Atypical Antipsychotics: Indications and How to Monitor
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August 28, 2015
Disclosure Statement

• I do not hold stock in any pharmaceutical companies, have no involvement with industry advisory boards, and have no participation in industry-sponsored clinical research.

• I cannot identify any potential conflict of interest.
Atypical Antipsychotics: Indications and How to Monitor

Objectives:

- Discuss briefly the history and pharmacology of atypical antipsychotics
- Discuss the Indications (FDA- and “off-label”) for prescribing atypical antipsychotics
- Discuss how to properly monitor patients prescribed atypical antipsychotics
Atypical Antipsychotics: Indications and How to Monitor

Typical, or First Generation Antipsychotics

- Common examples: Haldol (haloperidol), Prolixin (fluphenazine)- both available in long-acting injectable form, Thorazine (chlorpromazine, first introduced 1951). Good at treating “positive” symptoms of psychosis (hallucinations, delusions, disorganized thinking).

- **Side effects** – dry mouth is common, muscle rigidity, cramping, tremors, weight gain (less so than atypicals), EPS (more so than atypicals), Tardive Dyskinesia, Neuroleptic Malignant Syndrome

*Source: Primary Care Companion for CNS Disorders*
Atypical Antipsychotics: Indications and How to Monitor

What are the Atypical Antipsychotics?

• Also known as “second-generation antipsychotics”

• Developed due to concerning, intolerable extrapyramidal side effects (EPS) of typical antipsychotics

• “Atypical” primarily due to lower propensity to induce EPS

Source: Primary Care Companion for CNS Disorders
Atypical Antipsychotics: Indications and How to Monitor

What are the Atypical Antipsychotics?

• Clozaril (clozapine) introduced in 1971, FDA-approved 1989
  -Very effective, but associated w/ serious side effects
  (agranulocytosis, myocarditis/cardiomyopathy, seizures)
  & requires weekly blood draws

• Similar antipsychotics then developed, became available in the early 1990s

Source: Primary Care Companion for CNS Disorders
Atypical Antipsychotics: Indications and How to Monitor

What are the atypical antipsychotics?

- Block D₂ receptors- thought to decrease psychotic symptoms due to affect on the mesolimbic pathway. Side effects thought to be due to blocking receptors in other pathways (EPS – nigrostriatal pathway)

- Blocking serotonin receptors (5-HT₂A, 5-HT₂C, 5-HT₁A)- thought to affect symptoms of mood disorders (depression, mania)

Source: Primary Care Companion for CNS Disorders
Atypical Antipsychotics: Indications and How to Monitor

What are the atypical antipsychotics?

- Abilify (aripiprazole)
- Clozaril (clozapine)
- Geodon (ziprasidone)
- Fanapt (iloperidone)
- Invega (paliperidone)
- Latuda (lurasidone)
- Rexulti (brexpiprazole) *brand new*
- Risperdal (risperidone)
- Saphris (asenapine)
- Seroquel (quetiapine)
- Zyprexa (olanzapine)
Atypical Antipsychotics: Indications and How to Monitor

Indications

- **Abilify** (aripiprazole)
  - FDA
    - **Schizophrenia** (adults, adolescents 13-17 years **10-30mg**)
    - **Bipolar I Disorder**, Acute Manic & Mixed Episodes (adults **15-30mg**, children 10-17 years **10-30mg**), Maintenance Tx (also adjunctive with lithium or valproate)
    - **Major Depressive Disorder**, Adjunctive Tx with anti-depressant (adults **5-15mg**)
    - **Autism**, Irritability (6-17 years **5-15mg**)
    - Agitation associated with Schizophrenia or Mania (IM Injection **5.25-9.75mg** up to **30mg** total in 24 hrs)

- “Off-label”
  - Dementia (modest efficacy for Psychosis & Agitation)
  - Borderline Personality Disorder (low evidence)
  - Anxiety Disorders (2 open label trials)
  - ADHD, Depression monotherapy, Eating Disorders- no trials

*Source: Psychopharmacology Institute*
Atypical Antipsychotics: Indications and How to Monitor

Indications

• **Abilify** (aripiprazole)
  ❖ Special Considerations:
    - Partial agonist at D2
    - Long-acting injectable **Maintena**, orally disintegrating **Discmelt**
    - Dose should be reduced to 1/2 normal dose w/ strong inhibitors of CYP3A4 (ketoconazole, itraconazole)
    - Dose should be reduced to 1/2 normal dose w/ strong inhibitors of CYP2D6 (quinidine, fluoxetine, paroxetine)
    - Dose should be 2x when carbamazepine (CYP3A4 inducer) added
    - Pregnancy Category **B**: Potential benefit should outweigh potential risk.

