Psychiatric Medication Update

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Dr. Campbell does have financial or other relationships to disclose:

- UpToDate – Co-Author “Pharmacotherapy for schizophrenia: Long-acting injectable antipsychotic drugs”
- Sunovion Pharmaceuticals Inc. – Speakers bureau

None of which will be discussed today
Objectives

- Identify newly approved psychiatric medications and recent changes made to the United States Pharmacopeia
- Review new guidelines and pipeline treatments for the treatment of mental illness
- Briefly review the use and evidence for use of cannabidiol (CBD) products to manage mental health disorders
New/Newer Medications of Interest

The Long Road to a New Medicine

Idea

Exploratory Development

Discovery

Synthesis of Compounds

Screening

Project Team and Plans

Exploratory Development

Clinical Data Analysis

FDA Registration

Full Development

Studies in Healthy Volunteers (Phase 2)

Studies in 100-300 Patients (Phase I)

Medicine Tested in 3-10,000 Patients (Phase III)

EXPERIMENTAL Safety Studies
Is There Anything New Out There?

- Medications I’d like to talk about today
  - Dasotraline
  - Esketamine
  - Lumateperone
  - Droperidol
Dasotraline (SEP-225,289)

- Serotonin-dopamine-norepinephrine or Triple reuptake inhibitor (SNDRI)
- Originally evaluated for treatment of major depressive disorder (no longer)
- Submitted for review by the FDA for:
  - Treatment of ADHD in children > 6 years
  - Treatment of ADHD in adults
  - Treatment of binge eating disorder in adults
Dasotraline is a Stereoisomer of Desmethylsertraline

Solid Triangle: In front of the plane of molecule

Dotted Triangle: Behind the plane of molecule

Sertraline

Desmethylsertraline

Dasotraline


Slide courtesy of Stephen Saklad, PharmD, BCPP
# Dasotraline

## Comparison of Triple Monoamine Transporter Inhibition

<table>
<thead>
<tr>
<th>Compound</th>
<th>Transporter Inhibited (K_i or IC50; nM)</th>
<th>Norepinephrine (NET)</th>
<th>Dopamine (DAT)</th>
<th>Serotonin (SERT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centafadine (EB-1020)</td>
<td></td>
<td>6±1</td>
<td>38±6</td>
<td>83±12</td>
</tr>
<tr>
<td>Dasotraline (SEP-225,289)</td>
<td></td>
<td>4</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td></td>
<td>0.7</td>
<td>1400</td>
<td>43</td>
</tr>
<tr>
<td>Bupropion</td>
<td></td>
<td>2300</td>
<td>630</td>
<td>15600</td>
</tr>
</tbody>
</table>


**Primary Use:**
- A. Attention Deficit Hyperactivity Disorder
- B. Bulimia
- C. Depression

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*Slide courtesy of Stephen Saklad, PharmD, BCPP*
Dasotraline

- Doses most frequently studied: 4 or 8 mg
- Slow peak: 10-12 hrs
- Long T½: 47-77 hrs
- Possibly fewer drug interactions?
- Most common side effects:
  - Insomnia, decreased appetite, nausea, dry mouth
  - Likely to have warning for suicidal ideation
- Low abuse potential

Koblan KS, et.al. Drug and Alcohol Dependence. 2016; 159:26-34
“While Sunovion considers dasotraline to be a promising, novel treatment for BED and ADHD, we believe that further clinical studies would be needed to support a regulatory approval for dasotraline in these indications”
FDA News Release

FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor’s office or clinic

Approved nasal spray gives hope to patients with severe depression

Doctors Welcome New Depression Drug, Cautiously

Janssen Announces U.S. FDA Approval of SPRAVATO™ (esketamine) CIII Nasal Spray for Adults with Treatment-Resistant Depression (TRD) Who Have Cycled Through Multiple Treatments Without Relief
History of Ketamine

Esketamine (Spravato®)

- Is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist facilitates glutamate release, increases signaling of neurotrophic factors, and stimulating synaptogenesis
- Granted Fast Track and Breakthrough Therapy designations
- September 2018 Janssen submitted a New Drug Application
  - Based on five Phase 3 studies of esketamine nasal spray in patients with treatment-resistant depression
- FDA approved March 5, 2019 for the treatment of treatment-resistant depression in adults, in conjunction with an oral antidepressant
Response seen within hours to days

<table>
<thead>
<tr>
<th>Induction Phase (Weeks 1-4)</th>
<th>Maintenance Phase (Weeks 5-8)</th>
<th>Maintenance Phase (Weeks 9+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twice weekly</td>
<td>56mg OR 84mg weekly</td>
<td>56mg or 84mg every other week OR weekly*</td>
</tr>
<tr>
<td>First Dose: 56mg</td>
<td></td>
<td>*Least frequent dosing needed to maintain remission/response</td>
</tr>
<tr>
<td>Subsequent Doses:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56mg or 84mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Schedule III controlled substance (CIII)
Spravato Risk Evaluation and Mitigation Strategy (REMS)

