Patient Safety:
Psychosis as the Diagnosis,
Drugs as the Cause

Kristin Waters, PharmD, BCPS, BCPP
University of Connecticut
Assistant Clinical Professor

Disclosure

- Dr. Waters has no actual or potential conflict of interest associated with this presentation, nor does Dr. Waters have any relevant financial interests.
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Learning Objectives

- Differentiate between drug-induced psychosis vs. psychosis associated with a medical or mental illness
- Identify features of drug-induced psychosis
- Articulate which substances are most likely to contribute to psychotic symptoms, including prescription medications, over-the-counter (OTC) medications, and illicit substances
- Apply knowledge of drug-induced psychosis to patient case examples

What is Psychosis?

- Psychosis is a symptom (NOT an illness)
- Disruptions to thoughts and perceptions that make it difficult for person to recognize what is real and what is not
- 3 in 100 people will have a psychotic episode in their lifetime

<table>
<thead>
<tr>
<th>Hallucinations</th>
<th>Delusions</th>
<th>Paranoia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing (auditory), seeing (visual), smelling (olfactory) things that are not there</td>
<td>Strong beliefs not consistent with reality or the person’s culture or religion</td>
<td>Intense anxious or fearful feelings and thoughts often related to persecution, threat, or conspiracy</td>
</tr>
</tbody>
</table>

Causes of Psychosis

- Mental Illness: Schizophrenia, Schizoaffective disorder, Bipolar disorder, Major depressive disorder
- Substance or medication-induced: In drugs, OTC drugs, illicit drugs
- Other: Traumatic event, Hypothyroidism, Hypoglycemia, Delirium, Septis, Sleep deprivation, Nutritional deficiencies, COVID-19

Differential Diagnosis

- Considerations:
  - Age
  - Previous psychiatric and medical diagnoses
  - Temporal relation to potential causes:
    - Illicit drug use, new medication prescriptions, traumatic event, head injury, etc.
- Objective information (not all-inclusive):
  - Electrolyte, vitamin levels
  - Metabolic panel
  - Thyroid function tests
  - Urine toxicology
  - STD testing
Illicit Substance-Induced Psychosis

- May be associated with acute intoxication, chronic use, and/or withdrawal
- Most commonly implicated:
  - Synthetic cannabinoids
  - Stimulants:
    - Methamphetamine >> cocaine
  - Hallucinogens:
    - Ketamine
    - PCP
    - LSD
  - Synthetic cathinones (Bath salts)

Alcohol-Related Psychosis (Alcoholic Hallucinosis)

- Psychotic symptoms present during or shortly after heavy alcohol intake
- Relatively rare:
  - May affect up to 4% of patients with alcohol use disorder
- Risk factors:
  - Becoming dependent on alcohol at younger age
  - Low socioeconomic status
  - Unemployed
  - Living alone

Prescription Medications:

- Stimulants
- Corticosteroids (CS)
- Anticholinergics
- Parkinson’s disease (PD) medications
- Cardiovascular medications
- Opioids (withdrawal)
- Varenicline

Prescription Medications: Stimulants for ADHD

- Pathophysiology: Significant increase in synaptic dopamine (DA) levels
  1. Increased release of DA from neurons
  2. Inhibition of DA transporter (less reuptake)
- More common with amphetamine-based medications than methylphenidate-based
  - Amphetamine causes 4x the DA release of methylphenidate
  - Methylphenidate more potent inhibitor of DA transporter
  - Amphetamine more closely mimics primary psychotic disorders
- Ex: Patients with schizophrenia tend to have high presynaptic DA capacity (index of DA release) but no difference in DA transporter availability

Stimulants

<table>
<thead>
<tr>
<th>Methylphenidate-Based</th>
<th>Amphetamine-Based</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylin® Ritalin® Concerta®</td>
<td>Adderall®, Adderall XR®</td>
<td>Modafinil (Provigil®)</td>
</tr>
<tr>
<td>Lisdexamfetamine (Vyvanse®)</td>
<td>Metadate ER®</td>
<td>Nabilone (Cymbalta®)</td>
</tr>
<tr>
<td>Concerta®</td>
<td>Concerta®</td>
<td>Concerta®</td>
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<td>Concerta®</td>
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</table>
**Retrospective Review: Stimulants for ADHD**