*Source: Drugs.com*
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Indications

- **Clozaril** (clozapine)
  - FDA
    - Schizophrenia, Treatment Resistant (adults, 300-450mg, max 900mg)
    - Reduce Risk of Recurrent Suicidal Behavior (Schizophrenia/Schizoaffective Disorder), (adults, 300-450mg, max 900mg)

- “Off-label”
  - Bipolar Disorder
  - Borderline Personality Disorder
  - Children/Adolescents: Schizophrenia, Bipolar Disorder

Source: Drugs.com
Atypical Antipsychotics: Indications and How to Monitor

Indications

- **Clozaril** (clozapine)

  ❖ Special Considerations:
    - Dose adjustments may be necessary w/ strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, enoxacin)
    - contraindicated in patients with a history of clozapine-induced **agranulocytosis** (defined as ANC of < 500/mm3) or severe granulocytopenia
    - Pregnancy Category C: In animal studies, demonstrated developmental toxicity, including possible teratogenic effects in rats, rabbits

*Source: Drugs.com*
Atypical Antipsychotics: Indications and How to Monitor

Indications

• **Geodon** (ziprasidone)
  
  - **FDA**
  - **Schizophrenia** (adults 20-80mg BID)
  - **Bipolar I Disorder**, Acute Manic & Mixed Episodes (adults 40-80mg BID), Maintenance Tx (also adjunctive w/ lithium or valproate)
  - Agitation associated w/ Schizophrenia (IM Injection **10-20mg** up to **40mg** total in 24 hrs)

  - **“Off-label”**
    - Children/Adolescents: Schizophrenia, Bipolar Disorder, Irritability in Autism
    - Bipolar Depression
    - Major Depression
    - Anxiety/PTSD

*Source: Drugs.com*
Atypical Antipsychotics: Indications and How to Monitor

Indications

- **Geodon** (ziprasidone)

  - **Special Considerations:**
    - Take w/ **Food**! (absorption increased up to 2x)
    - Contraindicated in patients w/ known history of QT prolongation, recent MI, uncompensated heart failure
    - Caution w/ inducers of CYP3A4 (carbamazepine, ketoconazole)
    - Pregnancy Category C: In animal studies, demonstrated developmental toxicity, including possible teratogenic effects at doses similar to human therapeutic doses

*Source: Drugs.com*
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Indications

- **Fanapt** (iloperidone)
  - FDA
  - **Schizophrenia** (acute, adults 6-12mg BID)

- “Off-label”
  - Maintenance tx

*Source: Drugs.com*
Atypical Antipsychotics: Indications and How to Monitor

Indications

• **Fanapt** (iloperidone)

  ❖ **Special Considerations:**
  - modest increase in QTc interval
  - dose should be reduced by 1/2 w/ strong CYP2D6 inhibitors (fluoxetine, paroxetine)
  - dose should be reduced by 1/2 w/ strong CYP3A4 inhibitors (ketoconazole, clarithromycin)
  - Pregnancy Category C: no adequate, well controlled studies

*Source: Drugs.com*
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Indications

• **Invega** (paliperidone)
  
  ❖ FDA
  
  - **Schizophrenia** (acute & maintenance, adults *6-12mg*, adolescents 12-17 years *3-12mg*)
  - **Schizoaffective Disorder** (monotherapy & adjunctive, adults *6-12mg*)

  ❖ “Off-label”
  - Bipolar spectrum disorders

*Source: Drugs.com*
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Indications
• **Invega** (paliperidone)
  ❖ Special Considerations:
    - Long-acting injectable **Sustenna**
    - Is the major active metabolite of risperidone
    - On initiation of carbamazepine (strong inducer of CYP3A4), the dose of Invega should be re-evaluated & increased if necessary
    - Pregnancy Category C: caused developmental toxicity (but not teratogenic) in rats, rabbits

