Antipsychotic Update

Faculty
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This activity is an overview of the recent changes to FDA approved indications, for antipsychotics, as well as new formulations available for use and new approaches to using these agents. Those participating in this CE program will also experience a summarized detail of all the antipsychotic agents that are currently available in order to stay current of the full spectrum of treatment options.

Learning Objectives

Pharmacist
1. Identify the classification, related class effects and recent updates to the currently available antipsychotic agents
2. Describe the role and some new approaches to using antipsychotic agents for various conditions
3. Discuss the role of scales and clinical assessment tools when evaluating the effectiveness of antipsychotic agents in patients with complicated mental health conditions

Pharmacy Technician
1. Identify the classification, related class effects and recent updates to the currently available antipsychotic agents
2. Describe the role and some new approaches to using antipsychotic agents for various conditions
3. Discuss the role of scales and clinical assessment tools when evaluating the effectiveness of antipsychotic agents in patients with complicated mental health conditions

Nurse
1. Identify the classification, related class effects and recent updates to the currently available antipsychotic agents
2. Describe the role and some new approaches to using antipsychotic agents for various conditions
3. Discuss the role of scales and clinical assessment tools when evaluating the effectiveness of antipsychotic agents in patients with complicated mental health conditions
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Target Audience
Pharmacists, Pharmacist Technician, Nurse

Universal Activity Number
Pharmacist 0798-0000-19-102-L01-P
Pharmacy Technician 0798-0000-19-102-L01-T
Nurse 0798-0000-19-102-L01-P

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CE Broker Tracking Number
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OBJECTIVES

1. Identify the **classification, related class effects** and **recent updates** to the currently available antipsychotic agents
2. Describe the **role** and some **new approaches** to using antipsychotic agents for various conditions
3. Discuss the **role of scales and clinical assessment tools** when evaluating the effectiveness of antipsychotic agents in patients with complicated mental health conditions

OBJECTIVE #1

Identify the **classification, related class effects** and **recent updates** to the currently available antipsychotic agents
### First Generation Antipsychotic (FGA) - Class related side effects

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine (Thorazine)</td>
<td>Extrapyramidal side effects (EPS)</td>
</tr>
<tr>
<td>Fluphenazine (Prolixin)</td>
<td>QTc prolongation</td>
</tr>
<tr>
<td>Haloperidol (Haldol)</td>
<td>Prolactin elevation</td>
</tr>
<tr>
<td>Loxapine (Loxitane)</td>
<td>Dermatologic</td>
</tr>
<tr>
<td>Perphenazine (Trilafon)</td>
<td>Photosensitivity</td>
</tr>
<tr>
<td>Thiothixine (Navane)</td>
<td>Blue-gray skin</td>
</tr>
<tr>
<td>Trifluoperazine (Stelazine)</td>
<td>Orthostatic Hypotension</td>
</tr>
<tr>
<td>Thioridazine (Mellaril)</td>
<td>Altered thermoregulation</td>
</tr>
<tr>
<td></td>
<td>Black box: dementia related psychosis</td>
</tr>
</tbody>
</table>

### Second Generation Antipsychotic (SGA) - Class related side effects

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Asenapine (Saphris)</td>
<td>Hypertriglyceridemia</td>
</tr>
<tr>
<td>Brexipiprazole (Rexulti)</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Cariprazine (Vraylar)</td>
<td>Weight Gain (waist circumference)</td>
</tr>
<tr>
<td>Clozapine (Clozaril, others)</td>
<td>QTc prolongation</td>
</tr>
<tr>
<td>Illoperidone (Fanapt)</td>
<td>Blood dyscrasia/neutropenia</td>
</tr>
<tr>
<td>Lurasidone (Latuda)</td>
<td>Seizure threshold</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>Anticholinergic effects</td>
</tr>
<tr>
<td>Paliperidone (Invega)</td>
<td>Sedation</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>Prolactin elevation</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>Black box: Dementia related psychosis</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td></td>
</tr>
</tbody>
</table>
### New formulations of older agents

- **Aripiprazole**
  - Abilify Aristada monthly injection
  - Abilify Initio
    - One time injection used in combination with oral aripiprazole to start or restart Aristada treatment after a missed dose (675mg IM with one 30mg dose oral aripiprazole in conjunction with first Aristada injection or up to 10 days after. Can be used to re-initiate Aristada following missed dose but not meant for repeat dosing)
  - Abilify Mycite:
    - It should be noted that the use of Abilify Mycite to track drug ingestion in "real-time" or during an emergent event is not recommended because detection may be delayed or not occur-SMART phone app may take up to 2 hours to get signal.
SGA: FDA INDICATION UPDATE

