Doing More by Prescribing Less; 
Top Ten Drug Interactions that Limit Efficacy

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Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  – Dr. Zarkowski will be discussing off-label use of prescription medications in the presentation and will identify those issues.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

• This activity has been independently reviewed for balance.
Polypharmacy

- Increasing incidence of ≥ 2 concurrent prescriptions for
  - Antidepressants
  - Antipsychotics
  - Sedative-hypnotics
  - Antidepressant-antipsychotic combinations
    - But not other combinations
- Rare RPCDB studies of combinations
- Uncertain gains for quality of care and clinical outcomes

RPCDB = randomized placebo-controlled double-blind.
3 Types of Evidence

- Opposing clinical indications and side effects suggest an interaction limiting efficacy
- Underlying mechanism of action suggests an antagonistic interaction at receptors critical for efficacy
- Clinical studies with simultaneous administration of medications confirm decreased efficacy
  - Humans
  - Rats
  - Mice

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### Equilibrium Constant

<table>
<thead>
<tr>
<th>K (µM)</th>
<th>Drug X</th>
<th>Drug Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>0.5</td>
<td>6.200</td>
</tr>
<tr>
<td>5-HT1A</td>
<td>60</td>
<td>&gt;10.000</td>
</tr>
<tr>
<td>5-HT2A</td>
<td>0.1</td>
<td>105</td>
</tr>
<tr>
<td>5-HT2C</td>
<td>2.2</td>
<td>181</td>
</tr>
<tr>
<td>SERT</td>
<td>-</td>
<td>16</td>
</tr>
</tbody>
</table>
Example of Study Exclusion
Pramipexole and Antipsychotic Medication

Meets First 2 Criteria
- Pramipexole caused psychosis in patients treated for RLS
- Pramipexole is a dopamine agonist
  - Significant affinity for D_2
    - K_i = 3.1 nM
    - Antagonism of D_2 receptor is crucial for antipsychotic efficacy
  - More affinity for D_3
    - K_i = 0.23 nM
    - Proposed mechanism of action for treating psychosis

But RPCDB Supports Combination
- Augmenting antipsychotic medications with pramipexole to 4.25 mg (0.38 mg)
  - 24 participants (SC or SA) over 12 weeks
  - Completion ACT 82% vs PBO 62%
    - Includes 1 drop out in active arm with disorganization
    - 3 completers with new or worsening hallucinations at top dose
  - PANSS-Pos
    - ACT -9.5 (48); PBO +20.9 (60)*
    - P = .006
  - PANSS-Neg
    - ACT -9.2 (28); PBO -15.7 (16)

RLS = restless legs syndrome; SC = schizophrenia; SA = schizoaffective disorder; ACT = active; PBO = placebo; PANSS = Positive and Negative Syndrome Scale.
Ranking the Prevalence of Interactions that Limit Efficacy

- Electronic Chart Review
  - Genoa Healthcare Database
    - Largest provider of pharmacy services to behavioral health and addiction treatment communities
  - Multiple Community Mental Health organizations
    - All records between January 1, 2016 and May 20, 2018
- Inclusion based on concurrence of 3 types of evidence
  - Indications and side effects
  - Mechanism of action
  - Clinical studies of combination

Zarkowski P. 2018; In preparation.
#70 Fluoxetine and Cyproheptadine

#70 Fluoxetine & Cyproheptadine
#71 Sertraline & Cyproheptadine
#70 Paroxetine & Cyproheptadine
Fluoxetine FDA indication for Major Depression

Cyproheptadine Off-label treatment for Anorgasmia due to SSRIs

Sexual Dysfunction in 36% of patients on Fluoxetine

Case series of depressive relapse

SSRI = selective serotonin reuptake inhibitor.
Conflicting Mechanism of Action

<table>
<thead>
<tr>
<th>Equilibrium Constant</th>
<th>Cyproheptadine</th>
<th>Fluoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_i$ (nM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$H_1$</td>
<td>0.5</td>
<td>6200</td>
</tr>
<tr>
<td>5-HT$_{1A}$</td>
<td>69</td>
<td>&gt; 10,000</td>
</tr>
<tr>
<td>5-HT$_{2A}$</td>
<td>6.1</td>
<td>196</td>
</tr>
<tr>
<td>5-HT$_{2C}$</td>
<td>2.2</td>
<td>181</td>
</tr>
<tr>
<td>SERT</td>
<td>-</td>
<td>16</td>
</tr>
</tbody>
</table>

