Tolerability Is Key: Individualizing Treatment for Patients With Schizophrenia

page 145 in syllabus

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with additional support from: Assurex Health, Inc.; JayMac Pharmaceuticals, LLC; Neuronetics, Inc.. For further information concerning Lilly grant funding, visit www.lillygrantoffice.com.
Learning Objectives

- Implement evidence-based treatment strategies that address the long-term care of patients with schizophrenia
- Compare and contrast the safety, tolerability, and mechanisms of action of antipsychotics
- Identify strategies for the individualization of antipsychotic treatment for patients with schizophrenia
Mystery Medication 1: Who Am I?

- I am supposed to be given twice a day
- I am given sublingually
- If you swallow me, I will not be absorbed
- My dose is either 5 or 10 mg bid
- My cousin is mirtazapine

1. Clozapine
2. Olanzapine
3. Quetiapine
4. Asenapine
Mystery Medication 2: Who Am I?

• I am possibly more effective than other antipsychotics in schizophrenia
• I may cause more weight gain than other antipsychotics
• I am available in an acute injectable formulation and a 4-week injectable formulation

1. Clozapine
2. Olanzapine
3. Quetiapine
4. Asenapine
Mystery Medication 3: Who Am I?

- I was the first atypical antipsychotic
- I cause a lot of weight gain
- I am more effective than conventional antipsychotics and may be more effective than atypical antipsychotics
- I am the only antipsychotic proven to reduce suicide in schizophrenia
- I require the monitoring of blood counts

1. Clozapine
2. Olanzapine
3. Quetiapine
4. Asenapine
Pretest Question

Charles is a 30-year-old patient with schizoaffective disorder. Genotyping reveals that he is a poor metabolizer for the CYP450 1A2 enzyme. Based solely on this genotypic information, which of the following antipsychotics would be expected to have the greatest risk of intolerable side effects for this patient?

1. Asenapine
2. Iloperidone
3. Ziprasidone
Treatment Adherence

• Treatment adherence is the strongest predictor of relapse and rehospitalization in schizophrenia

• Tolerability is the primary cause for 20% of all drug discontinuation

• Most commonly reported intolerable side effects:
  – Cardiometabolic
  – Extrapyramidal symptoms (EPS)
  – Sedation/sleepiness
  – Cognitive dysfunction

Side Effects: What Can a Psychopharmacologist Do?

- Genes/aging: no options
- Lifestyle/diet: modest chance of success
- Choice of antipsychotic: most manageable option

Genetic Modification of Antipsychotic-Induced Side Effects: Cytochrome P450

- Liver enzymes
- Poor metabolizers may have dose-dependent increased risk of side effects
  - Most notably EPS and tardive dyskinesia
  - Poor metabolizers are also at an increased risk for treatment nonadherence

## CYP450 Substrates

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<tr>
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CARDIOMETABOLIC SIDE EFFECTS
Not All Cardiometabolic Issues in Schizophrenia Are Due to Treatment

**Comparison of First Episode, Drug-Naïve Schizophrenia Patients and Matched Controls**

NOTE: Cortisol levels in subjects with schizophrenia were elevated due to stress.

No difference in BMI

Genetic Modification of Antipsychotic-Induced Weight Gain

- The "A" allele of rs489693 on chromosome 18
  - Associated with greater SGA-induced weight gain
  - Located near the melanocortin 4 receptor (MC4R) gene
  - Previously associated with weight-related phenotypes in the general population

- The "T" allele of the 5HTR2C receptor gene
  - Associated with lower SGA-induced weight gain

Malhotra et al. Arch Gen Psychiatry 2012;69(9):904-12;
SNP rs489693 and Metabolic Changes Following 12-Week SGA Treatment

<table>
<thead>
<tr>
<th>Genotype at SNP rs489693 located on Chromosome 18</th>
<th>12 weeks treatment with quetiapine, risperidone, or aripiprazole</th>
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<tbody>
<tr>
<td><strong>Mean weight gain (kg)</strong></td>
<td>10.03</td>
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<tr>
<td>Mean increase in triglycerides (mg/dL)</td>
<td>51.67</td>
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<td>Mean increase in leptin (ng/mL)</td>
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<td>Mean increase in insulin (μIU/mL)</td>
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<tr>
<td>Mean increase in homeostasis model assessment insulin resistance (HOMA-IR) index</td>
<td>1.23</td>
</tr>
</tbody>
</table>
Meta-analysis of the 5HTR2C Gene

Favors T allele associated with less SGA-induced weight gain

MOVEMENT DISORDERS
Extrapyramidal Symptoms (EPS)

