What do you do when First-Line Antidepressants don't work? Treatment of Refractory Depression

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1

Objectives

Define	Define refractory depression
Review	Review the prevalence of refractory depression
Discuss	Discuss benefits and risks of second-line treatment options for major depressive disorder
Introduce	Introduce interventional options for refractory depression

2

Important Definitions

- Remission – 100% reduction in symptoms – THE GOAL!
- Response – 50% or more improvement in symptoms
- Partial response – 25% or more (but less than 50%) improvement
- Nonresponse – less than 25% improvement in symptoms

3

Difficult-to-Treat Depression

Form of depression for which traditional treatment, such as medication and psychotherapy, are not adequately effective

Ongoing depressive symptoms after adequate trials of evidence-based psychotherapy and **at least 2 antidepressants** from different classes

4

How Common is Difficult-to-Treat Depression?

Step 1
- Citalopram
- Remission rate: 33%

Step 2
- Switch to bupropion, sertraline, or venlafaxine
- Augment with bupropion or buspirone
- Remission rate: about 25%

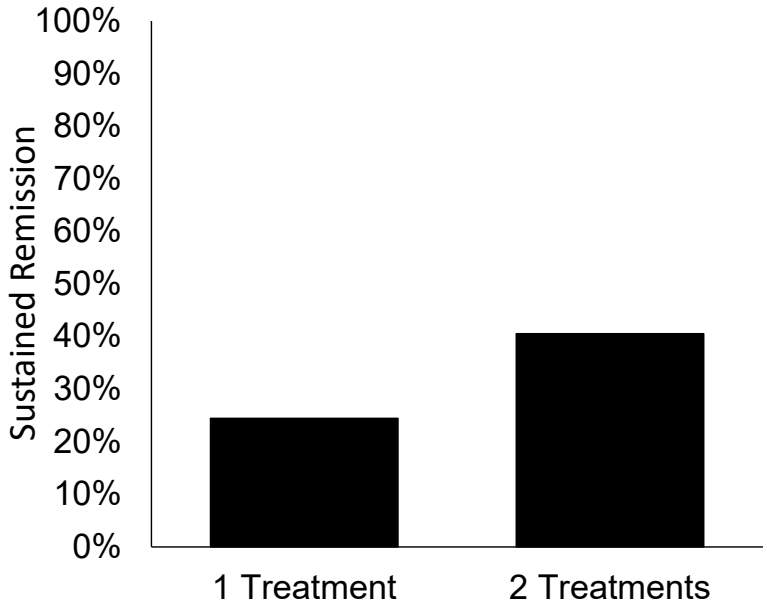
Step 3
- Switch to mirtazapine or nortriptyline
- Augment with lithium or triiodothyronine
- Remission rate: 26%

Step 4
- Switch to tranylcypromine or venlafaxine XR + mirtazapine
- Remission rate: 13%

Rush et al. 2006; Kennedy et al. 2010

5

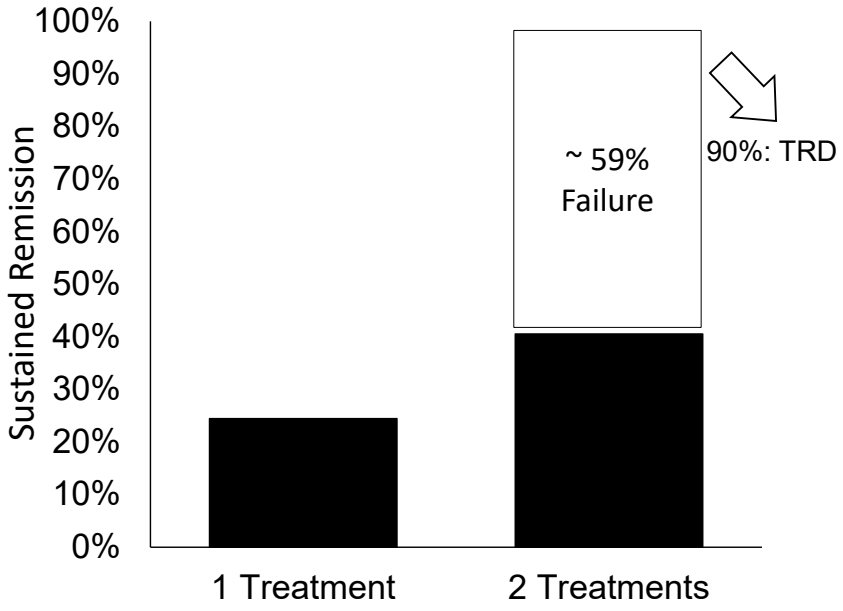
How Common is Difficult-to-Treat Depression?



