Multi-Therapy Resistant Depression: Clinical utility of the concept and treatment options to consider

R. Hamish McAllister-Williams, MD, PhD, FRCPsych

Reader in Clinical Psychopharmacology
Newcastle University
Hon. Consultant Psychiatrist
Regional Affective Disorders Service, RVI
Disclosure / conflict of interest

I work clinically in a tertiary level specialist affective disorders service in Northumberland Tyne and Wear NHS FT

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 the subject of this presentation. The relationships are summarised below:

<table>
<thead>
<tr>
<th>Interest</th>
<th>Name of organisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speaker fees</td>
<td>AstraZeneca, Bristol Myers-Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck Sharp &amp; Dohme, Pfizer, Servier, Wyeth</td>
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<td>Consultancy fees</td>
<td>AstraZeneca, Bristol Myers-Squibb, Cyberonics, Eli Lilly, Janssen-Cilag, <strong>LivaNova</strong>, Lundbeck, Merck Sharp &amp; Dohme, Servier, Wyeth</td>
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<tr>
<td>Independent investigator-led research support</td>
<td>AstraZeneca, Eli Lilly, Wyeth</td>
</tr>
</tbody>
</table>

I do not hold any shares in, nor have any ongoing financial relationship with, any pharmaceutical company.
Model of depression and treatment

Frank et al 1991
Guidelines – NICE & BAP

2009

Depression

The treatment and management of depression in adults

This is a partial update of NICE clinical guideline 23

2015

Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines

Anthony Cleare, CM Parfian and AH Young
With expert co-authors (in alphabetical order):
IM Anderson, D Christmas, R2 Cowen, C Dickens, IN Ferrier, J Geddes, S Gibbons, PM Haddad, C Katona, G Lewis, A Malizia, RH McIntosh-Williams, P Ramchandani, J Scott, D Taylor, R Uher and the members of the Consensus Meeting

Endorsed by the British Association for Psychopharmacology

Abstract

A revision of the 2008 British Association for Psychopharmacology evidence-based guidelines for treating depressive disorders with antidepressants was undertaken in order to incorporate new evidence and to update the recommendations where appropriate. A consensus meeting involving experts in depressive disorders and their management was held in September 2012. Key areas in treating depression were reviewed and the strength of evidence and clinical implications were considered. The guidelines were then revised after intensive feedback from participants and interested parties. A literature review is provided which identifies the quality of evidence upon which the recommendations are made. These guidelines cover the nature and detection of depressive disorders, acute treatment with antidepressant drugs, choice of drug versus alternative treatment, practical issues in prescribing and management, new-study treatment, relapse prevention, treatment of nausea, and stopping treatment. Significant changes since the last guidelines were published in 2008 include the availability of new antidepressant treatment options, improved evidence supporting certain augmentation strategies (e.g., rTMS and mono), management of potential long-term side effects, updated guidance for prevention in elderly and adolescent populations and updated guidance for optimal prescribing. Suggestions for future research priorities are also made.

Keywords

Antidepressants, depression, depressive disorders, treatment, evidence-based guidelines