- Large retrospective study of insurance claims databases included patients 13 to 25 years old with ADHD
  - Started taking prescription methylphenidate or amphetamine
- **Primary outcome:** New diagnosis of psychosis for which an antipsychotic medication was prescribed
- **Results:** N=221,846
  - 343 episodes of psychosis
    - Amphetamine: 237 (0.21%)
    - Methylphenidate: 106 (0.10%)
  - Overall: New-onset psychosis occurred in 1 in 660 patients

**Stimulants for Sleep Disorders**

- Modafinil, armodafinil indicated for treatment of excessive somnolence due to:
  - Narcolepsy
  - Obstructive sleep apnea
  - Sleep work sleep disorder
- Mechanism not completely understood → no effect on DA
- Multiple case reports of new-onset psychosis requiring antipsychotics with modafinil
  - Within ~4-5 days following initiation

**Treatment of Stimulant-induced Psychosis**

- Relapse may occur with continued stimulant use
  - Other stressors such as insomnia or heavy use of alcohol may contribute
- If psychotic symptoms persist may consider antipsychotics
- Can consider re-challenge of stimulants for ADHD treatment
  - Methylphenidate preferred

**Patient Case: Audience Question 1**

KR is a 53 year old female with no previous psychiatric history. Her past medical history includes hypothyroidism and hypertension. She presents to the emergency department with her husband and states that the FBI has been watching her through her computer for the past week and that she can hear them giving her secret instructions that her husband cannot hear.

All labs are WNL and her urine toxicology screen is negative.

Which of the following patient factors may indicate that KR’s psychotic symptoms are NOT associated with a mental illness?

A. The severity of her psychosis
B. Her age at onset of psychosis
C. Her comorbid hypothyroidism
D. The duration of her psychosis

**Corticosteroids (CS)**

- Effects are well-known but not well-documented
  - May occur in up to 20% of patients treated with high-dose CS (> 40 mg prednisone/day)
- Most commonly reported with prednisone
- Psychiatric effects may begin within 3-5 days of initiation
  - Most develop within first 6 weeks
Pathophysiology of CIPD

- Not completely understood
- Down-regulation of glucocorticoid receptors
- Altered levels of neurotransmitters
  - Decreased serotonin
  - Increased DA activity in some brain regions

Risk Factors for CIPD?

- 6x more common in women than men
- 2x more common with history of systemic lupus erythematosus
- Prednisone equivalent of > 40 mg/day

Mixed results:
- Age
- Previous psychiatric or medical illness
- Previous tolerance of CS does not correlate with reduced frequency upon reintroduction of the medication

CS Formulations and Dosing

- CIPD may occur at low doses, however risk increases dose:

<table>
<thead>
<tr>
<th>Prednisone Dose*</th>
<th>% of Patients CIPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 mg/day</td>
<td>1.3%</td>
</tr>
<tr>
<td>40-60 mg/day</td>
<td>4.6%</td>
</tr>
<tr>
<td>&gt; 80 mg/day</td>
<td>11.4%</td>
</tr>
</tbody>
</table>

*Prospective analysis of 1,717 hospitalized patients treated with prednisone

- Case reports of psychosis associated with:
  - Pulse-dosing (high-dose, short-term)
  - Alternate day dosing
  - Inhaled CS
  - One-time epidural injection, perioperative steroid administration
  - Sustained psychosis (> 5 months) following cessation has been reported

Anticholinergics "Mad as a Hatter"

Pathophysiology:
- Block presynaptic uptake of DA and increase release from presynaptic terminals
- Impaired cholinergic transmission may induce psychotic symptoms by weakening of the "sensory gating"
  - Brain has decreased ability to inhibit repetitive and irrelevant incoming sensory stimuli
- Most likely to affect elderly patients, especially with dementia
- Psychosis most common in setting of an overdose
- Cases at therapeutic doses have also been reported