Rush A, Trivedi M, Wisniewski S, et al. *Am J Psychiatry* 2006
Rush AJ, Aaronson ST, Demyttenaere K. *Aust N Z J Psychiatry* 2019

6

How Common is Difficult-to-Treat Depression?



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7

Is it Truly Difficult-to-Treat Depression?

Confirm the diagnosis of depression

Screen for substance use

Rule out medical causes that can look like depression or increase the likelihood of having depression

Ensure patient is taking their medications daily

8

Case

24 y/o female with a history of persistent depressive disorder with intermittent major depressive episodes since age 16 presents for management of her depressive symptoms.

- Did cognitive behavioral therapy for 1 year during early years of college with mild benefits in mood
- Has never trialed psychotropic medications

As her treating physician, what medication will you start?

9

Selective Serotonin Reuptake Inhibitors (SSRIs)

10

SSRI FDA Indications - page 1

SSRI	Adult	Child	Unique Information
Fluoxetine (Prozac) 10mg → 80mg	MDD, PMDD, OCD, bulimia, panic disorder, bipolar depression (in combination with Zyprexa)	MDD 8-17 Bipolar depression 10-17 OCD 7-17	- Better in patients with hypersomnia, apathy, fatigue, reduced positive affect, noncompliance - Tends to have more CYP interactions
Sertraline (Zoloft) 25mg → 200mg	MDD, PMDD, OCD, panic disorder, social anxiety, PTSD	OCD 6-17	- Higher rates of diarrhea and GI distress - Can cause false (+) for benzos on UDS - Safer in heart failure, stroke patients
Escitalopram (Lexapro) 5mg → 20mg	MDD, GAD	MDD 12-17 GAD 7-17	- Fewer CYP-mediated interactions

11

SSRI FDA Indications – page 2

SSRI	Adult	Child	Unique Information
Citalopram (Celexa) 10mg → 40mg	MDD		- Prolonged QTc at higher doses
Fluvoxamine (Luvox) 50mg → 300mg	OCD	OCD 8-17	- More likely to have withdrawal - Tends to have more CYP interactions
Paroxetine (Paxil) 10mg → 50mg CR 12.5mg → 62.5mg	MDD, PMDD, OCD, GAD, panic, social anxiety, PTSD		- Antimuscarinic – blurry vision, dry mouth, urinary retention, sedation - More likely to have withdrawal

12

SSRI Side Effects

- GI disturbances
- Sexual dysfunction
- Headache, dizziness
- Activation
- Bruxism
- Bleeding – when used with antiplatelets, anticoagulants, NSAIDs
- Hyponatremia

13

SSRI Side Effects

Black box warning – increased suicidal ideation under age 25

- 2% risk with antidepressant vs 1% with placebo in ages 18-24

Risk of mania or hypomania

Serotonin syndrome

- In the context of serotonergic agents like SSRIs and also linezolid, tramadol, methadone, fentanyl, triptans
- Autonomic instability – fever, tachycardia, elevated blood pressure
- Cognitive changes – confusion, agitation, delirium
- Neurological findings – myoclonus, hyperreflexia, tremor, muscle rigidity

14

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

15

SNRI FDA Indications

SNRI	Adult	Child	Unique Information
Duloxetine (Cymbalta) 30mg → 120mg	MDD, GAD, diabetic neuropathy, fibromyalgia, chronic musculoskeletal pain	GAD 7-17 Fibromyalgia 13-17	- Associated with severe drug induced liver injury, increase in ALT
Venlafaxine (Effexor) XR 37.5mg → 225mg	MDD, GAD, panic disorder, social anxiety		- Dose >150mg/day for the norepinephrine effect - More likely to have withdrawal
Desvenlafaxine (Pristiq) 25mg → 100mg	MDD		- Off label use for vasomotor symptoms in perimenopausal women
Levomilnacipran (Fetzima) 20mg → 120mg	MDD		- Higher potency for norepinephrine → more sweating, urinary hesitancy

16

SNRI Side Effects

- As with SSRIs
- Sexual dysfunction – possibly lower than SSRIs
- Hypertension at higher doses
- Increased heart rate

17

Back to the Case

- You start escitalopram 5mg daily
- You titrate this up to 20mg in 3 months
- She does not notice any improvement

What is the next best step?