1 Professor of Psychopharmacology & Affective Disorders, King’s College London, Institute of Psychiatry, Psychology and Neurosciences, Centre for Affective Disorders, London, UK
2 Professor of Bipolar Psychopharmacology and Intervention, Institute of Psychiatry, Psychology and Neurosciences, Centre for Affective Disorders, London, UK
3 Professor of Psychology and Chair of Mood Disorders, King’s College London, Institute of Psychiatry, Psychology and Neurosciences, Centre for Affective Disorders, London, UK
4 Professor and Honorary Consultant Psychiatrist, University of Manchester Department of Psychology, University of Manchester, Manchester, UK
5 Consultant Psychiatrist, Advanced Intervention Service, Middlesbrough Hospital and Medical School, Middlesbrough, UK
6 Professor of Psychopharmacology, Psychopharmacology Research Unit, Neuroscience Building, University Department of Psychiatry, University of Oxford, Oxford, UK
7 Professor of Psychological Medicine, University of Exeter Medical School and Exeter Partnership Trust, Exeter, UK
8 Professor of Psychiatry, Honorary Consultant Psychiatrist, School of Neurology, Neurology & Psychiatry, Royal Victoria Infirmary, Newcastle upon Tyne, UK
9 Consultant Psychiatrist, Sandwell House, Greater Manchester West Mental Health NHS Foundation Trust, Salford, UK
10 Consultant in Neuropsychopharmacology and Intervention, South Manchester NHS Trust, Wythenshawe Hospital, Manchester, UK
11 Reader in Clinical Psychopharmacology, Institute of Neuroscience, Newcastle University, Royal Victoria Infirmary, Newcastle upon Tyne, UK
12 Reader in Child and Adolescent Psychiatry, Centre for Mental Health, Imperial College London, London, UK
13 Associate Professor, Canada Research Chair in Early Interventions, Dalhousie University, Department of Psychiatry, Halifax, NS, Canada
14 Other members of the consensus meeting: Prof DavidSupported, Prof Thomas Dwyer, Dr David Offord, Prof Guy Goodwin, Prof Tony Hulse, Prof Louise Howard, Prof Brian Leonard, Dr Alan Lannan-Smith, Prof Keith Mottolese, Dr Stuart Montgomery, Prof Ian Reid, Prof Barbara J Tansley, Dr Tim White.

Corresponding authors: Anthony Cleare, King’s College London, Institute of Psychiatry, Psychology and Neurosciences, Centre for Affective Disorders, De Crespigny Park, London SE5 9M advertising campaigns for minor depression.

NICE clinical guideline 90

Developed by the National Collaborating Centre for Mental Health
Maximising outcomes in depression

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

Bauer et al. J Clin Psychopharmacol
“Measurement Based Care (MBC)” (guideline- and rating scale-based decisions)

- Outpatients with moderate to severe MDD
- Randomized to 24 weeks of either MBC (N=61) or standard treatment (N=59).
- Pharmacotherapy restricted to paroxetine (20–60 mg/day) or mirtazapine (15–45 mg/day)

The MBC group had significantly more treatment adjustments (44 compared with 23) and higher antidepressant dosages from week 2 to week 24.

BAP Guidelines – choice of antidepressant

• 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).
      – BUT NB factors influencing choice of antidepressant:
        presence of atypical features (responds less well to imipramine than phenelzine)

• In more severely ill patients, and where maximising efficacy is of overriding importance, consider:
  – Amitriptyline, clomipramine, venlafaxine (≥ 150 mg), escitalopram (20 mg), sertraline, mirtazepine
Augmentation options ‘sequenced’:

- First line: consider adding quetiapine (A), aripiprazole (A) or lithium (A)
- Second line risperidone (A), olanzapine (B), tri-iodothyronine (B) or mirtazapine (B)
- Other additions that could be considered bupropion (B), buspirone (B), lamotrigine (C) and tryptophan (C)
- Recommended for use in specialist centres with careful monitoring (S) modafinil (C), stimulants (C), oestrogen in perimenopausal women (C) and testosterone in men with low testosterone levels (C).
Preserving hope

• What do you do if you have exhausted all options included in the guidelines for routine use?
• Is it sensible to keep trying endless trials of monoaminergic treatments?
• What other treatment options are available?
• When should such treatments (and/or referral to specialist services) be considered?
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• What do you do if you have exhausted all options included in the guidelines for routine use?
• Is it sensible to keep trying endless trials of monoaminergic treatments?
• What other treatment options are available?
• When should such treatments (and/or referral to specialist services) be considered?
Patients with excessive fatigue or sleepiness despite adequate SSRI > 8 weeks

**All**

- 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.