*Source: Drugs.com*
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Indications

• Latuda (lurasidone)
  ❖ FDA
  -Schizophrenia (acute & maintenance, adults 40-160mg)
  -Bipolar Depression (monotherapy & adjunctive, adults 20-120mg)

❖ “Off-label”
  -Maintenance tx
  -Bipolar Mania, Mixed Episodes

Source: Psychopharmacology Institute
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Indications

• **Latuda** (lurasidone)

  ❖ **Special Considerations:**
  - Take w/ **Food**! (absorption increased up to 2x)
  - should not be used w/ strong CYP3A4 inhibitors or inducers
  - Pregnancy Category **B**: no adequate, well controlled studies

*Source: Drugs.com*
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**Indications**

- **Risperdal** (risperidone)
  - FDA
    - Schizophrenia (adults 4-16mg, adolescents 13-17 years 1-6mg)
    - Bipolar Disorder, Acute Manic & Mixed, adults 1-6mg, children 10-17 years 0.5-6mg
    - Autism, Irritability (children 5-17 years 0.5-3mg)
  - “Off-label”
    - Major depression, adjunctive (moderate-high evidence)
    - Dementia, associated behaviors & psychosis (moderate-high)
    - Generalized Anxiety (low)
    - OCD, augmentation w/ SSRI (moderate-high)
    - PTSD (moderate-high)
    - ADHD (low)
    - Tourette’s (low)

*Source: Psychopharmacology Institute*
Atypical Antipsychotics: Indications and How to Monitor

Indications

• **Risperdal** (risperidone)

  ❖ **Special Considerations:**

    - Long-acting injectable **Consta**, oral solution, orally disintegrating **M-TAB**
    - **Hyperprolactinemia** - can lead to sexual side effects, amenorrhea, gynecomastia, galactorrhea
    - should be reduced when used in combination w/ CYP2D6 enzyme inhibitors
    - Pregnancy Category C: no adequate, well controlled studies

*Source: Drugs.com*
Atypical Antipsychotics: Indications and How to Monitor

Indications

• Saphris (asenapine)
  ❖ FDA
  - Schizophrenia (acute & maintenance, adults 5-10mg BID)
  - Bipolar Mania (monotherapy & adjunctive, adults 5-10mg BID, children 10-17 years 2.5-10mg BID)

❖ “Off-label”
  - Bipolar Maintenance tx

Source: Psychopharmacology Institute
Atypical Antipsychotics: Indications and How to Monitor

Indications

- **Saphris** (asenapine)

  ❖ **Special Considerations:**
    - Sublingual tablet
    - Coadminister cautiously with drugs that are both substrates & inhibitors for CYP2D6
    - Pregnancy Category C: no human studies

*Source: Drugs.com*
Atypical Antipsychotics: Indications and How to Monitor

Indications

• **Seroquel** (quetiapine)

  ❖ **FDA**
  - **Schizophrenia** (acute & maintenance, adults 150-750mg, adolescents 13-17 years 400-800mg)
  - **Bipolar Mania** (monotherapy & adjunctive, adults, children 13-17 years 400-600mg)
  - **Bipolar Depression** (monotherapy, 300-600mg)
  - **Bipolar Maintenance** (adjunctive, 400-800mg)
  - **Major Depressive Disorder** (XR approved as adjunct to antidepressants 150-300mg)

  ❖ **“Off-label”**
  - Generalized Anxiety Disorder (moderate evidence)
  - OCD (low)
  - Dementia, associated psychosis & agitation
  - Parkinson's psychosis

*Source: Psychopharmacology Institute*
Atypical Antipsychotics: Indications and How to Monitor

Indications
• **Seroquel** (quetiapine)
  ❖ Special Considerations:
    - XR form
      -should be reduced to 1/6 original dose w/ potent CYP3A4 inhibitor (ketoconazole, itraconazole)
      -should be increased up to 5x original dose w/ chronic treatment (7-14 days) of potent CYP3A4 inducer (phenytoin, carbamazepine, rifampin, avasimibe, St. John’s wort)
      -Pregnancy Category C: no adequate, well-controlled studies

