Psychopharmacology in Treatment Resistant Depression

Stephanie Nichols, PharmD, MPH, FCCP
Board Certified Pharmacotherapy Specialist
Board Certified Psychiatric Pharmacist
Associate Professor, UNE School of Pharmacy
Adjunct Assistant Clinical Professor of Psychiatry, Tufts School of Medicine
Learning Objectives

- Describe treatment resistant depression (TRD) epidemiology and contributing factors, including bipolar disorder
- Compare and contrast practice guideline recommendations for TRD augmentation therapy
- Detail pharmacokinetics, pharmacodynamics, dosing, drug interactions, adverse effects, warnings, precautions, monitoring, and clinical pearls of use of non-first-line depression treatments, including combination/adjunctive therapies and evidence-based off-label medications for TRD
- Evaluate clinical-relevance of pharmacokinetic and pharmacodynamics drug interactions involving pharmacotherapy for TRD
Treatment Resistant Depression (TRD) Epidemiology

- TRD is an “inadequate response to at least two trials of antidepressant treatment at adequate dose and duration”
- Duration usually 4 - 6 weeks at maximum tolerated approved dose
- In one study, 60% of those with TRD who had no treatment response within 1 yr remained on unchanged treatment for longer

Incidence of TRD in STAR*D

## TRD Clinical Predictors

<table>
<thead>
<tr>
<th>Current episode predictors</th>
<th>Patient history predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater symptom severity</td>
<td>Comorbid anxiety</td>
</tr>
<tr>
<td>Psychotic symptoms present</td>
<td>Higher number of prior antidepressant trials</td>
</tr>
<tr>
<td>Longer duration of current episode</td>
<td>Higher number of lifetime depressive episodes</td>
</tr>
<tr>
<td>Higher suicide risk</td>
<td>Early age of onset of first episode</td>
</tr>
<tr>
<td>Inpatient status</td>
<td></td>
</tr>
</tbody>
</table>

Contributing factors to TRD

• **Dose and duration**
  - Did dose get titrated up to max tolerated and approved dose? Is 4 - 6 weeks sufficient?
  - Did “clock” start before max tolerated dose achieved?

• **Consistent medication intake barriers**
  - Intolerable adverse effects, incl. withdrawal?
  - Socioeconomic: cost, transport, time away from work or children
  - Depressive sx of cognitive impairment or psychomotor retardation

• **Medication selection**
  - Among 1st line meds, selection usually not most important factor for MDD
  - If depression secondary to bipolar d/o, tx is mood stabilizer

• Consider other conditions: hypothyroidism, B12 deficiency, etc
Possible bipolar disorder indicators

*(none should be taken in isolation)*

### Major indicators
- 1\textsuperscript{st} or 2\textsuperscript{nd} degree relative with bipolar disorder
- Hypomania/mania symptoms within the depressive episode

### Other possible indicators
- Early-onset depression (e.g., adolescent)
- Frequent recurrent episodes
- Nonresponse to antidepressants
- General family history of serious mental illness
- Suicide attempt: 20 - 50% of people with bipolar d/o attempted vs 15 - 17% with MDD
- Mood Disorder Questionnaire (right) score $\geq 7$
- Symptoms of psychomotor agitation

---


Sensitivity: 67% (85% type 1; 46% type II)
Specificity: 84%
STAR*D
Sequenced Treatment Alternatives to Relieved Depression

- NIMH funded
- Real World Trial
  - Choice regarding
    - Switch or augmentation
    - CBT
    - Medications un-desired
  - Flexible dosing
- 18 - 75 year old patients
- HAM-D17 (& QIDS-SR16)
- 4 levels
Lessons from STAR*D

- Onset of SSRI can take up to 12 weeks
  - 40% took 8+ weeks, thus adequate trial requires at least 6-8 weeks of robust dosing
- No strategy was clearly superior
- Remission rates were 67% after 4 med trials

Critics argue that when accounting for drop outs, remission rate may be <50% after 4 trials

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4314062/
Treating TRD: strategies