Anticholinergics (Rx or OTC)
Anticholinergic-Induced Psychosis: 2 Case Reports

<table>
<thead>
<tr>
<th>Case 1: Oxybutynin</th>
<th>Case 2: Diphenhydramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 y/o male developed auditory and visual hallucinations after 3 days of oxybutynin 15 mg po for nocturnal enuresis</td>
<td>26 y/o male with no medical or psych history</td>
</tr>
<tr>
<td>Brought in by police for agitation and confusion</td>
<td>Brought in by police for agitation and confusion</td>
</tr>
<tr>
<td>Re-trialed and hallucinations returned within one day along with delusions of persecution</td>
<td>2 episodes of acute paranoid delusions that both occurred 1-2 hours after ingestion of Tylenol PM (500 mg acetaminophen/25 mg diphenhydramine)</td>
</tr>
<tr>
<td>1 tab the previous night + 2 tabs the night of presentation</td>
<td>1 tab the previous night + 2 tabs the night of presentation</td>
</tr>
<tr>
<td>No previous history of taking Tylenol PM but had taken acetaminophen before</td>
<td>No previous history of taking Tylenol PM but had taken acetaminophen before</td>
</tr>
</tbody>
</table>

Other Implicated Anticholinergics

- Benztropine
- Scopolamine
- Trihexyphenidyl
- Atropine
  - Including eye drops

Parkinson's Disease Psychosis

- Parkinson's disease is associated with neuropsychiatric symptoms including psychosis (up to 30% of patients)
  - Well-formed visual hallucinations and delusions most common
  - Caused by neurodegenerative processes within the CNS
  - Most common in patients with more severe disease, cognitive impairment, mood disorders
  - Parkinson's disease (PD) medications may worsen psychotic symptoms however likely are not the sole cause

Treatment of Parkinson's Disease Psychosis

- Discontinue any non-essential non-PD meds that may be contributing
  - Anticholinergics, benzodiazepines, muscle relaxants, opioids
- Discontinue/modify PD drugs in the following order:
  1. Anticholinergics
  2. Monoamine oxidase B inhibitors (MAOB-Is)
  3. Amanitadine
  4. Dopamine agonists
  5. COMT inhibitors
  6. Levodopa

Parkinson's Disease Medications

<table>
<thead>
<tr>
<th>MAOB-Is</th>
<th>Dopamine Agonists</th>
<th>COMT† Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selegiline</td>
<td>Reboxetine</td>
<td>Entacapone</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>Pramipexole</td>
<td>Tolcapone</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Rotigotine patch</td>
<td>Opicapone</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Apomorphine</td>
<td>*Catechol-O-methyl transferase</td>
</tr>
</tbody>
</table>

* Catechol-O-methyl transferase
Treatment of Parkinson's Disease Psychosis

- **Antipsychotics:**
  - Quetiapine
  - Clozapine
  - Pimavanserin:
    - Selective serotonin 5-HT2A inverse agonist with no dopaminergic activity
    - Only FDA-approved medication

- **Anticholinesterase inhibitors:**
  - MOA: Atrophy of cholinergic brain structures in PD may contribute to hallucinations
  - Rivastigmine
  - Donepezil


Cardiovascular Medications

<table>
<thead>
<tr>
<th>Beta-Blockers</th>
<th>ACEIs</th>
<th>Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Action at beta-adrenergic receptors can have cognitive-behavioral effects</td>
<td></td>
</tr>
<tr>
<td><strong>Most common symptoms:</strong> Visual hallucinations, often hypnagogic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher risk in elderly patients and those with cognitive deficits, hepatic dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td>Propranolol, metoprolol, timolol, pindolol &gt; atenolol, carvedilol</td>
<td>Quinapril, enalapril, captopril</td>
</tr>
</tbody>
</table>

