PHARMACOLOGICAL MANAGEMENT OF TREATMENT-RESISTANT DEPRESSION

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Learning Objectives: Pharmacists

• Recognize the prevalence, risk factors, and clinical features of treatment-resistant depression

• Identify first-line treatment strategies for depressive disorders

• Describe treatment strategies for patients who do not respond to first-line therapies

• Identify evidence-based augmentation strategies for treatment resistant-depression

• Evaluate efficacy and tolerability of pharmacological agents used in treatment-resistant depression
Learning Objectives: Pharmacy Technicians

- Recognize the prevalence, risk factors, and clinical features of treatment-resistant depression

- Identify generic and brand names of commonly used antidepressants

- Identify common adverse drug reactions of antidepressants

- Recognize treatment strategies for patients who do not respond to first-line antidepressants

- Recognize evidence-based augmentation strategies for treatment-resistant depression
Background

• Depression is the most common mental disorder in the US, causing significant disability and disease burden

• Approximately 15.7 million (6.7%) adults experience at least one major depressive episode

• Lifetime prevalence of major depressive disorder (MDD) is 17%

• Annual health care costs
  • Depression: $200 Billion
  • Treatment-Resistant Depression (TRD): $64 Billion

Kessler et al. *JAMA*. 2003
SAMHSA, National Survey on Drug Use and Health. 2014
Prevalence of MDD

SAMHSA, National Survey on Drug Use and Health. 2013

*NH/OPI = Native Hawaiian/Other Pacific Islander
**AI/AN = American Indian/Alaska Native
Etiology: Monoamine Hypothesis

- Norepinephrine (NE)
  - Alertness
  - Concentration
  - Energy
  - BP/HR

- Serotonin (5-HT)
  - Obsessions
  - Compulsions
  - Memory
  - Nausea

- Dopamine (DA)
  - Reward
  - Pleasure
  - Motivation/Drive
  - Motor Function

Depression due to deficiency of neurotransmitters (NTs)
Other Possible Etiologies

• Desensitization – $\Delta$s receptor sensitivity

• 5-HT and NE link hypothesis – $\downarrow$ NTs

• Postsynaptic alteration theory – $\beta$-adrenergic receptors (hypersensitive)

• Dysregulation hypothesis – Failure of homeostatic NT regulation

• Brain-derived neurotrophic factor (BDNF) hypothesis – $\downarrow$ BDNF in hippocampus

• Alterations in GABA (Gamma ($\gamma$)-aminobutyric acid) and glutamate – $\Delta$s in levels in occipital and prefrontal cortex
DSM-5 Diagnostic Criteria for MDD

• Presence of symptoms
  • Symptoms persist ≥ 2 weeks
  • (Symptoms # 1 or 2 (or both) + ≥ 5 of 9 total symptoms
    1. Depressed mood
    2. Marked ↓ of interest or pleasure in activities
    3. Weight ↓ or ↑
    4. Insomnia or hypersomnia
    5. Psychomotor agitation or retardation
    6. Fatigue or ↓ of energy
    7. Feelings of worthlessness or excessive guilt
    8. ↓ cognitive function or ↓ concentration
    9. Suicidal ideation (SI)

Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5). 2013
## Select Rating Scales

### Hamilton Depression Rating scale (HAM-D)
- 17-item questionnaire
- Score interpretation
  - 0 – 7: Normal
  - 8 – 13: Mild
  - 14 – 18: Moderate
  - 19 – 22: Severe
  - ≥23: Very severe
- **Remission if ≤ 7**

### Montgomery-Asberg Depression Rating score (MADRS)
- 10-item questionnaire
- Score interpretation
  - 0 – 6: Normal
  - 7 – 19: Mild
  - 20 – 34: Moderate
  - ≥35: Severe
- **Remission if ≤ 10**

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Hamilton MJ. *Neurol Neurosurg Psychiatry* 1960
Montgomery SA & Asberg M. *British J Psychiatry*. 1979
Treatment Phases of Depression