*Source: Drugs.com*
Atypical Antipsychotics: Indications and How to Monitor

Indications
- **Zyprexa** (olanzapine)
  - FDA
  - **Schizophrenia** (acute & maintenance, adults & adolescents 13-17 years 10-20mg)
  - **Bipolar Disorder**, Acute & maintenance, Manic & Mixed, monotherapy & adjunctive, adults & children 10-17 years 10-20mg)
  - Agitation associated w/ Schizophrenia & Bipolar Mania (IM Injection 10 mg up to 30mg total in 24 hrs, 2-4 hrs apart)

  - “Off-label”
    - Depression augmentation
    - Anxiety, Panic, PTSD, OCD
    - Tourette’s
    - Dementia, associated psychosis & agitation

*Source: Psychopharmacology Institute*
Atypical Antipsychotics: Indications and How to Monitor

Indications
• Zyprexa (olanzapine)
  ❖ Special Considerations:
    - Oral disintegrating Zydis
    - Symbyax: Olanzapine/fluoxetine combination: Bipolar I Depression (adults 5mg/20mg, children 2.5mg/20mg), Tx-resistant depression (adults 5mg/20mg)
    - Caution w/ CYP1A2 inducers (carbamazepine) & inhibitors (fluvoxamine)
    - Pregnancy Category C: no evidence of teratogenicity in rats, rabbits

Source: Drugs.com
Atypical Antipsychotics: Indications and How to Monitor

**Indications**

- **Rexulti** (brexpoprazole)
  
  *Just approved by FDA 7/10/15 for Schizophrenia, Major depression tx augmentation*

  - Similar to Abilify except also affects 2 norepinephrine alpha receptors (which no other med does). Less affinity/activity at D₂ receptor compared to Abilify (less side effects like akathisia?)

  - Metabolized by same enzymes as Abilify (2D6, 3A4) so same dosing recommendations

  - MDD augmentation start 0.5 target 1mg; Schizophrenia start 1 target 2mg

  - Seeking approval for PTSD also
Atypical Antipsychotics: Indications and How to Monitor

Special Forms Available

**Liquid form:**
- Risperdal, Abilify, Clozaril, Haldol, Prolixin, Thorazine, Mellaril, Loxitane, Stelazine, Moban

**Dissolvable/Sublingual Tablets:**
- Risperdal M-tab, Zyprexa Zydis, Abilify Discmelt, Saphris

**IM (PRN):**
- Haldol, Prolixin, Zyprexa, Geodon

**Long-Acting Injectables:**
- Risperdal Consta, Invega Sustenna, Abilify Maintena, [Zyprexa Relprevv (only through a restricted distribution program)], Haldol Decanoate, Prolixin Decanoate
Atypical Antipsychotics: Indications and How to Monitor

**Black Box Warnings**

- **Elderly Patients with Dementia-Related Psychosis (all): Increased Mortality, Cerebrovascular Adverse Events (CVAE), Including Stroke**
  - A 2013 article from American Journal of Psychiatry argues morbidity/mortality related to mental illness & dementia severity, not medication side effects

- **Suicidal Thoughts and Behaviors in Adolescents and Young Adults (if FDA-approved for Depression):**
  “Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies”

*Source: Drugs.com*
Atypical Antipsychotics: Indications and How to Monitor

Monitoring Side Effects

- **Extrapyramidal side effects (EPS)**
  
  a) Dystonias- prolonged abnormal contractions of muscle groups
  
  b) Parkinsonism- symptom complex including tremor, slow movement, impaired speech, muscle rigidity
  
  c) Akathisia- feeling of inner restlessness and a compelling need to be in constant motion
  
  d) Tardive dyskinesia- involuntary movements of the face, jaw and tongue, can even affect limbs/digits. Usually seen with long-term use. Potentially irreversible. No known tx (sometimes remits if antipsychotic discontinued; low evidence that benzodiazepines reduce)

*Source: Primary Care Companion for CNS Disorders*
Atypical Antipsychotics: Indications and How to Monitor

Monitoring Side Effects

• **Neuroleptic Malignant Syndrome**
  – Rare, but potentially **fatal**

  – Fever, muscle rigidity, altered mental status, evidence of autonomic instability (irregular pulse/blood pressure, tachycardia, diaphoresis, cardiac dysrhythmia); elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), acute renal failure

