Update on drug treatment of treatment refractory depression

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Outcome of STAR*D: effect of treatment step

Entry: 80% recurrent or chronic depression
Mean episodes, 6; mean duration, 25 months

Patients (%) 80

- Citalopram: n=3671, Response 50%, Remission 30%
- Step 2: n=1439, Response 30%, Remission 30%
- Step 3: n=390, Response 20%, Remission 20%
- Step 4: n=123, Response 10%, Remission 10%

STAR*D, Sequenced Treatment Alternatives to Relieve Depression

Outcome of STAR*D: effect of treatment step

Entry: 80% recurrent or chronic depression
Mean episodes, 6; mean duration, 25 months

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Total (theoretical)</th>
<th>n=123 Step 4</th>
<th>n=390 Step 3</th>
<th>n=1439 Step 2</th>
<th>n=3671 Citalopram</th>
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<tbody>
<tr>
<td></td>
<td>Response</td>
<td>Remission</td>
<td>Response</td>
<td>Remission</td>
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<td>80</td>
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</tbody>
</table>

STAR*D, Sequenced Treatment Alternatives to Relieve Depression
Model of depression and treatment

Frank et al 1991

Partial remission
Non-response

Remission
Recovery
Relapse
Recurrence

Treatment Phases
Acute
Continuation
Maintenance

Time

Severity

“Normalcy”
Symptoms
Syndrome

progression
to disorder
Reasons for poor outcomes in MDD

- Patient related
- Doctor related
Reasons for poor outcomes in MDD

Patient related (assuming correct diagnosis!)

- Non-adherence
- Comorbidity
  - Personality
  - Substance misuse
  - Physical illnesses / Pain
  - Anxiety
  - Psychosis
  - Ongoing stress
- Chronicity
- Frequent relapse

Doctor related
STAR*D study N=2,876

Patients with MDD

Treated with citalopram for 12 weeks

Anxious patients defined as:
– ≥ 7 on anxiety/somatisation

Response and remission rated with HAMD and QIDS-SR

Addressing patient factors

Thorough assessment of predisposing, precipitating and perpetuating factors

Address any that are tractable – consider all interventions available

Ensure adequate prophylaxis
Reasons for poor outcomes in MDD

Patient related

Doctor related

- Lack of clarity of thought
- Lack of awareness of the evidence base
- Unsystematic approach
- Therapeutic nihilism
Addressing doctor-related factors

Avoid delays
Effect of duration of un-treated depression on response and remission

De Diego-Adelino et al. (2010) J Affect Disorders 120:221 - 225
Addressing doctor-related factors

- Avoid delays
- Clear pharmacological strategy
Which antidepressant?

AIM- find one that the patient makes at least some response to
Which antidepressant? Differences in efficacy?

- There is evidence of differences in efficacy between antidepressants but the effect size is small
- Meta-analysis support for\(^1,2\)
  - Amitriptyline vs SSRIs
  - Venlafaxine, escitalopram, mirtazepine and sertraline vs “second generation” antidepressants
- More than 1 RCT showing benefit over another AD for\(^3,4\)
  - Clomipramine, venlafaxine, escitalopram, agomelatine
- Theoretical support for blockade of both 5-HT and NA\(^5\)

Choice of antidepressant drug

- Match antidepressant to individual patient as far as possible (S)
- In the absence of special factors:
  - choose antidepressants that are better tolerated and safer in overdose (S).
    - most evidence for SSRIs
      - with other newer antidepressants these are first line choices
    - Older TCAs reserved for if first line drug treatment has failed (D)
    - MAOIs not first line and should only be initiated by practitioners with expertise in treating mood disorders (D).

- In more severely ill patients, and where maximising efficacy is of overriding importance, consider:
  - Amitriptyline, clomipramine, venlafaxine (≥ 150 mg), escitalopram (20 mg), sertraline, mirtazapine
Which antidepressant?  
**Patient past history**

- Is there evidence of preferential response to 5-HT uptake blockade?
  - try escitalopram, clomipramine or sertraline
- Is there evidence of preferential response to NA blockade?
  - try reboxetine or desipramine
- If neither (or in doubt) try a dual action drug
  - Venlafaxine, duloxetine, amitriptyline, mirtazepine
- Has there been response, but poor tolerability of a TCA?
  - try venlafaxine or duloxetine
- Issue with poor tolerability?
  - Escitalopram or agomelatine
- Has there been a trial of an MAOI?
- Do not forget ECT
Switch or Augment or Combine?