Taken from Dunn et al. AM J Manage Care. 2006
Terminology

- **Non-response**: poor response requiring a change in treatment plan
  - < 50% ↓ in symptom scores (i.e., HAM-D or MADRS)

- **Response**: incomplete response to treatment with residual symptoms
  - ≥ 50% ↓ in symptom scores (i.e., HAM-D or MADRS)

- **Remission**: 2 to 8 weeks of an “asymptomatic stage”
  - HAM-D ≤ 7
  - OR
  - MADRS ≤ 10 or ≤ 8

Treatment Goals of MDD

• Fully recovered state

• Remission of symptoms
  • 2 to 8 weeks of absence or ↓ of both depressed mood and interest

• No longer experiencing clinically significant symptoms and functional impairment

Rush AJ et al. Neuropsychopharmacology. 2006
Rates of Depression Non-Response

• Only 1 out of 3 depressed patients receiving 1st line treatment with a selective serotonin reuptake inhibitor (SSRI) will achieve remission

• STAR*D (Sequenced Treatment Alternative to Relieve Depression) study findings:
  • 50 to 66% did not achieve remission on 1st antidepressant
  • Approximately 30% did not respond to multiple treatments

Rush AJ et al. *CNS Drugs*. 2009
Treatment-Resistant Depression (TRD)

- No standard definition exists
- Failure to achieve response or remission
  - With $\geq 2$ trials of proven antidepressant monotherapy
  - Adequate dosing and duration of antidepressant therapy
TRD Risk Factors

- Comorbid medical or psychiatric disorders
  - i.e., anemia, hypothyroidism, anxiety, substance use, personality disorders
- Chronic pain
- Medications
  - i.e., interferon therapy, glucocorticoids
- Recurrent or severe depressive symptoms
- Suicidal thoughts and behavior
- Onset of major depression < 18 years of age
- Low socioeconomic status
- Genetic polymorphisms
  - i.e., CYP (cytochrome P450) enzymes, 5-HT transporter, NMDA (N-Methyl-D-aspartate)
- Abnormalities in specific brain regions and neural networks

Drozda K. *Pharmacotherapy*. 2014
Ionescu DF et al. *Dialogues CNS*. 2015
Thase ME. *J Clin Psychiatry*. 2011
First-line Antidepressant Treatments

- Greater evidence of efficacy and tolerability

<table>
<thead>
<tr>
<th>Selective serotonin reuptake inhibitors (SSRIs)</th>
<th>Serotonin norepinephrine reuptake inhibitor (SNRIs)</th>
<th>Atypical Antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram (Celexa®) Escitalopram (Lexapro®)</td>
<td>Duloxetine (Cymbalta®) Venlafaxine (Effexor®) Desvenlafaxine (Pristiq®)</td>
<td>Bupropion (Wellbutrin®) Mirtazapine (Remeron®)</td>
</tr>
<tr>
<td>Fluoxetine (Prozac®) Fluvoxamine (Luvox®) Paroxetine (Paxil®) Sertraline (Zoloft®)</td>
<td>Desvenlafaxine (Pristiq®)</td>
<td></td>
</tr>
</tbody>
</table>

TMAP MDD Algorithm. 2008
# SSRIs and SNRIs: ADRs and Management

<table>
<thead>
<tr>
<th>Adverse Drug Reaction (ADR)</th>
<th>Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/diarrhea</td>
<td>• Take with food or qHS</td>
</tr>
<tr>
<td>Insomnia/sedation</td>
<td>• Schedule dose qAM or qHS</td>
</tr>
</tbody>
</table>
| Headache                    | • OTC analgesics  
                              • APAP or NSAIDs  
                              • Schedule qHS |
| Sexual changes or dysfunction* | • Switch agents or add 5-HT\textsubscript{2A} antagonist |
| Bleeding or ↓ bone density  | • Monitor |
| SIADH (rare)                | • Discontinue |

