SAFETY FIRST: A COMPARISON OF THE SAFETY AND TOLERABILITY OF ANTIPSYCHOTICS

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Learning Objectives

• Discuss the hypothesized mechanisms of action behind troubling side effects often associated with antipsychotic use

• Differentiate antipsychotics based on their tolerability and safety

• Apply antipsychotic treatment strategies that address individual patient needs and improve adherence
Antipsychotic-Induced Weight Gain and Metabolic Disturbances
Metabolic Side Effects: What Should You Know?

• Increasingly predictable depending upon the antipsychotic prescribed
• Much more readily prevented than treated after the fact
• Child and adolescent patients are more susceptible
• Predictors of long-term problems?
  • Rapid weight gain of >5% in the first month of treatment
  • Immediate elevation of fasting triglycerides

Risk of Weight Gain Among Antipsychotics

- **LOW**
  - aripiprazole
  - brexpiprazole
  - cariprazine
  - lumateperone
  - lurasidone
  - ziprasidone

- **MODERATE**
  - asenapine
  - iloperidone
  - paliperidone
  - quetiapine
  - risperidone

- **HIGH**
  - clozapine
  - olanzapine

References:

Citrome L et al. CNS Spectr 2018;23(3):228-38;
Antipsychotic-Associated Weight Gain: Possible Neurobiological Mechanisms

• H1 receptor antagonism
  • Interferes with satiety signals from the gut
• 5-HT2C receptor antagonism
  • Increases food intake

Insulin Resistance / Elevated Triglycerides and Drugs for Psychosis: Caused by Tissue Actions at an Unknown Receptor?
Monitoring Along the Metabolic Highway

Stahl SM. Stahl’s essential psychopharmacology. 5th ed. CUP; 2021.
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Quarterly</th>
<th>Annually</th>
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*Non-fasting low-density lipoprotein cholesterol laboratory tests are available. Measurement of hemoglobin A1c is an acceptable diagnostic tool for diabetes.

Management of Metabolic Side Effects

• When possible, select agents with lower incidences of weight gain and/or dyslipidemia

• Monitor weight gain, appetite changes, and metabolic parameters

• Encourage healthy diet, exercise

• Consider olanzapine/samidorphan rather than olanzapine alone

• Consider using metformin when initiating treatment with either olanzapine or clozapine

Less Weight Gain With Olanzapine/Samidorphan Than Olanzapine Alone in Schizophrenia

Greater Weight Loss With Metformin in First-Episode Versus Chronic Schizophrenia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>Placebo</th>
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<td></td>
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<tr>
<td>Wu 2008 B AM J</td>
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<td>Wu 2008 JAMA</td>
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<td>Wu 2012</td>
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<td><strong>Subtotal (95% CI)</strong></td>
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</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 2.79, df = 4 (P = 0.59); I² = 0%
Test for overall effect: Z = 14.27 (P < 0.00001)

| **Chronic**       |           |         |                 |         |       |        |                       |
| Baptista 2006     | 5.5       | 3.3     | 19              | 6.3     | 2.3   | 18     | 9.4%                | -0.80 [-2.63, 1.03]   |
| Baptista 2007     | -1.4      | 3.2     | 36              | -0.18   | 2.8   | 36     | 10.2%               | -1.22 [-2.61, 0.17]   |
| Carrizo 2009      | -1.87     | 2.9     | 24              | 0.16    | 2.9   | 30     | 9.9%                | -2.03 [-3.59, -0.47]  |
| Chen 2012         | -3.2      | 3.1     | 28              | -0.2    | 2.1   | 27     | 10.2%               | -3.00 [-4.39, -1.61]  |
| de Silva 2015     | -1.56     | 4.16    | 34              | 1       | 2.26  | 32     | 9.8%                | -2.56 [-4.16, -0.96]  |
| Jarskog 2013      | -3        | 4.34    | 75              | -1      | 4.23  | 71     | 10.2%               | -2.00 [-3.39, -0.61]  |
| Klein 2006        | -0.13     | 2.88    | 15              | 4.01    | 6.23  | 15     | 6.4%                | -4.14 [-7.61, -0.67]  |
| **Subtotal (95% CI)** | 231       |         |                 |         |       | 229    | 65.9%               | -2.06 [-2.71, -1.41]  |

Heterogeneity: Tau² = 0.08; Chi² = 6.74, df = 6 (P = 0.35); I² = 11%
Test for overall effect: Z = 6.24 (P < 0.00001)

