Treating Antipsychotic-Induced Extrapyramidal Symptoms with Vitamin B6

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Disclosure Statement

I, Cassandra Abeyta, have no actual or potential conflict of interest in relation to this program.

Presentation is educational in nature and abides by non-commercial guidelines.

Learning Objectives

1. Describe the relationship between antipsychotic medications and incidence of extrapyramidal symptoms (EPS).
2. Evaluate the pros and cons of various common treatments of antipsychotic-induced EPS.
3. Analyze data supporting vitamin B6 as a potential treatment for antipsychotic-induced EPS.

Target Audience: Pharmacists
**Problem:** Antipsychotic Medications Can Cause EPS

**Types of EPS**

- **Dystonia:** sustained muscle activity; twisting, repetitive movements, abnormal postures, sometimes painful
- **Akathisia:** internal motor restlessness, distress, discomfort
- **Parkinsonism:** bradykinesia, rigidity, tremor, postural instability
- **Tardive Dyskinesia:** late onset movement disorder characterized by stereotypic movements of mouth, limbs, trunk, or upper face
  - Temporal criteria vary for tardive disorders vary; >30 days to >3 months

**Development of EPS**

- **Pathophysiology**
  - Exact mechanism unknown
  - Possibly related to antagonism of the dopaminergic D<sub>2</sub> receptor
  - Oxidative damage has also been implicated
- **Likelihood of occurrence is related to antipsychotic potency at the D<sub>2</sub> receptor**
  - High-potency typical antipsychotics: haloperidol, fluphenazine
  - High-potency atypical antipsychotics: paliperidone, risperidone
  - Lurasidone, asenapine, and aripiprazole have increased incidence of akathisia in particular compared to other SGAs
**Problem:** Many EPS Treatments Have Adverse Effects

### Common EPS Treatments

- **Propranolol**
- **Benzodiazepines** (diazepam, clonazepam, lorazepam)
- **Anticholinergics** (benztropine, trihexyphenidyl)
- **Diphenhydramine**
- **Clonidine**
- **Amantadine**
- **Trazodone**
- **5-HT2A antagonists** (mianserin, mirtazapine, cyproheptadine)

### Adverse Effects of Common EPS Treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Propranolol</strong></td>
<td>dizziness, bradycardia, hypotension, fatigue, depression</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>sedation, dizziness, depression, delirium</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td>dry mouth, constipation, nausea, blurred vision, urinary retention, tachycardia, confusion, hallucinations, sedation</td>
</tr>
<tr>
<td><strong>Diphenhydramine</strong></td>
<td>dry mouth, dizziness, somnolence, sedation</td>
</tr>
<tr>
<td><strong>Clonidine</strong></td>
<td>erythema, dry mouth, headache, dizziness, sedation, fatigue</td>
</tr>
<tr>
<td><strong>Amantadine</strong></td>
<td>hypotension, nausea, diarrhea, dry mouth, confusion, dizziness, headache, insomnia, hallucinations, depression, irritability, anxiety, fatigue</td>
</tr>
<tr>
<td><strong>Trazodone</strong></td>
<td>constipation, diarrhea, nausea, dry mouth, confusion, dizziness, headache, somnolence, nervousness, priapism</td>
</tr>
<tr>
<td><strong>5-HT2A antagonists</strong></td>
<td>increased appetite, weight gain, dry mouth, dizziness, somnolence</td>
</tr>
</tbody>
</table>

**Problem:** Psychotropic Medication Drug-Drug Interactions

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**Select Antipsychotic Drug-Drug Interactions w/ Common EPS Treatments**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Haloperidol</th>
<th>Fluphenazine</th>
<th>Paliperidone/paliperidone</th>
<th>Laroxetine</th>
<th>Aripiprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>X</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<tr>
<td>Aripiprazole</td>
<td>X</td>
<td>C</td>
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<tr>
<td>Anticholinergics</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>D</td>
<td>C</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>D</td>
<td>C</td>
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<tr>
<td>Clonidine</td>
<td>C</td>
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<tr>
<td>Antidepressives</td>
<td>D</td>
<td>D</td>
<td>D</td>
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<tr>
<td>Trazodone</td>
<td>X</td>
<td>C</td>
<td>X</td>
<td>X</td>
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<tr>
<td>5-HT2 antagonists</td>
<td>C</td>
<td>C</td>
<td>D</td>
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<td>C</td>
</tr>
</tbody>
</table>

Key to reaction types: X = major/avoid, D = consider modification, C = moderate/monitor, n/a = no interaction

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**Patient Case**

AL is a 36 yo female with schizophrenia suffering from **mild persistent akathisia** following switch from chlorpromazine to risperidone (also taking fluphenazine)

- >40 psychiatric hospitalizations
- Benefited from current regimen in the past, though notes h/o akathisia (treated with propranolol 10mg bid)
- Notable comorbidities and medications:
  - CHF, HTN: metoprolol tartrate
  - Pain: oxicodone, pregabalin
  - Respiratory: COPD, asthma, tobacco use, OSA (on CPAP), morbid obesity
  - Schizophrenia/personality disorder/anxiety/insomnia: fluphenazine, risperidone PO, risperidone LAI, hydroxyzine, melatonin, trazodone
- Patient has failed prior trials of anticholinergics
Possible Solution: Vitamin B6 (pyridoxine)

