Treating “treatment resistant” depression

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Declaration/disclaimer

Last 3 years

Consultancies
• Lundbeck, Servier, Alkermes

Honoraria/support for meetings
• Lundbeck, Servier

Grant support
• AstraZeneca, Servier

Some of the drug strategies describe off-label use

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What is TRD?

*Ruhe et al 2012* (J Aff Dis 137:35-45)

- Systematic review identified 5 staging models
- Evolution over time from single antidepressant adequacy ratings towards being multidimensional and continuum-based with disorder characteristics
- Reliability and predictive utility hardly assessed (latter best for Maudsley Staging Model)

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Problems with TRD as usually used

• Implies a cut-off where ‘resistance’ starts and the number of treatments (usually defined as 2 adequate) is arbitrary
• Assumes we know what constitutes a treatment
• Doesn’t include psychological treatments
• Doesn’t take into account:
  – treatment intolerance or partial response
  – patient and illness characteristics
  – psychosocial factors
  – treatment history in past episodes
• Message given to patient/ pejorative label

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“Although the term [TRD] is commonly used, and it can be seen as a useful ‘short-hand’ to refer to difficulties in achieving adequate improvement with treatment, it has problems that led the GDG to a move away from its use in this guideline update.

The GDG preferred to approach the problem of inadequate response by considering sequenced treatment options rather than by a category of patient.”

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Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2000 British Association for Psychopharmacology guidelines

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RH McAllister-Williams Reader in Clinical Psychopharmacology, Institute of Neuroscience, Newcastle University, Royal Victoria Infirmary, Newcastle upon Tyne, UK.
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J Scott Professor of Psychological Medicine, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK.
A Tylee Professor of Primary Care Mental Health, NIHR Biomedical Research Centre and Health Services and Population Research Department, Institute of Psychiatry, Kings College London, London, UK.

On Behalf of the Consensus Meeting; endorsed by the British Association for Psychopharmacology

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## Factors predicting response to antidepressant treatment

<table>
<thead>
<tr>
<th>Appears associated with poorer response</th>
<th>Not associated or inconsistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid anxiety</td>
<td>Age</td>
</tr>
<tr>
<td>Nonresponse to treatment in current episode</td>
<td>Age of onset</td>
</tr>
<tr>
<td>No partner/spouse</td>
<td>Duration of episode</td>
</tr>
<tr>
<td>Poorer social support</td>
<td>Gender</td>
</tr>
<tr>
<td>Severity of illness (especially in first episode)</td>
<td>Number of recurrences</td>
</tr>
<tr>
<td>Significant physical illness</td>
<td></td>
</tr>
<tr>
<td>Therapist factors</td>
<td></td>
</tr>
<tr>
<td>Unemployed, poorer education</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4.11 Factors predicting response to antidepressant treatment.** Adapted from Bagby et al [28] ©Canadian Medical Association.

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Routes to ‘non-response’

Sequential drugs first episode

Sequential drugs n’th episode

Treatment history

+ +

Relapse on treatment

Duration

Insufficient response to treatment

Severity
Dose
Adherence
Tolerance
Diagnosis
Comorbidity
Personality
Substances
Social

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Outcome of STAR*D: steps

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

Outcome of STAR*D: Tolerability

Deakin J & O’Loughlin C 2009 J Psychopharmacol. 23:605-12

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**Outcome of STAR*D: relapse**

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

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Rush et al 2006
Treatment of ‘non-response’

• How
• When
• What

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Effect of expectation on RCT outcome

- Meta-analysis of 90 RCTs

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Effect of preference on RCT outcome

Mergl et al 2011 Psychother Psychosom 80:39-47

- Primary care patients with preference determined before treatment.
- Randomised to sertraline or group CBT or patient choice

![Graph showing improvement in HAMD-17 total scores over time for sertraline and CBT-G groups.](image)
Placebo response: monitoring

Systematic review of placebo treatment arms of 41 RCTs
Group 1 = weekly FU (N=941)
Group 2 = skip wk 5 (N=1449)
Group 3 = skip wks 3+5 (N=673)

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Change in treatment at 6 weeks after non-response

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Response
Baseline

HDRS
0%
72%

sertraline
50mg
100mg

Weeks

Licht RW & Qvitza S 2002 Psychopharmacology 161:143–151
Blind switching to same drug after non-response

- Historical non-response + prospective 7 week treatment
- ‘Switching’ blindly to same antidepressant resulted in 30%-50% of non-responders becoming responders after 12 weeks