*Sexual Changes: Decreased libido, anorgasmia, delayed ejaculation  
AM: Morning; APAP: Acetaminophen; NSAIDs: Non-steroidal anti-inflammatory drugs;  
SIADH: Syndrome of inappropriate anti-diuretic hormone; q: Every
Atypical Antidepressants

- **Bupropion (Wellbutrin®)**
  - Inhibits reuptake of DA and NE
  - ADRs: insomnia, agitation, anxiety, headache, weight loss
  - Minimal sexual side effects
  - Contraindications: seizure disorder, h/o anorexia or bulimia

- **Mirtazapine (Remeron®)**
  - $\alpha_2$-antagonist, 5-HT$_2$/5-HT$_3$ antagonist
  - ADRs: sedation, weight gain, hyperlipidemia
  - Minimal sexual side effects
  - Minimal drug-drug interactions (DDIs)
Tricyclic Antidepressants (TCAs)

- Less favorable side effect profile
  - Also blocks histamine, α-adrenergic, and muscarinic receptors

<table>
<thead>
<tr>
<th>Secondary Amines</th>
<th>Tertiary Amines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nortriptyline (Pamelor®)</td>
<td>Amitriptyline (Elavil®)</td>
</tr>
<tr>
<td>Desipramine (Norpramin®)</td>
<td>Imipramine (Tofranil®)</td>
</tr>
<tr>
<td></td>
<td>Doxepin (Silenor®)</td>
</tr>
<tr>
<td></td>
<td>Clomipramine (Anafranil®)</td>
</tr>
<tr>
<td>ADR</td>
<td>Management Strategy</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Sedation</td>
<td>• Schedule dose qHS</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>• Switch agents</td>
</tr>
<tr>
<td>Weight gain</td>
<td>• Exercise and improve diet</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>• Improves over time, candy, ice chips</td>
</tr>
<tr>
<td>Constipation</td>
<td>• Diet high in fiber, adequate fluid</td>
</tr>
<tr>
<td>Dizziness/orthostasis</td>
<td>• Titrate dose slowly</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>• Monitor, lower dose</td>
</tr>
</tbody>
</table>
TCAs: Warnings/Precautions

- Lethal in overdose – avoid use in suicidal patients
- Caution in patients with cardiovascular (CV) disease
- May lower seizure threshold

Contraindications
- Use of Monoamine oxidase inhibitor (MAOI) within 14 days
- Recent myocardial infarction
- Glaucoma
- Urinary retention
Monoamine Oxidase Inhibitors (MAOIs)

- Inhibit the breakdown of 5-HT, NE, DA

- Phenelzine (Nardil®)
  - Tranylcypromine (Parnate®)
  - Selegiline patch (Ensam®)

- ADRs
  - Orthostatic hypotension, insomnia, weight gain, sexual dysfunction, dry mouth, constipation
MAOIs: Warnings/Precautions

• Avoid with tyramine-rich foods
  • Risk of hypertensive crisis
  • i.e., alcohol, aged cheese, aged meat, soy sauce

• High risk of serotonin syndrome
  • Requires 14-day wash-out period when starting other serotonergic compounds
Other Antidepressants

- Trazodone (Desyrel®)
  - 5HT reuptake, 5HT$\text{_{2A}}$, $\alpha_1$-H$_1$-antagonist

- Nefazodone (Serzone®)

- Vilazodone (Viibryd®) – 2011
  - Serotonin partial agonist and reuptake inhibitor (SPARI)

- Vortioxetine (Brintellix®) – 2013
  - 5HT reuptake inhibitor, 5HT$_3$ antagonism, 5HT$_{1A}$ agonist
Onset of Action

- **Full effect in ~ 6 to 8 weeks**

- **Week 1 - 2**: Improved sleep and appetite
- **Week 3 - 4**: Increased energy, improved concentration
- **Week 4 - 6**: Improved mood, less anhedonia and SI
Evaluating Patients with TRD

