Summary
Treatment-Resistant Depression

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<table>
<thead>
<tr>
<th>Tutorial title</th>
<th>Multimedia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Resistant Depression Part 1: Switching, Combining and Augmenting Antidepressants</td>
<td><a href="#">Access video and audio files here</a></td>
</tr>
<tr>
<td>Treatment-Resistant Depression Part 2: Experimental Treatments (Anti-Inflammatory Drugs, Ketamine, Psilocybin) and Neuromodulation (ECT, TMS, VNS, DBS)</td>
<td><a href="#">Access video and audio files here</a></td>
</tr>
</tbody>
</table>

Contents

Treatment-Resistant Depression Part 1: Switching, Combining and Augmenting Antidepressants ................................................. 2
Treatment-Resistant Depression Part 2: Experimental Treatments (Anti-Inflammatory Drugs, Ketamine, Psilocybin) and Neuromodulation (ECT, TMS, VNS, DBS) ........................................................................................................ 4
### Defining and Assessing Treatment-Resistant Depression

- Treatment resistance: when a patient fails to respond to at least two adequate courses of antidepressants
- In a depressed patient consider differential diagnoses, specifically: psychotic disorders, bipolar spectrum conditions, substance misuse and eating disorders
- If you don’t see any response after 4 weeks, it is unlikely the patient will improve with that medication

### Strategies: Switching Antidepressants

- When a first-line SSRI fails, most guidelines suggest switching to another antidepressant
  - Switching within the same class or to a different class seems to have little impact in outcomes
  - Consider switching to TCAs (amitriptyline, clomipramine) or MAO inhibitors (tranylcypromine) in treatment-resistant patients

### Strategies: Combination and Augmentation

- Adding a second drug (combination or augmentation):
  - Is slightly more effective and faster than switching
  - Has greater risks of drug interactions and side effects

### Combining Antidepressants

- Based on pharmacological reasoning, clinicians often use two specific antidepressant combinations:
  - Mirtazapine + SSRI or SNRI
  - Bupropion + SSRI or SNRI
- Even though these interventions have complementary mechanisms of action, the evidence base from actual clinical trials is limited
- When added as a second drug, it is prudent to start at low doses:
  - Mirtazapine 15 mg/day
  - Bupropion 150 mg/day

### Augmentation With Second-Generation Antipsychotics

- Second-generation antipsychotic augmentation:
  - Effective strategy
  - High burden of side effects
- Quetiapine:
  - Target symptoms: anxiety and sleeping difficulties
  - Side effects: sedation and weight gain
- Aripiprazole:
  - Target symptoms: anhedonia, reduced motivation
  - Side effects: movement disorders and anxiety
- When to augment versus switch?
  - Augmentation is favored in partial responders to antidepressant treatment
- The addition of an SGA allows the initial response to be maintained

| Use of Mood Stabilizers in Treatment-Resistant Depression | • Lithium’s ability to reduce suicidality is an important consideration in its use in treatment-resistant depression  
  • Best results are seen at plasma levels above 0.6 mEq/L |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Use of Stimulants and Dopamine Agonists: Methylphenidate, Amphetamines and Pramipexole | • According to a meta-analysis, modafinil augmentation increased remission rates in SSRI-resistant patients  
  • Evidence from a case series showed efficacy for pramipexole at high doses  
    • Nausea and sleepiness are common problems when starting pramipexole treatment |
| Other Augmenting Options: T3, SAMe, Folate and Omega-3 Fish Oils | • Evidence from a meta-analysis suggests benefit for omega-3 fish oils |
| Psychosocial Interventions | • Specific psychotherapies have demonstrated efficacy for treatment-resistant depression, these are: CBT, behavioral activation, psychodynamic psychotherapy and mindfulness-based CBT |
# Treatment-Resistant Depression Part 2: Experimental Treatments (Anti-Inflammatory Drugs, Ketamine, Psilocybin) and Neuromodulation (ECT, TMS, VNS, DBS)

<table>
<thead>
<tr>
<th>Video Title</th>
<th>Key Points</th>
</tr>
</thead>
</table>
| Experimental Treatments: Anti-Inflammatory Agents | • Inflammatory processes may play a role in depression  
  • A meta-analysis suggests celecoxib might be helpful as adjunct to serotonergic and noradrenergic antidepressants |
| Experimental Treatments: Ketamine | • Ketamine (an NMDA antagonist) is associated with a fast but transient antidepressant response in treatment-resistant patients  
  • Ketamine forms that are safer and able to overcome the transient effect limitation are being studied in clinical trials  
  • Ketamine’s mechanism of action could be linked to the metabolite hydroxynorketamine and its activity on glutamate AMPA receptors |
| Experimental Treatments: Psilocybin | • Psilocybin is a psychedelic agent with 5-HT2A agonist properties  
  • An open-label study in 12 patients showed that psilocybin produced improvement rapid improvement that lasted up to three months in half the group  
  • There are practical challenges around research and potential therapeutic use.  
  • Further research seems worthwhile. |
| Neuromodulation: ECT | • ECT is particularly effective in patients with depressive psychosis, problems maintaining adequate nutrition and hydration, and acute suicidality |
| Neuromodulation: TMS and VNS | • TMS is effective for treatment-resistant depression  
  • It may be less effective than ECT  
  • VNS is worthy considering for patients who have failed multiple antidepressant therapies, if facilities for its application and use are available |
| Neuromodulation: DBS | • DBS requires brain surgery and its efficacy hasn’t been shown in controlled studies |