5-HT$_{1A}$ Serotonin Receptor
- Fluoxetine inhibits the reuptake of serotonin
- Cyproheptadine is an antagonist at 5-HT$_{1A}$
- 5-HT$_{1A}$ and antidepressant efficacy
  - Shown to be crucial for efficacy in forced swim protocol in rats
  - Suggested intermediate role in the MOA of antidepressants
  - Relevance of receptor highlighted by vilazodone and vortioxetine

MOA = mechanism of action; SERT = serotonin transporter.
Clinical Interaction Supported by Case Studies

• Reversal of antidepressant activity of fluoxetine by cyproheptadine
  – Case study of 3 males treated for anorgasmia
• Loss of response of fluoxetine after addition of cyproheptadine
  – Case study of 2 patients taking fluoxetine for bulimia nervosa
• Interaction not limited to fluoxetine
  – Case study of cyproheptadine reversing antidepressant effect of paroxetine

Suggestions to Try Instead

• Dose reduction of fluoxetine
• Switch to antidepressant with less sexual side effects
  – Mirtazapine
    • 5-HT$_{2A}$ antagonist
  – Bupropion
    • No serotonergic activity
• Add trazodone to existing SSRI
  – Open-label study showed improvement in 4 dimensions of sexual function
    • Possible role of 5-HT$_{2A}$

#57 Amitriptyline and Naltrexone

#57 Amitriptyline & Naltrexone
#73 Nortriptyline & Naltrexone
Clinical Actions

Naltrexone
FDA indication for Alcohol and Opioid Use Disorder

Amitriptyline
FDA indication for Depression
Off-label use for Pain

Mechanism of Action

<table>
<thead>
<tr>
<th>Equilibrium Constant</th>
<th>Naltrexone</th>
<th>Naloxone</th>
<th>Amitriptyline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ki</strong> (nM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid-δ</td>
<td>26</td>
<td>52</td>
<td>-</td>
</tr>
<tr>
<td>Opioid-κ</td>
<td>1.75</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Opioid-μ</td>
<td>0.39</td>
<td>3.7</td>
<td>-</td>
</tr>
<tr>
<td>SERT</td>
<td>-</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>NET</td>
<td>-</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

Interaction via Opioid Receptors
- Naltrexone is a long-acting opioid blocker, similar to naloxone
- Amitriptyline inhibits the reuptake of serotonin and norepinephrine
- 10 days of amitriptyline blocks mechanically-induced allodynia from sciatic nerve cuffing in rats
  - No effect from sertraline
  - Effect reversed by naloxone
- μ and κ receptor knock out mice have localized MOA of TCAs to δ receptors

NET = norepinephrine transporter; TCA = tricyclic antidepressant.
Norepinephrine is the Missing Link

• 21 days of nortriptyline blocked mechanically-induced allodynia from sciatic nerve cuffing in rats
  – Effect was blocked by propranolol
    • β(2)-AR antagonist ICI 118,551
  – Not affected by
    • Yohimbine, α(2)-AR antagonist
    • Metoprolol or atenolol
    • β(3)-AR antagonist SR 59230A
  – Effect of nortriptyline was also totally absent in β(2)-AR-deficient mice

AR = adrenergic receptor.
Interaction Verified in Additional Pain Protocol

- Acetic acid-induced abdominal constriction assay in mice
  - Naloxone shifts the dose-response curve of amitriptyline to the right
- Studies on interaction in humans are scarce
  - In one case study 3 challenges of naltrexone caused depressive relapse 3 separate times in a patient that had responded to amitriptyline

**P<.01 vs amitriptyline and vehicle regression line.
Not All Pain Medications are Blocked by Naltrexone

- **NSAIDs**
  - Naloxone had no effect on the dose-response curve of ASA in mice
  - Pretreatment with naltrexone blocked the analgesic response of codeine but not IBU in patients undergoing dental surgery
- **AEDs**
  - Naltrexone blocked the antinociceptive properties of morphine but not gabapentin in mice injected with HSV-1
  - Replicated in sciatic nerve cuffing

NSAID = nonsteroidal anti-inflammatory drug; ASA = aspirin; IBU = ibuprofen; AED = anti-epileptic drug; HSV-1 = herpes simplex virus type-1.

