**Newer Atypical Antipsychotics: Novel Ideas or “Me Toos?”**

Sanaz Farhadian, Pharm.D., BCPP
Clinical Psychiatric Pharmacist
Veterans Affairs Healthcare System, San Diego, CA

**Objectives**
- Discuss new antipsychotics approved within the last five years
- Review new formulations of previously approved antipsychotics
- Recognize the clinical utility of new antipsychotic agents for the treatment of schizophrenia

**Pre-Test: Question 1**
Blockade of which receptor makes lurasidone a novel antipsychotic, due to the belief that it improves cognition?
A. 5-HT_{2A}
B. 5-HT_{1A}
C. 5-HT_{7}
D. D_{2}

**Pre-Test: Question 2**
Which of the following antipsychotics is NOT available as a long-acting injectable?
A. Olanzapine
B. Aripiprazole
C. Paliperidone
D. Quetiapine
**PRE-TEST: QUESTION 3**

Which of the following is a black box warning for Zyprexa Relprevv (olanzapine), requiring that a patient be observed for at least 3 hours after administration?

- A. Acute dystonia
- B. Post-injection delirium/sedation syndrome
- C. Hyperglycemia
- D. Increased mortality in elderly patients with dementia-related psychosis

---

**BACKGROUND**

- Antipsychotics introduced in 1950s to treat psychosis
- Atypical antipsychotics gained popularity in 1990s
  - More efficacious than typical agents
  - Decreased risk of movement disorders
- New atypical entities and formulations continue to be approved
- Account for large portion of pharmaceutical market share

---

**AVAILABLE ATYPICALS**

<table>
<thead>
<tr>
<th>GENERIC</th>
<th>BRAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine*</td>
<td>Clozaril</td>
</tr>
<tr>
<td>Risperidone*</td>
<td>Risperdal</td>
</tr>
<tr>
<td>Olanzapine*</td>
<td>Zyprexa</td>
</tr>
<tr>
<td>Quetiapine*</td>
<td>Seroquel</td>
</tr>
<tr>
<td>Ziprasidone*</td>
<td>Geodon</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Invega</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Fanapt</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Saphris</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Latuda</td>
</tr>
</tbody>
</table>

* Available generically

---

**SCHIZOPHRENIA PATHOPHYSIOLOGY**

[Image of brain with neurotransmitter labels: Abnormal Neurotransmission DA, 5-HT, Glu, GABA]
**DOPAMINE BRAIN PATHWAYS**

- Nucleus accumbens
- Substantia nigra
- Tegmentum
- Limbic cortex

1 – Mesolimbic
2 – Mesocortical
3 – Nigrostriatal
4 – Tuberoinfundibular

**SCHIZOPHRENIA CORE SYMPTOMS**

**POSITIVE**
- Hallucinations
- Delusions
- Disorganization
- Paranoia
- Combativeness/hostile
- Unusual behavior

**NEGATIVE**
- Alogia
- Anergia
- Avolition
- Anhedonia
- Restricted affect
- Social withdrawal
- Psychomotor retardation

**COGNITIVE**
- Difficulty with: Attention, Learning, Memory, Executive function

**ATYPICAL ANTIPSYCHOTICS**

- Postsynaptic D₂ receptor blockade with limbic specificity
  - Mesolimbic pathway – decreased positive symptoms
  - Tuberoinfundibular pathway – decreased risk of hyperprolactinemia

- Presynaptic 5-HT₂₅ autoreceptor blockade increases dopamine release that overcomes the postsynaptic blockade of the D₂ receptors in:
  - Mesocortical pathway – decreased negative symptoms
  - Nigrostriatal pathway – decreased risk of EPS