18

Back to the Case

- You start sertraline 50mg daily
- You titrate this up to 200mg in 4 months
- She notices a 20% improvement in depressive symptoms, specifically in anhedonia and energy level
- She continues to struggle with low mood and motivation

What is the next best step?

19

Augmentation Strategies

20

Augmentation Strategies

Bupropion	Mirtazapine	Buspirone	Lithium

L-Methylfolate	Triiodothyronine (T3)	Antipsychotics

21

Bupropion (Wellbutrin)

- Inhibits dopamine and norepinephrine reuptake
- For MDD, smoking cessation, seasonal affective disorder
- Helps with focus, energy level, apathy
- 100mg/day → 450mg/day; IR, SR, XL formulations
- Advantages
  - No sexual side effects
  - Minimal weight gain, if any
- Side effects
  - Lowers seizure threshold
  - Caution with eating disorder, recent head trauma, major alcohol use

22

Mirtazapine (Remeron)

- Presynaptic central alpha-2 antagonist, $5HT_{2A}$, $5HT_{2C}$, and $5HT_3$ blockers, histamine receptor blocker
- For MDD
- 15mg/day → 45mg/day; take at nighttime only
- Advantages
  - Less sexual side effects
  - Helps with sleep and appetite
- Side effects
  - Extra sedation
  - Weight gain, increases cholesterol and triglycerides

23

Buspirone (Buspar)

- Binds to serotonin 1A receptors
- Off-label use as an augmentation agent for antidepressants
- 15-20mg/day in 2-3 divided doses → max of 60mg/day
- Side effects
  - Dizziness
  - Headache
  - Possible sedation or activation

24

Lithium

- Has anti-suicide effects
- 300-600mg daily, can go up to 1200mg/day
- Common side effects: GI effects, hand tremor, sedation, increased appetite
- Rarer side effects
  - Renal: risk of diabetes insipidus, polyuria, polydipsia
  - Thyroid: elevated TSH, hypothyroidism
- Monitor trough lithium level 5 days after starting medication and with dose titrations

25

L-Methylfolate

- Regulator of monoamine synthesis
- Active form of folate in the body that helps form many coenzymes in the metabolic systems
- 7.5mg to 15mg daily for 6 months
- Deplin $60/month or MethylPro OTC $30/month

26

Triiodothyronine (T3)

- 20mcg to 62.5mcg daily
- Check TSH at baseline and again 6-8 weeks later
  - Target for TSH is about 1.0 and to ensure patient is getting some relief for depressive symptoms
- Side effects
  - Osteoporosis
  - Risk of adverse cardiovascular events like angina, arrhythmia

27

Antipsychotics – Aripiprazole (Abilify)

- D_2 and $5HT_{1A}$ receptor partial agonist, $5HT_{2A}$ receptor antagonist
- 2-5mg/day up to 20mg daily
- Advantages
  - Less sedating
- Side effects
  - Activation
  - Akathisia
  - Elevation in lipids and glucose

28

Antipsychotics – Quetiapine (Seroquel)

- D_2 and $5HT_{2A}$ antagonist
- 50mg/day up to about 300mg/day
- Side effects
  - More metabolic effects
  - Extra sedation
  - Anticholinergic effects

29

Augmentation Strategies

Bupropion	Mirtazapine	Buspirone	Lithium
L-Methylfolate	Triiodothyronine (T3)	Antipsychotics	

30

Tricyclic Antidepressants (TCAs)

31

TCA FDA Indications

TCA	Adult	Child	Unique Information
Amitriptyline (Elavil) 25mg → 300mg	MDD		- Most anticholinergic - Helpful for chronic pain, migraines
Imipramine (Tofranil) 25mg → 300mg	MDD	Nocturnal Enuresis 6-17	- Metabolized to desipramine
Doxepin (Silenor) 25mg → 300mg (max single dose 150mg)	Anxiety, MDD	Anxiety, MDD 12-17	Most histaminergic at low doses → most sedating
Clomipramine (Anafranil) 25mg → 250mg	OCD	OCD 10-17	Most serotonergic
Desipramine (Norpramin) 25mg → 200mg	MDD		Most noradrenergic so possible benefit in ADHD
Nortriptyline (Pamelor) 25mg → 150mg	MDD		