New formulations of older agents
• Risperidone
  • **Perseris** monthly subcutaneous injection
• Paliperidone
  • **Sustenna** monthly and every 3 months (quarterly) Trinza

New FDA approved uses for older agents
• Lurasidone (Latuda)
  • Updated label for BPD in pediatric patients 10 years and older

New agents available to manage side effects
• Valbenazine (Ingrezza)
• Deutetrabenazine (Austedo)
• Updates on the Management of Irritable Bowel Syndrome Management
RISPERIDONE

Formulation Dosing and equivalence

LAI dose-IM

- Consta (25-50mg IM every 2 weeks) oral overlap for 3 weeks

<table>
<thead>
<tr>
<th>IM dose</th>
<th>Oral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>25mg</td>
<td>2mg</td>
</tr>
<tr>
<td>37.5mg</td>
<td>4mg</td>
</tr>
<tr>
<td>50mg</td>
<td>&gt;6mg</td>
</tr>
</tbody>
</table>

LAI dose-SQ

- Perseris (90-120mg SQ once monthly) no oral overlap

<table>
<thead>
<tr>
<th>SQ dose</th>
<th>Oral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>90mg</td>
<td>3mg</td>
</tr>
<tr>
<td>120mg</td>
<td>4mg</td>
</tr>
</tbody>
</table>


PALIPERIDONE

Paliperidone (Invega)

MOA: antagonism D2/SHT2A
Metabolism: CYP3A4

Clinical pearls

- Metabolite of risperidone, similar ADR
- Deltoid or gluteal injection
- No PO overlap required
- Food increases bioavailability
- Must be maintained on Sustenna for at least 4 months before Trinza

Availability

PO: OROS Tablet ("ghost" may be seen in stool)
LAI: Invega Sustenna & Invega Trinza

Oral dose

Initial: 1.5-6 mg/day with usual range 3-12 mg/day

LAI dose

Sustenna usual initial dose: 234mg with 156mg week 2 (deltoid), then 117mg monthly*

<table>
<thead>
<tr>
<th>Oral dose</th>
<th>Sustenna dose (monthly)</th>
<th>Trinza dose (every 3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3mg</td>
<td>39 to 78mg</td>
<td>273mg</td>
</tr>
<tr>
<td>6mg</td>
<td>117mg</td>
<td>410mg</td>
</tr>
<tr>
<td>12mg</td>
<td>234mg</td>
<td>819mg</td>
</tr>
</tbody>
</table>

OBJECTIVE #2

Describe the **role** and some **new approaches** to using antipsychotic agents for various conditions.

USING ANTIPSYCHOTIC AGENTS FOR VARIOUS CONDITIONS

New role of antipsychotics in managing Behavioral and Psychological Symptoms of Dementia (BPSD)


NEW ROLE OF ANTIPSYCHOTICS IN MANAGING BPSD

- The 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) created an umbrella of neurocognitive disorders (NCDs):
  - Includes dementia, cognitive and amnestic disorders
  - Reported to occur in ~80% of patients with NCD (mild or major etiology subtypes)
  - NCDs can be frontotemporal, vascular, TBI, Parkinson’s disease, Huntington’s disease and Alzheimer’s disease (AD responsible for 70% of NCDs).
  - Roughly 50% of all patients with NCD have both AD and vascular features (mixed dementia)
  - Broad spectrum of symptoms


SPECTRUM OF SYMPTOMS ASSOCIATED WITH BPSD

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy</td>
<td>29-76%</td>
</tr>
<tr>
<td>Agitation/aggression</td>
<td>22-52%</td>
</tr>
<tr>
<td>Depression</td>
<td>20-57%</td>
</tr>
<tr>
<td>Irritability</td>
<td>20-55%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>17-45%</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>12-42%</td>
</tr>
<tr>
<td>Psychosis</td>
<td>10-35%</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>9-35%</td>
</tr>
</tbody>
</table>
Symptom Clusters Associated with BPSD