- Cause blockade of α₂, H₁, and mACH receptors

- Risk of metabolic side effects

**COMMON ADVERSE SIDE EFFECTS**

- Involuntary movements
  - Extrapyramidal symptoms
  - Tardive dyskinesia

- Hyperprolactinemia

- Sedation

- Orthostasis

- Anticholinergic side effects

- Metabolic abnormalities
  - Weight gain
  - Hyperglycemia and diabetes
  - Dyslipidemia
**RARE ADVERSE SIDE EFFECTS**

- Tachycardia
- QTc prolongation
- Seizures
- Cerebrovascular events
- Leukopenia, neutropenia, agranulocytosis
- Neuroleptic malignant syndrome
- Photosensitivity
- Thermoregulation
- Hepatic dysfunction

**BLACK BOX WARNINGS**

- Increased mortality in elderly patients with dementia-related psychosis due to cardiovascular or infectious causes
  - All atypical antipsychotics
- Suicidality in children and young adults due to depression indications
  - Aripiprazole
  - Quetiapine
- Myocarditis, seizures, agranulocytosis, orthostasis (± syncope)
  - Clozapine

**WHERE DO NEW AGENTS FIT IN?**

<table>
<thead>
<tr>
<th>APPROVAL DATE</th>
<th>ANTIPSYCHOTIC</th>
<th>BRAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 2009</td>
<td>Iloperidone</td>
<td>Fanapt</td>
</tr>
<tr>
<td>July 2009</td>
<td>Paliperidone IM Injection</td>
<td>Invega Sustenna</td>
</tr>
<tr>
<td>August 2009</td>
<td>Aripiprazole IM Injection</td>
<td>Akeeva</td>
</tr>
<tr>
<td>December 2009</td>
<td>Olanzapine IM Injection</td>
<td>Zyprexa Relprev</td>
</tr>
<tr>
<td>October 2010</td>
<td>Lurasidone</td>
<td>Latuda</td>
</tr>
<tr>
<td>February 2013</td>
<td>Aripiprazole IM Injection</td>
<td>Abilify Maintena</td>
</tr>
<tr>
<td>February 2013</td>
<td>Clozapine Oral Suspension</td>
<td>Versacloz</td>
</tr>
</tbody>
</table>

**FANAPT**

- (ILOPERIDONE)
- Oral tablet
  - 1mg, 2mg, 4mg, 6mg, 8mg, 10mg, 12mg
- Indication: acute treatment of schizophrenia
- Antagonist at α₂C receptors
- Twice daily dosing
  - 95% protein bound
  - Well absorbed, peak plasma concentrations 2-4 hours post-dose
  - Metabolized by CYP2D6 and CYP3A4 into P88 and P99
  - Elimination half-life: 18-33 hours for parent drug; 23-37 hours for metabolites
**Fanapt: Dosing**

*Iloperidone*

- Slow titration required due to orthostasis risk
- Initial dose: 1mg PO BID, titrating by 1-2mg BID daily
- Target dose: 6-12mg PO BID
- Maximum dose: 24mg/day in divided doses
- Dosage adjustments – reduce by 50%
  - CYP2D6 poor metabolizers
  - Strong CYP2D6 or CYP3A4 inhibitor
  - Hepatic impairment: NOT recommended

**Fanapt: Adverse Effects**

*Iloperidone*

- Hyperprolactinemia
- Orthostasis
- Medium metabolic risk
- QTc prolongation (~11.4 msec)
- Priapism