#38 Amphetamine-Dextroamphetamine and Haloperidol

#12 Amphetamine-Dextroamphetamine & Aripiprazole; #15 Amphetamine-Dextroamphetamine & Quetiapine; #16 Amphetamine-Dextroamphetamine & Risperidone; #27 Amphetamine-Dextroamphetamine & Olanzapine; 
#31 Amphetamine-Dextroamphetamine & Lurasidone; #38 Amphetamine-Dextroamphetamine & Haloperidol; #39 Amphetamine-Dextroamphetamine & Paliperidone; #48 Amphetamine-Dextroamphetamine + Asenapine
Opposing Clinical Actions and Side Effects

- Dextroamphetamine: FDA indication for ADHD
- Drug-Induced Psychosis in 8% to 46% of regular users depending on dose, method, and duration
- Haloperidol: effective Tx for Amphetamine-Induced Psychosis
- Opposite Effect on Clock Speed in Healthy Participants

ADHD = attention-deficit/hyperactivity disorder.
Conflicting Mechanism of Action

**Equilibrium Constant**

<table>
<thead>
<tr>
<th>$K_i$ (nM)</th>
<th>Haloperidol</th>
<th>Amphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_1$</td>
<td>121</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>$D_2$</td>
<td>2.7</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>$D_3$</td>
<td>5.7</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>DAT</td>
<td>&gt;10,000</td>
<td>140</td>
</tr>
<tr>
<td>SERT</td>
<td>2000</td>
<td>3000</td>
</tr>
<tr>
<td>NET</td>
<td>-</td>
<td>50</td>
</tr>
</tbody>
</table>

**Interaction at $D_2$ receptors**

- **Amphetamine**
  - Increases release of monoamines from presynaptic storage vesicles
  - Inhibits reuptake of monoamines
  - Facilitates release of cytoplasmic presynaptic monoamines
  - Weak MAO inhibitor
- **Haloperidol** is a dopamine antagonist
- **$D_2$ receptor** is essential for antipsychotic efficacy

DAT = dopamine transporter; MAO = monoamine oxidase.
Studies Confirm Mutual Interaction

- Amphetamine reduced locomotor activity in hyperactive Coloboma mice mutants
  - Haloperidol blocked this effect
- After 7 days of haloperidol, rats showed impaired sustained attention, increased reaction time, and more errors of omission
  - Amphetamine blocked this effect
  - Highest dose of amphetamine alone increased errors
    - Haloperidol blocked this effect
- Studies in humans are rare
  - A single dose of amphetamine increased activity in 21 participants with schizophrenia on haloperidol

Insurance Data Confirm Inferior Efficacy of Combination

- US medical/pharmacy claims database
  - 22,622 children started on AAP after Tx with stimulant
    • Excluded cases with indication for AAP
    • 2127 cases left after all exclusions
  - 84,588 children started on non-AAP after stimulant for comparison
    • Atomoxetine, clonidine, guanfacine
    • 16,508 cases left after same exclusions
  - 1857 matched pairs, 81% augmenters
- Significantly higher rates of subsequent augmentation, health care resource utilization, and total health care costs

AAP = atypical antipsychotic.
Risk of Hospitalization after Restarting Stimulants

- Ontario Drug Benefit Database
  - October 1, 1999 to March 31, 2013
  - 12,856 participants < 26 years old were hospitalized for psychosis or mania after starting a stimulant
  - 119 participants started stimulants < 60 days before first hospitalization
  - 64 controls between 120 and 180 days before first hospitalization
  - Odds ratio 1.86 (1.38–3.28)
  - 34% restarted on stimulants within 100 days of discharge
    - 45% were re-hospitalized within a median of 18 days