• SSRIs and SNRIs first-line treatment, mirtazapine bupropion considered 1st line
  • Consider starting with combination therapy in severe depression
• Non-response after 4 - 6 weeks options
  • Switch medication
  • wait a full 8 weeks and re-assess
• Lack of tolerability to adequate dose option
  • Switch medication
• Partial response after 4 - 6 weeks options
  • Combine antidepressant medication therapy
  • Add adjunctive medication therapy
  • Wait full 8 weeks and re-assess
Next-step treatment algorithm

• When switching, one suggested algorithm follows, but other options exist
  • SSRI -> SNRI, bupropion, or mirtazapine
  • SNRI -> SSRI, bupropion, or mirtazapine
  • Bupropion -> SNRI, SSRI, or mirtazapine
  • Mirtazapine -> SSRI, SNRI, or bupropion

• Selection depends on reason for switch: intolerable vs ineffective
• Be vigilant for drug interactions resolving or emerging with switching

Methods of switching

• Traditional: Taper A off; start B after washout is complete (~5 T_{1/2})
  • Depression continues untreated longer and withdrawal symptoms are common
  • Essential with MAOI switches and a full 2 weeks wash out must occur due to irreversible inhibition

• Cross taper A up and B down simultaneously
  • Over 1 - 2 weeks (degree of monitoring, history of w/d, disease severity)
  • Fluoxetine auto tapers, d/c <= 40mg; wait 7 days
  • Risk of withdrawal (not equivalent dose, genetic polymorphisms, DDIs)
  • Requires some clinical expertise but provides therapeutic levels of next more rapidly

• Abruptly switch to equivalent doses
  • Use for SRI switching (e.g., SSRI -> SSRI; not fluoxetine) on the inpatient setting (e.g., formulary restrictions)
  • High risk of w/d symptoms; can give add a smaller dose of A for a few days if sx develop
  • Caution with SSRI -> SNRI
TRD: Combination of monotherapy regimens

- If partial response, consider combination of 1st line options (usually 1+2 or 1+3)

1. SSRI or SNRI
2. Bupropion (NDRI)
3. Mirtazapine (alpha2 antagonist)

- If partial response to TCA -> TCA + mirtazapine
Guideline comparison:
TRD antidepressant augmentation
Tricyclic Antidepressants (brief review)

• (S)NRIs that bind to $\alpha_1$ and $H_1$ and muscarinic and fast Na$^+$ channels
• Amitriptyline/nortriptyline; imipramine/desipramine
• Effective, but very toxic in overdose
• Wide interpatient variability due to 2D6 polymorphisms -> Serum levels are obtainable

Log Scale of Receptor Affinity (Ki in nM)
## SSRI(+) medications

<table>
<thead>
<tr>
<th><strong>Vilazodone</strong></th>
<th><strong>Vortioxetine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• 5HT\textsubscript{1a} partial agonist and SERT inhibitor</td>
<td>• 5HT\textsubscript{1a} agonist, 5HT\textsubscript{1b} partial agonist, SERT inhibitor, 5HT\textsubscript{3a} and 5HT\textsubscript{7} antagonist</td>
</tr>
<tr>
<td>• May be useful for anxiolytic effects, reduced sexual dysfunction</td>
<td>• May be useful for anxiolytic effects, reduced sexual dysfunction</td>
</tr>
<tr>
<td>• AEs: diarrhea, nausea</td>
<td>• AEs: well tolerated; nausea</td>
</tr>
<tr>
<td>• $$$$$</td>
<td>• $$$$$</td>
</tr>
<tr>
<td>• Dose: 10 – 40mg/day</td>
<td>• Dose: 10 – 20mg/day</td>
</tr>
</tbody>
</table>
SNRI: Levomilnacipran

- NRI > SRI
- 1S, 2R enantiomer of milnacipran
- Higher incidence of noradrenergic effects
  - Tachycardia, sweating, tremor, nausea, urinary retention
- May be useful in co-morbid pain or atypical depression
- $$
- Dose: 20 – 120mg/day
- Dose adjust with renal dysfunction
MAOIs (brief review)