Beta-Blocker Induced Psychosis: 2 Case Reports

**Case 1: Carvedilol**
- 67 y/o male with PMH of diabetes, hypertension, hyperlipidemia, mild cognitive impairment
- Treated with amlodipine/benazepril + carvedilol added for better BP control
- Within a few days started complaining of seeing people by his bedside especially at night
- Also reported seeing "odd looking animals" and the fire hydrant wave to him and move around
- Went on for 10 months before he reported symptoms
- Quetiapine 25 mg nightly was started but visual hallucinations persisted
- Carvedilol tapered off, visual hallucinations disappeared 2-3 weeks after discontinuation

**Case 2: Metoprolol**
- 21 y/o male with htn and mild fatty liver
- Treated with amlodipine 2.5 mg daily, isosorbide mononitrate 10 mg po TID, and metoprolol 12.5 mg po BID
- Metoprolol increased to 25 mg po BID after 2 days pt because disoriented, paranoid, auditory hallucinations
- Metoprolol discontinued and 3 days later symptoms had disappeared


Opioids and Partial Opioids (Withdrawal)

- **Opioid Withdrawal Psychosis**
  - Some opioids may have antipsychotic properties
    - Opiate receptor agonism may modify DA flow and release → interferes with postsynaptic action of DA
  - Psychotic symptoms rarely reported following abrupt cessation of full and partial opioid receptor agonists following chronic use:
    - Oxycodone
    - Morphine
    - Tramadol
    - Methadone
    - Buprenorphine
    - Heroin

Varenicline (Chantix®): Boxed Warning Controversy

- Black box warning was added in 2009 but removed in 2016
- Removal of warning based on EAGLES study:
  - Study mandated by FDA to assess neuropsychiatric safety of bupropion, varenicline, and nicotine patches in patients with and without psychiatric disorders
  - Conducted by pharmaceutical company
  - ISMP recommended against removal of boxed warning due to high number of reported psychiatric adverse effects
  - Concerns about study design

Varenicline-Induced Psychosis

- Suicidal thoughts and behaviors more common than psychosis
- May induce psychosis by stimulating the mesolimbic dopamine system → increased release of dopamine
- Multiple case reports of exacerbating psychosis in patients with previous psychiatric history
- Case reports of patients with no psychiatric history requiring antipsychotic treatment also reported

Patient Case: Audience Question 2

Which of ILI’s medications is most likely to be contributing to her current presentation?
A. Acetaminophen
B. Amlodipine
C. Lisinopril
D. Metoprolol XL

Current medications:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen 165 mg po q6h prn</td>
<td>Headache, body aches</td>
<td>3 months</td>
</tr>
<tr>
<td>Amlodipine 10 mg po daily</td>
<td>Hypertension</td>
<td>1 month</td>
</tr>
<tr>
<td>Levithyroxine 17.5 mcg po daily</td>
<td>Hypothyroidism</td>
<td>2 years</td>
</tr>
<tr>
<td>Lisinopril 5 mg po daily</td>
<td>Hypertension</td>
<td>1 year</td>
</tr>
<tr>
<td>Metoprolol XL 150 mg po daily</td>
<td>Hypertension</td>
<td>1 month</td>
</tr>
</tbody>
</table>

Over-the-Counter Medication Induced Psychosis

Dextromethorphan-Induced Psychosis

- Non-narcotic antitussive in many combination cold products
- Blocks NMDA receptors similarly to ketamine, PCP
  - "Poor Man's PCP"
- Binds to serotonin receptors, sigma opioid receptors, and blocks reuptake of adrenergic neurotransmitters
- Psychosis usually attributed to excessive use
  - FDA-approved daily dose: 120 mg
Dextromethorphan Neuropsychiatric Symptoms