32

TCA Side Effects

Histaminergic	Anticholinergic	Alpha 1 & 2 Blockade	Blockade of Myocardial Fast Sodium Channels
• Sedation • Orthostatic hypotension • Weight gain	• Dry mouth • Constipation • Urinary retention • Blurred vision • Confusion	• Sedation • Orthostatic hypotension	• QT prolongation

33

Monoamine Oxidase Inhibitors (MAOIs)

34

MAOI FDA Indications

MAOI	Adult	Child	Unique Information
Phenelzine (Nardil) 15mg TID→ 20mg TID	MDD		- More sedating - More weight gain
Isocarboxazid (Marplan) 10mg BID → 60mg total/day	MDD	MDD 16-17	
Tranylcypromine (Parnate) 10mg TID → 60mg total/day	MDD		- Causes more activation, poor sleep
Transdermal Selegiline (Emsam) 6mg → 12mg/day	MDD		- Oral dose is selective for MAO-B - Transdermal patch inhibits MAO-A and MAO-B in the brain while largely bypassing inhibition of MAO-A in the liver → less dietary restrictions at lower doses

35

MAOI Side Effects

Hypertensive crisis due to tyramine

- Avoid dried, aged, smoked fermented spoiled meat, poultry, fish; aged cheese; unpasteurized beer, sauerkraut, kimchee
- If eating the above, may get palpitations, occipital headache, neck stiffness, nausea, vomiting, sweating, dilated pupils, tachycardia, photophobia
- Diet followed until 2 weeks after completely stopping the MAO inhibitor

Orthostatic hypotension → dizziness

Confusion

Cannot use with other serotonergic agents

- Washout period of 2 weeks before starting another medication

36

Back to the Case

- You add bupropion XL 150mg daily to the sertraline
- You titrate bupropion up to 300mg in 3 months with minimal additional benefit
- She continues to struggle with low mood, lack of motivation, some anhedonia

What do you recommend next?

37

Interventional Treatments

38

Interventional Options

Transcranial Magnetic Stimulation (TMS)	Esketamine	IV Ketamine
Electroconvulsive Therapy (ECT)	Vagus Nerve Stimulation (VNS)	

39

Transcranial Magnetic Stimulation (TMS)

Focused magnetic pulses to the dorsolateral prefrontal cortex → increased activation of this area
FDA approved for MDD and anxiety related to depression
36 treatments provided 3-5 times per week
Response rate of 58-69%, remission rate of 28-36%
Rare risk of seizures: in 1/1000 patients or 1/30,000 treatments
Contraindications: seizure history, metal/implanted devices in head or neck

40

Esketamine

- NMDA receptor antagonist → glutamate binds to this
- FDA approved for MDD in conjunction with an oral antidepressant
- Nasal spray, 28mg, 56mg, or 84mg
- Generally 12 treatments over 8 weeks
- Risk of temporary dizziness, sedation, headache, dissociation, elevated blood pressure, elevated heart rate
- Contraindications: aneurysm, arteriovenous malformation, intracranial hemorrhage

41

IV Ketamine

- NMDA receptor antagonist → glutamate binds to this
- Not FDA approved though effective for MDD, acute suicidality
- 40mg/kg infused over 40 minutes
- Generally 12 treatments over 8 weeks
- Risk of temporary dizziness, sedation, headache, dissociation, elevated blood pressure, elevated heart rate
- Contraindications: aneurysm, arteriovenous malformation, intracranial hemorrhage

42

Electroconvulsive Therapy (ECT)

Done by passing a limited amount of electricity between 2 electrodes placed on the head → induces a short seizure
Generally 12 treatments over 4 weeks
Higher likelihood of response/remission in older patients and those with psychotic or atypical features of depression
Response and remission rates about 50-80%
Requires general anesthesia
Cognitive risks and fatigue during acute treatment course

43

Vagus Nerve Stimulation (VNS)

- An adjustable pulse generator is implanted in the chest
- Connects to a wire beneath the skin and wound around the left vagus nerve
- Delivers timed electrical signals to change brain wave patterns
- FDA approved for unipolar and bipolar depression
- Positive effects are more gradual

44

Interventional Options

- Transcranial Magnetic Stimulation (TMS)
- Esketamine
- IV Ketamine
- Electroconvulsive Therapy (ECT)
- Vagus Nerve Stimulation (VNS)