Shelton RC et al 2005
J Clin Psychiatry 66:1289-97

Corya SA et al 2006
Depress Anxiety 23:364-72

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Structured treatment (algorithm-based) v TAU RCTs

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Principles:

• Systematic steps (with flexibility)
• Critical decision points (time defined)
• Standardised assessment
Structured treatment (algorithm-based) v TAU RCTs

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<table>
<thead>
<tr>
<th>Trivedi 2004</th>
<th>Yoshino 2009</th>
<th>Bauer 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>AD1</td>
<td>AD1</td>
</tr>
<tr>
<td>Step 2</td>
<td>AD2 or Li augmentation</td>
<td>AD2 or Li augmentation</td>
</tr>
<tr>
<td>Step 3</td>
<td>AD2 (diff class) or augmentation</td>
<td>TCA or Li augmentation</td>
</tr>
<tr>
<td>Step 4</td>
<td>Li augmentation</td>
<td>Combine AD</td>
</tr>
<tr>
<td>Step 5</td>
<td>Combine AD</td>
<td></td>
</tr>
<tr>
<td>Step 6</td>
<td>ECT</td>
<td></td>
</tr>
</tbody>
</table>
Structured treatment (algorithm-based) v TAU RCTs

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Outcomes:

- Trivedi MH et al 2004 Arch Gen Psychiatry 61:669-80
  - Greater response in algorithm group by week 12 with advantage sustained to 12 months (but relatively small effect)

  - Greater remission rate at 6 months in algorithm group but at cost of poorer tolerability and dropout

- Bauer A et al 2009 J Clin Psychopharmacol. 29:327-33
  - Greater remission rate at 12 weeks in algorithm group in inpatient setting
How long is an adequate trial?

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Malt et al 1999 BMJ 318(7192):1180-4
Natural history of depressive episodes - NIMH Collaborative Depression Study

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

When to change treatment

• Context
  – Stage of treatment
  – Duration
  – Social factors/life events

• Trajectory (needs accurate assessment)

• Severity

• Nature of change

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Difficulties in assessing the evidence for next-step treatment

- Natural course of response
- Study limitations
  - Very limited number of comparisons between options,
  - Very few adequately controlled studies for dose increase or switching
  - Small non-replicated studies for augmentation/combination
- Different methodologies make comparisons difficult
  - Timing of intervention
  - Patient inclusion criteria
  - Number of failed trials
  - Response definition
- Absence of long-term data

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Considerations in choosing next-step strategy

- **Treatment optimisation/dose increase**
  - Low/moderate dose so far
  - Side-effects minimal
  - Short(ish) duration
  - Patient choice

- **Switch**
  - No response
  - Side-effects
  - Past history of non-response to same treatment
  - Patient choice

- **Augment/combine**
  - Partial response
  - Side-effects minimal
  - Time constraints
  - Patient choice

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Optimisation/dose increase

- **Antidepressants**
  - Lack of evidence for most SSRIs, if present small effect
  - Escitalopram 20mg > 10mg
  - Venlafaxine 300mg > 150mg
  - Tricyclics doses 300mg > 150mg
  - MAOIs: phenelzine 90mg > 45mg

Cost is increase in side effects

(Burke et al 2002 J Clin Psychiatry. 63:331-6
Thase et al 2006 J Clin Psychopharmacol 26:250–258

- **Lithium**
  - Li+ >0.6mM/L (Bauer et al 2013 J Aff Dis 151: 209–219)
Switch treatment

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- Little evidence to choose between antidepressants or for pharmacological rationale to switch to a different mechanism of action

- However, modest effect switching from SSRI to venlafaxine (Ruhe et al 2006 Br J Psychiatry 189:309-16)

- Quetiapine monotherapy non-inferior to lithium augmentation (Bauer et al 2013 J Aff Dis 151: 209–219)
Add a treatment

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- **CBT** (? other psychological treatments) (Wiles et al 2014 HTA 18 (31))

- **Atypical antipsychotics**


- **Second antidepressant**
  - ?Mirtazapine (Carpenter et al 2002 Biol Psychiatry 51:183–188), otherwise evidence lacking

- **ECT**
CBT + AD vs AD (not after treatment failure)