- Involved in >100 enzyme reactions for metabolism
- Proposed benefits: heart disease, cancer, cognitive function, PMS, N/V in pregnancy, immune function, brain development
- Recommended daily intake: 0.1-2mg (varies by age and gender)
- Signs of deficiency: anemia, rash/itching, scaly skin
- Signs of toxicity: nerve damage/uncontrolled movements, patches on skin, sensitivity to sunlight, nausea, heartburn
  - Data suggests doses >2g daily may be toxic

Vitamin B6 (pyridoxine)

Theorized MOA of Vitamin B6 in EPS

- Recall that EPS development may be related to antagonism of the D2 receptor or oxidative damage
- Pyridoxine is converted to pyridoxal-5-PO₄, a cofactor in the conversion of L-dopa dopamine
- Pyridoxine is also an antioxidant and free radical scavenger


Vitamin B6 for Treating Tardive Dyskinesia

- 4-week open-label clinical trial of vitamin B6 100mg/day in 5 patients with tardive EPS (3 dyskinesia, 1 akathisia, 1 parkinsonism)
- Severity of movement assessed using AIMS, BARS, and SAS
  - 4/5 patients demonstrated clinically significant (>30%) improvement in involuntary movement with no side effects
  - Comparing week 4 to baseline there were average improvements of 62.4% on AIMS, 67% on BARS, and 60% on SAS
  - 2 patients showed dramatic return to baseline upon discontinuation of vitamin B6

AIMS: Abnormal Involuntary Movement Scale
BARS: Barnes Akathisia Rating Scale
SAS: Simpson-Angus Scale


Vitamin B6 for Treating Tardive Dyskinesia (Part II)

- Same authors as previous study, almost a decade later
- Double-blind 26-week crossover study of 50 patients with TD
  - Patients were assigned to either vitamin B6 600mg bid or placebo for 12 weeks followed by 2-week washout period then switch
- ESRS used to assess severity of movement
  - 91% of patients treated with vitamin B6 demonstrated statistically significant clinical improvement of >20% (p<0.0001)
  - 1 patient experienced acne, 1 patient developed itch

ESRS: Extrapyramidal Symptom Rating Scale


Vitamin B6 for Treating Akathisia

- Randomized, double-blind study of 20 patients with akathisia assigned to either 5 days of vitamin B6 300mg bid or placebo
- BARS was used to assess akathisia objectively
  - Objective measures did not achieve statistical significance (p=0.079).
    80% of patients in vitamin B6 group had a reduction of ≥2 points on BARS (vs. 30% of placebo patients)
  - Significant improvements in subjective awareness of restlessness (p=0.0004) and distress (p=0.01)

BARS: Barnes Akathisia Rating Scale

Vitamin B6 Drug-Drug Interactions

- Levodopa: ≥ 5mg B6 may reverse effects of levodopa. **Risk D**
  - Using concurrent carbidopa eliminates this interaction
- Barbiturates: ≥ 200mg B6 may increase metabolism. **Risk C**
- Phenytoin/fosphenytoin: B6 may increase metabolism. **Risk C**


Select Antipsychotic Drug-Drug Interactions w/ Common EPS Treatments

<table>
<thead>
<tr>
<th></th>
<th>Haloperidol</th>
<th>Fluphenazine</th>
<th>Risperidone/ paliperidone</th>
<th>Lamotrigine</th>
<th>Aripiprazole</th>
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</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>X</td>
<td>C</td>
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<td>AKIs</td>
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<tr>
<td>Anticholinergics</td>
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<tr>
<td>Diphenhydramine</td>
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<td>C</td>
<td>C/D</td>
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<td>Dibenzepine</td>
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<td>Clonidine</td>
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<tr>
<td>Trazodone</td>
<td>X</td>
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<td>5-HT2 Agonists</td>
<td>C</td>
<td>C</td>
<td>Q</td>
<td>C</td>
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</tbody>
</table>

Vitamin B6

- n/a = no interaction

Select Antipsychotic Drug-Drug Interactions w/ Common EPS Treatments

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Patient Case Conclusion

AL is a 36 yo female with schizophrenia suffering from mild persistent akathisia following switch from chlorpromazine to risperidone (also taking fluphenazine)

- Interested in simplification of medication regimen, and “natural” alternatives whenever available
- Initiated on vitamin B6 100mg daily with recommendations to provider to increase dosage if insufficient response
- Experienced relief of akathisia with vitamin B6 100mg daily
Post-Test Questions

1. True or false: Because vitamin B6 is water-soluble, it is impossible to experience toxicity.
   ✘ False – potential toxicities may manifest in nerves, skin, or GI tract

2. True or false: Vitamin B6 has fewer drug-drug interactions than other common therapies for antipsychotic-induced EPS.
   ✔ True – vitamin B6 has only a handful of potential drug-drug interactions, and for the most part these are with seldom-used medications

3. Studies have demonstrated potential efficacy of vitamin B6 in treating which of the following types of antipsychotic-induced EPS? (Select all that apply).
   ✔ a. Tardive dyskinesia
   ✗ b. Akathisia
   ✔ c. Parkinsonism
   ✗ d. Dystonia

Summary

- Vitamin B6 may have some benefits in reducing the severity of antipsychotic-induced EPS
  - But the evidence is sparse, and limited by small sample sizes, short trials, and minimal follow-up
- Vitamin B6 has minimal adverse effects, and few theoretical drug-drug interactions

Consider trial of vitamin B6 for patients with mild antipsychotic-induced EPS

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Thank you!