- Reassess diagnosis
  - MDD w/ psychotic features vs. melancholic depression
  - Medical comorbidities

- Psychiatric comorbidities
  - OCD (obsessive-compulsive disorder), PTSD (post-traumatic stress disorder), substance use disorder

- Medication adherence
  - Ambivalence to treatment, cognitive deficits, cost, side effects

- Pharmacokinetics
  - Drug-drug interaction, rapid metabolizers, smokers

- Dose and duration

Ionescu DF et al. *Dialogues CNS*. 2015
Treatment Strategies

- **Optimize** antidepressant
  - Increase to maximum dose, as tolerated
  - 6 to 12 week trial
- **Switch** to another antidepressant
  - Within class or between class
- **Combine** with antidepressant from a different class
- **Augment** with non-antidepressant agent

Ionescu DF et al. *Dialogues CNS*. 2015
Shelton RC et al. *CNS Drugs*. 2010
Thase ME. *J Clin Psychiatry*. 2011
Optimization of Antidepressant Therapy

- “Pseudoresistance” due to suboptimal dose or short trial period
- Evaluate response to SSRI treatment after 6 to 12 weeks
- If no response, increase dose until:
  1. Remission of depression symptoms
  2. Unable to tolerate dose-related side effects
  3. Reached maximum recommended dose
- Assess for other contributing factors to lack of response
  - Medication adherence
  - DDIs, food effects, rapid metabolism

Shelton RC et al. *CNS Drugs*. 2010
Switching Strategies

• Consider switching to alternative SSRI or SNRI if:
  • Unable to tolerate at adequate doses
  • No improvement at adequate doses
  • Concern for non-adherence and monotherapy preferred
  • Concern for DDIs with combination therapy
Switching Antidepressants

- **Within-class switching**
  - SSRI $\rightarrow$ SSRI

- **Between-class switching**
  - SSRI $\rightarrow$ SNRI
  - SSRI $\rightarrow$ bupropion or mirtazapine
  - SSRI $\rightarrow$ TCA
  - SSRI $\rightarrow$ MAOI
Switching Antidepressants

- Standard approach is to cross-taper
  - Over 1 to 2 weeks
  - Switching to MAOI requires washout period of 14 days

- Direct switch between SSRI/SNRI at equivalent doses

- If switching to MAOI, taper and discontinue current SSRI with 14-day washout period (6 weeks for fluoxetine)
Combination Strategies

• Addition of antidepressant from different class
  • SSRI/SNRI + Mirtazapine OR Bupropion
  • Bupropion + Mirtazapine

• Lower risk of discontinuation syndrome compared with cross-titration during antidepressant switch

• Possible synergistic effect

Lopes RF et al. *J Affect Disord.* 2013
Carvalho AF et al. *Psychother Psychosomat.* 2014
Combination Strategies

- Conflicting evidence
  - Meta-analysis of four RCTs (randomized controlled trials) found remission was 3x more likely with combination treatment
  - Systematic review of five RCTs of patients with TRD found that combination treatment did not improve response or remission rates

Lopes RF et al. *J Affect Disord.* 2013
Carvalho AF et al. *Psychother Psychosomat.* 2014
Medications Used to Augment Antidepressants

- AAPs (i.e., risperidone, aripiprazole, etc.)
- Lithium (Li⁺)
- Thyroid hormone (T₃)
- Buspirone
- Anticonvulsants (i.e., lamotrigine, topiramate)
- NSAIDs (celecoxib)
- Stimulants (i.e., methylphenidate, lisdexamfetamine)
- Stimulant-like agents (modafinil)
- Dopamine Agonists (pramipexole)
- Supplements: L-methyl folate (5-MTHF), omega-3 fatty acids, SAMe
Atypical Antipsychotics (AAPs)