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>
</tr>
</thead>
<tbody>
<tr>
<td>02 HRSD scores post-treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hautzinger (in-pats)</td>
<td>20</td>
<td>9.30 (7.50)</td>
<td>22</td>
<td>11.30 (7.60)</td>
<td></td>
</tr>
<tr>
<td>Murphy 1984 (US)</td>
<td>22</td>
<td>8.23 (7.00)</td>
<td>24</td>
<td>10.92 (8.22)</td>
<td></td>
</tr>
<tr>
<td>Miller 1989 (US)</td>
<td>14</td>
<td>15.30 (13.84)</td>
<td>17</td>
<td>23.80 (14.84)</td>
<td></td>
</tr>
<tr>
<td>Hautzinger 1996 (Ge)</td>
<td>32</td>
<td>8.00 (5.50)</td>
<td>24</td>
<td>8.80 (6.80)</td>
<td></td>
</tr>
<tr>
<td>Scott 1997 (UK)</td>
<td>18</td>
<td>13.50 (5.30)</td>
<td>16</td>
<td>16.50 (6.80)</td>
<td></td>
</tr>
<tr>
<td>Keller 2000 (US)</td>
<td>226</td>
<td>10.80 (9.47)</td>
<td>220</td>
<td>15.80 (9.49)</td>
<td></td>
</tr>
<tr>
<td>Thompson 2001 (US)</td>
<td>36</td>
<td>12.00 (6.90)</td>
<td>33</td>
<td>15.00 (6.20)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>368</td>
<td></td>
<td>356</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 2.64, df = 6 (P = 0.85), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 6.10 (P &lt; 0.000001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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NICE Guideline 2009
CBT+AD vs AD after one treatment failure

Patients randomised to CBT in addition to AD or usual care (continuing AD) after failure to respond to >6 weeks AD treatment in primary care.

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Wiles et al 2014 Health Technol Assess 18(31)
Atypical antipsychotic augmentation

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### Antipsychotic studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Placebo n/N</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman 2007 [75]</td>
<td>47/181</td>
<td>27/172</td>
<td>1.88 (1.11 – 3.19)</td>
</tr>
<tr>
<td>Berman 2009 [82]</td>
<td>48/174</td>
<td>24/169</td>
<td>2.30 (1.33 – 3.97)</td>
</tr>
<tr>
<td>Marcus [76]</td>
<td>47/185</td>
<td>28/184</td>
<td>1.90 (1.13 – 3.19)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>142/540</td>
<td>79/523</td>
<td>2.01 (1.48 – 2.73)</td>
</tr>
</tbody>
</table>

Heterogeneity: $Q = 0.34, I^2 = 0\%, p = .84$

### Olanzapine/fluoxetine studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Placebo n/N</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corya [25]</td>
<td>58/230</td>
<td>23/114</td>
<td>1.33 (0.77 – 2.30)</td>
</tr>
<tr>
<td>Shelton 2001 [27]</td>
<td>4/10</td>
<td>2/10</td>
<td>2.67 (0.36 – 19.71)</td>
</tr>
<tr>
<td>Shelton 2005 [26]</td>
<td>19/146</td>
<td>29/210</td>
<td>0.89 (0.48 – 1.67)</td>
</tr>
<tr>
<td>Thase 1 [85]</td>
<td>24/110</td>
<td>18/102</td>
<td>1.45 (0.73 – 2.89)</td>
</tr>
<tr>
<td>Thase 2 [85]</td>
<td>30/97</td>
<td>16/101</td>
<td>2.38 (1.20 – 4.72)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>135/584</td>
<td>88/537</td>
<td>1.42 (1.01 – 2.00)</td>
</tr>
</tbody>
</table>

Heterogeneity: $Q = 4.72, I^2 = 15.19\%, p = .32$

### Quetiapine studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Placebo n/N</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer [81]</td>
<td>110/327</td>
<td>38/160</td>
<td>1.62 (1.06 – 2.50)</td>
</tr>
<tr>
<td>El-Khalili [83]</td>
<td>112/289</td>
<td>35/143</td>
<td>1.95 (1.24 – 3.05)</td>
</tr>
<tr>
<td>McIntyre [84]</td>
<td>9/29</td>
<td>5/29</td>
<td>2.16 (0.62 – 7.49)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>231/645</td>
<td>78/332</td>
<td>1.79 (1.33 – 2.42)</td>
</tr>
</tbody>
</table>