**HAMD$_{17} >14$**

- 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>
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<tbody>
<tr>
<td>Abolfazli et al, 2011</td>
<td>-1.52 [-2.19 to -0.85]</td>
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<td>DeBattista et al, 2003</td>
<td>-0.10 [-0.44 to 0.24]</td>
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<td>Dunlop et al, 2007</td>
<td>-0.19 [-0.65 to 0.28]</td>
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<tr>
<td>Fava et al, 2005</td>
<td>-0.21 [-0.44 to 0.01]</td>
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<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: -0.35 [-0.61 to -0.10]

Bipolar depression

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
    • 2 RCTs for modafinil – positive
    • No clear evidence for efficacy of other stimulants

• Lavretsky et al. 2015 Am J Psych
  – RCT of citalopram vs methylphenidate vs combo in elderly depressed patients (n=47-48 in each group)
  – Largest response in combo group. Well tolerated.
Transdermal selegiline

- Pooled analysis of 5 PC-RCTs of STS
  - 352 atypical; 932 non-atypical patients
  - Overall significant benefit of STS
  - Effect numerically larger in atypical patients

Pae et al. 2013 CNS Spectrums 19, 324–329

- STS approved by US FDA in 2006

**Figure 1.** Placebo-subtracted mean change in HAMD-28 total score ($-2.11 \pm 1.01$ vs $-1.0 \pm 0.60$, p = 0.34) in atypical versus nonatypical subtypes treated with STS. Abbreviations: HAMD, Hamilton Depression Rating Scale; STS, selegiline transdermal system.
Pramipexol augmentation in TRD
Cusin et al. 2013 (n = 60)

Response – 40% vs 27%
Remission – 33% vs 23%

Dose:
Start at 0.25mg bd
Increase by 0.25mg bd weekly
Target 1.5mg bd
Mean = 1.35mg/day
Single dose of ketamine in TRD

Zarate et al 2006
Single dose of ketamine: Metanalysis

Xu et al. 2016
<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of participants</th>
<th>Standardised effect size (95% CI)</th>
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<tr>
<td>Steiner 1978</td>
<td>12</td>
<td>0.369 (-0.840 to 1.578)</td>
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<td>Wilson 1963</td>
<td>12</td>
<td>-0.513 (-1.663 to 0.637)</td>
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<tr>
<td>Davidson 1978</td>
<td>19</td>
<td>-1.389 (-2.449 to -0.328)</td>
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<td>McDonald 1966</td>
<td>22</td>
<td>-0.930 (-1.813 to -0.047)</td>
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<td>Gangadhar 1982</td>
<td>32</td>
<td>1.287 (0.406 to 2.169)</td>
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<td>MacSweeney 1975</td>
<td>27</td>
<td>-0.714 (-1.492 to 0.065)</td>
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<td>Dinan 1989</td>
<td>30</td>
<td>-0.196 (-0.926 to 0.534)</td>
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<tr>
<td>Janakiramaiah 2000</td>
<td>30</td>
<td>-1.095 (-1.863 to -0.328)</td>
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<tr>
<td>Folkerts 1997</td>
<td>40</td>
<td>-1.336 (-2.032 to -0.640)</td>
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<tr>
<td>Herrington 1974</td>
<td>43</td>
<td>-1.497 (-2.174 to -0.821)</td>
</tr>
<tr>
<td>Stanley 1962</td>
<td>47</td>
<td>-1.342 (-2.047 to -0.638)</td>
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<tr>
<td>Medical Research Council 1965</td>
<td>204</td>
<td>-0.559 (-0.883 to -0.234)</td>
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<tr>
<td>Greenblatt 1964</td>
<td>242</td>
<td>-1.683 (-2.020 to -1.346)</td>
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<tr>
<td>Pooled fixed effects</td>
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<td>-1.010 (-1.170 to -0.856)</td>
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<tr>
<td>Pooled random effects</td>
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<td>-0.802 (-1.290 to -0.289)</td>
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Meta-Review of Metanalytic Studies with Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Major Depression

Bernardo Dell’Osso*, Giulia Camuri, Filippo Castellano, Vittoria Vecchi, Matteo Benedetti, Sara Bortolussi and A. Carlo Altamura

