Additional options for difficult-to-treat depression: the long and the short of it

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Hon. Consultant Psychiatrist, Regional Affective Disorders Service, Cumbria, Northumberland Tyne and Wear NHS FT
Disclosure / conflict of interest

I am employed by Newcastle University. I also work clinically in a tertiary level specialist affective disorders service in Cumbria, Northumberland Tyne and Wear NHS Foundation Trust.

I have had 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>
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<tr>
<td>Speaker fees</td>
<td>AstraZeneca, Bristol Myers-Squibb, Eli Lilly, Ferrer, GlaxoSmithKline, Janssen-Cilag, LivaNova, Lundbeck, Merck Sharp &amp; Dohme, OM Pharma, Otsuka, Pfizer, Pulse, Roche, Servier, SPIMACO, Sunovian, Wyeth</td>
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<tr>
<td>Independent investigator-led research support</td>
<td>AstraZeneca, Eli Lilly, Lundbeck, Wyeth</td>
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<tr>
<td>Commercial research support</td>
<td>COMPASS pathways, MagStim</td>
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I do not hold any shares in, nor have any ongoing financial relationship with, any pharmaceutical company.
Aims/Objectives

• Review some of the elements of the consensus recommendations for the management of DTD
• Illustrate with some exemplar treatments
• Share some clinical tips and anecdotes regarding the use of these treatments

• Focus on TIME scales
Effect of duration of untreated depression on outcomes

- Short duration = 8 weeks or less.
- Sample includes both first episode and recurrent depressive patients

De Diego-Adelino et al. (2010) J Affect Disorders 120:221 - 225
BAP Guidelines Treatment Trial Duration

• Lack of significant improvement with standard antidepressants after 2–4 weeks treatment substantially reduces the probability of eventual sustained response

• After 4 weeks adequate treatment:
  – if there is at least some improvement continue for another 2–4 weeks
  – if there is no trajectory of improvement undertake a next-step treatment
    • in patients who have failed a number of treatments consider longer trials

• 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
    • in patients who have failed a number of treatments consider longer trials before changing treatment

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Management of Depression: DTD Model

Review article

The identification, assessment and management of difficult-to-treat depression: An international consensus statement


Northern Centre for Mood Disorders, Newcastle University, UK
Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, Newcastle upon Tyne, UK
Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (ISGIM), CIBERSAM, School of Medicine, Universidad Complutense, Madrid, Spain
Royal Ottawa Institute of Mental Health Research, University of Ottawa, Canada
University Psychiatric Center KU Leuven, Faculty of Medicine KU Leuven, Belgium

DTD, difficult-to-treat depression.

Principles and practice of managing DTD

- Enhance engagement and retention in services
- Shared decision making
- Implement measurement-based care
- Support self-management strategies
- Integrated Service Pathway
- Frequent re-assessment and consideration of treatment direction

DTD, difficult-to-treat depression; ECT, electroconvulsive therapy.

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1. Optimise symptom control
2. Target symptoms associated with poor outcomes
3. Target symptoms to maximise quality of life
4. Manage comorbidities
5. Optimise prophylaxis
6. Encourage self management
7. Integrated service pathways
8. Regular reviews

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DTD, difficult-to-treat depression; ECT, electroconvulsive therapy.

**Principles and practice of managing DTD**

1. **Optimise symptom control**
   - Use self-management strategies and empowering patients

2. **Target symptoms associated with poor outcomes**
   - Use of conventional treatments
   - Use of non-conventional treatments

3. **Target symptoms to maximise quality of life**
   - Integrated service pathways

4. **Manage comorbidities**
   - Encourage self-management

5. **Optimise prophylaxis**

6. **Encourage self-management**
   - Behavioural activities
   - Active community reintegration

7. **Integrated service pathways**

8. **Regular reviews**

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DTD, difficult-to-treat depression; ECT, electroconvulsive therapy.

DTD: Putting principles into practice

1. Achieve optimal symptom control using measurement-based treatment

- Use of conventional treatments
- First line medication, psychotherapy or neurostimulation
  - Antidepressant increased dose, switch or augmentation
  - High intensity psychotherapy with/without medication
  - (Alternate) neurostimulation (e.g. ECT)

Use of non-conventional treatments

- Novel medication and psychotherapies, neuromodulation

DTD, difficult-to-treat depression; ECT, electroconvulsive therapy.