<table>
<thead>
<tr>
<th>Dextromethorphan Dose</th>
<th>Psychiatric Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5-2.5 mg/kg</td>
<td>MDMA-like perceptual alterations</td>
</tr>
<tr>
<td>2.5-7.5 mg/kg</td>
<td>Impairment of motor, cognitive, perceptual functioning</td>
</tr>
<tr>
<td>7.5-15 mg/kg</td>
<td>Intense hallucinations; dissociative symptoms; agitation</td>
</tr>
</tbody>
</table>
| >15 mg/kg             | Complete psychophysical dissociation with violent behavior, elevated temperatures, possible death from cardiac or respiratory arrest | Comparable to high-dose ketamine

Weight Loss Supplement-Induced Psychosis

- FDA banned products that contained ephedrine in 2004 due to cardiovascular and neurologic reactions
- Newer generally products touted as safe however many case reports of psychosis and mania

Implicated substances:
- Synephrine is one of the most common active ingredients in current weight loss products
  - Structurally similar to ephedrine and other amphetamines (may have (+) amphetamine on Utox)
  - Contained in bitter orange
- Sibutramine
  - Structurally similar to amphetamine
- Caffeine
  - Adenosine antagonist → affects dopamine neurotransmission

Weight-Loss Supplement-Induced Psychosis: Case Report

HPI: 52 year old Caucasian woman who worked in the OR as a nurse with PMH of anxiety, depression, hypothyroidism. Presented to the ED when she “saw occult messages on her identification badge from Satan that read ‘You will die.’” Headed body ‘ticking’ and saw ‘laser-writing from aliens on the hospital floor, door, arm.”

Physical exam: Tachycardia, htn, unsteady gait
- Urine drug screen positive for amphetamines

Psychiatric exam: Disoriented, anxious, depressed, paranoid, guarded, suspicious, labile, disorganized

Medications prior to admission:
- Buspirone
- Levothyroxine
- Jillian Michaels’ Fat Burner and Calorie Control pills

Admitted to inpatient psychiatric unit where she remained psychotic with auditory and visual hallucinations for ~2 days
- Symptoms improved on hospital day 4 when urine drug screen no longer positive for amphetamines
- Admitted to increasing doses of weight loss pills for more energy 4 days prior to admission

Weight-Loss Supplement-Induced Psychosis: Case Report

Jillian Michaels’ Fat Burner ingredients (at the time of case):
- Citrus aurantium (aka Bitter orange, Sour orange, Seville orange)
- Caffeine 400 mg
- Ingredients appear to have been modified following several lawsuits

Caffeine-Related Psychosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Name</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Clinical Presentations</th>
<th>50 mg</th>
<th>100 mg</th>
<th>150 mg</th>
<th>200 mg</th>
<th>250 mg</th>
<th>300 mg</th>
<th>350 mg</th>
<th>400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADHD</td>
<td>## Hallucinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearn JK, et al.</td>
<td>2020</td>
<td>Jillian Michaels’ Fat Burner ingredients</td>
<td>14</td>
<td>Male</td>
<td>## Tactile hallucinations</td>
<td>Year</td>
<td>Year</td>
<td>Year</td>
<td>Year</td>
<td>Year</td>
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<td>Year</td>
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</tbody>
</table>

Audience Question 3

A 14 year old male patient is brought to the ED by his parents who are very concerned. He has been saying that he does not “feel real” and has been experiencing auditory, visual, and tactile hallucinations. He was recently started on clonidine and Adderall XR for ADHD. His parents insist that he does not use illicit drugs or alcohol, however his Utox is positive for PCP and his brother states that he has found boxes of “some cough medicine” in the patient’s room.

Which of the following substances is the least likely to be contributing to the patient’s current symptoms?
- A. Adderall XR
- B. Clonidine
- C. Dextromethorphan
- D. PCP
Summary

- It can be difficult to differentiate between drug-induced psychosis vs. psychosis associated with other medical or psychiatric conditions.
- Commonly used prescription and over-the-counter medications have been associated with psychosis in patients without psychiatric history.
- Patients with medication-induced psychosis may require inpatient psychiatric admission and pharmacologic treatment.

Questions?

Psychosis as the Diagnosis, Drugs as the Cause

Kristin Waters, PharmD, BCPS, BCPP
University of Connecticut
Assistant Clinical Professor