#34 Donepezil and Oxybutynin

#21 Donepezil & Benztropine; #28 Donepezil & Ranitidine; #34 Donepezil & Oxybutynin; #40 Donepezil & Hydroxyzine; #58 Donepezil & Amitriptyline; #59 Donepezil & Diphenhydramine; #60 Donepezil & Doxepin; #61 Donepezil & Hydroxyzine
Donepezil
FDA indication for Alzheimer’s Disease

7% of patients develop Urinary Incontinence

Oxybutynin
FDA indication for Bladder Muscle Dysfunction

ACB “definite class” associated with 0.33 greater decline in MMSE over 2 years

ACB = anticholinergic cognitive burden; MMSE = Mini-Mental State Examination.
Conflicting Mechanism of Action

### Equilibrium Constant

<table>
<thead>
<tr>
<th>$K_i$ (nM)</th>
<th>Oxybutynin</th>
</tr>
</thead>
<tbody>
<tr>
<td>M₁</td>
<td>5.9</td>
</tr>
<tr>
<td>M₂</td>
<td>15</td>
</tr>
<tr>
<td>M₃</td>
<td>5.3</td>
</tr>
</tbody>
</table>

### Antagonism at Muscarinic Receptors

- **Donepezil** is a reversible acetylcholinesterase inhibitor
  - MOA via an increase in the concentration of acetylcholine
  - Activity at M₁ and M₂ relevant for cognition
- **Oxybutynin** is an antagonist at muscarinic receptors
  - M₃ receptors are primarily responsible for detrusor contraction

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Prospective Study Confirms Loss of Efficacy

- 3536 Nursing Home Residents
  - Higher functioning residents lost 1.08 per quarter on a 28-item ADL scale
    - Donepezil 70.5%, rivastigmine 19.9%, and galantamine 16.5%
    - No other anticholinergic medications
  - 376 residents with Tx for urine incontinence
    - Residents on oxybutynin lost an additional 0.54 per quarter
    - Similar findings with tolterodine
    - Combined significance $P=0.01$

ADL = activity of daily living.
Avoiding Cognitive Effects in Overactive Bladder

- Agents with low lipid solubility are correlated with less cognitive effects
  - Darifenacin and trospium have the lowest lipid solubility with poor CNS penetration
  - Oxybutynin crosses the blood brain barrier freely
- Solifenacin is selective for $M_3$
  - Reduced cognitive effects
- Mirabegron is a $B_3$ agonist
  - No effect on anticholinergic load

CNS = central nervous system.
#23 Amphetamine-Dextroamphetamine & Alprazolam

#10 Amphetamine-Dextroamphetamine & Clonazepam; #11 Atomoxetine & Clonazepam; #13 Amphetamine-Dextroamphetamine & Lorazepam; #14 Methylphenidate & Lorazepam; #23 Amphetamine-Dextroamphetamine & Alprazolam; #24 Atomoxetine & Lorazepam; #29 Methylphenidate & Alprazolam; #30 Methylphenidate & Clonazepam; #37 Amphetamine-Dextroamphetamine & Diazepam; #45 Atomoxetine & Alprazolam; #46 Methylphenidate & Diazepam
Opposing Clinical Actions and Side Effects

Amphetamine
FDA indication for ADHD

Anxiety in 8% leading to discontinuation in 2.1%

Alprazolam
FDA indication for Anxiety

Somnolence in up to 76%
Memory Impairment in 33%
Cognitive Disorder in 29%

Mechanism of Action

Amphetamine

Alprazolam

Some direct receptor agonist actions may contribute

Note: Amphetamine reverses DAT, SERT & NET

Opposing Effect on Performance

• Computerized task to assess focus
  – 18 fully rested human participants
  – Dextroamphetamine 10 mg induced enhancement on behavioral measures compared to placebo
  • Also increased tunnel vision
  – Alprazolam impaired performance compared to placebo

Persisting Memory Impairment with Alprazolam

• Memory impairment 24 hours after a single 1 mg oral dose of alprazolam
  – 16 words in 8 practice trials
  – Alprazolam 9.8 words (1.2) group differed significantly from
  – Placebo 14.3 (0.7) at 24 hours

