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

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Disclosure

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- Dr. Waters has no actual or potential conflict of interest associated with this
 presentation, nor does Dr. Waters have any relevant financial interests.
- This activity may contain discussion of unlabeled/unapproved use of drugs. The
 content and views presented in this educational program are those of the faculty
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 School of Pharmacy. Please refer to the official prescribing information for each
 product for discussion of approved indications, contraindications, and warnings.

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Learning Objectives

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- 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

Hallucinations	Delusions	Paranoia
Hearing (auditory), seeing (visual), feeling (tactile), or smelling (olfactory) things that are not there	Strong beliefs not consistent with reality or the person's culture or religion	Intense anxious or fearful feelings and thoughts often related to persecution , threat , or conspiracy

Erain injury:
Traumatic brain injury
Stroke
Brain tumor
Parkinson's disease
Alzheimer's disease
Alzheimer's disease
HIV

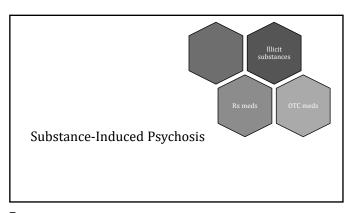
Mental Illness:
Schizophrenia
Schizoaffective disorder
Bipolar disorder
Major depressive disorder
Major d

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

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riswold KM, et al. Am Fam Physician. 2015



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)

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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



Stankowicz HA, et al. Stat Pearls (Internet). 2020; Massood B, et alo. Alcohol Alcohol. 2018

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Prescription Medications

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

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Stimulants | Methylin® | Adderall®, Adderall XR® | Metadate ER® | Concerta® | Daytrana® (patch) | Daytrana® (patch) | Concerta® | Concert

Simulant

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

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Retrospective Review: Stimulants for ADHD

- \blacksquare 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

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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 \rightarrow no effect on DA
- Multiple case reports of new-onset psychosis requiring antipsychotics with modafinil
 - · Within ~4-5 days following initiation

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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 a 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

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Corticosteroids (CS)

Neuropsychiatric Disorders (CIPD)

- Effects are well-known but not welldocumented
 - 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

CS Formulations and Dosing

CPID may occur at low doses, however risk increases dose:

Prednisone Dose*	% of patients CIPD	
≤ 40 mg/day	1.3%	
41-80 mg/day	4.6%	
≥ 80 mg/day	18.4%	

*Prospective analysis of 717 hospitalized patients treated with prednisone

- Case reports of **psychosis** associated with:
 - · Pulse-dosing (high-dose, short-term)
 - Alternate day dosing
 - Inhaled CS

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- · One-time epidural injections, perioperative steroid administration
- Sustained psychosis (> 5 months) following cessation has been reported

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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

Case 1: Sustained Psychosis: 2 Case Reports

Case 1: Sustained Psychosis after CS
Discontinuation

• 58 y/o male with no previous psych history
except 1 episode of general anxiety disorder
• PMH of idiopathic thrombocytopenic purpura
treated with 3 courses of high-dose prednisone
over 9 years

• Brought to ED during 4th lifetime steroid
treatment for unusual behavior (delusions,
pressured speech, disorganization)
• 40 mg dexamethasone x 4 day bursts (267 mg
prednisone equivalent) every 3 weeks
• Required inpatient psych admission following
steroid cessation
• Treated with high-dose quetiapine and
electroconvulsive therapy
• Gradual improvement over 5 months

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Anticholinergics (Rx or OTC)

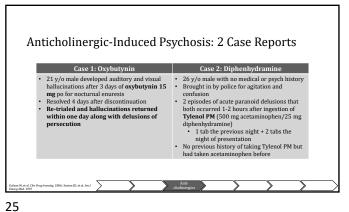
Anticholinergics: "Mad as a Hatter"



- Pathophysiology:
- $\, \blacksquare \,$ 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

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Other Implicated Anticholinergics Benztropine Scopolamine Trihexyphenidyl Atropine · Including eye drops

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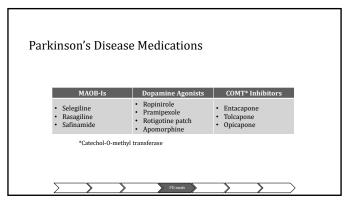
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Parkinson's Disease (PD) Medications

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 · Parkinson's disease (PD) medications may worsen psychotic symptoms however likely are not the sole cause

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Treatment of Parkinson's Disease Psychosis \blacksquare Discontinue any $non\text{-}essential\ non\text{-}PD\ meds\ that\ may\ be\ contributing\ }$ · Anticholinergics, benzodiazepines, muscle relaxants, opioids Discontinue/modify PD drugs in the following order: 1. Anticholinergics 2. Monoamine oxidase B inhibitors (MAOB-Is) 3. Amantadine 4. Dopamine agonists 5. COMT inhibitors 6. Levodopa t Neurol 2020; Chang A, et al. Drugs. 2016; harmocother. 2017; Friedman JH. Expert



Treatment of Parkinson's Disease Psychosis

• Antipsychotics:

• Quetiapine

• Clozapine

• Pimavanserin:

• Selective serotonin 5-HTZA inverse agonist with no dopaminergic activity

• Only FDA-approved medication

• Anticholinesterase inhibitors:

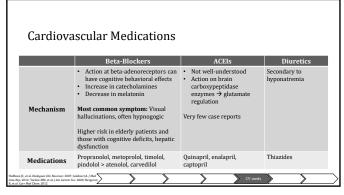
• MOA: Atrophy of cholinergic brain structures in PD may contribute to hallucinations

• Rivastigmine

• Donepezil

Cardiovascular Medications

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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

**Metoprolol discontinued and 3 days later symptoms had disappeared

**Metoprolol discontinued and 3 days later symptoms had disappeared

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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

**Canada Deputab NM, et al. for the Mathematical 2015.

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Varenicline (Chantix®)

Varenicline (Chantix®): Boxed Warning Controversy Black box warning was added in 2009 but removed in 2016 WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS See full prescribing information for complete

- 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

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Varenicline-Induced Psychosis

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- Suicidal thoughts and behaviors more common than psychosis
- ullet May induce psychosis by stimulating the mesolimbic dopamine system etaincreased 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

Current medications:

Medication	Indication	Duration of Treatment	
Acetaminophen 650 mg po q6h prn	Headache, body aches	3 months	
Amlodipine 10 mg po daily	Hypertension	1 month	
Levothyroxine 37.5 mcg po daily	Hypothyroidism	2 years	
Lisinopril 10 mg po daily	Hypertension	1 year	
Metoprolol XL 50 mg po daily	Hypertension	1 month	

Which of KR's medications is most likely to be contributing to her current presentation?

- A. Acetaminophen
- Amlodipine
- Lisinopril Metoprolol XL

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Over-the-Counter Medication Induced **Psychosis**

Dextromethorphan-Induced Psychosis

- Non-narcotic antitussive in many combination cold products
- Blocks NMDA receptors similarly to ketamine, PCP
- $\,\blacksquare\,$ Binds to seroton in 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

Dextromethorphan Dose	Psychiatric Effect
1.5-2.5 mg/kg	MDMA-like perceptual alterations
2.5-7.5 mg/kg	Impairment of motor, cognitive, perceptual functioning Comparable to alcohol + cannabis
7.5-15 mg/kg	Intense hallucinations, dissociative symptoms, agitation Comparable to low-dose ketamine
>15 mg/kg	Complete psychophysical dissociation with violent behaviors, 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 most common active ingredient in current weight loss products
 - Structurally very similar to ephendrine and other amphetamines (may have (+) amphetamine on Utox)
 - · Contained in Bitter orange
 - · Sibutramine
 - Structurally similar to amphetamine
 - Caffeine
 - Adenosine antagonist → affects dopamine transmission

mero C, et al. Psychosomatics. 2011; Hedger DW, et al. CNS Spectr. 2009; Nafk S, et al. Prog Neuropsychopharmacol Biol Psychiotry. 2010

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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."" Heard 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

Psychiatric exam: Disoriented, anxious, depressed, paranoid, guarded, suspicious, lat **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
- $\bullet \quad \text{Admitted to increasing doses of weight loss pills for more energy 4 days prior to admission} \\$

Retamero C, et al. Psychosomotics 2011

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

Returnero C. et al. Psychosomotics

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Caffeine-Related Psychosis

Author	Sex	Age, y	Clinical Presentation	Caffeinated Beverage	Estimated Daily Caffeine Intake, mg	Preexisting Psychiatric Diagnosis
Quadri et af ^o	Female	17	Mania	Energy drinks	600 × 1 week	None
Krankl and Gitlin ¹⁰	Female	69	Mania	Coffee/cola	840	None
Cruzado et al ¹¹	Female	31	Mania	Energy drinks	1,000-1,810	None
Ogawa and Ueki12	Male	43	Mania	Coffee	660-1,320	None
Kunitake et al ¹³	Male	54	Mania	Coffee	1,300-2,000	Bipolar spectrum
Machado-Vieira et al ¹⁴	Male	36	Mania	Energy drinks	300-400	Bipolar spectrum
Tondo and Rudas ¹⁵	Female	50	Mania	Espresso	900-1,500	Bipolar spectrum
Hernandez-Huerta et al ¹⁶	Male	18	Psychosis	Energy drinks	480	None
Govil ¹⁷	Male	35	Psychosis	Source unclear	1,600	None
Görgülü et al ^{e s}	Male	21	Psychosis	Energy drinks	Unknown	None
Hedges et al ¹⁹	Male	47	Psychosis	Coffee	"High intake"	None
Shaul et al ^{co}	Female	18	Psychosis	Diuretic/caffeine pill	4,800	Anorexia nervosa no history of psychosis
Peng et aF1	Male	49	Psychosis	Coffee	600	Schizophrenia
Menkes ²²	Male	27	Psychosis	Coffee, energy drinks	600-1,305	Schizophrenia
Cerimele et al ²³	Male	43	Psychosis	Energy drinks	1,280-1,600	Schizophrenia
Tibrewal and Dhillon ²⁴	Male	52	Psychosis	Coffee	960-5,000	Schizophrenia
Lucas et al ²⁵	12 male, 1 female	18-36	Psychosis (exacerbation)	Intravenous; double-blind placebo, controlled	10 mg/kg	Schizophrenia

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 \boldsymbol{least} likely to be contributing to the patient's current symptoms?

- A. Adderall XR
- B. Clonidine
- C. Dextromethorphan
- D. PCP

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Summary

- It can be difficult to differentiate between drug-induced psychosis vs. psychosis associated 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



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Psychosis as the Diagnosis, Drugs as the Cause

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