Psychiatric Medication Update
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Pharmacy & Behavioral Health Programs Manager

Objectives
- Identify newly approved psychiatric medications
- Discuss medications currently in the pipeline
- Review pertinent FDA MedWatch Alerts
- Evaluate new treatment guidelines for schizophrenia

Abbreviations
- ADHD: Attention Deficit Hyperactivity Disorder
- AP: Antipsychotic
- CNS: Central Nervous System
- FDA: Food and Drug Administration
- FGA: First Generation Antipsychotic
- SGA: Second Generation Antipsychotic
- VMAT2: Vesicular monoamine transporter 2
FDA Drug Approval Process
✓ Drug developed
✓ Animals tested
✓ Investigational New Drug (IND) application
✓ Phase 1 → Phase 2 → Phase 3 trials
✓ Review meeting: FDA + drug sponsor
✓ New Drug Application
✓ FDA NDA Review
✓ Drug Labeling
✓ Manufacturer facility inspection
✓ Drug Approval
✓ Post-Marketing monitoring

FDA Drug Approval Process
► Faster Approval Options
  ➢ Accelerated Approval
  ➢ Fast Track
► Prescription Drug User Fee Act (1992)
► FDA MedWatch
  ➢ Voluntary system for physicians and consumers to report adverse events

Azstarys™
(serdemethylphenidate/dexmethylphenidate)
► FDA Approval: March 2, 2021
► CNS stimulant for treatment of ADHD in patients 6 years of age and older
► Norepinephrine dopamine reuptake inhibitor; Schedule II substance
► KemPharm, Inc.
  ➢ LAT® (Ligand Activated Therapy) technology

**Azstarys™**
(serdexmethylphenidate/dexmethylphenidate)

- Novel once-daily oral capsule
  - First and only product with dexmethylphenidate prodrug
- Three strengths available
  - 26.1mg/5.2mg, 39.2mg/7.8mg, 52.3mg/10.4mg
- Warnings & Precautions
  - Abuse/dependence, cardiovascular, psychiatric, growth suppression

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**Azstarys™ Clinical Efficacy**

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**BXCL501**
(dexmedetomidine)

- Acute treatment of agitation associated with schizophrenia and bipolar disorders
- Orally dissolving film formulation of dexmedetomidine
  - Selective alpha2a receptor agonist
- Granted Fast Track Designation by FDA
- New drug application: March 11, 2021
  - Based on two Phase 3 studies
SPN-812 (viloxazine hydrochloride)

- Novel, non-stimulant treatment for ADHD in pediatric patients 6-17 years of age
- Serotonin norepinephrine modulating agent
- New drug application: February 8, 2021
  - Original NDA: November 11, 2019
  - FDA Complete Response Letter: Nov. 2020
  - Supplemental NDA planned for adults

ALKS 3831 (olanzapine/samidorphan)

- Novel, once-daily oral treatment for schizophrenia & bipolar I disorder in adults
- Combination of an established atypical antipsychotic + novel µ-opioid antagonist
  - Mitigates weight gain from olanzapine
- New drug application: December 29, 2020
  - Original NDA: November 19, 2019

FDA MedWatch Alerts

- Drug Safety Communication: Benzodiazepine Drug Class — Boxed Warning Updated to Improve Safe Use
  - September 2020
  - Boxed Warning to include risks of abuse, misuse, addiction, dependence and withdrawal reactions
  - Updates to patient Medication Guide
  - Changes to prescribing information
FDA MedWatch Alerts

- Opioid Pain Relievers or Medicines to Treat Opioid Use Disorder – FDA Recommends Health Care Professionals Discuss Naloxone with All Patients when Prescribing
  - July 2020
  - Updating prescribing information and patient Medication Guides

Schizophrenia Guideline Update

- Focuses on evidence-based pharmacological and nonpharmacological treatments
- Includes statements related to assessment and treatment planning for patient-centered care

Schizophrenia

- Significant health, social, occupational and economic burdens due to early onset and severe, persistent symptoms
- One of the top 20 causes of disability worldwide
- Estimated cost of > $150 billion annually in United States
- Increased mortality, with shortened life span, common comorbidities, suicide risk
Schizophrenia Guideline Update

- Goal: Enhance the treatment of schizophrenia to reduce mortality, morbidity and significant psychosocial and health consequences

- Topics not addressed in this update
  - Attenuated psychosis syndrome
  - Schizoaffective disorder
  - Cost-effectiveness considerations


Schizophrenia Guideline Update

- Rating Strength of Statement
  - Recommendation (Numeral 1)
  - Suggestion (Numeral 2)

- Rating Strength of Research Evidence
  - A: High Confidence
  - B: Moderate Confidence
  - C: Low Confidence


