Treatment Resistant Depression: Where Are We

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Conflict of Interest

I have an interest in relation to one or more organisations that could be perceived as a possible conflict of interest in the context of this presentation. The organisations are:

Astra-Zeneca, GlaxoSmithKline, Lilly, Lundbeck, Servier
‘Real world’ efficacy of SSRIs (STAR*D)

- 2876 patients with major depression treated in primary care and psychiatric settings
- Flexible dose of citalopram up to 14 weeks (mean dose 42 mg daily)
- 80% of patients had chronic or recurrent depression
- Response rate 47%; remission rate 28%

SSRI, selective serotonin reuptake inhibitor; STAR*D, Sequenced Treatment Alternatives to Relieve Depression

Trivedi et al 2006
Which antidepressant?
Probability of being ranked as among the 4 most effective treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirtazapine</td>
<td>24.4</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>23.7</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>22.3</td>
</tr>
<tr>
<td>Sertraline</td>
<td>20.3</td>
</tr>
<tr>
<td>Citalopram</td>
<td>3.4</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>0.7</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>0.1</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>0.0</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Cipriani et al 2009
Increased efficacy of combination antidepressant treatment

Remission

- Fluoxetine (n=28): 25%
- Fluoxetine + mirtazapine (n=25): 52%
- Venlafaxine + mirtazapine (n=26): 58%
- Bupropion + mirtazapine (n=26): 48%

HAM-D, Hamilton Depression Rating Scale
Negative Study of Combination Treatment

Rush et al, 2011
Early Pharmacological Approaches to TRD (NICE)

1. Consider raising dose (allows time for natural recovery to start and to carry out further assessments)

2. Switch (initially another SSRI, or a better tolerated new generation antidepressant)

3. An antidepressant of a different pharmacological class that may be less well tolerated (eg a TCA (but not dosulepin), venlafaxine, or an MAOI)
Different Class vs SSRIs Switch in SSRI-Resistant patients

Poirier and Boyer, 1999
Lenox-Smith et al, 2001
Thase et al, 2001
Rush et al, 2006

Favors within-class switch
Favors across-class switch

Combined

Risk Ratio

Papakostos et al 2007
Amitriptyline v. the rest: still the leading antidepressant after 40 years of randomised controlled trials

CORADDU BARBUI AND MATTHEW HOTOPF

*British Journal of Psychiatry* 178, 129-144

A systematic review of 187 randomised trials of amitriptyline v. tricyclics/heterocyclics and SSRIs showed a 2.5% difference in the proportion of responders in favour of amitriptyline (number needed to treat 40; OR 1.12).
Further Management (NICE Guidelines)

1. Add CBT
2. Lithium Augmentation
3. Antidepressant combination (mirtazapine with SSRI or SNRI)
4. Atypical antipsychotic augmentation
5. Augmentation with anticonvulsants, T3, pindolol, buspirone NOT recommended
Lithium Augmentation of Antidepressant treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Lithium, N/N</th>
<th>Control, N/N</th>
<th>Fixed Effects OR and 95% CI</th>
<th>Fixed Effects OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heninger et al (1983)</td>
<td>5/8</td>
<td>0/7</td>
<td></td>
<td>23.57 (1.00 to 556.08)</td>
</tr>
<tr>
<td>Kantor et al (1986)</td>
<td>1/4</td>
<td>0/3</td>
<td></td>
<td>3.00 (0.09 to 102.05)</td>
</tr>
<tr>
<td>Zusky et al (1988)</td>
<td>3/8</td>
<td>2/8</td>
<td></td>
<td>1.80 (0.21 to 15.41)</td>
</tr>
<tr>
<td>Schöpf et al (1989)</td>
<td>7/14</td>
<td>0/13</td>
<td></td>
<td>27.00 (1.35 to 541.57)</td>
</tr>
<tr>
<td>Browne et al (1990)</td>
<td>3/7</td>
<td>2/10</td>
<td></td>
<td>3.00 (0.35 to 25.87)</td>
</tr>
<tr>
<td>Stein and Bernadt (1993)</td>
<td>2/16</td>
<td>4/18</td>
<td></td>
<td>0.50 (0.08 to 3.19)</td>
</tr>
<tr>
<td>Joffe et al (1993)</td>
<td>9/17</td>
<td>3/16</td>
<td></td>
<td>4.88 (1.01 to 23.57)</td>
</tr>
<tr>
<td>Katona et al (1995)</td>
<td>15/29</td>
<td>8/32</td>
<td></td>
<td>3.21 (1.09 to 9.48)</td>
</tr>
<tr>
<td>Baumann et al (1996)</td>
<td>6/10</td>
<td>2/14</td>
<td></td>
<td>9.00 (1.27 to 63.89)</td>
</tr>
<tr>
<td>Nierenberg et al (2003)</td>
<td>2/18</td>
<td>3/17</td>
<td></td>
<td>0.58 (0.08 to 4.01)</td>
</tr>
<tr>
<td>Total</td>
<td>53/131</td>
<td>24/138</td>
<td></td>
<td>3.11 (1.80 to 5.37)</td>
</tr>
</tbody>
</table>