- Parkinsonism and akathisia
- 30-50% less risk with second-generation antipsychotics (SGAs) compared to first-generation antipsychotics (FGAs)
  - However, risk is still clinically substantial with many SGAs

Tardive Dyskinesia

- Prevalence is as high as 33% in patients treated with FGAs
- Risk of tardive dyskinesia is 80% lower for SGAs; however, it does still occur
- Tardive dyskinesia will reverse in approximately one-third of patients over a 6-month period after the offending medication is discontinued

Genetic Modification of Antipsychotic-Induced Tardive Dyskinesia: DRD2

- Rs1800497 polymorphism in the dopamine D2 receptor gene (DRD2)
  - A1 allele
    - Associated with a 40% reduction in striatal D2 receptor density
    - Protective against tardive dyskinesia
  - A2 homozygotes have an 80% increased risk of tardive dyskinesia compared to A1 homozygotes

- Rs1799732 -141C insertion/deletion in DRD2
  - Each Del allele significantly decreases the risk of tardive dyskinesia

Genetic Modification of Antipsychotic-Induced Tardive Dyskinesia: DRD3

- Rs6280 polymorphism in the DRD3 gene
  - Serine (Ser) to glycine (Gly) substitution
  - Gly variant is associated with 4X greater binding affinity for dopamine
  - Gly carriers have a significantly increased risk of tardive dyskinesia

Genetic Modification of Antipsychotic-Induced Tardive Dyskinesia: COMT

- Catechol-O-methyltransferase (COMT) degrades dopamine
- Met allele of the COMT gene: one-fourth of the enzymatic activity of the Val allele
  - Val carriers have decreased synaptic dopamine due to more rapid dopamine clearance
- Val allele is associated with a moderately increased risk for tardive dyskinesia

Genetic Modification of Antipsychotic-Induced Tardive Dyskinesia: HTR2A

- Rs6313 polymorphism in the serotonin 5HT2A receptor gene (HTR2A)
  - C allele is associated with a significantly increased risk of tardive dyskinesia
  - C allele theoretically leads to reduced expression of 5HT2A receptors

MAXIMIZING TREATMENT EFFICACY WHILE MINIMIZING SIDE EFFECTS
Cardiometabolic side effects, including weight gain, insulin resistance, and increased fasting triglycerides.
Maximize Treatment Efficacy While Minimizing Side Effects for the Individual Patient

<table>
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<th>Drug</th>
<th>D2 Antag</th>
<th>D2 PA</th>
<th>D3</th>
<th>5HT1A</th>
<th>5HT2A</th>
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Therapeutic Effects
- Reduced positive symptoms
- Reduced positive symptoms
- Reduced positive symptoms: Reduced negative symptoms: Procognitive: Antidepressant
- Reduced EPS: Reduced hyperprolactinemia: Antidepressant: Anxiolytic
- Reduced EPS: Reduced hyperprolactinemia
- Antidepressant
- Reduced circadian rhythm dysfunction: Reduced negative symptoms: Procognitive
- Reduced nightmares
- Reduced EPS
- Reduced EPS
- Hypnotic

Side Effects
- EPS: Hyperprolactinemia; increased negative symptoms: increased cognitive deficits: Sedation
- Relatively lower risk of EPS
- Unknown
- Cardiometabolic
- Cardiometabolic
- Unknown
- Dizziness: Sedation: Hypotension
- Constipation: Sedation: Dry mouth: Blurred vision
- Cardiometabolic: Constipation: Sedation: Dry mouth: Blurred vision

+ weak binding affinity (100>K<1000)
++ moderate binding affinity (10>K<100)
 +++ strong binding affinity (1>K<10)
++++ very strong binding affinity (Ki<1)
? No data yet available
* Binding property due primarily to the metabolite norquetiapine
Antipsychotics Target 60-80% Dopamine D2 Receptor Occupancy

- Antipsychotic effect threshold
- EPS threshold
In general, the "pines" are more sedating and carry more cardiometabolic risk than the "dones"

- Asenapine may be the exception
Clozapine

- The first and prototypical atypical antipsychotic
- Typically dosed to occupy <60% of D2 receptors
- Not recommended first line
- Best choice for treatment-resistant or highly aggressive patients
- May reduce suicidality
- Associated with agranulocytosis in 0.5-2% of patients
Olanzapine

- Low risk of EPS, even at high doses
- High risk of cardiometabolic side effects
- May improve mood in schizophrenia, bipolar disorder, and depression
- Available as a long-acting depot and ODT "Zydis"
Quetiapine