**Total (95% CI)**
371 372 100.0% -3.24 [-4.55, -1.92]

Favours [Metformin] Favours [Placebo]

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• Improves weight, waist circumference, fasting glucose, insulin, HbA1c, HOMA-IR, triglycerides, and total cholesterol
• Average weight loss: 6.5 lbs
• Hypoglycemia is rare with metformin, and the risk of lactic acidosis is extremely low until eGFR is < 30 mL/min
  • Reevaluate metformin if eGFR < 45 mL/min, and stop if < 30
• Standard titration: 500 mg qam the first week; increase by 500 mg/wk if tolerated to 1000 mg BID; use extended-release formulation if GI adverse effects

Weight Gain Management: Other Options

- **Naltrexone + bupropion**
  - Approved weight loss treatment for patients with obesity
- **Aripiprazole**
  - May be effective for mitigating clozapine-induced weight gain
- **Liraglutide**
  - Weight loss in clozapine- or olanzapine-treated patients
  - Expensive and requires injections

Weight Gain Management: Other Options

• **Topiramate**
  - Prevents antipsychotic-induced weight gain, but has drug interactions and central side effects (e.g., cognitive dysfunction, sedation)

• **Amantadine**
  - May be effective for preventing/stabilizing olanzapine-induced weight (inconsistent results)

• **Behavioral interventions** (i.e., nutritional intervention, CBT)
  - Effective in individuals motivated to improve physical health

Switching to Aripiprazole or Ziprasidone May Reduce Weight Gain

- Meta-analysis: 59 studies reporting weight and metabolic alterations after antipsychotic switching vs. staying on the previous antipsychotic
- Switching to aripiprazole significantly reduced weight, improved fasting glucose, and triglycerides
- Switching to olanzapine significantly increased weight
- Drop-out and psychosis ratings did not differ significantly between aripiprazole and olanzapine
- In before-to-after switch meta-analyses, aripiprazole and ziprasidone were associated with weight loss, while olanzapine was associated with weight gain

Drug-Induced Parkinsonism and Akathisia
Drug-Induced Parkinsonism (DIP)

- DIP represents a spectrum of symptoms including tremor, bradykinesia, and muscle stiffness or rigidity.
- Occurs more frequently with typical antipsychotics and across a spectrum of atypical antipsychotics.
- Risk factors include age and female gender.
- Inadequate relief of DIP is a major reason why patients stop their medication.

DIP Treatment Strategies

• Withdraw or reduce the antipsychotic drug, if possible
• Switch to antipsychotic with lower D2 affinity
• Anecdotal evidence and small trials support the use of anticholinergic drugs (e.g., benztropine)
• Overuse of anticholinergics can lead to excessive tolerability burden
• Amantadine may also be helpful, but empirical evidence supporting its use is also limited

Akathisia

• Condition characterized by a subjective feeling of inner restlessness accompanied by mental distress and an inability to be still

• Akathisia severity is negatively correlated with quality of life in patients with schizophrenia

• The distress associated with akathisia reduces treatment adherence

Risk of Akathisia/DIP Among Antipsychotics

LOW
- clozapine
- iloperidone
- lumateperone
- quetiapine

MODERATE
- aripiprazole
- asenapine
- brexpiprazole
- cariprazine
- lurasidone
- olanzapine
- ziprasidone

HIGH
- paliperidone
- risperidone

NOTE: Treatment-emergent akathisia is generally higher with typical than atypical antipsychotics

Abbas A, Roth BL. Expert Opin Pharmacother 2008;9(18):3251-9;
**Dose reduction**

**Change to lower-risk antipsychotic**

**Initiate adjunctive medication**

* Withdrawal akathisia can occur; allow at least 6 weeks before judging effectiveness of dose reduction/medication switch
Adjunctive Medications for Akathisia

- **Beta-adrenergic blockers** (e.g., propranolol)
- **Benzodiazepines** (e.g., clonazepam)
- **5HT2A antagonists** (e.g., mirtazapine, cyproheptadine)

**NOTE**: anticholinergics (e.g., benztropine) should not be routinely used for the treatment of akathisia

Antipsychotic-Induced Sedation
Sedating Properties of Antipsychotics

- Sedation is most pronounced in the initial phases of treatment; many patients develop some tolerance.
- May be a beneficial therapeutic effect in acute psychosis and insomnia.
- Antagonistic action at serotonergic, adrenergic, muscarinic, dopaminergic, and histaminergic receptors is associated with sedation.
- Unwanted daytime sedation is associated with long-term adverse effects on cognitive performance and metabolic disturbances.