Department of Psychiatry, University of Milan, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Milano, Italy

Abstract: Background: Major Depression (MD) and treatment-resistant depression (TRD) are worldwide leading causes of disability and therapeutic strategies for these impairing and prevalent conditions include pharmacological augmentation strategies and brain stimulation techniques. In this perspective, repetitive transcranial magnetic stimulation (rTMS) is a widely investigated stimulation technique in psychiatry. Several studies have showed preliminary evidence for the antidepressant efficacy of rTMS stimulation. Results: First meta-analyses on the efficacy of rTMS for the treatment of MD and TRD have shown mixed results. On the other hand, more recent meta-analytic studies seem to support the antidepressant efficacy of the technique to a greater extent, also in light of longer periods of stimulation (e.g. > 2 weeks). Conclusion: rTMS seems to be an effective and safe brain stimulation technique for the treatment of medication refractory depression. Nevertheless, further studies are needed to better define specific stimulation-related issues, such as duration of treatment as well as durability of effects and predictors of response.
Change in MADRS scores in patients with severe depression currently in amitriptyline (n= 46)
Rumi et al. 2005
<table>
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<tr>
<th>Author</th>
<th>Year</th>
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<th>Frequency</th>
<th>%</th>
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<th>Total</th>
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<tr>
<td>Avery et al</td>
<td>1999</td>
<td>Yes</td>
<td>10</td>
<td>80</td>
<td>5</td>
<td>10,000</td>
<td>1.80 (-7.96, 11.56)</td>
<td>1.27</td>
</tr>
<tr>
<td>Berman et al</td>
<td>2000</td>
<td>No</td>
<td>20</td>
<td>80</td>
<td>2</td>
<td>8,000</td>
<td>11.00 (1.01, 21.99)</td>
<td>1.28</td>
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<tr>
<td>Boutros et al</td>
<td>2002</td>
<td>Yes</td>
<td>20</td>
<td>80</td>
<td>2</td>
<td>8,000</td>
<td>4.70 (-6.80, 16.20)</td>
<td>0.93</td>
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<tr>
<td>Holtzheimer et al</td>
<td>2004</td>
<td>No</td>
<td>10</td>
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<td>Mosheim et al</td>
<td>2004</td>
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<td>2</td>
<td>16,000</td>
<td>1.10 (-5.64, 7.84)</td>
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<tr>
<td>Su et al</td>
<td>2005</td>
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<td>20</td>
<td>100</td>
<td>2</td>
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<td>Loc et al</td>
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<td>O’Reardon et al</td>
<td>2007</td>
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<td>2010</td>
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<td>10</td>
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<td>Triggs et al</td>
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<td>Fitzgerald et al</td>
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<td>10</td>
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<td>2012</td>
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<td>Chen et al</td>
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<td>20</td>
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<td>2</td>
<td>8,000</td>
<td>1.30 (-0.51, 3.11)</td>
<td>18.94</td>
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<tr>
<td>Overall (I²-squared = 19.8%, p = 0.233)</td>
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<td>2.31 (1.19, 3.43)</td>
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Heterogeneity chi-squared = 17.46 (df = 14), p = 0.233
Test of WMD = 0; z = 4.04; p = 0.000

Health Quality Ontario, 2016
### rTMS

#### Health Quality Ontario, 2016

**Table:**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>AD (Hz)</th>
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<th>Duration (s)</th>
<th>Total</th>
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<tr>
<td>Avery et al</td>
<td>1999</td>
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<td>2000</td>
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<td>Boutros et al</td>
<td>2002</td>
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<td>20</td>
<td>80</td>
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<td>Mosimann et al 2004</td>
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<td>Holtzheimer et al 2004</td>
<td>No</td>
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<td>3.2 (5.39, 7.63)</td>
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<tr>
<td>Su et al</td>
<td>2005</td>
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<td>20</td>
<td>100</td>
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<td>8.6 (9.82, 7.9)</td>
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<td>Triggs et al</td>
<td>2010</td>
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<td>8</td>
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<td>Chen et al</td>
<td>2013</td>
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<td><strong>Subtotal</strong></td>
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#### Subtotal (I-squared = 39.5%, p = 0.116)

