Treatment-resistant depression in primary care

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Take Home Points

• About 30% of depressed patients experience treatment-resistant depression: failure of multiple first-line treatments

• Approach to treatment resistance in primary care
  • Differential diagnosis
  • Suicide risk assessment
  • Measurement-based care
  • Optimize medication adherence, dose, duration
  • Complementary approaches

• Specialty consultation for advanced psychopharmacology, psychotherapy, or brain stimulation therapies
Depression

Disease of mind, brain, and body

Not normal sadness

Caused by genetic factors, early environment, recent stress

A leading cause of disability worldwide, and the burden is increasing
(World Health Organization, 2015)

The standard of care for moderate-to-severe depression is antidepressant medication, often with psychotherapy
(American Psychiatric Association, 2010)
Depression is not one thing

Unfortunately, we use “depression” to describe a wide range of syndromes, from psychotic melancholia to a normal reaction to loss

“The opposite of depression is not happiness, but vitality, and it was vitality that seemed to seep away from me in that moment.”

Andrew Solomon
TED talk: Depression, the secret we share
Epidemiology

Major depressive disorder
- 15% lifetime prevalence in US
- Twice as common among women

Bipolar disorder
- 2% lifetime prevalence in US
- Roughly equal in men and women

Most patients with depression are treated in primary care

Depression is over-represented among primary care patients
- Mental health diagnosis in about half of patients seen at U of U
DSM-5 Criteria: Major Depressive Disorder

- At least 5 symptoms, for at least 2 weeks, nearly every day:
  1) Depressed mood most of the day*
  2) Markedly diminished pleasure or interest in almost all activities*
  3) Unintentional weight loss (5%), or decrease/increase in appetite
  4) Insomnia or hypersomnia
  5) Psychomotor agitation or retardation (observable by others)
  6) Fatigue or loss of energy
  7) Inappropriate worthless or guilty feelings
  8) Diminished concentration or indecisiveness
  9) Recurrent thoughts of death or suicide

* Depressed mood or anhedonia must be present
DSM-5 Criteria: Persistent Depressive Disorder (Dysthymia)

Depressed mood for at least 2 years, for more days than not

Presence of at least two symptoms while depressed:
1) Poor appetite or overeating
2) Insomnia or hypersomnia
3) Fatigue or loss of energy
4) Low self-esteem
5) Diminished concentration or indecisiveness
6) Hopeless feelings

Never without symptoms for more than 2 months

Criteria for a MDE may be present continuously for more than 2 years
DSM-5 Criteria: Manic Episode

Distinct period of elevated, expansive, or irritable mood and persistently increased goal-directed activity or energy, lasting at least 1 week, and present most of the day, nearly every day

During the disturbance of mood and energy, at least 3 symptoms present:

1) Inflated self-esteem or grandiosity
2) Decreased need for sleep
3) Talkative or pressured speech
4) Racing thoughts or flight of ideas
5) Distractibility (reported or observed)
6) Increased goal directed activity or psychomotor agitation
7) Excessive involvement in pleasurable activities

“Have you ever experienced a period of days or weeks during which you felt excessively high or hyper, or so full of energy that other people thought you weren’t acting like your usual self?”
Case: Mr. D.

Mr. D. is a 68 year old retired engineer with a family history of depression and completed suicide.

His first clear depressive episode occurred in his 50’s in the context of work stress. He experienced full recovery with antidepressant medication and psychotherapy, then tapered off medication and remained well for a decade.

His second episode occurred two years ago without a clear precipitant and eventually resolved with a combination of two antidepressants.
Natural history

Onset at any age

Adult course
  MDD recurrent > 50%
  Bipolar recurrent ~ 90%

Earlier episodes are more strongly linked to stressful life events
  First episode 45–75%, later episodes 15–50%
  Later episodes tend to be longer, more severe, more difficult to treat

Mortality and morbidity
  Suicide 5–15%
  Cardiovascular disease, obesity, tobacco
Case: Mr. D. (continued)

One year ago, Mr. D. discontinued one medication, then sustained a bicycling injury, with pain lasting 1-2 months. His depression recurred.