Test for Heterogeneity: $\chi^2 = 11.90$, df = 9, $p = .22$, $I^2 = 24.4\%$
Test for Overall Effect: $Z = 4.06$, $p < .0001$

Crossley and Bauer 2007
Mirtazapine augmentation of SSRI Treatment

26 patients on SSRI-like-drugs, randomised to either mirtazapine augmentation (15-30mg at night) or placebo for 4 weeks

<table>
<thead>
<tr>
<th>Mirtazapine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>7/11 (64%)</td>
</tr>
</tbody>
</table>

p = 0.048

(Carpenter et al, 2002)
Outcome of STAR*D: augmentation

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

![Graph showing outcomes of different treatments]

Trivedi et al 2006; Madhukar et al 2006; Nierenberg et al 2006; McGrath et al 2006
Antipsychotic drugs in Depression

• Antipsychotic drugs have an established role in the treatment of depressive psychosis
• Role of antipsychotic drugs in treatment of refractory depression less clear.
• Now good evidence that certain atypical antipsychotic drugs can augment ineffective SSRI treatment at doses probably too low to block dopamine receptors significantly
Meta-analysis of atypical antipsychotic augmentation of SSRI treatment

Agent and study | Treatment, n | Control, n | Odds ratio (fixed) (95% CI) | Odds ratio (fixed) (95% CI)
--- | --- | --- | --- | ---
**Olanzapine studies**
Shelton et al | 6 / 10 | 2 / 10 | 6.00 (0.81, 44.35) | 1.42 (0.74, 2.74)
Shelton et al | 25 / 146 | 18 / 142 | 1.97 (0.94, 4.13) | 1.47 (0.74, 2.91)
Corya et al | 69 / 230 | 10 / 56 | 2.37 (1.20, 4.70) | 1.83 (1.30, 2.56)
Thase et al I | 24 / 102 | 18 / 104 |  |  |
Thase et al II | 30 / 98 | 16 / 102 |  |  |
Subtotal | 586 | 414 |  |  |
**Risperidone studies**
Mahmoud et al | 26 / 137 | 12 / 131 | 2.32 (1.12, 4.83) |  |
Keitner et al | 32 / 62 | 8 / 33 | 3.33 (1.30, 8.53) | 2.25 (0.32, 15.76)
Reeves et al | 4 / 12 | 2 / 11 |  |  |
Subtotal | 211 | 175 |  |  |
**Quetiapine studies**
Khullar et al | 3 / 8 | 0 / 7 | 9.55 (0.40, 225.19) |  |
Mattingly et al | 11 / 24 | 2 / 13 | 4.65 (0.84, 25.66) |  |
McIntyre et al | 9 / 29 | 5 / 29 | 2.16 (0.62, 7.49) |  |
Earley et al | 110 / 327 | 38 / 160 | 1.63 (1.06, 2.50) |  |
El-Khalilii et al | 112 / 289 | 35 / 143 | 1.95 (1.25, 3.06) |  |
Subtotal | 677 | 352 | 1.89 (1.41, 2.54) |  |
**Aripiprazole studies**
Berman et al | 47 / 181 | 27 / 172 | 1.88 (1.11, 3.19) |  |
Berman et al | 64 / 174 | 32 / 169 | 2.49 (1.52, 4.08) |  |
Marcus et al | 47 / 185 | 28 / 184 | 1.90 (1.13, 3.19) |  |
Subtotal | 540 | 525 | 2.09 (1.55, 2.81) |  |
**Total** | 2014 | 1466 | 2.00 (1.69, 2.37) |  |