Esketamine nasal spray: TRANSFORM 2 study in patients with TRD: Outcomes*

*As measured by change in MADRS score compared with placebo nasal spray + oral antidepressant; **Difference of LS means (95% CI); †MMRM analysis with change from baseline as the response variable and the fixed effect model terms for treatment (Esketamine nasal spray + antidepressant, placebo + antidepressant), day, country, class of oral antidepressant and treatment-by-day, and baseline value as a covariate; ‡Esketamine nasal spray + antidepressant minus placebo + antidepressant.

CI, confidence interval; LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures; SD, standard deviation; SE, standard error; TRD, treatment-resistant depression.


### MADRS total score at baseline

<table>
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<tr>
<th></th>
<th>Esketamine nasal spray + antidepressant</th>
<th>Placebo + antidepressant</th>
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<tbody>
<tr>
<td>n</td>
<td>114</td>
<td>109</td>
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<tr>
<td>Mean (SD)</td>
<td>37.0 (5.7)</td>
<td>37.3 (5.7)</td>
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### Change from baseline to Day 28 in MADRS total score

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<th>Esketamine nasal spray + antidepressant</th>
<th>Placebo + antidepressant</th>
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<tr>
<td>n</td>
<td>101</td>
<td>100</td>
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<tr>
<td>Mean (SD)</td>
<td>−21.4 (12.3)</td>
<td>−17.0 (13.9)</td>
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### MMRM analysis†

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<th>Esketamine nasal spray + antidepressant</th>
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<tr>
<td>Difference of LS means (SE)‡</td>
<td>−4.0 (1.7)</td>
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<tr>
<td>95% CI on difference</td>
<td>−7.3, −0.6</td>
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<tr>
<td>Two-sided p-value</td>
<td>0.020</td>
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At Day 28, 66.7% of patients were receiving the 84 mg dose
VNS in patients with TRD: 5-year LivaNova registry data

Primary endpoint – response rate based on MADRS\textsuperscript{1}

Cumulative first-time responders by visit month and treatment group: MADRS – VNS D-21 + D-23, TAU (ITT Population)\textsuperscript{1}

<table>
<thead>
<tr>
<th>Follow-up visit month</th>
<th>VNS (22.3% - 67.6%)</th>
<th>TAU (22.3% - 40.9%)</th>
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<tbody>
<tr>
<td>3</td>
<td>VNS 22.3%</td>
<td>TAU 22.3%</td>
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<tr>
<td>6</td>
<td>VNS 34.4%</td>
<td>TAU 34.4%</td>
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<tr>
<td>9</td>
<td>VNS 42.8%</td>
<td>TAU 34.4%</td>
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<tr>
<td>12</td>
<td>VNS 50.4%</td>
<td>TAU 42.8%</td>
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<tr>
<td>15</td>
<td>VNS 57.2%</td>
<td>TAU 42.8%</td>
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<tr>
<td>18</td>
<td>VNS 60%</td>
<td>TAU 50.4%</td>
</tr>
<tr>
<td>21</td>
<td>VNS 67.6%</td>
<td>TAU 57.2%</td>
</tr>
</tbody>
</table>

Cumulative response rate at 5 years\textsuperscript{1}

67.6% for VNS + TAU

vs.

40.9% for TAU (P<0.001; NNT=4)


What threshold should be used to consider “non-standard” treatments?

MTR-MDD criteria
Aims to identify as early as possible the point when “non-standard” treatments should be considered.

Multiple-therapy-resistant major depressive disorder: a clinically important concept

Summary
Many novel therapeutic options for depression exist that are either not mentioned in clinical guidelines or recommended only for use in highly specialist services. The challenge faced by clinicians is when it might be appropriate to consider such ‘non-standard’ interventions. This analysis proposes a framework to aid this decision.