- Monitor for dissociation and sedation for at least 2 hrs
- Only approved clinics/pharmacies able to order
Esketamine

- August 2020 the US Food and Drug Administration (FDA) approved the supplemental new drug application for esketamine nasal spray to treat depressive symptoms in adults with major depressive disorder (MDD) and acute suicidal ideation or behavior.
- First and only drug to carry this indication.
Lumateperone (Caplyta®)

- Approved December 2019 for the treatment of schizophrenia in adults
- Second generation antipsychotic (SGA)
- Potentially novel mechanism of action?
  - Dopamine 2 (D$_2$) and serotonin 2A (5-HT2A) receptor antagonist
  - Much higher binding affinity for 5-HT2A over D$_2$
  - Possible effects on D$_1$, D$_4$, NMDA, and glutamate
- Metabolized mostly through CYP3A4
Lumateperone

- **Dosing:** 42 mg once daily with food
  - Lower and higher doses did not separate from placebo trials
  - Possible narrow therapeutic window or the result of a high placebo response rate

- **Side effects**
  - Drowsiness and sedation (24%), nausea (9%), EPS (7%)
  - Possible advantages in EPS
  - Appears to have neutral metabolic effects
Droperidol

- First generation antipsychotic (FGA) and antiemetic
  - Butyrophenone (similar to haloperidol)
- Mechanism of action, primarily dopamine blockade (D2)
  - Also causes peripheral vascular dilation
- FDA indicated for postoperative nausea/vomiting
  - Used off label for headaches and undifferentiated agitation
- FDA Box warning for QTc prolongation

Wait... Haven’t I heard of this before?
History

- FDA approval 1988
- Black box warning added in 2001
- Removed from market
- Manufacturing restarted in 2019
Class A: “There is currently insufficient evidence to recommend for mandating an ECG or telemetry monitoring for doses <2.5 mg given either IM or IV”
- Recommendation based on 5 studies of droperidol that used ECG or telemetry monitoring
- Findings of significant QT prolongation were rare

Class B: “IM doses of up to 10 mg of droperidol appear to be as safe and as effective as other medication used for sedation of agitated patients”
- Recommendation based on 6 studies using droperidol doses 2.5 – 10 mg
- No reported cases of Torsades

Droperidol

- Dosing (off-label agitation): IM/IV 2.5 – 10 mg
- Possible advantages in treatment of agitation?
  - Quick time to onset (3-10 minutes)
    - Decreased need for repeat doses???
    - Decreased need for concomitant medication???
- Frequency of side effects not well defined on package labeling
  - Comparable to haloperidol with possibly slightly lower risk of EPS but more dizziness and sedation
  - Lower doses appear safe (1.25 – 2.5 mg)
Practice Guideline: Treatment for Insomnia and Disrupted Sleep Behavior in Children and Adolescents with Autism Spectrum Disorder

Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Endorsed by:
- American Academy of Sleep Medicine
- Autism Speaks
- Child Neurology Society
- Society for Developmental and Behavioral Pediatrics.
Between 44% and 83% of children and adolescents with ASD report coexisting sleep abnormalities, adversely affecting daily functioning.

Guidelines are targeted to support primary care providers treating children with ASD.

Recommendations for addressing sleep issues:
1. Caused by medication or other medical condition?
2. Offer strategies for healthy sleep habits
3. Referral for cognitive behavioral therapy
4. Melatonin supplementation
There is a dearth of evidence-based treatments for sleep dysregulation in ASD

- No identified studies examined pharmacologic approaches, and the identified literature could not inform what population might be most likely to respond to treatment
- The best studies examined pharmacologic treatment with melatonin and used study-specific formulations to overcome limitations of unknown purity in OTC formulations
- No medications for insomnia are FDA approved for pediatric use.
Melatonin is the most commonly dispensed hypnotic drug in children. However, melatonin concentrations in OTC formulations differ, and some formulations are contaminated with other products. Look for these logos:

- NSF
- USP
- ConsumerLab.com

Pediatric melatonin safety/tolerability trials are limited but there is no evidence that short-term melatonin use has serious adverse events. Adverse events include: morning drowsiness, increased enuresis, headache, dizziness, diarrhea, rash, and hypothermia.
A new Treatment For ADHD

- Endeavor Rx
- June 2020, FDA cleared digital therapeutic device to improve attention function in children with attention deficit hyperactivity disorder (ADHD)
- First game-based therapeutic granted marketing authorization by the FDA for any type of condition
Endeavor Rx

- First prescription-only game-based device indicated for pediatric patients ages 8 to 12 years old with primarily inattentive or combined-type ADHD
- Improve attention function as measured by computer-based testing in over 600 children
- Intended for use as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs
- Most common adverse events:
  - Frustration, headache, dizziness, emotional reaction, and aggression
New Medication Delivery System