He presents with a pervasive, low, apprehensive mood; loss of interest and pleasure; insomnia; loss of appetite; 15 pound weight loss; hopelessness; and increasing suicidal ideation with a plan to drown himself.

Depression persists despite psychotherapy and a series of 3 adequate medication trials:
- venlafaxine 225 mg/d
- sertraline 150 mg/d
- bupropion 450 mg/d
Treatment Resistant Depression (TRD)

30% of individuals recover with a single antidepressant medication trial

50% recover with 1 or 2 adequate trials

70% recover with 1 - 4 adequate trials

Failure of multiple trials = treatment-resistant depression (TRD)

Annual prevalence of TRD is ~2% (~5 million Americans)

Many individuals experience intolerable side effects from medications

In naturalistic studies, ~10% of patients with TRD recover at 1 year
Overview: Approach to TRD

Assessment
- Differential diagnosis and comorbidities
- Suicide risk
- Measurement-based care

Primary care
- Optimize medication adherence, dose, & duration
- Complementary approaches

Specialty care
- Advanced psychopharmacology
- Psychotherapy
- Brain stimulation therapies
Differential diagnosis of depression

Major depressive disorder
Bipolar disorder
Dysthymic disorder
Schizoaffective disorder
  Psychotic symptoms independent of mood symptoms
Adjustment disorder with depressed mood
  Mild depression that resolves within 6 months of a stressor
Normal bereavement
  Depression lasting less than 2 months after significant loss
Dementia (vs pseudodementia)
Secondary mood disorder
  General medical condition (CBC, comprehensive metabolic panel, TSH, vit B12)
  Neurological (epilepsy, Parkinson’s disease, stroke)
  Medication (interferon, corticosteroids)
  Recreational drugs (alcohol, sedatives, cocaine withdrawal)
Personality disorder
Anxiety disorder
Suicide risk assessment


Suicide risk factors

Prior suicidal ideas, plans, and attempts, including
Attempts that were aborted or interrupted
Prior intentional self-injury
Anxiety, panic attacks
Hopelessness
Impulsivity
Past hospitalizations and emergency department visits
Recent use of alcohol or other substances
Presence of psychosocial stressors
Lack of social support
Painful, disfiguring, or terminal medical illness

(American Psychiatric Association, 2016)
Measurement-based care

**Depression**
Patient Health Questionnaire (PHQ-9)
Quick Inventory of Depressive Symptomatology (QIDS-SR-16)

**Anxiety**
Generalized Anxiety Disorder Scale (GAD-7)

**Mania**
Altman Self-Rating Mania Scale (ASRM)
**Measurement-based care: PHQ-9**

*Over the last 2 weeks, how often have you been bothered by any of the following problems?*

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself- or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead, or of hurting yourself.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Principals of antidepressant medication management

“Adequate” trial = moderate to high dose for at least 4 weeks

Adherence: non-judgmental inquiry

Treat to remission and continue at least 9 months

Individual responses vary widely

Effectiveness is similar across medication classes – on average

Choice of antidepressant guided by:
  - past response
  - side effects
  - comorbidities
Antidepressant classes

A. Selective serotonin reuptake inhibitors (SSRIs)
citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vortioxetine, vilazodone

B. Serotonin norepinephrine reuptake inhibitors (SNRIs)
venlafaxine, duloxetine, desvenlafaxine, levomilnacipran

C. Bupropion

D. Mirtazapine

E. Tricyclic and tetracyclic antidepressants (TCAs)
nortriptyline, amitriptyline, desipramine, imipramine, clomipramine, doxepin, etc

F. Monoamine oxidase inhibitors (MAOIs)
tranylcypromine, isocarboxazid, phenelzine, selegiline
## Antidepressants: Side effects