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence</th>
<th>Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy</td>
<td>29-76%</td>
<td>Not defined</td>
</tr>
<tr>
<td>Agitation/aggression</td>
<td>22-52%</td>
<td>Hyperactivity</td>
</tr>
<tr>
<td>Depression</td>
<td>20-57%</td>
<td>Affective</td>
</tr>
<tr>
<td>Irritability</td>
<td>20-55%</td>
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<tr>
<td>Hallucinations/delusions</td>
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<td>Psychosis</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>9-35%</td>
<td>Not defined</td>
</tr>
</tbody>
</table>

Recognizing the truth

- Most patients will have at least one of these symptoms
- Reported to be among the most distressing factors to caregivers and may result in otherwise avoidable institutionalization
- Other factors such as unaddressed pain, constipation and adverse drug have been associated with BPSD
- Non-pharmacologic behavioral interventions can be effective and are considered first line
- Despite best efforts, antipsychotic medications may still be needed
NEW ROLE OF ANTIPSYCHOTICS IN MANAGING BPSD

Recognizing the truth

• Black box warning highlighting the risks of using APS in patients with dementia
• Increased thromboembolic risk, accelerated cognitive decline & metabolic syndrome are also associated with use
• Alternatives to APS include cholinesterase inhibitors, memantine and SSRIs, however these have only demonstrated modest effects
• Other medications with risk greater than potential benefit: benzodiazepines and AED mood stabilizers due to high probability of adverse effects and low probability of meaningful clinical improvement
• APS are considered modestly effective with data supporting use when symptoms are considered dangerous or distressing

What does the data say?

• APS are considered modestly effective with data supporting use when symptoms are considered dangerous or distressing
• Target psychosis, aggression and agitation
• Response generally seen 1 to 4 weeks
• SGA: risperidone, olanzapine, aripiprazole and quetiapine all have data with overall improvements of up to 35% NPI scale improvement
• FGA: haloperidol most widely studied but newest guidelines advise against use of FGAs due to risk of higher mortality when compared to SGA

References:
NEW ROLE OF ANTIPSYCHOTICS IN MANAGING BPSD

What does the data say?

- Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer’s Disease (CATIE-AD) found SGA modestly effective for BPSD
- NPI improvement of 15 points
- 82% of subjects (study participants) discontinued the APS before 9 months (study concluded) due to adverse effects vs placebo (p=0.009)
- Discontinuation rates for all cause: Risperidone (77%), olanzapine (80%), quetiapine (82%) vs placebo (85%)
- Aripiprazole not included and current use is limited

NEW ROLE OF ANTIPSYCHOTICS IN MANAGING BPSD

Antipsychotic discontinuation is advisable and may not result in decompensation

• If no benefit seen at 4 weeks, taper and discontinue
• If response is noted, consider continuation for up to 6 months, then trial taper
• Ruths et al. found no difference in scale scores 30 days after patients were tapered off (85% of those patients remained symptom free)
• Ballard et al. reported no significant changes after taper and discontinuation
• Devanand et al. however did report relapse and worsening when patients were tapered and discontinued when compared to those who remained on risperidone


Antipsychotic discontinuation is often necessary

• Dose reduction is mandated by the Centers for Medicare and Medicaid Services (CMS) for patients in long term care facilities
• Minimum of 2 gradual dose reductions are required during first year of treatment, with each attempt being 3 to 6 months apart

Using Antipsychotic Agents for Various Conditions

New role of antipsychotics in managing depression


NEW ROLE OF ANTIPSYCHOTICS IN MANAGING DEPRESSION

Recognizing the truth

- SGAs have become increasingly popular augmentation agents for MDD (4 agents with current FDA approval)
- APS augmentation is associated with the same side effects when used for psychotic symptoms
- New additions to the MDD course specifiers in DSM-5 have allowed consideration for clinical features of the current episode

NEW ROLE OF ANTIPSYCHOTICS IN MANAGING DEPRESSION

Recognizing the truth

• Mixed features specifier allows co-occurring MDD with at least 3 manic symptoms but not meeting strict criteria for a manic episode

• Although considered less common than anxious distress specifier, the impact is significant and disabling.