- AAPs are the only FDA-approved agents for depression augmentation

- No head-to-head trials comparing AAP augmentation

- Growing use of AAP for nonpsychotic depression
  - 8.6% of MDD clinic visits included AAP prescriptions

- High rates of discontinuation are due to ADRs
  - Sedation
  - Weight gain
  - Metabolic disturbances (i.e., diabetes, hyperlipidemia)
  - Extrapyramidal motor symptoms (i.e., dystonia, akathisia, pseudoparkinsonism, tardive dyskinesia)

Aripiprazole (Abilify®)

- Open-label and retrospective chart reviews show significant ↓ in MADRS score
  - “less impairment in family/home responsibilities and social activities”

- Effective antidepressant augmentation agent
  - Response rates up to 70%
  - Remission rates up to 53%

- Significant discontinuation rates due to akathisia

Hellerstein DJ et al. *Prog Neuropsychopharmacol.* 2008
Papakostas GI et al. *J Clin Psychiatry.* 2005
Olanzapine

- Olanzapine-fluoxetine (Symbyax®) FDA-approved for TRD and bipolar depression
  - Superior to monotherapy with olanzapine or fluoxetine
  - More rapid treatment response than monotherapy
  - 76-week long-term study revealed remission rate of 44%
  - Usual dose: Olanzapine 6 mg to 18 mg/fluoxetine 25 mg to 50 mg

- Higher incidence of adverse events vs. placebo
  - Sedation
  - Weight gain, increased appetite
  - Elevated glucose levels
  - Hypercholesterolemia
  - QT interval prolongation

Quetiapine (Seroquel®)

• Augmentation improves mood, insomnia, and anxiety

• Metabolized to active metabolite norquetiapine
  • Selectively inhibits NE reuptake
  • Partial 5-HT$_{1A}$ receptor agonist
  • Potential antidepressant effects

• Response rate in TRD about 70% after augmentation

• Adverse effects include sedation, weight gain, dizziness, dry mouth and headache

Sagud M et al. Psychopharmacology. 2008
Lopez-Munoz et al. Front Psychiatry. 2013
Devarajan et al. Psychopharmacology. 2006
Risperidone (Risperdal®)

- Only AAP not FDA-approved for depression augmentation
- Improvements in insomnia, suicidality, and depressive mood
- Remission rate up to 52%
- Increases time to relapse of depressive symptoms
- ↑ incidence of prolactinemia compared to other AAPs

Rapaport MH et al. Neuropsychopharmacology. 2006
Keitner GI et al. APA Annual Meeting. 2006
## AAP Efficacy: Response

<table>
<thead>
<tr>
<th>AAP Adjunct</th>
<th># of Trials</th>
<th># of Subjects</th>
<th>OR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>3</td>
<td>1065</td>
<td>2.07 (1.58-2.72)</td>
<td>7 (5-12)</td>
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<tr>
<td>Olanzapine/fluoxetine</td>
<td>5</td>
<td>1121</td>
<td>1.30 (0.87-1.93)</td>
<td>NS</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>3</td>
<td>977</td>
<td>1.52 (1.17-2.0)</td>
<td>10 (6-26)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2</td>
<td>363</td>
<td>1.83 (1.16-2.88)</td>
<td>8 (5-33)</td>
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<tr>
<td><strong>All AAPs Pooled</strong></td>
<td><strong>13</strong></td>
<td><strong>3526</strong></td>
<td><strong>1.61 (1.33-1.95)</strong></td>
<td><strong>9 (7-16)</strong></td>
</tr>
</tbody>
</table>