Schizophrenia Guideline Update

- Assessment & Treatment Planning
  - Statements 1 – 3

- Pharmacotherapy
  - Statements 4 – 14

- Psychosocial Interventions
  - Statements 15 – 21

Schizophrenia Guidelines

Assessment & Treatment Planning

- Initial psych assessment specifications (1C)
  - Quantitative measure for symptoms (1C)
- Assessments to monitor physical status, detect physical comorbidities and medication side effects (1C)
- Documented, comprehensive, person-centered treatment plan (1C)

Schizophrenia Guidelines

Pharmacotherapy

- Treat with antipsychotic, monitoring for effectiveness and side effects (1A)
  - Benefits of antipsychotics reducing positive symptoms consistently shown
  - Limited info from head-to-head trials showing superiority of specific AP
  - No FGA vs SGA preference shown
  - May be meaningful distinctions in response and tolerability

Schizophrenia Guidelines

- Choice of antipsychotic should occur in discussion with patient about benefits and possible side effects
  - Patient preferences
  - Past responses to treatment
  - Typical side effect profile
  - Comorbid physical health conditions
  - Other med factors: Formulations, drug interactions, pharmacokinetics
Schizophrenia Guidelines

- Antipsychotic Treatment Considerations
  - Initial Goal: Reduce acute symptoms; return to baseline level of functioning
  - Maintenance Goal: Prevent recurrence of symptoms; maximize functioning and quality of life
  - Strategies for initial nonresponse and/or partial response
  - Monitoring throughout treatment

First Generation APs

<table>
<thead>
<tr>
<th>First Generation Antipsychotic Formulations</th>
<th>Trade Name</th>
<th>Tablet or Capsule</th>
<th>Oral Concentrate, Solution or Eligir</th>
<th>Short-Acting Injection</th>
<th>Other Formulation</th>
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<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
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Second Generation APs

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<th>Trade Name</th>
<th>Tablet or Capsule</th>
<th>Rapidly Dissolving Tablet</th>
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<th>Short-Acting Injection</th>
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<tr>
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<tr>
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<td>Seroquel</td>
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<tr>
<td>Paliperidone</td>
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</tbody>
</table>

Side Effect Profiles

- Allergic & Dermatological
- Cardiovascular
- Endocrine
- Gastrointestinal
- Hematological
- Neurological
- Ophthalmological
- Other


Antipsychotic Side Effects

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Antipsychotic</th>
<th>Sedative</th>
<th>Sclerotic</th>
<th>Orthotropic</th>
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<td>Aripiprazole</td>
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<tr>
<td>Bromperidone</td>
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Antipsychotic Side Effects

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Prolactin</th>
<th>Weight Gain</th>
<th>Hyperprolactinaemia</th>
<th>Sedation</th>
<th>Other</th>
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<tbody>
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<td>Clozapine</td>
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<td>Risperidone</td>
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</tr>
<tr>
<td>Haloperidone</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Long-Acting Injectables

<table>
<thead>
<tr>
<th>Long-Acting Injectable Antipsychotics</th>
<th>Trade Name</th>
<th>Available strengths in the U.S. (mg, أجل, equivalent oral)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroleptics</td>
<td>Paliperidone</td>
<td>Disperon 50 mg (1 mL), 75 mg (1 mL), 100 mg (1 mL)</td>
<td>Monitor for hypotension. In some cases of allergy, avoid injection site.</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>Aripiprazole</td>
<td>Abilify 25 mg, 30 mg, 37.5 mg</td>
<td>Not to be used with paliperidone. Avoid concurrent injection of Abilify and paliperidone into the same muscles.</td>
</tr>
<tr>
<td>Deposedrone</td>
<td>Aripiprazole</td>
<td>AriSoma 17 mg, 21 mg, 23 mg</td>
<td>Not to be used with paliperidone. Avoid concurrent injection of AriSoma and paliperidone into the same muscles.</td>
</tr>
<tr>
<td>Long-Acting Injectable Antipsychotics</td>
<td>Gepirone</td>
<td>250 mg, 300 mg (1 mL)</td>
<td>Requires use of DAS RMS program due to risk of post-injection delirium/delirious syndrome. Must be given in hospital setting with ready emergency response access. Patient must be observed for at least 3 hours post injection and accompanied upon discharge.</td>
</tr>
<tr>
<td>Long-Acting Injectable Antipsychotics</td>
<td>Paliperidone</td>
<td>Paludol 30 mg, 60 mg (1 mL)</td>
<td>This may cause fluid retention. Loop diuretics may be required to enhance diuresis.</td>
</tr>
<tr>
<td>Long-Acting Injectable Antipsychotics</td>
<td>Quetiapine</td>
<td>Seroquel XR 200 mg, 400 mg (1 mL)</td>
<td>Alternative injection sites.</td>
</tr>
<tr>
<td>Long-Acting Injectable Antipsychotics</td>
<td>Clozapine</td>
<td>Geodon 25 mg, 50 mg, 100 mg (1 mL)</td>
<td>Alternative injection sites.</td>
</tr>
<tr>
<td>Long-Acting Injectable Antipsychotics</td>
<td>Olanzapine</td>
<td>Zyprexa 5 mg (1 mL)</td>
<td>Additional subcutaneous injection only in alternate injection sites. Inject only in areas without skin conditions, irritation, swelling, bruising, inflammation, or scarring.</td>
</tr>
</tbody>
</table>
Schizophrenia Guidelines

