Treating Antipsychotic-Induced Extrapyramidal Symptoms with Vitamin B6

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Disclosure Statement

VA Portland Health Care System

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

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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*

Dayalu P, Chou K. *Expert Opinion on Pharmacotherapy.* 2008;9(9):1451-1462.

Development of EPS

- Pathophysiology
  - *Exact mechanism unknown*
  - Possibly related to antagonism of the dopaminergic D_2 receptor
  - Oxidative damage has also been implicated
- Likelihood of occurrence is related to antipsychotic potency at the D_2 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

Dayalu P, Chou K. *Expert Opinion on Pharmacotherapy.* 2008;9(9):1451-1462.
Yoshida K, Bies RR, Suzuki T, et al. *Schizophr Res.* 2014;153(1-3):184-8.
Kane JM, Fleischhacker WW, Hansen L, et al. *J Clin Psychiatry*. 2009;70(5):627-43.

Problem: Many EPS Treatments Have Adverse Effects

Common EPS Treatments

- Propranolol
- Benzodiazepines (diazepam, clonazepam, lorazepam)
- Anticholinergics (benztropine, trihexyphenidyl)
- Diphenhydramine
- Clonidine
- Amantadine
- Trazodone
- 5-HT2$_A$ antagonists (mianserin, mirtazapine, cyproheptadine)

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Kane JM, Fleischhacker WW, Hansen L, et al. *J Clin Psychiatry*. 2009;70(5):627-43.

Adverse Effects of Common EPS Treatments

- Propranolol: *dizziness, bradycardia, hypotension,* ***fatigue***, ***depression***
- Benzodiazepines: ***sedation***, *dizziness,* ***depression***, ***delirium***
- Anticholinergics: *dry mouth, constipation, nausea, blurred vision, urinary retention, tachycardia,* ***confusion***, ***visual hallucinations***, ***sedation***
- Diphenhydramine: *dry mouth, dizziness,* ***somnolence***, ***sedation***
- Clonidine: *erythema, dry mouth, headache, dizziness,* ***sedation***, ***fatigue***
- Amantadine: *hypotension, nausea, diarrhea, dry mouth,* ***confusion***, *dizziness, headache,* ***insomnia***, ***hallucinations***, ***depression***, ***irritability***, ***anxiety***, ***fatigue***
- Trazodone: *constipation, diarrhea, nausea, dry mouth,* ***confusion***, *dizziness, headache,* ***insomnia***, ***somnolence***, ***nervousness***, *priapism*
- 5-HT2$_A$ antagonists: ***increased appetite***, ***weight gain***, *dry mouth, dizziness,* ***somnolence***

DRUGDEX System. Greenwood Village, CO: Truven Health Analytics: Available at www.micromedexsolutions.com. Accessed October 18, 2016.

Problem: Psychotropic Medication Drug-Drug Interactions

Select Antipsychotic Drug-Drug Interactions w/ Common EPS Treatments

	Haloperidol	Fluphenazine	Risperidone/ paliperidone	Lurasidone	Aripiprazole
Propranolol	X	C	C	C	C
BZDs	C	C	C	C	C
Anticholinergics	C	C	C	C	C
Diphenhydramine	C	C	C/D	C	C
Clonidine	C	C	C	C	C
Amantadine	D	D	D	D	D
Trazodone	X	C	X	X	X
5-HT2$_A$ antagonists	C	C	D	C	C

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

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Lexicomp Drug Interactions. Waltham, MA: UpToDate. Available from www.uptodate.com. Accessed October 18, 2016.

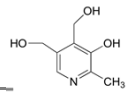
Patient Case

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: oxycodone, 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)

Vitamin B6 (pyridoxine)

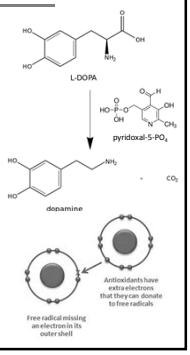


- Involved in >100 enzyme reactions for metabolism
- Proposed benefits: heart disease, cancer, cognitive function, PMS, N/V in pregnancy, immune function, brain development
- Recommended daily intake: 0.1-2mg (varies by age and gender)
- Signs of deficiency: anemia, rash/itching, scaly skin
- Signs of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

Vitamin B6. NIH Office of Dietary Supplements. Available from ods.od.nih.gov/factsheets/VitaminB6-Consumer. Accessed December 9, 2016.
Lerner V, Miodownik C, Kaptsan A, et al. *J Clin Psychiatry*. 2007;68(11):1648-54.

Theorized MOA of Vitamin B6 in EPS

- *Recall that EPS development may be related to antagonism of the D_2 receptor or oxidative damage*
- Pyridoxine is converted to pyridoxal-5-PO_4, a cofactor in the conversion of *L*-dopa dopamine
- Pyridoxine is also an antioxidant and free radical scavenger



Lerner V, Kaptsan A, Miodownik C, et al. *Clin Neuropharmacol*. 1999;22(4):241-3.
Lerner V, Bergman J, Statsenko N, et al. *J Clin Psychiatry*. 2004;65(11):1550-4.
Miodownik C, Lerner V, Statsenko N, et al. *Clin Neuropharmacol*. 2006;29(2):68-72.

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

Lerner V, Kaptsan A, Miodownik C, et al. *Clin Neuropharmacol*. 1999;22(4):241-3.

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

Lerner V, Miodownik C, Kaptsan A, et al. *J Clin Psychiatry*. 2007;68(11):1648-54.

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

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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***

Vitamin B6. NIH Office of Dietary Supplements. Available from ods.od.nih.gov/factsheets/VitaminB6-Consumer. Accessed December 9, 2016.
Pyridoxine. DRUGDEX System. Greenwood Village, CO: Truven Health Analytics: Available from www.micromedexsolutions.com. Accessed October 16, 2016.
Vitamin B6 (pyridoxine) Drug Information. Waltham (MA): UpToDate. Available from www.uptodate.com. Accessed December 9, 2016.

Select Antipsychotic Drug-Drug Interactions w/ Common EPS Treatments

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Diphenhydramine	C	C	C/D	C	C
Clonidine	C	C	C	C	C
Amantadine	D	D	D	D	D
Trazodone	X	C	X	X	X
5-$HT2_A$ antagonists	C	C	D	C	C
Vitamin B6	n/a	n/a	n/a	n/a	n/a

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

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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!