- Gastrointestinal synthetic epithelial lining (GSEL)
- New oral solution designed to form a biofilm
  - Targets the small intestine epithelium – layer of cells that protects against bacteria and provides main nutrient absorption
  - Identified an enzyme (catalase) that can convert individual molecules into polymeric film
  - Use dopamine to form polydopamine: similar to what muscles use to attach to rocks
GSEL

A. Oral monomer solution

Step 1

Step 2

Step 3

Polymeric coating on the small intestine (SI)

Oral GSEL solution administered to SI

Endogenous enzyme catalyzed oxidation

Polymer deposited and coated on epithelium
GSEL Potential Applications

- Liquid system that can help deliver medication over the entire day, vs. 2-4 times daily dosing
  - Tested on praziquantel (usually 3 times daily dosing)
  - Able to give once daily – Drug remained on intestinal surface longer and half-life of the medication was increased by 10 fold
- Treating lactose intolerance
  - Enhanced lactase breakdown 20 times over baseline
- Regulating blood glucose
  - Effectively created a barrier to glucose absorption
Cannabis Use in Mental Health
Focus on Use in Children Autism Spectrum Disorder (ASD)
All would legalize medical marijuana to individuals with qualifying medical condition

<table>
<thead>
<tr>
<th></th>
<th>Amendment 2</th>
<th>Amendment 3</th>
<th>Proposition C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oversight and Management</td>
<td>Department of Health and Senior Services</td>
<td>Brad Bradshaw</td>
<td>Division of Liquor Control</td>
</tr>
<tr>
<td>Tax</td>
<td>4%</td>
<td>15%</td>
<td>2%</td>
</tr>
<tr>
<td>Funding for</td>
<td>Veterans’ health services</td>
<td>Cancer research institute</td>
<td>Drug treatment, education, and public safety</td>
</tr>
</tbody>
</table>
Amendment 2

- Legalizes growing, manufacturing, selling, and consuming marijuana for medical use.
- Patients must apply to the state:
  - Require recommendation from licensed prescriber
  - Qualifying diagnosis
- Individuals wanting to grow require separate licensing:
  - Patients may grow up to 6 plants
  - Caretakers may grow up to 18 plants
Amendment 2

- Smoke ‘em if you got ‘em???
  - **DOES NOT** include recreational use
- Must be Missouri resident
- Qualifying diagnoses:
  - Cancer, epilepsy, intractable migraines, HIV/AIDS, terminal illness, illnesses causing severe muscle spasms, **debilitating psychiatric disorders**, **other chronic debilitate disease** as determined by physician
As of November 2020, how many states have “legalized” medical marijuana?

33
Marijuana is classified as a Schedule I

“Drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse”

- Examples: heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote
Cannabis Components

- THC (tetrahydrocannabinol): the psychoactive component
- CBD (cannabidiol): the therapeutic component
  - Most medical promise
  - FDA Approved June of 2018 (Epidiolex®) for treatment of intractable seizures (Lennox-Gastaut syndrome)
  - Schedule V controlled substance
- These are just 2 of the more than 100 identified compounds found in cannabis
- Concentrations can be HIGHLY variable
Common side effects (>10%): drowsiness, lethargy, fatigue, insomnia, sleep disorder, decreased appetite, weight loss, diarrhea

Serious side effects (>10%): increased liver enzymes, risk of infection

Psychiatric effects (1-10%): agitation, irritability, aggressive behavior

…and this is with the regulated, well studied, FDA approved product
Nonprescription Products

- Considered herbal product or dietary supplement
  - No required quality control or good manufacturing practices
- What you don’t know can hurt you
- Blinded analysis of 20 popular CBD products in California
  - Only 3 products contained what was on their label
  - 8 products contained less than 20% of the CBD claimed
  - 2 products contained none at all
  - High levels of potentially dangerous solvents/gases in numerous

Rubin R. JAMA. 2019
Multiple studies have demonstrated an increased risk of psychosis in cannabis users:
- Meta-analyses have shown odds ratios between 1.4 to 4.8
- Findings are consistent with a dose-response effect:
  - Frequency of use
  - Increased potency
  - Age of onset of use (before or after age 16)
Outside of seizure disorders, larger randomized controlled trials are still sparse.

Most evidence is considered anecdotal but some is promising.

2018 study of CBD oil in 60 children with ASD and severe behavioral problems followed for 7 – 13 months:
- 61% reported improved on caregiver CGI scale
- 51% reported adverse effects

2019 study collected data on 188 ASD patients treated with CBD:
- 83% of those completing the study reported moderate symptom improvement
- 25% reported adverse effects

Both studies possess significant limitations.

National Academies of Science report

- Use in ASD and associated comorbid disorders considered to have **limited or no evidence** for efficacy
- ASD not mentioned as having any compelling evidence at the time of report

That... was a lot...
Questions?