Pharmacotherapy

- Those with symptom improvement with an antipsychotic should continue to be treated with an antipsychotic (1A)
  - Benefits: Lower relapse rate, rehospitalization and death
  - Risks: Greater rates of weight gain, sedation and movement disorders


- Those with symptom improvement with an antipsychotic should continue to be treated with the same antipsychotic (2B)
  - Studies showed earlier treatment discontinuation with med switches
  - Gradual cross-taper needed if switching
  - Careful monitoring to avoid nonadherence and destabilization


- Clozapine recommended for
  - Treatment-resistant schizophrenia (1B)
  - Risk of suicide attempts or suicide (1B)
  - Risk for aggressive behavior (2C)
  - Slow titration essential
  - Clozapine REMS Program required
Schizophrenia Guidelines

Pharmacotherapy

- Suggest use of **long-acting injectable** antipsychotic if preferred or history of nonadherence (2B)
  - Subjective sense of better symptom control, take fewer daily meds, reduced conflict with family re: med reminders

Schizophrenia Guidelines

Pharmacotherapy

- For **acute dystonia** associated with AP, treat with anticholinergic med (1C)
  - Diphenhydramine IM or IV (emergent)
  - Benztropine IM
  - Once acute dystonia resolved, may need to continue oral med, such as benztropine or trihexyphenidyl, to prevent recurrence

Schizophrenia Guidelines

Pharmacotherapy

- For **parkinsonism** associated with AP, suggest lowering AP dosage, switching AP or treating with anticholinergic (2C)
  - Acute: PO/IM diphenhydramine
  - Short or long term: Benztropine or trihexyphenidyl
Schizophrenia Guidelines

Pharmacotherapy

- For akathisia associated with AP, suggest lowering AP dosage, switching AP, adding a benzodiazepine or beta blocker (2C)
  - BZD: Lorazepam and clonazepam
  - β-blocker: Propranolol
  - Short or long term: Benztropine or trihexyphenidyl


Schizophrenia Guidelines

Pharmacotherapy

- Treat moderate to severe tardive dyskinesia (TD) associated with AP with VMAT2 inhibitor (1B)
  - Deutetrabenazine or valbenazine preferred over tetrabenazine
  - Consider initiation with mild TD
  - Anticholinergic meds may worsen TD


Schizophrenia Guidelines

- Tardive Dyskinesia Pocket Guide

| Reversible inhibitors of human vesicular monoamine transporter type 2 (VMAT2) |
|-----------------------------------|----------|----------|----------|
| **Generic name** | **Trade name** | **Deutetrabenazine** | **Tetrabenazine** | **Valbenazine** |
| Available formulations (mg) | Tablet: 6, 9, 12 | Tablet: 12, 25 | Capsule: 40, 80 |
| Typical dose range (mg/day) | 12-48 | 25-75 | 40-80 |

Schizophrenia Guidelines

Psychosocial Intervention
- Treatment of first episode psychosis to include coordinated specialty care program (1B)
- Cognitive-behavioral therapy for psychosis (1B)
- Psychoeducation (1B)
- Supported employment services (1B)
- Assertive community treatment for poor engagement leading to frequent relapse or social disruption (1B)


Schizophrenia Guidelines

Psychosocial Intervention
- Family interventions (2B)
- Self-management skills (2C)
- Cognitive remediation (2C)
- Social skills training (2C)
- Supportive psychotherapy (2C)


Schizophrenia Guidelines

Areas for Further Research: Medications
- Comparative effectiveness (and harms) of newer SGAs vs other SGAs and FGAs
- Optimal treatment for suicidal/aggression
- Risks/benefits of concomitant meds with AP
- Optimal approach to making med changes
- Relationship between AP blood levels and therapeutic response
- Efficacy and comparative efficacy of neurostimulation approaches