<table>
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<th>Author</th>
<th>Year</th>
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<td>Loos et al</td>
<td>2007</td>
<td>Yes</td>
<td>10</td>
<td>110</td>
<td>5</td>
<td>30,000</td>
<td>1.50 (-2.64, 6.44)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.17 (0.69, 3.64)</td>
<td>43.72</td>
</tr>
</tbody>
</table>

#### Subtotal (I-squared = 1.5%, p = 0.398)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>AD (Hz)</th>
<th>MT</th>
<th>Duration (s)</th>
<th>Total</th>
<th>WMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Reardon et al 2007</td>
<td>No</td>
<td>10</td>
<td>120</td>
<td>4</td>
<td>90,000</td>
<td>5.85 (8.89, 11.9)</td>
<td>3.30 (0.21, 6.39)</td>
</tr>
<tr>
<td>Bakım et al 2012</td>
<td>Yes</td>
<td>20</td>
<td>110</td>
<td>2</td>
<td>24,000</td>
<td>5.8 (8.38, 12.56)</td>
<td>6.37 (0.11, 12.63)</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.17 (-0.28, 6.62)</td>
<td>21.72</td>
</tr>
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#### Overall (I-squared = 19.8%, p = 0.233)

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<th>MT</th>
<th>Duration (s)</th>
<th>Total</th>
<th>WMD (95% CI)</th>
<th>Weight</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.31 (1.19, 3.43)</td>
<td>100.09</td>
</tr>
</tbody>
</table>

**Significance test(s) of WMD = 0**
- 10 sessions: z = 2.01, p = 0.044
- 15-20 sessions: z = 2.87, p = 0.004
- 30 sessions: z = 1.80, p = 0.072
VNS

The lead connects to the vagus nerve, which then carries this stimulation the rest of the way to the brain.

A pacemaker-like device (called a generator) sends stimulation through a flexible wire (called a lead).
VNS

- Meta-analysis of non-randomised longitudinal studies (Berry et al. 2013)
- 96 weeks of treatment with VNS + TAU (n = 1035) versus TAU (n = 425)

<table>
<thead>
<tr>
<th>Response rate</th>
<th>Remission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>weeks</td>
<td>weeks</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>VNS + TAU</td>
<td>VNS + TAU</td>
</tr>
<tr>
<td>12%</td>
<td>3%</td>
</tr>
<tr>
<td>18%</td>
<td>5%</td>
</tr>
<tr>
<td>28%</td>
<td>10%</td>
</tr>
<tr>
<td>32%</td>
<td>14%</td>
</tr>
<tr>
<td>TAU</td>
<td>TAU</td>
</tr>
<tr>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>12%</td>
<td>2%</td>
</tr>
<tr>
<td>14%</td>
<td>4%</td>
</tr>
</tbody>
</table>
VNS: LivaNova Registry data (in Press in Am J Psych)

Primary Endpoint – **Response Rate** based on MADRS

Cumulative First-Time Responders by Visit Month by Treatment Group: MADRS – VNS D-21 + D-23, TAU (ITT Population)

Cumulative Response Rate at 5 years

67.8% for VNS Therapy vs. 40.9% for TAU (P<0.001) (NNT=4)

Follow-up Visit Month

Data provided by LivaNova
VNS: LivaNova Registry data (in Press in Am J Psych)

Exploratory Analysis – Response based on MADRS

Cumulative First-Time Response by Visit Month by Treatment Group: MADRS – VNS D21+D23 vs. TAU (ITT Population) based on Length of Current Episode (<5 or >5 years)

Follow-up Visit Month

Cumulative Response Rate Based on Length of Current MDE (5 year Threshold) at 5 Years
- VNS (<5 yrs) (n=194) 72.5%
- TAU (<5 yrs) (n=62) 43.0%
- VNS (≥ 5yrs) (n=136) 61.7%
- TAU (≥ 5yrs) (n=50) 39.1%

Data provided by LivaNova
Anterior cingulotomy

Comparison of lesions (overlaid as regions of interest) for responders (n=4 – lighter grey) and non-responders (n=6 – darker grey).