Heterogeneity: $Q = 0.42, I^2 = 0\% p = .81$

### Risperidone studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Placebo n/N</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keimer [73]</td>
<td>22/62</td>
<td>6/33</td>
<td>2.48 (0.89 – 6.91)</td>
</tr>
<tr>
<td>Mahmoud [44]</td>
<td>26/137</td>
<td>12/131</td>
<td>2.32 (1.12 – 4.83)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>48/199</td>
<td>18/164</td>
<td>2.37 (1.31 – 4.30)</td>
</tr>
</tbody>
</table>

Heterogeneity: $Q = .01, I^2 = 0\% p = .92$

Total: 556/1968 vs 263/1558

Heterogeneity: $Q = 9.20, I^2 = 0\% p = .69$

Figure 2. Remission rates by drug and overall.
Lithium augmentation in TRD: placebo controlled studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Lithium n/N</th>
<th>Control n/N</th>
<th>OR (fixed) 85% CI</th>
<th>OR (fixed) 85% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heninger 1983</td>
<td>5/8</td>
<td>0/7</td>
<td>23.57 [1.00, 556.08]</td>
<td></td>
</tr>
<tr>
<td>Kantor 1986</td>
<td>1/4</td>
<td>0/3</td>
<td>3.00 [0.09, 162.05]</td>
<td></td>
</tr>
<tr>
<td>Zusky 1988</td>
<td>3/8</td>
<td>2/8</td>
<td>1.80 [0.21, 15.41]</td>
<td></td>
</tr>
<tr>
<td>Schoepf 1989</td>
<td>7/14</td>
<td>0/19</td>
<td>27.00 [1.35, 541.57]</td>
<td></td>
</tr>
<tr>
<td>Browne 1990</td>
<td>3/7</td>
<td>2/10</td>
<td>3.00 [0.35, 25.87]</td>
<td></td>
</tr>
<tr>
<td>Stein 1993</td>
<td>2/16</td>
<td>4/18</td>
<td>0.50 [0.08, 3.19]</td>
<td></td>
</tr>
<tr>
<td>Joffe 1993</td>
<td>9/17</td>
<td>3/16</td>
<td>4.88 [1.01, 23.57]</td>
<td></td>
</tr>
<tr>
<td>Kalona 1995</td>
<td>15/29</td>
<td>8/32</td>
<td>3.21 [1.09, 9.48]</td>
<td></td>
</tr>
<tr>
<td>Baumann 1998</td>
<td>6/10</td>
<td>2/14</td>
<td>9.00 [1.27, 63.89]</td>
<td></td>
</tr>
<tr>
<td>Nierenberg 2003</td>
<td>2/18</td>
<td>3/17</td>
<td>0.58 [0.08, 4.01]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>131</td>
<td>138</td>
<td>3.11 [1.80, 5.37]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 53 (Lithium), 24 (Control)
Test for heterogeneity: Chi^2 = 11.90, df = 9 (P = 0.22), I^2 = 24.4%
Test for overall effect: Z = 4.06 (P < 0.0001)

Response 40% 17%

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Lithium augmentation v quetiapine monotherapy and augmentation after 1-2 treatment failures


Response
24%
27%
32%

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Outcome of a 4-step algorithm in depressed inpatients

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35% psychotic, 41% duration >1 year, 44% failed adequate treatment (excluding a TCA or fluvoxamine)

A treatment algorithm:
warning: weak evidence base + adapt to gaps and history

SSRI/s → SNRI → TCA → MAOI → Review options
- escitalopram (20mg)
- venlafaxine (→high dose)
- amitriptyline
- clomipramine (→high dose)
- phenelzine (→high dose)

+ Atypical APS (mirtazapine)
+ lithium
+ tryptophan
+ ECT
+ CBT
+ CBT/BA

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Conclusions

- Evidence is poor for choosing between next-step treatments
- There is evidence for the importance of having a structured treatment plan, not just fire-fighting
- Individualise treatments to your patient’s circumstances
- Assume that your patient will not respond and plan the next-step treatment from the start
- Use standardised assessments and planned follow-up
- Be clear about the timescale and do something
- Always combine drug treatment with psychosocial approaches
- Consider ECT relatively early
- Consider tertiary referral
- Prioritise relapse prevention

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Monitoring outcomes

Symptom scores
- Personal Health Questionnaire (9-item): PHQ-9
- Hospital Anxiety and Depression Scale: HADS
- Beck Depression Inventory: BDI
- Quick Inventory of Depressive Symptomatology (Self-Report): QIDS-SR 16
- Observer ratings: MADRS, HAMD, CGI

Other
- Euroqol (EQ5D) for quality of life
- Global Assessment of Functioning (GAF)