<table>
<thead>
<tr>
<th></th>
<th>SSRIs</th>
<th>SNRIs</th>
<th>bupropion</th>
<th>mirtazapine</th>
<th>TCAs</th>
<th>MAOIs</th>
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<tr>
<td>anti-cholinergic</td>
<td>0 - 1</td>
<td></td>
<td></td>
<td>1</td>
<td>1 - 4</td>
<td>1</td>
</tr>
<tr>
<td>sedation</td>
<td>0 - 1</td>
<td></td>
<td></td>
<td>4</td>
<td>1 - 4</td>
<td>0 - 2</td>
</tr>
<tr>
<td>insomnia/agitation</td>
<td>1 - 2</td>
<td>2</td>
<td>1</td>
<td>0 - 4</td>
<td>1 - 2</td>
<td></td>
</tr>
<tr>
<td>orthostatic hypotension</td>
<td></td>
<td></td>
<td></td>
<td>1 - 4</td>
<td>1 - 3</td>
<td></td>
</tr>
<tr>
<td>cardiac arrhythmia</td>
<td></td>
<td></td>
<td>1</td>
<td>1 - 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI distress</td>
<td>1 - 3</td>
<td>1 - 3</td>
<td>1</td>
<td>0 - 1</td>
<td>0 - 1</td>
<td></td>
</tr>
<tr>
<td>weight gain</td>
<td>0 - 2</td>
<td></td>
<td></td>
<td>4</td>
<td>0 - 4</td>
<td>0 - 2</td>
</tr>
<tr>
<td>sexual dysfunction</td>
<td>2 - 3</td>
<td>1 - 2</td>
<td>1</td>
<td>1 - 2</td>
<td>1 - 2</td>
<td></td>
</tr>
</tbody>
</table>
Switch, combine, or augment?

If no improvement, then switch (often to a different class)
If partial improvement, combine or augment

Augmenting agents

T3 (triiodothyronine) 25 – 50 mcg
lithium 300 – 900 mg
atypical antipsychotics
    aripiprazole 2 – 15 mg
    olanzapine 2.5 – 15 mg
    quetiapine 50 – 300 mg
lamotrigine 200 mg
buspirone 45 – 60 mg
modafinil 200 mg
stimulants
Medication management of bipolar disorder

Lithium (gold standard)

Anticonvulsants
  valproate
  carbamazepine
  lamotrigine

Antipsychotics
  atypical
  conventional

Antidepressants
  may be helpful or destabilizing
Complementary approaches

- Stress reduction
- Sleep hygiene
- Exercise, physical activity
- Omega-3 fatty acids (EPA, DHA)
- Folate, SAMe
- Vitamins B12 and D
- Phototherapy for seasonal mood disorders
When psychiatric specialty consultation is recommended

High suicide risk
Psychosis
Mania or hypomania (i.e., bipolar disorder)
Co-morbid substance abuse
Secondary to neurological illness
Severe personality disorder

Highly-treatment resistant illness (3 or more failed trials)
- Advanced psychopharmacology
- Psychotherapy
- Brain stimulation therapies
Psychotherapies for depression

Typically weekly for at least 12 weeks

When combined with medications, generally more effective than either treatment alone

Evidence-based therapies
   Cognitive behavioral therapy (CBT)
   Interpersonal therapy (IPT)
   Brief psychodynamic psychotherapy
   Mindfulness-based therapies
   others
Brain stimulation therapies

Also known as Neuromodulation or Neurostimulation

Application of electromagnetic stimuli to alter brain activity

Three established therapies for depression

- Electroconvulsive therapy (ECT)
- Repetitive transcranial magnetic stimulation (TMS or rTMS)
- Vagus nerve stimulation (VNS) therapy
Electroconvulsive therapy (ECT)