Declaration of interest
In the past 3 years R.H.M.W. has received support for research, expenses to attend conferences and fees for lecturing and consultancy work (including attending advisory boards) from various pharmaceutical companies including AstraZeneca, Cyberonics, Eli Lilly, Janssen, LivaNova, Lundbeck, MyTomorrows, Otsuka, Pfizer, Roche, Servier, SPIMACO and Sunovion. D.M.B.C. has received fees from LivaNova for attending an advisory board. In the past 3 years A.I.G. has received fees for lecturing from AstraZeneca and Lundbeck; fees for consulting from LivaNova, Janssen and Allergan; and research grant support from Lundbeck.
In the past 3 years A.C. has received fees for lecturing from pharmaceutical companies namely Lundbeck and Sunovion. In the past 3 years A.L.M. has received support for attending seminars and fees for consultancy work (including advisory board) from Medtronic Inc and LivaNova. R.M. holds joint research grants with a number of digital companies that investigate devices for depression including Alpha-stim, Big White Wall, Pivotal, Intel, Johnson and Johnson and Lundbeck through his mindTech and CLARIC EM roles. M.S. is an associate at Blueriver Consulting providing intelligence to NHS organisations, pharmaceutical and devices companies. He has received honoraria for presentations and advisory boards with Lundbeck, Eli Lilly, URGO, AstraZeneca, Phillips and Sanofi and holds shares in Johnson and Johnson. In the past 3 years P.R.A.S. has received support for research, expenses to attend conferences and fees for lecturing and consultancy work (including attending an advisory board) from life sciences companies including Concept Therapeutics, Indivior and LivaNova. In the past 3 years P.S.T. has received consultancy fees as an advisory board member from the following companies: Galen Limited, Sunovion Pharmaceuticals Europe Ltd, myTomorrows and LivaNova. A.H.Y. has undertaken paid lectures and advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders and LivaNova. He has received funding for investigator initiated studies from AstraZeneca, Eli Lilly, Lundbeck and Wyeth.

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Proposed MTR-MDD Criteria  
(McAllister-Williams et al. BJPsych May 2018 212:274)

The Patient: Diagnosed with MDD (using the Diagnostic and Statistical Manual, 5th edition (DSM-5))

Their depression: MDD of at least moderate severity.

Their treatment:
a failure to respond, achieve remission, maintain a response/remission, tolerate, refused or contra-indication of the following:

- **Psychotherapy.** At least two trials of structured, evidence-supported psychological therapy.

- **Antidepressants.** Four adequate trials of antidepressants. At least two trials are using antidepressants that are viewed as being potentially more efficacious in severe depression and/or compared to other antidepressants, for example as listed by BAP guidelines (clomipramine, venlafaxine (>150 mg), escitalopram (20 mg), sertraline, amitriptyline or mirtazapine).² We would also recommend consideration of a traditional MAOI (e.g. phenelzine), especially for patients with atypical symptoms.

- **Pharmacological augmentation.** At least two adequate trials Ideally these should both be agents listed as first line options in BAP Guidelines (lithium (ideally with a plasma level of 0.6 – 1.0 mmol/l), quetiapine and aripiprazole).²

- **ECT.** A trial of ECT (at least 8 treatments, and ideally bilateral if tolerated).

Given evidence for possible greater efficacy of a structured psychological treatment in combination with medication, a period of combined treatment, possibly over a period of 9-15 months, is recommended.
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DTD, difficult-to-treat depression; ECT, electroconvulsive therapy.
Vortioxetine mediated an improvement in cognitive performance in depression in three clinical trials

DSST – Replication: Number of correct symbols, change from baseline at Week 8 (FAS, ANCOVA, LOCF, path analysis)

* p<0.05, *** p<0.001 vs placebo; path analysis mediated via MADRS total score; duloxetine was included as active reference in the CONNECT and Elderly studies for study validation, not for comparison of effect sizes; DSST scores were assessed as a predefined primary outcome of CONNECT, secondary outcome of FOCUS, and exploratory outcome of the Elderly study, with path analyses performed post hoc

Effect of modafinil on episodic memory in patients with depression in remission

Double-blind RCT of a **single dose** of modafinil 200mg vs placebo in 60 patients