Table 4  Changes in rating scales following anterior capsulotomy (n=20)

<table>
<thead>
<tr>
<th>Rating scale</th>
<th>Baseline</th>
<th>Postop</th>
<th>12 months</th>
<th>Long term follow-up</th>
<th>Percentage change at long term</th>
<th>p Value (baseline to long term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRSD-17 (actual scores)</td>
<td>26.8±3.9  (n=6)</td>
<td>20.8±10.6  (n=4)</td>
<td>15.3±10.7  (n=6)</td>
<td>13.3±12.0  (n=18)</td>
<td>−50.7</td>
<td>0.101 (n=6)</td>
</tr>
<tr>
<td>HRSD-17 (imputed scores)</td>
<td>23.3±4.6  (n=18)</td>
<td>15.8±7.0   (n=16)</td>
<td>16.2±7.0   (n=12)</td>
<td>13.8±11.6  (n=20)*</td>
<td>−44.2</td>
<td>0.004 (n=18)</td>
</tr>
<tr>
<td>MADRS (not imputed)</td>
<td>39.6±6.5  (n=18)</td>
<td>24.2±11.6  (n=16)</td>
<td>24.1±12.2  (n=12)</td>
<td>22.6±16.4  (n=20)</td>
<td>−42.9</td>
<td>0.001 (n=18)</td>
</tr>
<tr>
<td>LQoLP (mean satisfaction scores)</td>
<td>3.9±1.1   (n=12)</td>
<td>N/A</td>
<td>4.5±0.92   (n=7)</td>
<td>4.9±0.9   (n=17)</td>
<td>+25.6</td>
<td>0.049 (n=11)</td>
</tr>
<tr>
<td>HADS (anxiety subscale)</td>
<td>14.7±5.0  (n=10)</td>
<td>8.5±6.9    (n=6)</td>
<td>8.4±8.0    (n=5)</td>
<td>10.4±4.9   (n=17)</td>
<td>−28.3</td>
<td>0.132 (n=9)</td>
</tr>
</tbody>
</table>

*Data not imputed at long term follow-up.
Paired samples t-test used to calculate p values.
HADS, Hospital Anxiety and Depression Scale; HRSD, Hamilton Rating Scale for Depression; LQoLP, Lancashire Quality of Life Profile; MADRS, Montgomery Asberg Depression Rating Scale.

David Christmas et al. J Neurol Neurosurg Psychiatry 2011;82:594-600
Preserving hope

• What do you do if you have exhausted all options included in the guidelines for routine use?

• Is it sensible to keep trying endless trials of serotonergic/noradrenergic treatments?

• What other treatment options are available?

• When should such treatments (and/or referral to specialist services) be considered?
What threshold should be used to consider non-standard treatments?

“Treatment resistant depression” - a concept that has had its time

• There is no consistent definition of TRD
  – Most commonly failure to respond to two adequate courses of different antidepressants
  – Utility as the point of referral from primary into secondary care?
• However there are a number of issues with the definition
  – No good evidence of qualitative difference in demographics, clinical characteristics or biological measures in patients with and without TRD
  – Lack of tolerability is usually not considered
  – Non-sustained response is not considered
  – Usually only medication is considered in the definition
  – Unclear if this relates to all major depressive episodes (MDE)
  – Limited clinical utility
    • NICE recommendations for referral to secondary care not based on number of treatment failures
The need for an additional or alternative threshold