## AAP Efficacy: Remission

<table>
<thead>
<tr>
<th>AAP Adjunct</th>
<th># of Trials</th>
<th># of Subjects</th>
<th>OR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>3</td>
<td>1065</td>
<td>2.01 (1.48-2.73)</td>
<td>9 (6-18)</td>
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<tr>
<td>Olanzapine/fluoxetine</td>
<td>5</td>
<td>1121</td>
<td>1.42 (1.01-2.0)</td>
<td>19 (9-713)</td>
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<tr>
<td>Quetiapine</td>
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<td>977</td>
<td>1.79 (1.33-2.42)</td>
<td>9 (6-19)</td>
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<tr>
<td>Risperidone</td>
<td>2</td>
<td>363</td>
<td>2.37 (1.31-4.30)</td>
<td>9 (5-35)</td>
</tr>
<tr>
<td><strong>All AAPs Pooled</strong></td>
<td><strong>13</strong></td>
<td><strong>3526</strong></td>
<td><strong>1.77 (1.49-2.09)</strong></td>
<td><strong>10 (8-15)</strong></td>
</tr>
</tbody>
</table>

## AAPs: Risk vs. Benefit

<table>
<thead>
<tr>
<th>AAP Adjunct</th>
<th># of Trials</th>
<th>Major ADR</th>
<th>ADR NNH (95% CI)</th>
<th>Remission NNT (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>3</td>
<td>akathisia</td>
<td>4 (3-6)</td>
<td>9 (6-18)</td>
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<tr>
<td>Olanzapine/fluoxetine</td>
<td>5</td>
<td>weight gain</td>
<td>9 (5-20)</td>
<td>19 (9-713)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>3</td>
<td>metabolic disturbances</td>
<td>6 (4-9)</td>
<td>9 (6-19)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2</td>
<td>↑ appetite, weight gain</td>
<td>NS</td>
<td>9 (5-35)</td>
</tr>
</tbody>
</table>

## AAPs: Monitoring Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Quarterly</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Waist circumference</td>
<td></td>
<td>X</td>
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<td></td>
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<tr>
<td>Blood pressure</td>
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<td>X</td>
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<tr>
<td>Fasting plasma glucose</td>
<td>X</td>
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<td></td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Fasting lipid profile</td>
<td>X</td>
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<td></td>
<td>X</td>
<td></td>
<td>X</td>
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</tbody>
</table>
Lithium (Li⁺)

- FDA-approved for treatment of acute mania and maintenance in bipolar disorder

- Antidepressant effects involved hypothalamic-pituitary-thyroid axis

- STAR*D results of Li⁺ augmentation with citalopram
  - Remission rate of 15.9%

- Higher rates of discontinuation due to side effects
  - Polyuria, polydipsia, tremor, thyroid dysfunction

- Requires monitoring of serum Li⁺ level, electrolytes, renal and thyroid function, ECG

Bauer M et al. *CNS Drugs*. 2014
Liothyronine (T₃)

• Mechanism of action (MOA) of T₃ augmentation not fully understood

• Preferred over levothyroxine (T₄) due to bioactivity in the central nervous system (CNS)

• STAR*D results of T₃ augmentation with citalopram
  • Remission rate of 24.7%

• Usual dose: 25 to 50 mcg/day

• Minimal adverse effects

• Generally well-tolerated

Iosifescu DV et al. *Biol Psychiatry* 2008
Aronson R et al. *Arch Gen Psychiatry*. 1996
Buspirone (Buspar®)

- FDA-approved for treatment of generalized anxiety disorder

- $5\text{-HT}_{1A}$ agonist thought to modulate serotonergic neurotransmission and affect cognition and mood

- STAR*D trial compared buspirone and bupropion augmentation with citalopram
  - Similar remission rate of 30%

- Common adverse effects
  - Nausea
  - Drowsiness
  - Headache

# Efficacy of Other Adjuncts: Response

<table>
<thead>
<tr>
<th>Adjunct</th>
<th># of Trials</th>
<th># of Subjects</th>
<th>Response (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>10</td>
<td>269</td>
<td>OR 3.11 (1.80-5.37)</td>
<td>5</td>
</tr>
<tr>
<td>Liothyronine (T₃)</td>
<td>8</td>
<td>1121</td>
<td>RR 2.09 (1.37-3.32)</td>
<td>4.3</td>
</tr>
<tr>
<td>Buspirone</td>
<td>3</td>
<td>317</td>
<td>RR 0.98 (0.80-1.21)</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Lithium and T₃ studies used TCAs > SSRI/SNRI
- T₃ safer and better tolerated than lithium