Modafinil augmentation: meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges g [95% CI]</th>
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<tbody>
<tr>
<td>Abofazli et al, 2011</td>
<td>-1.52 [-2.19 to -0.85]</td>
</tr>
<tr>
<td>DeBattista et al, 2003</td>
<td>-0.10 [-0.44 to 0.24]</td>
</tr>
<tr>
<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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<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: -0.35 [-0.61 to -0.10]

Goss et al. 2013 J Clin Psychiatry 74:1101-1107
Aripiprazole augmentation after inadequate response to SSRI/SNRIs

Using modafinil and aripiprazole: Clinical anecdotes

<table>
<thead>
<tr>
<th>Aripiprazole</th>
<th>Modafinil</th>
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</thead>
<tbody>
<tr>
<td>• Start low and go gently (but you can be quick)</td>
<td>• Be bold (but don’t go too quick)</td>
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<tr>
<td>– Initiate at 5mg (or even 2.5mg)</td>
<td>– Initiate at 100mg bd (or 200mg mane)</td>
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<tr>
<td>– Increase in 2.5mg steps</td>
<td>– Assess effect on mood, energy and pleasure vs insomnia, agitation (acutely GI effects)</td>
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<tr>
<td>– Target range - 5-15mg</td>
<td>– Assess over 4-6 weeks</td>
</tr>
<tr>
<td>– Titrate mood, energy and pleasure vs agitation, anxiety</td>
<td>– If partial response, or non-sustained response increase to 200mg bd (second dose at noon)</td>
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<tr>
<td>– Increase and decrease dose to find sweet spot</td>
<td>– Probably don’t increase above 400mg/day</td>
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<tr>
<td>– Use liquid to get titration down to 1mg steps if needed</td>
<td>– Be more cautious in frail elderly – 100mg steps</td>
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<tr>
<td>– Steps can be every 3-7 days</td>
<td>– Once at optimal dose, trial over further couple of weeks</td>
</tr>
</tbody>
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Esketamine nasal spray treatment model

**Induction phase**
- **Esketamine**: 2 times per week for 4 weeks
- **Euthymic**

**Maintenance phase**
- **REDUCE** frequency of administration to once weekly for 4 weeks following clinical evaluation by a physician
- **CONTINUE** administration every 2 weeks or once weekly (dosing frequency should be individualised to the lowest frequency to maintain remission/response)
- Periodically re-examine the need for continued treatment
- After depressive symptoms improve, treatment is recommended for at least 6 months

**Variable duration**
- Evaluate evidence of therapeutic benefit at the end of the induction phase

AD, antidepressant.

# VNS and maintenance ECT: A case series

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1 – Number of admissions per year
2 – Number of ECT treatments per month

Aaronson et al. 2021 in press
# VNS and maintenance ECT: A case series

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1 – Number of admissions per year  
2 – Number of ECT treatments per month  

Aaronson et al. 2021 in press
Principles and practice of managing DTD

1. Optimise symptom control
2. Target symptoms associated with poor outcomes
3. Target symptoms to maximise quality of life
4. Manage comorbidities
5. Optimise prophylaxis
6. Encourage self management
7. Integrated service pathways
8. Regular reviews

Frequent re-assessment and consideration of treatment direction

DTD, difficult-to-treat depression; ECT, electroconvulsive therapy.
Schematic of management of DTD over time

**Pharmacotherapy**
- Initial serial acute treatments
- Holding pharmacotherapy
  - Steady while exploring other modalities
- Acute trials of ‘new’ treatments alongside long term treatments

**Psycho-social interventions**
- e.g. SSRI then SNRI (e.g. augmentation)
- e.g. CBT or IPT (e.g. CBASP)
- e.g. behavioural activation

**Neurostimulation**
- e.g. TMS
- e.g. ECT
- e.g. VNS
- e.g. supported self-management

**Time**
- Suspected DTD
- DTD
Principles and practice of managing DTD

Conclusions

**Time** is a critical element:
- When to make changes to medication
- How long trials should be
- Whether the target is acute or chronic symptom control
- When to consider change in direction of treatment

For more details see:

DTD, difficult-to-treat depression; ECT, electroconvulsive therapy.