SSRI, selective serotonin reuptake inhibitor; CI, confidence interval

Nelson JC, Papakostas GI. Am J Psychiatry 2009;166:980-91
Meta-Analysis of Atypical Antipsychotic augmentation of SSRI Treatment (ii)

- Response rate 44.2% vs 29.9%
- Remission rate 30.7% vs 17.2%
- For Response NNT= 9
- For Remission NNT= 9
- Discontinuation (adverse effects) NNH= 17

(Papakostas and Nelson, 2009)
Response Rate of 51 Patients with Depressive Psychosis to three treatments

% Response

0 20 40 60 80 100

Amitrip  Perphen  Ami+Per

Spiker et al 1985
Meta-Analysis in Depressive Psychosis

- Tricyclic antidepressants are more effective than second generation antidepressants
- Antidepressants alone are more effective than antipsychotic drugs given alone
- Uncertain if antidepressant drugs combined with antipsychotic agents are more effective than antidepressants alone

Wijkstra et al 2006
Efficacy of Antidepressant-Antipsychotic Combination in Depressive Psychosis

Wijkstra et al, 2010

Response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean HRSD (ITT)</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipramine</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Venlafaxine + Quetiapine</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>

(42) (39) (41) (33%) (52%) (66%)

Wijkstra et al, 2010
## NNTs of Some Treatments for Resistant Depression

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine vs SSRI (switch)</td>
<td>13</td>
</tr>
<tr>
<td>Lithium Augmentation (low n)</td>
<td>5</td>
</tr>
<tr>
<td>Triiodothyronine Augmentation</td>
<td>13</td>
</tr>
<tr>
<td>Atypical Augmentation</td>
<td>9</td>
</tr>
</tbody>
</table>
Neural Circuitry of Depression and Deep Brain Stimulation

Deep Brain Stimulation (DBS) is an established treatment for Parkinson’s Disease

DBS is undergoing trials for patents with refractory depression as an alternative to psychosurgery

Efficacy depends on selection of most appropriate target region for stimulation
Abnormal Brain Circuitry in Mood Disorder

Proposed **reduced responsiveness** in areas of brain associated with cognitive control.

Proposed **increased responsiveness** in areas of brain involved in emotional regulation.

DLPFC: Dorsolateral prefrontal cortex
VLPFC: Ventrolateral prefrontal cortex
DMPFC: Dorsomedial prefrontal cortex
ACG: Anterior cingulate gyrus

Langham and McDonald 2009
Increased Activity in the ACC in Depression

Drevets et al, 1997
Effect of Subcallosal DBS in 20 Patients with Refractory Depression

Change in HRSD-17 Score From Baseline

Total HAM-D 17 Score

All time points
p < 0.001

(Lozano et al, 2008)
From: Deep Brain Stimulation for Treatment-Resistant Depression: Follow-Up After 3 to 6 Years


Figure Legend:

Hamilton Depression Rating Scale (HAM-D) Scores for Patients With Treatment-Resistant Depression (N=20) at Baseline, at 1, 2, and 3 Years After Surgery for Deep Brain Stimulation, and at Last Follow-Up Visita

a Error bars indicate standard error of the mean.
DBS studies

• By six months 60% of patients responded and 35% met remission. Response maintained at three years although two non-responders died by suicide
• Adverse effects. Wound infection in five patients. One peri-operative seizure.
• DBS study in Depression at Queens Square starting later this year
Ketamine as an Antidepressant

• Ketamine is an antagonist at glutamate NMDA receptors
• Ketamine prevents ECS induced changes in LTP in rats (Stewart and Reid, 1994)
• Intravenous ketamine can provide some temporary relief from depression in resistant depression (bipolar and unipolar)
Ketamine blocks the NMDA Receptor ion channel

Ketamine produces a rapid alleviation of depression in TRD

Conclusions

- First line treatment of depression with SSRIs has a modestly useful effect but many patients are still symptomatic after several weeks treatment.
- In non-responders switching antidepressants is generally safe and about a further 25% of patients will be helped. It’s be worth trying older drugs (TCAs/MAOIs) in some patients.
- The use of mirtazapine and SSRIs is probably the safest antidepressant combination and may be helpful in SSRI-resistant depression. Lithium still has a role, as do atypical antipsychotic drugs.
- There is a need to develop innovative and acceptable treatments for resistant depression.