- Many binding properties are due to the metabolite, norquetiapine
- Available in both immediate and extended release formulations
- May have different properties at different doses
- Strong antidepressant evidence (NRI?)
Quetiapine and the Three Bears

- **Papa Bear**
  - 800 mg
  - Antipsychotic

- **Mama Bear**
  - 300 mg
  - Antidepressant

- **Baby Bear**
  - 50 mg
  - Hypnotic
Asenapine

- **Not** absorbed once swallowed; must be administered sublingually
  - Common side effect: oral hypoesthesia
- Not approved for depression but may have antidepressant properties
- May be useful as a rapid-onset prn since rapidly absorbed after sublingual administration
Asenapine and Mirtazapine

= mirtazapine

= asenapine
The "Dones"

- **Risperidone**
- **Paliperidone**
- **Ziprasidone**
- **Iloperidone**
- **Lurasidone**
Risperidone

- May act more as a conventional at higher doses
- May increase prolactin levels, even at low doses (PGP substrate)
- Available as a long-acting depot
Paliperidone

- Active metabolite of risperidone; OROS delivery system
- Not hepatically metabolized
- May be more tolerable than risperidone
- Available as a long-acting depot
- Has a lower incidence of EPS than risperidone
Ziprasidone

- Must be given twice daily with food
- Does not cause dose-dependent QTc prolongation
- Not approved for depression, but binding profile suggests possible antidepressant properties
Iloperidone

- Recommended twice daily, but dosing not well studied
- Must be titrated to avoid orthostasis and sedation due to strong alpha-1 binding
- Not approved for mania or depression, but potentially effective
- Potent alpha-1 antagonism suggests utility in PTSD
- Has lowest EPS/akathisia, possibly linked to alpha-1 antagonism (blocking properties)
Lurasidone

- Lack of H1 binding suggests reduced risk of metabolic side effects and sedation
- 5HT7 antagonism may be beneficial for mood and cognition
- Dose once daily with food
- Schizophrenia dosing now up to 160 mg/day
- Two new positive studies in bipolar depression:
  - Monotherapy
  - Augmentation to Li or VPA
Tandospirone and Lurasidone
The "Pip": Aripiprazole

- D2 partial agonist
- Acts as an agonist in the presence of a D2 antagonist
- Acts as an antagonist in the presence of a D2 agonist such as dopamine
- Approved as an adjunctive treatment for depression
- Has moderate 5HT1A and 5HT7 properties
# Minimizing the Risk of Side Effects

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<tr>
<th>SEDATION</th>
<th>WEIGHT GAIN</th>
<th>EPS</th>
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*Best choice*

*Worst choice*
Antipsychotic Algorithm for Schizophrenia: Efficacy

4-6-wk trial of a single atypical antipsychotic or, if unavailable, a trial of haloperidol, chlorpromazine, or another conventional antipsychotic

- Inadequate response
  - 4-6-wk trial of another atypical or conventional antipsychotic
    - Inadequate response
      - 6-month trial of clozapine (≤900 mg/day)
        - Inadequate response
          - Optimize clozapine and/or add ECT, adjunct prescription, or alternate strategies

- Adequate response
  - Maintenance phase

Antipsychotic Algorithm for Schizophrenia: Tolerability

4-6-wk trial of a single atypical antipsychotic or, if unavailable, a trial of haloperidol, chlorpromazine, or another conventional antipsychotic

Intolerable movement disorder
- Clozapine, iloperidone, or quetiapine

Intolerable metabolic syndrome
- LOWEST RISK: Aripiprazole, lurasidone, or ziprasidone
- LOWER RISK: Asenapine, iloperidone, or paliperidone ER

Intolerable sedation
- LOWEST RISK: Aripiprazole, iloperidone, or ziprasidone
- LOWER RISK: Lurasidone or paliperidone ER

SWITCHING FROM ONE ANTIPSYCHOTIC TO ANOTHER
Switching From One Pine or Done to Another: Pines to Pines or Dones to Dones

Switching From a Pine to a Done: Stop the Pine Slowly

Always Stop Clozapine Slowly

Switching From a Done to a Pine: Start the Pine Slowly

Switching From a Pine to Aripiprazole

Start a middle (not a low) dose when adding aripiprazole

3-7 days to add pip

2 weeks to taper pine

Time

Dose

pine

pip


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Switching From a Done to Aripiprazole