• Longer trials of alprazolam lead to more persistent impairment
  – Marked impairment in word recall after 8 weeks of alprazolam vs placebo in patients with panic disorder
  – Persisting impairment at 24 weeks
  – No relative impairment at 3.5 years

Alprazolam Impairs Discriminative Ability in Amphetamine Users

- Pretreatment with alprazolam blocked the discriminative ability for dose of amphetamine and some of the self-reported effects
  - 6 healthy individuals became > 80% accurate on 4 consecutive days in discriminating dose
  - Amphetamine 0, 2.5, 5, 10, and 15 mg
  - Alprazolam 0.5 mg pretreatment significantly attenuated discriminative ability to detect the highest dose of 15 mg

- Pretreatment with alprazolam enhanced self-administration of methamphetamine in rats, shifting inverted “U” to left

Synergistic Impact in Impaired Driving and Accidents

• Once alprazolam is detected, the most common additional substance in those pulled over for DUI of drugs is amphetamine
  – Sweden, 2001–2005
  – Alprazolam-amphetamine combination prevalent in fatal accidents
• Elevated prevalence of amphetamine-benzodiazepine combination in DUI cases
  – Finland, 1997–2008
• Amphetamine-benzodiazepine combination commonly found in seriously injured drivers
  – Denmark, 2007–2010

<table>
<thead>
<tr>
<th>Drugs co-ingested</th>
<th>Traffic DUI, n = 773 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>354 (46)*</td>
</tr>
<tr>
<td>Diazepam</td>
<td>275 (36)</td>
</tr>
<tr>
<td>THC</td>
<td>244 (32)</td>
</tr>
<tr>
<td>Morphine</td>
<td>108 (14)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>99 (13)</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>94 (12)</td>
</tr>
<tr>
<td>Codeine</td>
<td>55 (7.1)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>53 (6.9)</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>42 (5.4)</td>
</tr>
<tr>
<td>Methadone</td>
<td>41 (5.3)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>41 (5.3)</td>
</tr>
</tbody>
</table>

DUI = driving under the influence.
In Contrast to the Absence of Clinical Studies Showing Efficacy...

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**Xanax and adderall: The best combination ever**

https://www.reddit.com/r/Drugs/..../xanax_and_adderall_the_best_combination_ever/ •

Apr 25, 2016 • 7 posts • 4 authors

Ok I like to call myself a veteran to drugs. I've literally done everything except MDMA and heroin. And I gotta say this combination right here is...  

**I plan on taking Xanax and Adderall together. How should I dose**

https://www.reddit.com/r/.../i_plan_on_taking_xanax_and_adderall_together_how/ •

Jan 17, 2016 • 6 posts • 4 authors

So when I only take Adderall in social situations it relieves anxiety, makes me chatty, happy, and overall more energetic. Although, sometimes I...

**The Beauty of Adderall and Xanax**

https://www.reddit.com/r/benzodiazepines/.../the_beauty_of_adderall_and_xanax/ •

Mar 31, 2016 • 10 posts • 6 authors

Lately, I've been sporadically using Adderall. It hasn't been for recreational purposes, I've just been using it when I have lots of work...

**Adderall + Xanax = I literally turn into God**

https://www.reddit.com/r/Drugs/comments/.../adderall_xanax_i_literally_turn_into_go... •

Jul 19, 2017 • Second day rolls in I'm like fuck it so I took 40 mg of Adderall and 1.5 mg of Xanax. I've done both of these drugs before but never at the same time. Now, adderall by itself usually helps me become more talkative and proactive but I feel like I kind of become an uptight douche when I'm wired. Xanax by itself...