- Very effective, but many drug and dietary interactions
  - Serotonergic burden (SSRIs, TCAs, and many more)
  - Sympathomimetic burden (pseudoephedrine, amphetamines)
  - Tyramine burden: Chocolate, cheese, wine, beer, soybeans
- AE: orthostatic hypotension; hypertensive crisis
- Phenelzine, isocarboxazid, tranylcypromine: irreversible and non-selective
- Selegilene daily patch: MAO-B selective at lower doses (6mg patch)

“I ate his liver with some fava beans and a nice Chianti.”
# Antipsychotic therapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA status</th>
<th>Goal dose</th>
<th>comments</th>
<th>Common adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>aripiprazole</td>
<td>FDA approved: oral form Off label: Long acting injection (LAI)</td>
<td>5-10mg daily</td>
<td>LAI q1 - 2 months helps w adherence</td>
<td>akathisia</td>
</tr>
<tr>
<td>quetiapine</td>
<td>FDA approved: XR form Off label: IR form</td>
<td>150-300mg nightly</td>
<td>Titrate up</td>
<td>Sedation, dizziness, weight gain</td>
</tr>
<tr>
<td>risperidone</td>
<td>Off label but well supported by evidence</td>
<td>1-2mg daily</td>
<td>LAI q2 - 4 weeks helps w adherence</td>
<td>EPS, weight gain, dizziness</td>
</tr>
<tr>
<td>brexipiprazole</td>
<td>FDA approved</td>
<td>2mg daily</td>
<td></td>
<td>akathisia</td>
</tr>
<tr>
<td>cariprazine</td>
<td>Off label: FDA application submitted Feb 2022</td>
<td>2 - 4.5mg daily</td>
<td></td>
<td>akathisia</td>
</tr>
<tr>
<td>Olanzapine/fluoxetine</td>
<td>FDA approved</td>
<td>6 - 12mg / 25 - 50mg daily</td>
<td>Use monotherapy</td>
<td>Weight gain, sedation</td>
</tr>
</tbody>
</table>
NMDA antagonists

- Role in both bipolar and unipolar depression
- **Rapid** onset of action
- (es)ketamine
  - Ketamine infusion 0.5mg/kg thrice weekly for 2 weeks (off label)
  - Esketamine nasal inhalation (FDA approved)
    - twice weekly x4 weeks then weekly x4w then q2w
    - FDA REMS requires 2hrs monitoring post dose
- Dextromethorphan/bupropion (FDA approved Aug 2022)
  - Also sigma1 agonist and more
  - bupropion increases levels of dextromethorphan via 2D6 inhibition
- Esmethadone (REL-1017 in phase 2a RDBPCT)
Other adjunctive off label therapy

- Lithium ER: start at 600 - 900mg nightly
  - goal level 0.5 - 0.8 meq/L (lower is safer long term)
  - Reduces the risk of suicide 64% in unipolar depression
  - Monitor renal, parathyroid, and thyroid functions

- Liothyronine ($T_3$): 25 - 50 mcg daily

- Lamotrigine: 200 - 400 mg daily

- Psilocybin assisted psychotherapy
  - FDA designated as "breakthrough therapy" for treatment-resistant depression in 2018 because it “may demonstrate substantial improvement over available therapy”
  - Current phase 2 RCT
    - psilocybin at point-of-care in adults with TRD (MDD or bipolar II disorder)
    - estimated completion Feb 2023 - https://clinicaltrials.gov/ct2/show/NCT05029466
Inhibitory (a) excitatory ionotropic & GPCR targets (b) inhibitory pre- & post-synaptic receptor targets of interest

Log Scale of Receptors (Ki in nM)

↑partial agonist or activator ↔ antagonist or inhibitor

Stephanie Nichols, PharmD BCPP

Borbely et al. BJP. 2021.
Understanding and evaluating drug interactions
Pharmacodynamic interactions

- What the drug does to the body
  - Receptor binding, cellular influence
  - must be considered for additive effects, synergy, and oppositional effects
- Anticholinergic - TCAs
- Sedation - TCAs, quetiapine, mirtazapine
- Dizziness/OH - risperidone, quetiapine, TCAs
- QTc prolongation - TCAs, citalopram, risperidone
- Seizures - bupropion, TCAs, antipsychotics
- Sympathomimetic - bupropion, SNRIs (esp levomilnacipran), MAOIs
- Serotonin syndrome
5-HT toxicity