Risk of Sedation Among Antipsychotics

- **LOW**
  - aripiprazole
  - brexipiprazole
  - cariprazine
  - lumateperone
  - pimavanserin

- **MODERATE**
  - amisulpride
  - iloperidone
  - lurasidone
  - paliperidone
  - risperidone
  - ziprasidone

- **HIGH**
  - asenapine
  - clozapine
  - olanzapine
  - quetiapine

Citrome L et al. CNS Spectr 2018;23(3):228-38;
Management of Sedation

- Consolidate antipsychotic doses into one evening dose
- Reduce total daily antipsychotic dose
- Switch to less sedating antipsychotic agent
- Caffeine in the morning (may interact with medications)
- Rule out comorbid conditions contributing to sedation
- Discontinue other sedating medications

Stroup TS, Gray N. World Psychiatry 2018;17(3):341-56;
Antipsychotic-Induced Sexual Dysfunction
Mechanism and Prevalence

• Sexual dysfunction is common with antipsychotics, especially those that raise prolactin levels.

• The most common side effects of hyperprolactinemia are impaired libido, orgasmic, and arousal functioning.

• Patients do not tend to report sexual problems spontaneously, but 16–60% of patients report sexual dysfunction when asked.

De Boer MK et al. Schizophr Bull 2015;41(3):674-86;
Treatment Strategies

• Select or switch to antipsychotic agent with low propensity to elevate prolactin (e.g., lurasidone, lumateperone, quetiapine, clozapine) or to lower prolactin (e.g., aripiprazole, brexpiprazole, cariprazine)

• Aripiprazole may also be added in low doses to another antipsychotic that is causing hyperprolactinemia and sexual dysfunction

• Psychosocial strategies to treat antipsychotic-induced sexual dysfunction include psychoeducation and relationship counseling

General Considerations for Dose Lowering

More effective

Very dose sensitive  
- Sedation
- Drug-induced Parkinsonism
- Akathisia

Moderate sensitivity
- Sexual dysfunction

Not very dose sensitive
- Metabolic disturbances

Less effective

General Considerations for AP Switching

• Following antipsychotic (AP) switch, side effects are predictable, but efficacy is not.

• Switching for side effects when the person has achieved good efficacy means accepting the risk of unpredictable efficacy.

• Risk needs to be understood and accepted by patient, family, and clinician.

• Many of the short-term side effect benefits go on to provide greater side effect relief over time.

General Considerations for Adding Adjuncts

Add
• Target side effect is not dose-related
• Side effect is dose-related, but current medication cannot be lowered easily

Don’t Add
• Side effect is likely to be transient
• Side effect is dose-related, and dose lowering has not been tried
• Adjunct may impair efficacy of primary treatment
• Switching antipsychotics is feasible and likely to be more effective

Summary

• Antipsychotic selection may be the single most powerful tool in a clinician’s armamentarium for reducing antipsychotic-induced adverse effects

• Dose reduction of many antipsychotics can help ameliorate some side effects, especially DIP, akathisia, and sedation

• Metabolic effects
  • Initiate or switch to an agent with lower risk
  • Metformin or the new combination olanzapine/samidorphan show promise for prevention of weight gain

• Drug-induced movement disorders
  • Anticholinergics for DIP, beta blockers for akathisia

• Sexual dysfunction
  • Switching antipsychotics or possibly adding aripiprazole
A patient with schizophrenia is about to begin treatment with olanzapine. Is it a reasonable strategy to also prescribe metformin at the start of treatment?

1. Yes, metformin can be prescribed to prevent weight gain
2. No, metformin should only be prescribed to mitigate existing weight gain
Joseph is experiencing a good therapeutic effect with an antipsychotic but is constantly shifting positions while standing and moving his feet while sitting. He also rocks back and forth and occasionally jumps out of the chair. When asked to describe his symptoms he has tremendous difficulty and says he “feels anxious and has constant itching.”

What is the best treatment intervention for Joseph?

1. Discontinue his antipsychotic
2. Reduce the dose of his antipsychotic
3. Increase the dose of his antipsychotic
4. Add an anticholinergic
Mary is a 44-year-old patient who is experiencing sedation with her antipsychotic administered twice a day, and that is interfering with her cognitive function. Which of the following management strategies would be appropriate to minimize sedation?

1. Reduce the total daily dose
2. Consolidate her dose into a single nighttime dose
3. Switch to a less sedating antipsychotic
4. 1 and 3
5. All of the above