Bauer M et al. *CNS Drugs*. 2014
Aronson R et al. *Arch Gen Psychiatry*. 1996
Lamotrigine (Lamictal®)

- FDA-approved for epilepsy and maintenance of bipolar disorder
  - Off-label use in bipolar depression

- Randomized controlled trials (n=2) show mixed results for depression augmentation

- Requires careful titration due to risk of serious skin rash (i.e., Stevens-Johnson syndrome)

Topiramate (Topamax®)

- FDA-approved for epilepsy and prevention of migraine headaches
  - Off-label use in alcohol use disorder, binge eating disorder, and essential tremor

- RCT of female patients with MDD (n=64)
  - Reduced depressive symptoms and anger versus placebo

- ADRs include dizziness, paresthesias, memory impairment, and weight loss

- May worsen depressive symptoms

Methylphenidate (Ritalin®)  
Lisdexamfetamine (Vyvanse®)

- May improve energy level and concentration

- Methylphenidate and lisdexamfetamine comparable to placebo in reducing depressive symptoms when combined with antidepressant
  - Minimal evidence to support use in TRD

- Contraindicated in patients with psychosis, anxiety, insomnia, and substance use disorder

Modafinil (Provigil®)

• FDA-approved for narcolepsy and shift work sleep disorder
  • Off-label use in ADHD and cancer-related fatigue

• CNS stimulant which may reduce depressive symptoms such as fatigue and sleepiness

• Meta-analysis of six RCTs
  • Improvements in depressive and fatigue symptoms
  • Higher remission rates compared to placebo
  • Similar rates of adverse events compared to placebo

• ADRs include nausea, headache, dizziness

Goss AJ. J Clin Psychiatry. 2013
Pramipexole (Mirapex®)

- FDA-approved for Parkinson's disease and restless leg syndrome
- Dopamine agonist at D_3_ receptor in mesolimbic system
- Open label studies report response rate of 68 to 74% and remission rate of 61% after 22 weeks
- RCT indicate modest but statistically significant benefit vs. placebo
  - Average dose: 1 mg per day
- Poorly tolerated at higher doses
  - Reports of nausea, fatigue, somnolence, insomnia

Lattanzi L et al. *Bipolar Disord.* 2002
Cassano P et al. *Depress Anxiety.* 2004
Franco-Chaves JA. *J Affect Disord.* 2013
Celecoxib (Celebrex®)

• Non-steroidal anti-inflammatory drug (NSAID)

• Inflammatory processes suggested to play a role in pathophysiology of depression

• Meta-analysis of 4 trials (n=150) of adjunctive celecoxib showed significant antidepressant efficacy compared to placebo
  • ↓ HAM-D score, higher response and remission rates
  • GI and CV effects similar for celecoxib and placebo
  • Duration of treatment possibly too short for ADRs to manifest

• SSRI + NSAIDs associated with ↑ bleeding risk

Kohler O et al. JAMA Psychiatry. 2014
Faridhosseini F et al. Hum Psychopharmacol. 2014
S-adenosyl methionine (SAMe)

- Marketed as nutritional supplement
- Essential metabolic precursor of neurotransmitter synthesis
- Data from a RCT (n=73) found patients with TRD had ↑ response and remission rate with SAMe augmentation
- Open-label studies show remission rates of 22 to 43%
  - No response with SAMe monotherapy

Papakostas GI et al. Am J Psychiatry. 2010
L-Methyl Folate (5-MTHF)