- Triad of: altered Mental Status, neuromuscular excitability, and autonomic Instability
  - Iatrogenic and dose related
  - Threshold varies widely amongst individuals
- SRIs (SSRIs, SNRIs, many TCAs)
- MAOIs - Reversible vs irreversible; Selective vs non selective
- 5HT2a agonists
- “Hidden” 5HT medications
  - Dextromethorphan
  - Linezolid
    - Risk is lower than previously thought; likely between 0.5 and <3%
    - Combine with caution and consider the SS sx of AMS
- Methylene blue
- Tramadol, meperidine

Very uncommon with SSRI only (even in overdose incidence is only about 15%)

Trouble lies in the combinations, especially SRI + MAOI...
Essence of Pharmacokinetic CYP450 interactions: *active to inactive*

- **Substrate** (drug)
- **P450 enzyme**
- **Metabolite**
- **Inhibitors**: grapefruit, lurasidone
- **Inducers**: rifampin, methadone

**Normal**

**Inhibition**

**Induction**

- What happens to the medication effect with inhibition?
- Induction?
Essence of CYP450 interactions:

**Prodrugs**

<table>
<thead>
<tr>
<th>Substrate (drug)</th>
<th>P450 enzyme</th>
<th>Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td></td>
<td>Active</td>
</tr>
<tr>
<td>Inactive</td>
<td></td>
<td>Active</td>
</tr>
<tr>
<td>Inactive</td>
<td>P450 enzyme</td>
<td>Active</td>
</tr>
</tbody>
</table>

**Normal**

**Inhibition**

**Induction**

Codeine, morphine
Inh: tamoxifen, paroxetine
Ind: acetaminophen, alcohol (not prodrug, but toxin activation)

What happens to the medication effect with inhibition?
Induction?
Making it a tiny bit more complicated...

• What happens when both inhibition and induction are present?
  a. Substrate levels are equalized to be normal
  b. Substrate levels are lower
  c. Substrate levels are higher

• Time course
  • Inhibition follows inhibitor’s half life
  • Induction is delayed
    • Rifampin $T_{1/2} = 4h$ but takes about 10 - 14 days for new SS enzyme function
    • Phenobarbital can take up to 3 weeks
<table>
<thead>
<tr>
<th>Parent</th>
<th>Metabolite vs. Parent</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>↑ Activity</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Active</td>
<td>↔ Activity</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risperidone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Active</td>
<td>↓ Activity</td>
<td>Quetiapine</td>
</tr>
<tr>
<td>Active</td>
<td>Opposite activity</td>
<td>Nefazodone</td>
</tr>
<tr>
<td>Active</td>
<td>Inactive</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Inactive</td>
<td>Active</td>
<td>Tamoxifen</td>
</tr>
</tbody>
</table>
Common examples

CYP450 Substrates

- Nicotine
- Bupropion
- methadone
- Diazepam
- Losartan
- NSAIDs
- Warfarin
- Phenytoin
- Some TCAs/SSRIs
- Fentanyl/methadone
- Buprenorphine
- Quinidine
- Erythromycin/clarithromycin
- Antipsychotics

Inhibitors

- Azoles
- Macrolides
- Cimetidine
- Grapefruit
- Barbs
- Rifampin
- Disulfiram
- Quinidine
- Methadone
- Paroxetine
- Duloxetine
- Fluoxetine
- Bupropion
- Cimetidine

Inducers

- Azoles
- Macrolides
- Cimetidine
- Grapefruit
- Barbs
- Rifampin
- Dextromethorphan
- Ethanol
- Isoniazid
- Rifampin