**Fanapt: Efficacy**

*Iloperidone*

All studies were randomized, double-blind, placebo-, active controlled

<table>
<thead>
<tr>
<th>Study Duration</th>
<th>Iloperidone Regimen</th>
<th>Active Comparator</th>
<th>Primary Outcome (Baseline to Endpoint)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks</td>
<td>24mg/day</td>
<td>Ziprasidone</td>
<td>↓ PANSS-T in ilo vs plac (p&lt;0.019) and zlpr vs plac (p&lt;0.05)</td>
</tr>
<tr>
<td>6 weeks</td>
<td>4, 8, or 12 mg/day</td>
<td>Haloperidol</td>
<td>↓ PANSS-T in ilo 12mg/day vs plac (p&lt;0.047) and halo vs plac (p&lt;0.001)</td>
</tr>
<tr>
<td>6 weeks</td>
<td>4-8mg/day 10-16mg/day</td>
<td>Risperidone</td>
<td>↓ BPRS-d in all ilo groups and risp Sign. improv. in both ilo groups vs plac.</td>
</tr>
<tr>
<td>6 weeks</td>
<td>12-24mg/day 20-24mg/day</td>
<td>Risperidone 6-8mg/day</td>
<td>↓ BPRS-d in all ilo groups and risp Sign. improv. in ilo 20-24mg vs plac (p&lt;0.01)</td>
</tr>
</tbody>
</table>

ilo = iloperidone, zlpr = ziprasidone, halo = haloperidol, risp = risperidone, plac = placebo, sign. improv = significant improvement

**Fanapt: Clinical Utility**

*Iloperidone*

**Pros**

- Low EPS risk

**Cons**

- Slow titration
- BID dosing
- QTc prolongation
**INVEGA SUSTENNA**

(PALIPERIDONE PALMITATE)

- Long-acting formulation of paliperidone
  - 39mg/0.25ml, 78mg/0.5ml, 117mg/0.75ml, 156mg/1.0ml, 234mg/1.5ml
- Indication: acute and maintenance treatment of schizophrenia
- Once monthly injection
  - 74% protein bound
  - Paliperidone palmitate hydrolyzed to paliperidone
  - Metabolized by CYP2D6 and CYP3A4 to 9-hydroxyrisperidone
  - Peak plasma concentrations at 13 days
  - Elimination half-life: 25 days (39mg), 48 days (234mg)

**INVEGA SUSTENNA: DOSING**

(PALIPERIDONE PALMITATE)

- Must establish efficacy/tolerability on risperidone or oral paliperidone first
  - First two doses must be given in deltoid
    - Day 1: 234mg IM; Day 8: 156mg IM
  - Then, 117mg IM (deltoid or gluteal) q4 weeks
    - Maintenance dose may range from 39-234mg
- Dosage adjustments
  - CrCl 50-79mL/min: day 1 - 156mg, day 8 - 117mg, q4 weeks - 78mg
  - CrCl ≤ 49mL/min: NOT recommended
  - Strong CYP3A4 inducer: decrease paliperidone dose

**SWITCHING TO INVEGA SUSTENNA**

(PALIPERIDONE PALMITATE)

- Oral antipsychotic to paliperidone palmitate
  - Stop oral antipsychotic, initiate as discussed on previous slide
  - If switching from oral paliperidone, use following conversion for maintenance dose

<table>
<thead>
<tr>
<th>PO QD</th>
<th>IM Q4 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>3mg</td>
<td>39-78mg</td>
</tr>
<tr>
<td>6mg</td>
<td>117mg</td>
</tr>
<tr>
<td>9mg</td>
<td>156mg</td>
</tr>
<tr>
<td>12mg</td>
<td>234mg</td>
</tr>
</tbody>
</table>

- Long-acting injection to paliperidone palmitate
  - If at steady state, initiate with maintenance dose q4 weeks when next injection is due

**INVEGA SUSTENNA: ADMINISTRATION**

(PALIPERIDONE PALMITATE)

- Visually inspect prefilled syringe for particles/discholoration
  - White to off-white suspension
- Shake syringe vigorously for at least 10 seconds
- Attach appropriate needle based on injection site
  - Hold syringe upright to de-aerate by moving plunger rod forward
- Inject entire contents IM slowly into selected muscle
**INVEGA SUSTENNA: ADVERSE EFFECTS**

(PALIPERIDONE PALMITATE)

- Injection site reaction
- Dose-related EPS
- Hyperprolactinemia
- Sedation
- Orthostasis
- Medium metabolic risk
- Priapism