Google search: adderall and xanax reddit.
#20 Propranolol and Atomoxetine

#20 Atomoxetine & Propranolol
#52 Amphetamine-Dextroamphetamine & Metoprolol
#53 Amphetamine-Dextroamphetamine & Propranolol
#54 Atomoxetine & Carvedilol
#55 Atomoxetine & Metoprolol
Opposing Clinical Actions and Side Effects

Atomoxetine
FDA indication for ADHD

- 22.4% with increase in Heart Rate of 20 bpm,
- 12.4% with increase systolic BP of 20 mm Hg

Propranolol
FDA indication for Hypertension

- Decreased Performance on Neuropsychometrics

bpm = beats per minute; BP = blood pressure.
Conflicting Mechanism of Action

<table>
<thead>
<tr>
<th>Equilibrium Constant</th>
<th>Propranolol</th>
<th>Atomoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_i$ (nM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$B_1$</td>
<td>1.3</td>
<td>-</td>
</tr>
<tr>
<td>$B_2$</td>
<td>0.33</td>
<td>-</td>
</tr>
<tr>
<td>NET</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>SERT</td>
<td>-</td>
<td>77</td>
</tr>
</tbody>
</table>

Adrenergic $\beta$ Receptors
- Atomoxetine has a preferential effect on reuptake of norepinephrine
  - Less affinity for serotonin transporter
- Propranolol is a non-cardioselective lipid soluble noradrenergic antagonist
- Contrary action verified in extinction training in rats
  - Atomoxetine increased strength of learning
  - Propranolol had opposite effect

Propranolol and Depressive Symptoms

Early Case Studies Suggest Link
• Depressive symptoms are linked to starting propranolol or subsequent dose increases
  • Depressive symptoms resolved after stopping propranolol
  – No recurrence with starting atenolol as a substitute for propranolol

Meta-Analysis Results Conflict
• Meta-analysis of RPCDB studies of β-blockers in the Tx of MI, HF, or HTN
  – Increased incidence of fatigue
  – No increased risk of depression
• An earlier meta-analysis including studies comparing propranolol to other β-blockers reported contrary results
  – Organic mood disorder, depressed type
  • Propranolol was associated with more fatigue, decreased energy, decreased libido, anorexia, and poor concentration

MI = myocardial infarction; HF = heart failure; HTN = hypertension.
Propranolol Abolishes Effect of Atomoxetine

• β-adrenoceptor blockade blocks atomoxetine-induced risk taking
  – Rats performed a probabilistic discounting task as a model for risk taking
    • 1 lever guaranteed a single pellet
    • Other lever delivered 4 pellets with decreasing chance from 100% to 12.5%
  – Atomoxetine increased risk taking
    • More pulls of risky lever, less likely to pull safe lever after loss
  – Co-administration of propranolol blocked this effect
    • Prazosin did not

Avoiding Cardiac Effects and Polypharmacy

- Dose reduction of atomoxetine
- Switch atomoxetine to guanfacine
  - Less risk of hypertension
- Switch propranolol to a non-lipid soluble β-blocker
  - Atenolol has lower levels in CSF
  - Atenolol has been reported to have less impact on cognitive function
    - Similar to ACE inhibitors
  - Other studies have highlighted atenolol’s anticholinergic activity and impact on cognitive function
  - Blood brain barrier changes with age

<table>
<thead>
<tr>
<th>Lipid Solubility</th>
<th>Cardio-selective</th>
<th>Non-selective</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>-</td>
<td>Propranolol, Labetalol*</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Metoprolol</td>
<td>Carvedilol*</td>
</tr>
<tr>
<td>Low</td>
<td>Atenolol</td>
<td>Nadolol</td>
</tr>
</tbody>
</table>

CSF = cerebrospinal fluid; ACE = angiotensin-converting enzyme.

#17 Ropinirole and Olanzapine

- #17 Ropinirole & Olanzapine
- #41 Ropinirole & Paliperidone
- #42 Ropinirole & Risperidone
- #66 Ropinirole & Perphenazine
Opposing Clinical Actions and Side Effects

Ropinirole
FDA indication for RLS

Psychosis in 8% of Parkinson's Disease patients treated with Ropinirole
2 of 35 treated for RLS

Olanzapine
FDA indication for Schizophrenia

Case series of RLS

10% on 15 mg qd report Akathisia

Conflicting Mechanism of Action

Dopamine D₂ Receptors
- D₂ receptor is essential for antipsychotic efficacy
- Akathisia associated with blockade of D₂ receptors
- RLS symptoms
  - Absent during the day during hyper-dopaminergic state
  - Worse during the evening during hypo-dopaminergic state