CYP450 Initiators

- 2B6
- 2A6
- 2C19
- 2C9
- 3A4/5
- 1A2
- 2E1
- 2D6
- 2C8

- Paclitaxel
- Azoles
- Macrolides
- Cimetidine
- Grapefruit
Take home points

- TRD is extremely common and can be first addressed by ensuring proper dose and duration, lack of med barriers, and that treatment fits
- Strategies include antidepressant combination, augmentation, or switch
- Strategies for switch include traditional taper-washout, cross taper, and abrupt conversion
- Several second generation antipsychotics are effective as augmentation therapy and are recommended by all ten TRD augmentation guidelines
- Ketamine has been a breakthrough in TRD and NMDA receptors are now a significant pharmacological target of ongoing interest
- Lithium and (probably) (es)ketamine are effective in treating acute suicidality
- Serotonin syndrome is the most common PD drug interaction associated with TRD
- Pharmacokinetic interactions are predictable and involve a substrate which is impacted by an inhibitor or an inducer which will alter medication levels accordingly
Thank you!

What are you wondering?

snichols6@une.edu
<table>
<thead>
<tr>
<th>STAR*D level</th>
<th>Medication (mean dose)</th>
<th>Remission rate (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Citalopram (42 mg)</td>
<td>27 - 33% (47% sx 50% ↓)</td>
</tr>
<tr>
<td>• Mean time to response 47 days (~7 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 2a</td>
<td>Sertraline (136 mg)</td>
<td>18 - 27%</td>
</tr>
<tr>
<td>• No difference in RR between groups (p&gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Shorter time to response with medications vs CBT (mean 40 vs 55 days, p=0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Shorter time to response with medications vs CBT (mean 40 vs 55 days, p=0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 2b</td>
<td>Venlafaxine XR (194 mg)</td>
<td>25%</td>
</tr>
<tr>
<td>• No difference in RR between groups (p&gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Greater QIDS-SR reduction with bupropion (p&lt;0.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 3a</td>
<td>Bupropion SR (283 mg)</td>
<td>21 - 26%</td>
</tr>
<tr>
<td>• No difference in RR between groups (p&gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 3b</td>
<td>Citalopram + Buspirone (41 mg)</td>
<td>30 - 33%</td>
</tr>
<tr>
<td>• No difference in RR between groups (p&gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Greater QIDS-SR reduction with bupropion (p&lt;0.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 4</td>
<td>Citalopram + Bupropion (268 mg)</td>
<td>30 - 39%</td>
</tr>
<tr>
<td>• No difference in RR between groups (p&gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lower d/c rate with liothyronine (p=0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 5</td>
<td>Citalopram + CBT</td>
<td>31%</td>
</tr>
<tr>
<td>• No difference in RR between groups (p&gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 6</td>
<td>Mirtazapine (42 mg)</td>
<td>8 - 12%</td>
</tr>
<tr>
<td>• No difference in RR between groups (p&gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 7</td>
<td>Nortriptyline (97 mg)</td>
<td>12 - 20%</td>
</tr>
<tr>
<td>• No difference in RR between groups (p&gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 8</td>
<td>Lithium</td>
<td>13 - 16%</td>
</tr>
<tr>
<td>• No difference in RR between groups (p&gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lower d/c rate with liothyronine (p=0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 9</td>
<td>Liothyronine</td>
<td>25%</td>
</tr>
<tr>
<td>• No difference in RR between groups (p&gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 10</td>
<td>Mirtazapine (36 mg) &amp; venlafaxine XR (210 mg)</td>
<td>14 - 16%</td>
</tr>
<tr>
<td>• No difference in RR between groups (p&gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lower d/c rate with liothyronine (p=0.03)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Important Terms: we’ll dive into each in more detail, but here’s the first seed.

- **Substrate**: medication (substance) that uses a specific enzyme for metabolism
  - E.g., simvastatin is a CYP450 3a4 substrate so it is metabolized by 3a4

- **Inhibitor**: a medication (substance) that inhibits a specific enzyme so that it becomes much less active, which reduces metabolism of any substrates
  - E.g., ketoconazole is a 3a4 inhibitor so when it is combined with simvastatin, the levels will increase and can be toxic
  - Story: simvastatin and ketoconazole

- **Inducer**: a medication (substance) that causes a specific enzyme to become expressed more, which increases the metabolism of any substrates
  - E.g., st Johns Wart is a 3a4 inducer so when it is combined with simvastatin, the levels (and effectiveness) of simvastatin will lower
Anti-psychotics for MDD

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3595214/