**INVEGA SUSTENNA: EFFICACY**

(PALIPERIDONE PALMITATE)

- 13-week randomized, double-blind/dummy, non-inferiority trial
  - Long-acting paliperidone 78-234mg
  - Long-acting risperidone 25-50mg with oral risperidone x3 weeks

**INVEGA SUSTENNA: CLINICAL UTILITY**

(PALIPERIDONE PALMITATE)

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helps with adherence</td>
<td>Dose-related EPS</td>
</tr>
<tr>
<td>Administered monthly</td>
<td>Two dose initiation</td>
</tr>
<tr>
<td>No oral overlap required</td>
<td></td>
</tr>
</tbody>
</table>

**SAPHRIS**

(ASENAPINE)

- Sublingual tablet
  - 5mg, 10mg
- Indications
  - Acute and maintenance treatment of schizophrenia
  - Acute treatment of bipolar manic or mixed episodes
- Antagonist at 5-HT2C, 5-HT3, 5-HT7, and α2 receptors
- Twice daily dosing
  - 95% protein bound
  - Bioavailability: 35% sublingually, 2% orally
  - Peak plasma concentrations 0.5-1.5 hours post-dose
  - Metabolized by CYP1A2 and UGT1A4
  - Elimination half-life: 24 hours
**Saphris: Dosing**

**Asenapine**
- Regular flavor or black cherry
- Initial dose: 5mg SL BID
- Maintenance: increase to 10mg SL BID after 7 days
- Maximum dose: 20mg/day in divided doses
- Avoid eating or drinking for 10 minutes after administration
  - Reduces bioavailability
- Dosage adjustments
  - NOT recommended in severe hepatic impairment

**Saphris: Administration**

**Asenapine**
- Remove immediately before administration with dry hands
- Peel back colored tab to remove tablet
- Place under tongue and allow to dissolve fully
- Do not eat or drink for 10 minutes post-administration
- Slide tablet pack into case until it clicks

**Saphris: Adverse Effects**

**Asenapine**
- Oral hypoaesthesia
- Bitter taste
  - Black cherry flavor developed
- Akathisia
- Somnolence
- Low metabolic side risk

**Saphris: Efficacy**

**Asenapine**

All studies were randomized, double-blind, placebo-, active controlled

<table>
<thead>
<tr>
<th>Study Duration</th>
<th>Asenapine</th>
<th>Active Comparator</th>
<th>Primary and Secondary Outcomes (Baseline to Endpoint)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>5mg BID</td>
<td>Risperidone 3mg BID</td>
<td>↓ PANSS-T in asen vs plac (p&lt;0.005) Asen superior for PANSS-P and PANSS-N Asen &gt; plac for improvement on cognition</td>
</tr>
<tr>
<td>6 weeks</td>
<td>5mg BID</td>
<td>Haloperidol 4mg BID</td>
<td>↓ PANSS-T in asen 5mg and halo vs plac</td>
</tr>
<tr>
<td>6 weeks</td>
<td>5mg BID</td>
<td>Olanzapine 15mg daily</td>
<td>↓ PANSS-T in olan vs plac ↓ PANSS-P in asen 5mg and olan vs plac</td>
</tr>
</tbody>
</table>

Asen = iloperidone, risp = risperidone, halo = haloperidol, olan = olanzapine, plac = placebo
PANSS-T = Positive and Negative Symptom Scale, Total
PANSS-P = Positive and Negative Symptom Scale, Positive subscale
PANSS-N = Positive and Negative Symptom Scale, Negative subscale
**SAPHRIS: CLINICAL UTILITY**

(ASENAPINE)

**PROS**
- Low metabolic risk

**CONS**
- Akathisia
- BID dosing
- Patients without insight may swallow it instead of use it sublingually
- Eating and drinking affects bioavailability

**ZYPREXA RELPREVV**

(OLANZAPINE PAMOATE)