Start a middle (not a low) dose when adding aripiprazole

3-7 days to add pip
1 wk to taper done

1 week 1 week 1 week 1 week 1 week

done pip
time

Switching From Aripiprazole to a Pine

Immediate stop of aripiprazole

Start a middle (not a low) dose when adding to aripiprazole

2 weeks to add pine

Switching From Aripiprazole to a Done

Immediate stop of aripiprazole

Start a middle (not a low) dose when adding to aripiprazole

1 week to add done

WHEN SWITCHING IS NOT POSSIBLE
Treatment Options: Cardiometabolic Issues

• Lifestyle changes
  – Smoking
  – Exercise
  – Diet

• Augment with a weight loss agent
  – Metformin
  – Topiramate + phentermine (Qnexa®, Qsymia®)
  – Lorcaserin (Belviq®)
  – Bupropion + naltrexone (Contrave®)*

*Not FDA approved

Stahl et al. CNS Spectrums 2013; Epub ahead of print.
### "Meta-guidelines": Cardiometabolic Monitoring Recommendations

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Initial or Baseline</th>
<th>Follow-Up</th>
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<tbody>
<tr>
<td>Body weight and</td>
<td>Body weight, height, and calculated BMI; waist circumference when possible</td>
<td>BMI every visit for 6 months after changing antipsychotic medications and at least quarterly thereafter for outpatients; monthly for inpatients</td>
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<tr>
<td>height</td>
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<tr>
<td>Diabetes</td>
<td>Screening for diabetes risk factors; fasting blood glucose</td>
<td>Fasting blood glucose or hemoglobin a1c at no longer than 4 months after initiating a new treatment and annually thereafter for outpatients; more frequently (monthly to quarterly) for inpatients, depending on the agent (with high-risk agents such as clozapine and olanzapine assessed more frequently)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>Lipid panel</td>
<td>At least every 5 years recommended by APA/ADA but no longer followed; now at least semi-annually and more frequently for high-risk agents such as clozapine and olanzapine</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Assessed monthly for the first 3 months</td>
<td>Assess annually once treatment is stabilized or more frequently for high-risk agents</td>
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Stahl et al. CNS Spectrums 2013;Epub ahead of print.

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Treatment Options: EPS and Akathisia

- Anticholinergic agents can improve drug-induced parkinsonism but may exacerbate or unmask tardive dyskinesia
  - Procyclidine
  - Benztropine
  - Diphenhydramine
  - Trihexyphenidyl

- Benzodiazepines
  - Use with caution due to risk of dependence

- Beta blockers (propranolol)

- Amantadine
  
Treatment Options: Tardive Dyskinesia

• Generally, recommendations are to discontinue the offending antipsychotic and stop or minimize any anticholinergic medications

• Once these medications are stopped, it is possible that tardive dyskinesia will reverse

• If tardive dyskinesia does not reverse…

Treatment Options: Tardive Dyskinesia

- **Tetrabenazine and reserpine**
  - Dopamine-depleting agents
  - Considered first-line agents to treat tardive dyskinesia

- **Amantadine, benzodiazepines, beta blockers, and levetiracetam**
  - May have more tolerable side effect profiles

- **Botulinum toxin injections**
  - Option for patients with focal symptoms

- **Vitamin E**
  - May not improve tardive dyskinesia but may protect against deterioration
Treatment Options: Tardive Dyskinesia

• Suppressive therapy
  – Reinstating the offending antipsychotic
  – A controversial option, but it may be appropriate for some patients
  – Although this can make tardive dyskinesia worse in the long run, the short-term benefits may justify the risk for certain patients
Summary

• Intolerability is one of the leading causes of treatment nonadherence in patients with schizophrenia

• Movement disorders, cardiometabolic issues, and sedation are among the most commonly reported adverse effects of antipsychotics

• Genetic factors and lifestyle choices may predispose or protect individuals from the adverse effects of antipsychotics

• Side effects that may be intolerable for the individual patient can often be minimized by choosing antipsychotic agents based on their unique molecular binding profiles and using the lowest effective doses

• If an antipsychotic agent is intolerable, treatment strategies include switching to a different antipsychotic agent or augmenting with a side effect-mitigating agent
Mystery Medication 1: Who Am I?

• I am supposed to be given twice a day
• I am given sublingually
• If you swallow me, I will not be absorbed
• My dose is either 5 or 10 mg bid
• My cousin is mirtazapine

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Charles is a 30-year-old patient with schizoaffective disorder. Genotyping reveals that he is a poor metabolizer for the CYP450 1A2 enzyme. Based solely on this genotypic information, which of the following antipsychotics would be expected to have the greatest risk of intolerable side effects for this patient?

1. Asenapine
2. Iloperidone
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