Antagonistic Action
- Olanzapine is a dopamine antagonist at D₂
- Ropinirole is a dopamine agonist
  - Highest affinity for D₂, D₃, D₄
- Antagonistic interaction verified via recruitment of β-arrestin2 to the dopamine D₂ receptor

Clinical Studies of Combination are Scarce

- Case Study
  - Onset of RLS with olanzapine
    - Symptoms resolved with reduction of dose of olanzapine and addition of ropinirole
  - No long-term follow-up on antipsychotic efficacy

Alternative Treatments for Monotherapy

• RLS
  – Alternative treatments to consider
    • Fe replacement at < 75 mcg/L
    • Pregabalin
    • Gabapentin enacarbil
    • Pneumatic compression

• Psychosis
  – Onset of RLS is dose dependent
    • Often resolves with dose reduction
    • Resolved with discontinuation
  – RLS did not recur with switch to different antipsychotic
  – EPS/RLS modulated by type of AAP

EPS = extrapyramidal symptoms.

#4 Clonididine and Mirtazapine

#4 Mirtazapine & Clonididine
#62 Mirtazapine & Guanfacine
Opposing Clinical Actions and Side Effects

Clonidine
Off-label treatment for ADHD
Inattention

Mirtazapine
FDA indication for
Major Depression

Half of studies report increase in incidence of Major Depression —usually 1.5% to 2.3%

Sedation in 54%
Half-life of 22 hours

Conflicting Mechanism of Action

### Equilibrium Constant

<table>
<thead>
<tr>
<th>$K_i$ (nM)</th>
<th>Clonidine</th>
<th>Mirtazapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-2A</td>
<td>43</td>
<td>20</td>
</tr>
<tr>
<td>α-2B</td>
<td>106</td>
<td>-</td>
</tr>
<tr>
<td>α-2C</td>
<td>233</td>
<td>18</td>
</tr>
<tr>
<td>5-HT$_2$A</td>
<td>&gt;10,000</td>
<td>69</td>
</tr>
<tr>
<td>H$_1$</td>
<td>-</td>
<td>1.3</td>
</tr>
</tbody>
</table>

### α-2A Adrenoceptors
- Clonidine’s positive effect on attention is mediated via stimulation of postsynaptic α-2A receptors
- Mirtazapine enhances serotonergic transmission by blocking presynaptic α-2A heteroreceptors

Sallee FR. The Role of Alpha 2 Agonists in the Attention Deficit/Hyperactivity Disorder Treatment Paradigm. 2008.
Studies Confirm an Interaction

• Mirtazapine blocks a discriminative stimulus protocol in rats
  – Clonidine has opposite effect
• Mirtazapine blocks the antihypertensive effect of clonidine
  – 2 case reports of hypertensive urgency

Strategies for Avoiding Polypharmacy

• For treating HTN, select an anti-hypertensive medication with less association with inducing depressive symptoms
  – ACE inhibitors
  – Angiotensin receptor blockers
• For treating major depression, select an antidepressant with efficacy for treating inattention
  – Bupropion

#2 Clozapine and Sertraline

- #2 Clozapine & Sertraline
- #5 Clozapine & Citalopram
- #6 Clozapine & Fluoxetine
- #9 Clozapine & Paroxetine
- #19 Clozapine & Escitalopram
- #26 Clozapine & Fluvoxamine
Opposing Clinical Actions and Side Effects

Clozapine
FDA indication for Schizophrenia

21% with emergence or worsening of Obsessions vs 1.3% on other antipsychotics

Sertraline
FDA indication for OCD

OCD = obsessive-compulsive disorder.
Conflicting Mechanism of Action

### Equilibrium Constant

<table>
<thead>
<tr>
<th>$K_i$ (nM)</th>
<th>Clozapine</th>
<th>Nor clozapine</th>
<th>Sertraline</th>
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</thead>
<tbody>
<tr>
<td><strong>D$_1$</strong></td>
<td>215</td>
<td>14.3</td>
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<tr>
<td><strong>D$_2$</strong></td>
<td>128</td>
<td>100</td>
<td>-</td>
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<tr>
<td><strong>D$_3$</strong></td>
<td>240</td>
<td>153</td>
<td>-</td>
</tr>
<tr>
<td>5-HT$_{1A}$</td>
<td>160</td>
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<td>&gt;10,000</td>
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<tr>
<td>5-HT$_{2A}$</td>
<td>2.6</td>
<td>10.9</td>
<td>-</td>
</tr>
<tr>
<td>5-HT$_{2C}$</td>
<td>4.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SERT</td>
<td>1600</td>
<td>316</td>
<td>1.5</td>
</tr>
</tbody>
</table>