- Long-acting formulation of olanzapine
  - 210mg, 300mg, 405mg
- Indication: schizophrenia
- Once to twice monthly injection
  - 93% protein bound
  - Metabolized by glucuronidation and CYP1A2
  - Peak plasma concentrations within 7 days
  - Elimination half-life: 30 days

**ZYPREXA RELPREVV: DOSING**

(OLANZAPINE PAMOATE)

- Must establish efficacy/tolerability on oral olanzapine first

<table>
<thead>
<tr>
<th>Initial Oral Dose</th>
<th>IM (Gluteal) Dose in First 8 Weeks</th>
<th>IM (Gluteal) Dose After 8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mg/day</td>
<td>210mg q2 weeks OR 405mg q4 weeks</td>
<td>150mg q2 weeks OR 300mg q4 weeks</td>
</tr>
<tr>
<td>15mg/day</td>
<td>300mg q2 weeks OR 405mg q4 weeks</td>
<td></td>
</tr>
<tr>
<td>20mg/day</td>
<td>300mg q2 weeks OR 405mg q4 weeks</td>
<td></td>
</tr>
</tbody>
</table>

- Dose adjustments
  - Geriatric or debilitated patients, and those with hypotension risk
    - Starting dose 150mg IM q4 weeks
  - Clearance may be impaired in severe hepatic dysfunction

**ZYPREXA RELPREVV: ADMINISTRATION**

(OLANZAPINE PAMOATE)

- Loosen powder in the vial by light tapping
- Withdraw desired diluent volume and inject into powder vial
- Pad a hard surface and tap vial firmly until no powder is visible
- Shake vigorously until suspension is homogenous
  - Yellow and opaque
- Inject immediately after reconstitution
  - Otherwise, shake vigorously to re-suspend; stable for 24 hours
- Using 19 gauge or larger needle, inject into gluteal muscle
- Aspire for several seconds to ensure not in blood supply
- Administer injection at steady, continuous pressure
**POST-INJECTION DELIRIUM/SEDATION (PDSS) – BLACK BOX WARNING**

- Incidence <0.1% per injection, 2% per patient
- Related to excessive olanzapine plasma concentrations

![Graph showing approximate onset times of PDSS events in clinical trials](image)

**ZYPREXA RELPREVV REGULATIONS (OLANZAPINE PAMOATE)**

- Must be given in registered healthcare facility with ready access to emergency response services
- Must observe patient for at least 3 hours once administered
- Prior to releasing patient, healthcare professional must confirm alertness, orientation, and lack of signs/symptoms of PDSS
- DO NOT administer if patient will not be accompanied on release
- REMS medication distributed through Zyprexa Relprevv Patient Care Program, which requires registration of:
  - Prescriber, healthcare facility, patient, and pharmacy

**ZYPREXA RELPREVV ADVERSE EFFECTS (OLANZAPINE PAMOATE)**

- Injection site reaction
- PDSS
- Sedation
- Orthostasis
- Anticholinergic
- High metabolic risk

**ZYPREXA RELPREVV: EFFICACY (OLANZAPINE PAMOATE)**

- Similar to oral olanzapine and haloperidol in symptom reduction
- Similar to Risperdal Consta in 1 year treatment-completion rates
- Dose-related rate of discontinuation due to lack of efficacy
### Zyprexa Relprevv: Clinical Utility

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helps with adherence</td>
<td>Registration requirements</td>
</tr>
<tr>
<td>Up to once monthly dosing</td>
<td>Long observation period</td>
</tr>
<tr>
<td>No oral overlap required</td>
<td>High metabolic risk</td>
</tr>
<tr>
<td></td>
<td>Unclear guidance for doses greater 20mg orally</td>
</tr>
</tbody>
</table>