Treating Depression After Initial Treatment Failure
Directly Comparing Switch and Augmenting Strategies in STAR*D

Bradley N. Gaynes, MD, MPH,* Stacie B. Dussetzina, PhD,† Alan R. Ellis, MSW,‡ Richard A. Hansen, PhD,§||
Joel F. Farley, PhD,||| William C. Miller, MD, PhD,¶¶ and Til Stürmer, MD, MPH¶¶

• 1292 patients who did not remit with citalopram and opted to go with medication at level 2
  – N = 565 augmentation (cit.+bupropion (279); cit.+buspirone (286))
  – N = 727 switch (bupropion (239); sertraline (238); venlafaxine (250)

• When matched, no difference in RR for remission:
• If had received 12 weeks of initial therapy:
  – Augmentation > switch: RR 1.9 (95% CI 1.16–3.11)
• Patients with residual symptoms:
  – Augmentation > switch: RR 1.32 (95% CI 1.03–1.70)

Clin Psychopharmacol 2012; 32: 114-119
RCTs of switching antidepressants: SSRI to SSRI vs SSRI to another AD (remission)

Remission rates 28% (for non-SSRIs) and 23.5% (for SSRIs)

Papakostas et al 2008
Lithium augmentation in TRD: 1\textsuperscript{st} vs 2\textsuperscript{nd} generation ADs

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Lithium Events Total</th>
<th>Placebo Events Total</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto, Fixed, 95% CI</th>
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<tbody>
<tr>
<td>1.1.1 TCAs or 1st Generation Agents</td>
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<td>Kantor et al 1986</td>
<td>1</td>
<td>4</td>
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<td>8</td>
<td>2</td>
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<td>Schöpf et al 1989</td>
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<td>Brown et al 1990</td>
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<td>7</td>
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<td>Joffe et al 1993</td>
<td>9</td>
<td>17</td>
<td>3</td>
<td>16.0%</td>
</tr>
<tr>
<td>Katona lofepramine 1995</td>
<td>9</td>
<td>12</td>
<td>11</td>
<td>17.0%</td>
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<td>Nierenberg et al 2003</td>
<td>2</td>
<td>17</td>
<td>3</td>
<td>8.9%</td>
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<tr>
<td>Total events</td>
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<td>Heterogeneity: Chi² = 6.52, df = 6 (P = 0.37); I² = 8%</td>
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<td>Test for overall effect: Z = 2.92 (P = 0.003)</td>
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<td>1.1.2 SSRIs or 2nd Generation Agents</td>
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<tr>
<td>Katona fluoxetine 1995</td>
<td>10</td>
<td>17</td>
<td>7</td>
<td>16.0%</td>
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<tr>
<td>Baumann et al 1996</td>
<td>6</td>
<td>10</td>
<td>2</td>
<td>14.0%</td>
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<tr>
<td>Joffe et al 2006</td>
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<td>9</td>
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<td>Total events</td>
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<td>Heterogeneity: Chi² = 1.59, df = 2 (P = 0.45); I² = 0%</td>
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<td>Test for overall effect: Z = 2.31 (P = 0.02)</td>
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<tr>
<td>Total (95% CI)</td>
<td>115</td>
<td>122</td>
<td>100.0%</td>
<td>2.89 [1.65, 5.05]</td>
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<tr>
<td>Total events</td>
<td>53</td>
<td>31</td>
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<td>Heterogeneity: Chi² = 8.13, df = 9 (P = 0.52); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 3.72 (P = 0.00002)</td>
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<tr>
<td>Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%</td>
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</table>

Response to lithium within and outside normal levels

post hoc analysis

LOCF, last observation carried forward; LSM, least squares means; MADRS, Montgomery-Åsberg Depression Rating Scale; MITT, modified intent-to-treat

Bauer et al 2010
Atypical antipsychotic augmentation in TRD/inadequate response to ADs

Figure 1. Primary Meta-Analytic Findings: Remission

Papakostas et al 2007

NOTE: Olanzapine and risperidone do not have a licence for augmentation of antidepressants in unipolar depression in Europe
Quetiapine augmentation of antidepressants following sub-optimal response

Aripiprazole augmentation after inadequate response to SSRI/SNRIs


Aripiprazole does not have a licences for augmentation in refractory depression in Europe
Modafinil augmentation of SSRIs

Patients with excessive fatigue or sleepiness despite adequate SSRI ≥ 8 weeks

All

HAMD$_{17} \geq 14$

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*Modafinil, N = 151; placebo, N = 149 at endpoint.  
*p = .07; mean difference in change = 1.1.  
†p = .06; mean difference in change = 1.1.  
‡p < .08; mean difference in change = 1.2.

*Modafinil, N = 85; placebo, N = 65 at endpoint.  
*p = .04; mean difference in change = 1.9.  
†p = .04; mean difference in change = 2.4.  
‡p = .05; mean difference in change = 2.2.