There are no FDA approved treatments that specifically focus on mixed features

• Clinicians have extrapolated data used similar treatment strategies as TRD

• Attempt to pursue indication for lurasidone (Latuda) for mixed features was not successful (FDA noted enrollment criteria did not meet diagnostic criteria)

• However lurasidone was later approved for bipolar depression in 2018


NEW ROLE OF ANTIPSYCHOTICS IN MANAGING DEPRESSION

Recognizing the truth

- Additional studies have supported use of aripiprazole, asenapine, cariprazine, quetiapine and ziprasidone based on efficacy in BPD.

- Currently aripiprazole, brexpiprazole, olanzapine and quetiapine are FDA approved augmentation SGAs

OBJECTIVE #3

Discuss the **role of scales and clinical assessment tools** when evaluating the effectiveness of antipsychotic agents in patients with complicated mental health conditions
ROLE OF SCALES

There are many scales available for mental health assessment
• Brief Psychiatric Rating Scale (BPRS)
• Positive and Negative Syndrome Scale (PANSS)
• NPI
• AIMS, Barnes Akathisia Rating Scale
• Montgomery-Asberg Depression Rating Scale (MADRS)
• Can be used to as an initial clinical indicator, but also to see how effective medication intervention is
• Need to know what the scale is appropriate for
• Need to know what the number means (ie 30% improvement in NPI is minimum acceptable threshold for “clinical observable change” with mean total improvement as threshold of 4 points to be clinically significant)
• Best to have a baseline before assessing changes


BEST IN CLASS....

• Can you give an example of the impulsivity associated with ability?
• Could you elaborate on oral challenge
• Have you had any success in decreasing the overuse of SGA’s for sleep?
• When initiating antipsychotic therapy in a patient in seemingly perfect physical health, which agent would be your first choice and why?
• What would be appropriate to treat agitation related to dementia psychosis
• How do you tell the difference between NMS and serotonin syndrome in someone on a neuroleptic and SSRI?
• How does the efficacy of Ingrezza (valbenazine) compare to Austedo (deutetabenazine)? is there a reason you would choose one over the other?
## BENAZINE DIFFERENCES

<table>
<thead>
<tr>
<th></th>
<th>Valbenazine</th>
<th>Deutetrabenazine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>40 mg/d x 1 week then 80 mg/d</td>
<td>6 mg twice daily (12 mg/d) x 1 week then the dose of deutetrabenazine may be increased by 6 mg weekly until week 7 to a dose of 24 mg twice daily (48 mg/d)</td>
</tr>
<tr>
<td><strong>Dosage special</strong></td>
<td>Moderate or severe hepatic impairment (Child-Pugh score 7 to 15) = 40 mg/d</td>
<td>Hepatic Impairment contraindicated</td>
</tr>
<tr>
<td></td>
<td>Not recommended in severe renal impairment (CrCl&lt; 30mL/min)</td>
<td>In CYP2D6 poor metabolizers, dose should not exceed 18 mg twice daily</td>
</tr>
<tr>
<td><strong>Special instructions</strong></td>
<td>Take with or without food</td>
<td>Take with food</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tablets should not be crushed, chewed, or broken</td>
</tr>
</tbody>
</table>

- Valbenazine metabolized by CYP3A4/5 and by hydrolysis to form an active metabolite. The active metabolite is metabolized in part by CYP2D6
- Deutetrabenazine is primarily metabolized by CYP2D6

<table>
<thead>
<tr>
<th>Factors</th>
<th>Dose Adjustments for Valbenazine</th>
<th>Dose Adjustments for Deutetrabenazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use with MAOIs</td>
<td>Concomitant use not recommended</td>
<td>Concomitant use not recommended</td>
</tr>
<tr>
<td>Use with strong CYP3A4 inducers (e.g.,</td>
<td>Concomitant use not recommended</td>
<td>N/A</td>
</tr>
<tr>
<td>carbamazepine, phenytoin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of strong CYP3A4 inhibitors (e.g.,</td>
<td>Reduce dose to 40 mg</td>
<td>N/A</td>
</tr>
<tr>
<td>ritonavir, ketoconazole)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of strong CYP2D6 inhibitors (e.g.,</td>
<td>Consider dose reduction based on</td>
<td>Reduce dose to 18 mg twice daily</td>
</tr>
<tr>
<td>fluoxetine, paroxetine, bupropion)</td>
<td>tolerability</td>
<td></td>
</tr>
<tr>
<td>QTc Prolongation</td>
<td>May increase QTc interval</td>
<td>May increase QTc interval</td>
</tr>
</tbody>
</table>
THANK YOU!

Questions?