### Latuda (Lurasidone)

- **Pros**
  - Oral tablet
  - 20mg, 40mg, 80mg, 120mg
- **Cons**
  - Indication: schizophrenia
  - Partial agonist at 5-HT<sub>1A</sub> and antagonist at 5-HT<sub>7</sub> and α<sub>2c</sub> receptors
  - Once daily dosing
    - 99% protein bound
    - Poor absorption: 9-19%, peak plasma concentrations 1-3 hours
    - Metabolized by CYP3A4 into ID-14283 and ID-14326
    - Elimination half-life: 18 hours

### Latuda: Dosing (Lurasidone)

- Initial dose: 40mg PO daily
- Target dose: 40-160mg PO daily
- Maximum dose: 160mg/day
- Take with food (at least 350 calories)
- Dosage adjustments
  - CrCl ≤ 49ml/min - reduce 50%
  - Moderate hepatic impairment – reduce 50%
  - Severe hepatic impairment – initiate 20mg, max 40mg/day
  - Moderate CYP3A4 inhibitor – reduce 50%
  - CONTRAINDI CATED with strong CYP3A4 inhibitors or inducers

### Latuda: Adverse Effects (Lurasidone)

- Akathisia
- Parkinsonism
- Somnolence
- Dizziness
- Low metabolic risk
- Nausea
- Dizziness
**Latuda: Efficacy (Lurasidone)**

- Comparable to olanzapine, quetiapine XR, and ziprasidone in decreasing PANSS-T from baseline to endpoint at 6 weeks

<table>
<thead>
<tr>
<th>Study Duration</th>
<th>Lurasidone Regimen</th>
<th>Active Comparator</th>
<th>Outcome (Baseline to Endpoint)</th>
</tr>
</thead>
</table>
| 6 weeks        | 80mg/day 160mg/day| Quetiapine XR 600mg/day | Sign. improv in MADRS for all groups vs plac  
|                |                   |                   | (p<0.001)                      |
| 6 months       | 80mg/day 160mg/day| Quetiapine XR 600mg/day | Luras 160mg superior to plac and QXR on composite cognitive functioning measure  
|                |                   |                   | UPSA-B scores superior to plac for all groups  
| 21 days        | 120mg/day         | Ziprasidone 80mg BID | Statistical trend for luras to improve SCoRS  
|                |                   |                   | (p=0.058)                      |

* Luras = lurasidone, QXR = quetiapine XR, plac = placebo, sign. improv = significant improvement  
* MADRS = Montgomery-Asberg Depression Rating Scale  
* UPSA-B = UCSD Performance-based Skills Assessment, Brief  
* SCoRS = Schizophrenia Cognition Rating Scale

**Latuda: Clinical Utility (Lurasidone)**

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Once daily dosing</td>
<td>Must take with food</td>
</tr>
<tr>
<td>Low metabolic risk</td>
<td></td>
</tr>
</tbody>
</table>

**Abilify Maintena (Aripiprazole)**

- Long-acting formulation of aripiprazole
  - 300mg, 400mg
- Indication: schizophrenia
- Partial agonist at D2 and 5-HT1A receptors  
  - Potential to lower prolactin levels and improve mood
- Once monthly injection  
  - 99% protein bound  
  - Metabolized by CYP2D6 and CYP3A4 to dehydro-aripiprazole  
  - Peak plasma concentrations at 5-7 days  
  - Elimination half-life: 29.9 days (300mg), 46.5 days (400mg)

**Abilify Maintena: Dosing (Aripiprazole)**

- Must establish efficacy/tolerability on oral aripiprazole first
- 300-400mg IM (gluteal) q4 weeks
- Oral aripiprazole overlap x2 weeks  
  - Upon initiation or if missed dose occurs
- Dose adjustments  
  - CYP2D6 poor metabolizers  
  - Strong CYP2D6 or CYP3A4 inhibitor >14 days  
  - Combination of CYP2D6 or CYP3A4 inhibitor >14 days  
  - AVOID use with CYP3A4 inducers >14 days
**Abilify Maintena: Administration (Aripiprazole)**