  – **1) Discontinue antipsychotic 2) Intensive symptomatic treatment/medical monitoring 3) Treat any concomitant serious medical problems**

*Source: Primary Care Companion for CNS Disorders*
Atypical Antipsychotics: Indications and How to Monitor

Monitoring Side Effects

• **Orthostatic Hypotension**
  – Drop in blood pressure upon suddenly standing
  – associated w/ dizziness, tachycardia, bradycardia, even syncope

*Source: Drugs.com*
Atypical Antipsychotics: Indications and How to Monitor

Monitoring Side Effects

• **Somnolence**
  - Common, often dose-related
  - Use particular caution in elderly/dementia

Source: Drugs.com
Atypical Antipsychotics: Indications and How to Monitor

Monitoring Side Effects

• Metabolic Changes

a) Hyperglycemia/Diabetes Mellitus

b) Dyslipidemia

c) Weight Gain

Source: Primary Care Companion for CNS Disorders
Atypical Antipsychotics: Indications and How to Monitor

Monitoring Side Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight gain</th>
<th>Dyslipidemia</th>
<th>Hyperglycemia</th>
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</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Risperidone</td>
<td>++</td>
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<td>Quetiapine</td>
<td>++</td>
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<tr>
<td>Ziprasidone</td>
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<td>Paliperidone</td>
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<td>Asenapine*</td>
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</tr>
<tr>
<td>Lurasidone*</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

+++: significant; ++: intermediate; +: low; +/-: low or neutral
\*Limited data and/or long-term data are not available

Source: Current Psychiatry
Atypical Antipsychotics: Indications and How to Monitor

Monitoring Side Effects

ADA/APA Guideline Revised for Non-fasting Labs

<table>
<thead>
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<th>Assessment Parameter</th>
<th>Cut-offs</th>
<th>Baseline</th>
<th>4 wks</th>
<th>8 wks</th>
<th>12 wks</th>
<th>Quarterly</th>
<th>Annually</th>
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<td>Medical and Family History, Including DVD</td>
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<tr>
<td>Weight, BMI (kg/m²)</td>
<td>&gt;7% gain over baseline or &gt;25 kg/m²</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<td>Waist Circumference</td>
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<td></td>
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<td>Hemoglobin A1c</td>
<td>Pre-DM: &gt;6.7%, DM: &gt;6.5%</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Random Plasma Glucose</td>
<td>Pre-DM: &gt;140 mg/dL, DM: &gt;200 mg/dL</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Blood Pressure</td>
<td>&gt;140/90 mmHg</td>
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<td>Non-Fasting TC and HDL</td>
<td>Non-HDL: &gt;220 mg/dL or 10-yr risk &gt;7.5%</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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</tr>
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</table>

Atypical Antipsychotics: Indications and How to Monitor

Monitoring Side Effects

• **Metabolic Changes**
  Several strategies help minimize adverse metabolic effects of antipsychotics:

  o Healthy lifestyle interventions

  o Switching to lower risk antipsychotic

  o Addition of medications that may lower body weight and/or lipid & glucose parameters (**metformin** has the most evidence for weight reduction, lowering triglycerides & HgB A1C)

*Source: The American Journal of Psychiatry*
Atypical Antipsychotics: Indications and How to Monitor

Monitoring Side Effects

• Clozaril
  – Prior to initiating treatment with Clozaril, obtain a complete blood count (CBC) w/ differential.

  – Absolute neutrophil count (ANC) must be \( \geq \) to 2000/mm\(^3\) + WBC must be \( \geq \) 3500 mm\(^3\) in order to initiate.

  – To continue, ANC + WBC must be monitored Weekly x 6 months, Every 2 weeks x 6 months then every 4 weeks.

Source: Drugs.com
Summary

- Discussed briefly the history and pharmacology of atypical antipsychotics
- Discussed the Indications (FDA- and “off-label”) for prescribing atypical antipsychotics
- Discussed how to properly monitor patients prescribed atypical antipsychotics
Thank You

For Your Participation!

Questions?
Thank you for attending!

The recording of the webinar will be available at: youtube.com/LSQIN

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12:30-1 p.m. ET

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