45

Therapy Options for Depression

46

Therapy

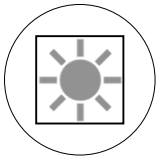
Generally cognitive behavioral therapy and behavioral activation therapy

Effective on its own for mild depression

Effective with medications for moderate to severe depression

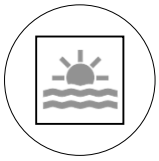
47

Light Therapy

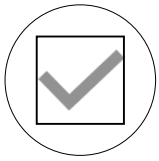


For seasonal pattern of low mood though can help in the summer too

Artificial light can help correct circadian rhythm



Lightbox intensity 5000-10,000 lux for 30-60 minutes per day is optimal



To be used only in the mornings

48

Back to the Case

- You send her to psychiatry for a full course of TMS
- She notices a 70% improvement in depressive symptoms with overall improvement in mood, anhedonia, energy level, and motivation
- She says that being able to feel positive emotions and enjoy things again has been life-changing!

49

Summary

2+ medication trials at therapeutic doses from different classes is considered difficult-to-treat depression (refractory depression)

Augment with another agent if there is partial benefit with the original agent vs switch the antidepressant if no improvement

Therapy on its own and also with medication can be quite effective

Start thinking about 2nd line and interventional treatment options sooner

50

References

- Friedman RA, Leon AC (2007). Expanding the Black Box – Depression, Antidepressants, and the Risk of Suicide. *The New England Journal of Medicine*, 356(23): 2343-2345.
- Gelenberg AJ, Freeman MP, Markowitz JC, et al (2010). Practice Guideline for the Treatment of Patients with Major Depressive Disorder. *American Psychiatric Association*, 3rd edition:1-152.
- Hammad TA, Laughren T, Racoosin J (2006). Suicidality in Pediatric Patients Treated with Antidepressant Drugs. *Archives of General Psychiatry*, 63(3):332-339.
- Kaur U, Pathak BK, Singh A, et al (2021). Esketamine: A Glimmer of Hope in Treatment-Resistant Depression. *European Archives of Psychiatry and Clinical Neuroscience*, 271:417-429.
- Leslie LK, Newman TB, Chesney J, et al (2005). The Food and Drug Administration's Deliberations on Antidepressant Use in Pediatric Patients. *Pediatrics*, 116(1):195-204.
- Little, A (2009). Treatment-Resistant Depression. American Family Physician, 80(2):167-172.
- McGrath PJ, Stewart JW, Fava M, et al (2006). Tranylcypromine versus Venlafaxine Plus Mirtazapine Following Three Failed Antidepressant Medication Trials for Depression: A STAR*D Report. American Journal of Psychiatry, 163: 1531-1541.
- Rima (2020). Tricyclic Antidepressants. Biopharma Notes, retrieved on 5 January 2024 from https://biopharmanotes.com/tricyclic-antidepressants/.

51

References

- Rosenquist PB, McCall WV, Youssef N (2016). Charting the Course of Electroconvulsive Therapy. Journal of Psychosocial Nursing, 54(12):39-43.
- Rush AJ, Trivedi MH, Wisniewski SR, et al (2006). Bupropion-SR, Sertraline, or Venlafaxine-XR after Failure of SSRIs for Depression. The New England Journal of Medicine, 354(12):1231-1242.
- Sackeim HA, Aaronson ST, Carpenter LL, et al (2020). Clinical Outcomes in a Large Registry of Patients with Major Depressive Disorder treated with Transcranial Magnetic Stimulation. *Journal of Affective Disorders*, 277:65-74.
- Trivedi MH, Rush AJ, Wisniewski SR, et al (2006). Evaluation of Outcomes with Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. American Journal of Psychiatry, 163: 28-40.
- Uher R, Perlis RH, Placentino A, et al (2013). Self Report and Clinician-Rated Measures of Depression Severity: Can One Replace the Other? *Depression Anxiety*, 29(12):1043-1049.
- Various medications on UpToDate for FDA indications
- Voineskos D, Daskalakis ZJ, Blumberger DM (2020). Management of Treatment-Resistant Depression: Challenges and Strategies. Neuropsychiatric Disease and Treatment, 16: 221-234.
- Zisook S, Ganadjian K, Moutier C, et al (2008). Sequenced Treatment Alternatives to Relieve Depression (STAR*D): Lessons Learned. Journal of Clinical Psychiatry, 69:1184-85.

52