- Suspend Abilify Maintena with appropriate amount of sterile water for injection
- Shake vigorously for 30 seconds until suspension is uniform
  - Visually inspect for particles/discoloration
  - Opaque and milky white
- Inject immediately after reconstitution
  - Otherwise, keep at room temperature and shake at least 60 seconds to re-suspend
- Attach vial adapter to syringe and draw up recommend volume
- Attach 21 gauge needle and slowly administer into gluteal muscle

**Abilify Maintena: Adverse Effects (Aripiprazole)**

- Injection site reaction
- Akathisia
- Low metabolic risk

**Abilify Maintena: Efficacy (Aripiprazole)**

- 52-week randomized, double-blind, placebo-controlled trial
  - Terminated early
- Time to impending relapse significantly delayed (p<0.0001)
- Relapse rates significantly lower (10.0% arip. vs 39.6% placebo)

**Abilify Maintena: Clinical Utility (Aripiprazole)**

**Pros**

- Helps with adherence
- Administered monthly
- Depot formulation with lowest metabolic risks
- May improve mood
- Reduces prolactin levels

**Cons**

- More akathisia compared to other antipsychotics
- Oral overlap required
VERSACLOZ (CLOZAPINE)
- Oral suspension formulation
  - 50mg/ml
- Indications:
  - Treatment-resistant schizophrenia
  - Recurrent suicidal behavior in schizophrenia & schizoaffective disorder
- Slow dose titration similar to other clozapine formulations
- Side effects similar to other clozapine formulations
- REMS program due to agranulocytosis risk
  - Prescribers, patients, and dispensing pharmacies must be registered

VERSACLOZ: CLINICAL UTILITY (CLOZAPINE)
- Pros
  - Effective for treatment-resistant schizophrenia
- Cons
  - Registration requirements
  - Frequent blood monitoring
  - Multiple black box warnings
  - Slow dose titration
  - High metabolic risk

ATYPICAL FORMULATIONS

<table>
<thead>
<tr>
<th>Atypical Antipsychotic</th>
<th>PO</th>
<th>ODT</th>
<th>Oral Liquid</th>
<th>Short-Acting IM</th>
<th>Long-Acting IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iloperidone</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aserpine</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ODT = orally disintegrating tablet; IM = intramuscular
IR = immediate release; XR/AL = extended release; SL = sublingual

RELATIVE METABOLIC RISK

- High risk
- Medium risk
- Low risk

* Limited long-term data exists

* Limited long-term data exists

CONCLUSIONS

- Place in therapy of newer agents largely limited by lack of head-to-head trials
- Fanapt, Saphris, and Latuda appear to be “me-too” agents
  - Dosing and administration restrictions
  - More data needed for efficacy of negative and cognitive symptoms
- Sustenna, Relprevv, and Maintena have provided for longer dosing interval of q4 weeks compared to previous IMs
  - Relprevv use limited due to need for registration and monitoring
  - Maintena has low metabolic risk, but still requires oral overlap
- Versacloz provides another formulation option for patients with treatment-resistant schizophrenia

POST-TEST: QUESTION 1

Blockade of which receptor makes lurasidone a novel antipsychotic, due to the belief that it improves cognition?

A. 5-HT_7
B. 5-HT_2A
C. 5-HT_1A
D. D_2

POST-TEST: QUESTION 2

Which of the following antipsychotics is NOT available as a long-acting injectable?

A. Olanzapine
B. Aripiprazole
C. Paliperidone
D. Quetiapine

POST-TEST: QUESTION 3

Which of the following is a black box warning for Zyprexa Relprevv (olanzapine), requiring that a patient be observed for at least 3 hours after administration?

A. Acute dystonia
B. Post-injection delirium/sedation syndrome
C. Hyperglycemia
D. Increased mortality in elderly patients with dementia-related psychosis