Fava et al 2005
Modafinil augmentation: meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges g [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abolfazli et al, 2011</td>
<td>-1.52 [-2.19 to -0.85]</td>
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<tr>
<td>DeBattista et al, 2003</td>
<td>-0.10 [-0.44 to 0.24]</td>
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<tr>
<td>Dunlop et al, 2007</td>
<td>-0.19 [-0.65 to 0.28]</td>
</tr>
<tr>
<td>Fava et al, 2005</td>
<td>-0.21 [-0.44 to 0.01]</td>
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<tr>
<td>Calabrese et al, 2010</td>
<td>-0.25 [-0.50 to 0.00]</td>
</tr>
<tr>
<td>Frye et al, 2007</td>
<td>-0.46 [-0.88 to -0.03]</td>
</tr>
</tbody>
</table>

Random-Effects Model

Favors Modafinil: -0.35 [-0.61 to -0.10]

Goss et al. 2013 J Clin Psychiatry 74:1101-1107
Other psychostimulants?

• Systematic review – Abbasowa et al. 2013 Nordic J Psych
  – Examined modafinil, methylphenidate, dexamphetamine, methylamphetamine and pemoline
    • Positive RCTs for modafinil
    • No clear evidence for efficacy of other stimulants
Pramipexol augmentation

Figure 1. Mixed-Effects Linear Regression Analysis of Montgomery-Asberg Depression Rating Scale (MADRS) Scores Over Time, by Treatment Group

N=60
p = 0.038
remission and response NS

Cusin et al. 2013 J Clin Psychiatry 74: e636-e641
# RCTs of lamotrigine augmentation of antidepressants

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnoses</th>
<th>N</th>
<th>Interventions</th>
<th>Duration</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
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<tbody>
<tr>
<td>Normann et al. J Clin Psychiatry. 2002</td>
<td>Acute depressive episode, 7 with bipolar disorder; variable treatment resistance</td>
<td>40</td>
<td>Parox 40 mg/d + lamot 200 mg/d or placebo</td>
<td>9 weeks</td>
<td>NS on HAM-D</td>
<td>Sign. on CGI-S and other secondary outcomes</td>
</tr>
<tr>
<td>Barbosa et al. J Clin Psychiatry. 2003</td>
<td>MDD (n=15) or bipolar II disorder (n = 8); failed at least 1 previous trial of an antidepressant</td>
<td>23</td>
<td>Fluox 20 mg/d + lamot 100 mg/d or placebo</td>
<td>6 weeks</td>
<td>NS on HAM-D</td>
<td>Sign. on CGI-S and CGI-I (responders: lamotrigine 85%, placebo 30%)</td>
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<tr>
<td>Santos et al. Prim Care Companion J Clin Psychiatry. 2008</td>
<td>MDD with nonresponse to 2 antidepressants</td>
<td>34</td>
<td>AD + lamot or plac</td>
<td>8 weeks</td>
<td>NS on MADRS</td>
<td>NS of CGI</td>
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<tr>
<td>Barbee et al. J Clin Psych 2011</td>
<td>MDD with failure of ≥ 1 antidepressant and HAM-D ≥ 15 after 8 weeks of prospective treatment with paroxetine</td>
<td>96</td>
<td>Parox (up to 62.5 mg/d) + lamot (up to 400 mg/d) or placebo</td>
<td>10 weeks</td>
<td>NS on MADRS</td>
<td>NS on HAM-D, CGI-Severity and CGI-I</td>
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</table>

AD – Antidepressant; NS - not statistically significant; HAM-D - Hamilton Depression Rating Scale; CGI - Clinical Global Impression Scale; CGI-S - CGI Severity; CGI-I - CGI Improvement; MADRS - Montgomery Asberg Depression Rating Scale.
Augmentation with l-tryptophan

• Tryptophan alone may have antidepressant properties (RCT, n=28 over 12/52: Thomson et al. 1982)

• Only one RCT as augmentation (Levitan et al. 2000)
  – N= 30, fluoxetine +/- tryptophan 2-4g over 8/52
  – Improved response at 1/52 and increased SWS

• Case series of:
  – Newcastle cocktail (Phenelzine+Li+tryp: Barker et al. 1987)
  – London cocktail (Clomip+Li+tryp: Hale et al. 1987)
  – Dalhousie cocktail (nefaz+pind+tryp: Dursun et al. 2001)

  Should only be initiated by practitioners with expertise in treating mood disorders (D).