### Serotonergic Receptors

- 5-HT$_{2A}$ and 5-HT$_{2C}$ are crucial for efficacy of SSRIs in treating OCD
- Sertraline blocks the reuptake of serotonin
- Clozapine is an antagonist at serotonergic receptors

Case Reports Document Efficacy

- Worsening OCD symptoms in clozapine treated 39-year-old male after augmenting with fluvoxamine
  - Associated with elevation in clozapine serum levels
  - OCD symptoms improved after addition of sertraline
    - No CYP1A2 inhibition
- Additional case of treating OCD induced from clozapine with sertraline

Meta-Analysis on Reverse Combination Adding Antipsychotics to SSRIs

- Augmentation Strategies for OCD
  - Antipsychotics added to SSRIs
  - 12 RPCDB with 394 participants
  - Percentage of responders
  - Risperidone with significant effect size

- Antipsychotic augmentation shown more effective for comorbidities
  - Tic-related OCD
  - Schizotypal symptoms
  - Poor insight

#1 Prazosin and Venlafaxine

#1 Venlafaxine & Prazosin
#3 Duloxetine & Prazosin
#32 Duloxetine & Tamsulosin
#33 Venlafaxine & Tamsulosin
Opposing Clinical Actions and Side Effects

Venlafaxine
FDA indication for Major Depression

Prazosin
Off-label treatment for PTSD and Nightmares

7% of patients treated with Venlafaxine had Nightmares vs 2% on placebo

PTSD = posttraumatic stress disorder.
Conflicting Mechanism of Action

### Equilibrium Constant

<table>
<thead>
<tr>
<th>$K_i$ (nM)</th>
<th>Prazosin</th>
<th>Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$-1A</td>
<td>0.37</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>$\alpha$-1B</td>
<td>0.32</td>
<td>-</td>
</tr>
<tr>
<td>$\alpha$-1D</td>
<td>0.22</td>
<td>-</td>
</tr>
<tr>
<td>$\alpha$-2A</td>
<td>302</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>$\alpha$-2B</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>$\alpha$-2C</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>SERT</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>NET</td>
<td>-</td>
<td>385</td>
</tr>
</tbody>
</table>

### Antagonism at $\alpha$-Adrenoceptors

- Venlafaxine is a serotonin and norepinephrine reuptake inhibitor
- Prazosin is a antagonist at $\alpha$-1 receptors

Neurophysiological Cancelation

- Prazosin blocks the discriminative stimulus of a specific norepinephrine reuptake inhibitor, reboxetine in rats
  - Full substitution was attained with venlafaxine
- Prazosin attenuates the venlafaxine induced increase in serotonergic activity in the prefrontal cortex of rats

Avoiding Nightmares and Polypharmacy

- Noradrenergic medications are to be avoided in PTSD
- The Best Practices task force of the American Academy of Sleep Medicine for the treatment of nightmare disorder
  - Prazosin is recommended, level A
  - Fluvoxamine may be considered, level C
  - Venlafaxine is not suggested, level B
- Based on a large placebo-controlled study in which most symptoms of PTSD improved with a 12-week course, disturbing dreams did not

Practical Take-Aways

• We have an impressive number of medications in our psychiatric formulary, but a limited number of neurotransmitters of interest to modulate. Often more extensive medication regimens are associated with inferior results.

• Anticholinergic medications are often prescribed for geriatric patients for numerous indications, but limit the efficacy of acetylcholinesterase inhibitors. Anticholinergics are not all the same. Know which can be safely prescribed.

• Although stimulants are commonly prescribed to increase focus and improve attention, concurrent prescription of benzodiazepines is associated with increased risk of automobile collisions and other accidents.