- Biologically active precursor of SAMe
- Readily crosses blood-brain barrier
- Two published RCTs (n=223) of adjunctive 5-MTHF in TRD
  - Results conflicting (effective in TRD vs no difference from placebo)
  - 5-MTHF generally well-tolerated
- Response made be affected by biomarkers and genetic markers of metabolic dysfunction
  - Methylene tetrahydrofolate reductase (MTHFR) genotype variant
- Folic acid has not been shown to be effective as antidepressant augmentation agents

Omega-3 Fatty Acids

- Inverse correlation between fish intake and prevalence of depression

- Augmentation in with recurrent or persistent MDD
  - Omega-3 fatty acids: 53 to 60% response rate
  - Placebo: 10 to 29% response rate
  - No difference in rates of adverse events

Review of Augmentation Strategies

- **Strong evidence**
  - Atypical antipsychotics
  - Lithium
  - Thyroid hormone ($T_3$)

- **Potential benefit**
  - Celecoxib
  - Modafinil
  - Pramipexole
  - Omega-3 fatty acids
  - SAMe

- **Mixed or minimal evidence**
  - Buspirone, L-methyl folate, lamotrigine, topiramate, methylphenidate, lisdexamphetamine
Ketamine: The Future of TRD Treatment?

- Dissociative anesthetic with NMDA receptor antagonist properties
  - Disinhibition of glutamate transmission → glutamate burst leading to ↑ BDNF
  - Anti-inflammatory properties

- IV administration provides rapid, robust, and relatively sustained antidepressant efficacy
  - Likely to require repeated doses to extend antidepressant response

- ↓ anhedonia and suicidal ideation

- Studies currently ongoing to determine appropriate duration and dose of ketamine

- Safe and well tolerated given subanesthetic dose
  - 0.5 mg/kg IV over 40 min

Summary: TRD Management

- One-third of depressed patients will not remit after multiple medication trials

- TRD influenced by a variety of factors and pathophysiological processes

- Difficult to predict which therapy will produce significant response
Summary: TRD Management

- Ensure adequate initial antidepressant medication trial before switching or augmenting
- Identify comorbid conditions and residual symptoms before considering augmentation strategies
- Given potential long-term use for depression, consider agents with good efficacy and better tolerability profiles
  - $\text{Li}^+$ or $\text{T}_3 > \text{AAP}$
Questions?
Abbreviations

• \( \Delta \): Change/s
• 5-HT: Serotonin
• 5-MTHF: L-methyl folate
• ADR: Adverse drug reaction
• AAP: Atypical antipsychotics
• AM: Morning
• APAP: Acetaminophen
• BN: Billion
• BDNF: Brain-derived neurotrophic factor
• CNS: Central nervous system
• CV: Cardiovascular
• CYP: Cytochrome P450 enzymes
• DA: Dopamine
• ECG: Electrocardiogram
• GAD: Generalized anxiety disorder
Abbreviations

- GI: Gastrointestinal
- HAM-D: Hamilton depression rating scale
- HS: Bedtime
- M: Million
- MOA: Mechanism of action
- MADRS: Montgomery-Asberg depression rating score
- MAOI: Mono-amine oxidase inhibitor
- MDD: Major depressive disorder
- NMDA: N-Methyl-D-aspartate
- OCD: Obsessive compulsive disorder
- GABA: Gamma (γ)-aminobutyric acid
- MTHFR: Methylene tetrahydrofolate reductase
- NE: Norepinephrine
Abbreviations

• NMDA: N-methyl-D-aspartate
• NSAIDs: Non-steroidal anti-inflammatory drugs
• NT: Neurotransmitter
• PTSD: Post-traumatic stress disorder
• RCT: Randomized controlled trial
• SAMe: S-adenosyl methionine
• SI: Suicidal ideation
• SIADH: Syndrome of inappropriate antidiuretic hormone
• SNRI: Serotonin norepinephrine reuptake inhibitor
• SSRI: Selective serotonin reuptake inhibitor
• STAR*D: Sequenced Treatment Alternative to Relieve Depression
• TCA: Tricyclic antidepressant
• TRD: Treatment-resistant depression
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