• N.B. tryptophan discontinuation
Antidepressant combinations

Baseline   25
            20
            15
            10
             5
             0

HAM-D scores

Day of treatment

Fluoxetine (n=28)
Fluoxetine + mirtazapine (n=25)
Venlafaxine + mirtazapine (n=26)
Bupropion + mirtazapine (n=26)

p=0.011, difference between fluoxetine monotherapy and all combination treatment groups

CO-MED – Outcomes

Single dose of ketamine in TRD

Zarate et al 2006
24h response

NNT for remission:
24h: 5
3 days: 6
7 days: 7
(McGirr et al 2014)
Other lines of research

• Antiglucocorticoid treatments
  – Some positive data, but ADD study (metyrapone) negative

• N-acetylcysteine
  – Mainly been explored in bipolar depression

• L-methylfolate
  – 2 studies, 1 positive 1 negative

• NSAIDs
Celecoxib augmentation

Faridhosseini et al. 2014 Hum Psychopharmacol 29: 216-223

- Significant benefit on endpoint remission rates
- But....
  - n=160
  - Not TRD
  - Just for those with raised cytokines?
  - Trials just 4-6 weeks – how long should treatment be for?? (NB cardiac risks)
Addressing doctor-related factors

- Avoid delays
- Clear pharmacological strategy
- Use adequate trials of medication
Standard v high dose venlafaxine after SSRI failure/intolerance

**FIGURE 1.** Time to remission during treatment with standard or higher dose venlafaxine XR.

Thase et al 2006
Lack of significant improvement after 2–4 weeks treatment substantially reduces the probability of eventual sustained response (A).

After 4 weeks adequate treatment:
- if there is at least some improvement continue treatment with the same antidepressant for another 2–4 weeks (B),
- if there is no trajectory of improvement undertake a next-step treatment (B);
  - in patients who have failed a number of treatments consider longer trials (D).

After 6–8 weeks adequate treatment:
- if there is moderate or greater improvement continue the same treatment,
- if there is minimal improvement undertake a next-step treatment (B)
  - in patients who have failed a number of treatments consider longer trials before changing treatment (D).
Treatment trial duration

- Lack of significant improvement after 2–4 weeks treatment substantially reduces the probability of eventual sustained response (A).

- After 4 weeks adequate treatment:
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- After 6–8 weeks adequate treatment:
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  - if there is minimal improvement undertake a next-step treatment (B)
    - in patients who have failed a number of treatments consider longer trials before changing treatment (D).
Addressing doctor-related factors

- Avoid delays
- Clear pharmacological strategy
- Use adequate trials of medication
- Holistic treatment
CBT + AD v AD

Review: Dep Up: Psychology: Cognitive and behavioural therapies
Comparison: 09 Cognitive and behavioural therapies + ADs v ADs (with clinical management or GP care)
Outcome: 04 Depression scores: continuous measures post-treatment

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>Treatment Mean (SD)</th>
<th>N</th>
<th>Control Mean (SD)</th>
<th>SMD (fixed) 95% CI</th>
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<td>9.30 (7.50)</td>
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<td>11.30 (7.60)</td>
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<td>Murphy 1984 (US)</td>
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<td>8.23 (7.00)</td>
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<td>10.92 (8.22)</td>
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<td>Miller 1989 (US)</td>
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<td>15.30 (13.84)</td>
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<td>23.80 (14.84)</td>
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<td>Hautzinger 1996 (Ge)</td>
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<td>8.00 (5.50)</td>
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<td>Scott 1997 (UK)</td>
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<td>13.50 (5.30)</td>
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<td>Keller 2000 (US)</td>
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<td>10.80 (9.47)</td>
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<td>356</td>
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</table>

Test for heterogeneity: Chi² = 2.64, df = 6 (P = 0.85), I² = 0%
Test for overall effect: Z = 6.10 (P < 0.00001)

Total (95% CI)

Test for heterogeneity: Chi² = 2.64, df = 6 (P = 0.85), I² = 0%
Test for overall effect: Z = 6.10 (P < 0.00001)
Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis
Heijnen et al

7 Cohort studies n=958

Remission rates
Overall 61%
Without medication resistance 65%
With medication resistance 48%

Conclusions
1. ECT should be given early
2. ECT works in TRD
However observational studies may have multiple confounders e.g. length of episode etc.
Addressing doctor-related factors

- Avoid delays
- Clear pharmacological strategy
- Use adequate trials of medication
- Holistic treatment
- Monitor response and use critical decision points
Algorithm (ALGO) vs treatment as usual (TAU)

Rate of non-remitted patients (%)

Study duration (weeks)

TAU (N=74)  ALGO (N=74)

HR=2.0 (p=0.004)
Survival analysis (ITT group)

Addressing doctor-related factors

- Avoid delays
- Clear pharmacological strategy
- Use adequate trials of medication
- Holistic treatment
- Monitor response and use critical decision points
- Avoid therapeutic nihilism and instil (realistic) hope
Conclusions

• Beware malignant psychodynamics
• All antidepressants are not the same
• Have non-response strategies
  – Instil (realistic) hope
  – Do something!!
  – Work to an algorithm with critical decision points
  – Consider ECT
  – If stuck then get second opinion/refer