• There is an expanding number of highly specialised treatments for patients with resistant depression
  – Augmentation strategies that BAP recommends for “specialist centres”
  – Expensive drug options e.g. transdermal selegiline
  – Controversial treatments e.g. maintenance ECT
  – Other physical non-drug treatments e.g. VNS and ablative neurosurgery

• When should a patient be considered suitable for consideration of such options??
  (the concern is that currently such options are not considered at all)
“Multi-therapy resistant-major depressive disorder” (MTR-MDD)

- Concept based on consensus group views
  - Publication under review
- Higher threshold than traditional TRD
- Specific to MDD (MTR-BD criteria being worked on)
- Takes into account
  - Multiple therapies (drugs, psychotherapy, ECT)
  - Intolerance
  - Non-sustained response
- Aim to identify as early as possible the point where further trials of “standard” (mainly monoaminergic) treatments are likely to be of limited benefit
  - i.e. the point in time when “non-standard” treatments should be considered.
  - The actual point at which different “non-standard” treatments are used is likely to be different between different treatments
Proposed MTR-MDD Criteria

**Episode of MDD of at least moderate severity for \( \geq 2 \) years or \( \geq 3 \) documented episodes of moderate-to-severe depression (DSM-5 criteria)**

Since the last period of recovery (defined as remission for at least 12 months), or since illness onset if there has been no period of recovery, there has been a failure of the following interventions to lead to a response, maintain a response, or be tolerated:

(Note that interventions from (a), (b) and (c) may have occurred concurrently)

(a) A substantial trial (e.g. at least 16 hours) of a structured, evidence-supported psychological therapy. Ideally there should have been at least 1 trial in combination with pharmacotherapy.

(b) 4 adequate trials of antidepressants (at least 1 from at least 3 classes):
   i) 5-HT reuptake inhibitors (e.g. SSRIs, clomipramine)
   ii) NA reuptake inhibitors (e.g. reboxetine, lofepramine, nortriptyline)
   iii) 5-HT & NA reuptake inhibitors (e.g. SNRIs, amitriptyline, imipramine)
   iv) MAOI (e.g. phenelzine, moclobemide)
   v) Others (e.g. mirtazapine, vortioxetine, agomelatine, bupropion)

(c) At least 2 adequate trials of different evidence based augmentation/combination agents:
   i) Atypical antipsychotics (aripiprazole or quetiapine are preferred)
   ii) Lithium (ideally with a plasma level of 0.6 – 1.0 mmol/l)
   iii) Tri-iodothyronine

(d) A trial of ECT (at least 8 treatments, and ideally bilateral if tolerated). The requirement for a course of ECT may be waived if there is a recognised contraindication to ECT or the patient has, despite extensive discussions and the provision of information, declined a trial of ECT, or there have been well-documented adverse effects that have limited tolerability.
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Conclusions

• It is easy to fall into the trap of therapeutic nihilism when managing depression
• Hope can be maintained by remembering the rapidly expanding number of treatment options for MDD
• However, the use of many of these options is likely to be primarily in specialist centers
• MTR-MDD criteria provides:
  – A prompt for consideration of what conventional treatments should be considered
  – A threshold for consideration of possible use of non-standard therapies and/or referral
MTR-MDD Consensus Group

• Hamish McAllister-Williams
  — Tertiary care, Newcastle
• David Christmas
  — Tertiary care, Dundee
• Tony Cleare
  — Tertiary care, London
• Alan Currie
  — Secondary (now tertiary) care, Newcastle
• John Gledhill
  — Primary care, Co. Durhma
• Lisa Insole
  — Secondary care, Newcastle
• Andrea Malizia
  — Tertiary care, Bristol
• Mari McGeever
  — Primary Care, Newcastle
• Richard Morriss
  — Secondary and tertiary care, Nottingham
• Lucy Robinson
  — Clinical Psychologists, tertiary care, Newcastle
• Mike Scott
  — Primary care, Newcastle
• Paul Stokes
  — Tertiary care, London
• Peter Talbot
  — Tertiary Care, Manchester
• Allan Young
  — Tertiary care, London