Therapeutic, electrically-induced seizure

General anesthesia and muscle relaxation

Typically 8-12 treatments over 3-4 weeks

Response rate ~70% at 4 weeks
ECT risks and side effects

Short-term cognitive impairment (common)

No long-term cognitive impairment (controversial)

Adverse effects of anesthetic or muscle relaxant (rare)

Nausea, headache, myalgia (common, manageable)

No absolute contraindications
ECT indications

Major depressive episode
  Melancholia
  Psychosis
  Catatonia
  Severe/suicidal
  Refractory 60% response at 3-4 weeks

Other
  Mania (e.g., bipolar disorder)
  Schizophrenia and related psychoses
  Secondary depression, psychosis, or catatonia
  Neuroleptic malignant syndrome

\{ > 80% response
ECT take-home points

Very effective for certain psychiatric syndromes

Not a “last resort”

Very safe across the life span

Sometimes life-saving

Stigma continues but is improving

Education and awareness are needed
Repetitive transcranial magnetic stimulation (TMS)

FDA approved in 2008

Magnetic pulses induce currents in prefrontal cortex

Office procedure; no anesthesia

Typically 20-30 treatments

Response rate 40-50% at 6 weeks

Minimal side effects; no surgical risks
TMS risks and side effects

Seizure risk (rare): contra-indicated for individuals at high risk of seizure

Pain with stimulation (35-50%): managed with changes in coil position

Scalp muscle contractions (20%)

Toothache (7%)

Theoretical hearing risk (earplugs used)

In pivotal trial, discontinuation rate of 4.5% was not different from sham stimulation
TMS for TRD: meta-analysis

Remission (HDRS < 7)
relative risk vs sham = 5.1
(95% CI, 2.5 to 10.3)

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Figure 2. Mean Difference Meta-Analysis of Changes in Depressive Severity Comparing rTMS and Sham: Tier 1 Trials

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*Random-effects meta-analysis, $I^2 = 65\%$.  
Abbreviations: MDD = major depressive disorder, rTMS = repetitive transcranial magnetic stimulation.*
TMS take-home points

Relatively non-invasive and safe

Low burden of side effects

Time intensive: typically >20 one-hour treatments

Response rates are about half that of ECT

Best for patients with medication intolerance or low treatment-resistance

TMS techniques are still evolving… stay tuned
Case: Mr. D. (continued)

ECT was recommended, and after discussion with his family, Mr. D. decided to start ECT.

After 1 week (3 treatments), he experienced significant short-term memory impairment and mild confusion. Treatments were spaced to 2 per week.

After 2 weeks (5 treatments), his suicidal ideation had completely resolved. Cognitive impairment persisted.

After 4 weeks (9 treatments), his mood and neurovegetative signs had improved, and ECT was discontinued.

He started nortriptyline and titrated to a therapeutic serum level. Lithium augmentation was added.

Cognitive impairment improved 90% within 4 weeks of the last ECT treatment.

At two years, he remained well with nortriptyline monotherapy.
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Quiz

1. All the following patient characteristics increase the risk of suicide except:

   a. Male gender
   b. Panic attacks
   c. Agoraphobia
   d. Chronic pain
2. All the following are important in evaluating whether an antidepressant medication trial is adequate except:

a. Duration of the trial
b. Antidepressant class
c. Patient adherence
d. Daily dose
Quiz

3. Which of the following is irrelevant in choosing a medication for a patient with depression?

   a. Each medication's mechanism of action
   b. Each medication's typical side effects
   c. The patient's diagnoses
   d. The patient's past response to antidepressants
4. Specialty consultation should be sought for each of the following patients except:

a. 33-year-old acutely depressed man who was hospitalized for mania 15 years ago
b. 25-year-old postpartum woman who starts acting paranoid and neglecting her baby
c. 46-year-old man with depression and opioid addiction who attempted suicide two weeks ago
d. 51-year-old woman with severe depression for 5 months despite sertraline 50 mg/d and bupropion 150 mg/d