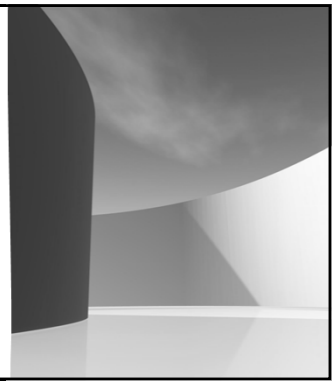
Mental Illness and Substance Use Disorders: Background



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University of Connecticut
Assistant Clinical Professor

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Disclosures

Dr. Waters is a consultant with Janssen Pharmaceuticals. She will discuss all drugs without bias. All financial interests with ineligible companies (as noted) have been mitigated.

2

Learning Objectives

- Describe the prevalence, pathophysiology, clinical features, and diagnostic criteria of:
  - Schizophrenia
  - Bipolar disorder
  - Substance use disorders
- Differentiate between signs and symptoms of these disorders

3

Schizophrenia

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Schizophrenia Background

- Psychosis can be a component of many disorders (not just schizophrenia)
- High hospital readmission rate associated with schizophrenia spectrum disorders
- Mortality rate 2-3x higher than general population
- High morbidity:
  - Comorbid conditions: CV disease, dyslipidemia, obesity, hypertension, diabetes, substance use disorders, depression
  - Reduced quality of life
  - Treatment adverse effects
  - Homelessness
  - Stigma, social isolation
  - Family/caregiver burden

Millier A, et al. Journal of Psychiatric Research, 2014;54:85-93

5

Clinical Features of Schizophrenia

Positive Symptoms	Negative Symptoms	Cognitive Symptoms
Hallucinations	**Blunted affect:** Reduction in intensity of affect	Difficulty maintaining attention
Delusions	**Alogia:** Inability to speak	Deficits in working memory and long-term memory
Disorganized speech	**Avolition:** Lack of desire or motivation to pursue reasonable goals	Deficits in executive function
Grossly disorganized or catatonic behavior	**Anhedonia:** Inability to experience pleasurable emotions	
	Amotivation: Inability or unwillingness to participate in normal social situations	

Depression is NOT a negative symptom of schizophrenia.
Depression = a mood symptom

Jauhar S, et al. *Lancet*. 2022; Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association, 201

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Diagnosis of Schizophrenia: DSM-5

A. ≥ 2 symptoms for a significant percent of time during a 1 month period (less if treated). At least one symptom must be **delusions, hallucinations, or disorganized speech.**
   1. **Delusions:** Fixed, false beliefs generally outside of cultural or societal norms
   2. **Hallucinations:** A sensory perception with no basis in external stimulation
   3. **Disorganized speech**: Frequent derailment or loose associations, tangentiality, incoherence, or repetition of words
   4. **Grossly disorganized/catatonic behavior:** May range from silliness to catatonia to purposeless movement to agitation
   5. **Negative symptoms:**
      a. Blunted affect
      b. Alogia
      c. Avolition
      d. Anhedonia
      e. Amotivation

Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association, 2013

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Diagnosis of Schizophrenia: DSM-5 (Cont.)

B. One or more **areas of function** (work, interpersonal relations, self-care) must be **markedly below the previous level** for significant portion of time as evidence by **social isolation**, difficulty maintaining **employment** or employment below educational level, **impaired self-care**, impaired or diminished family or social **relationships**

C. Duration of ≥ 6 months including ≥ 1 month of symptoms as noted above

D. Does not better meet criteria for **schizoaffective or mood disorders**

E. Origin of symptoms **not solely due to a substance** and/or general medical condition

F. Prominent hallucinations or delusions must be present if history of autism spectrum disorder

Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association, 2013

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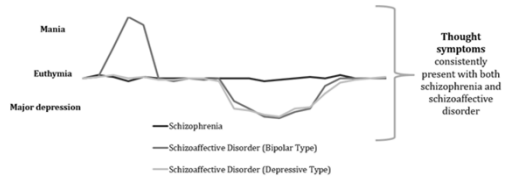
Schizophrenia vs. Schizoaffective Disorder

- **Schizoaffective disorder:** Combination thought disorder and mood disorder
  - Must have delusions or hallucinations for ≥ 2 weeks **in absence of mood symptoms**
  - Uninterrupted period of illness containing either a **major depressive or manic episode concurrent with symptoms meeting criteria for schizophrenia**



Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association, 2013

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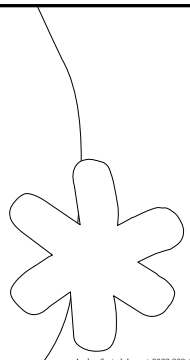
Etiology and Risk Factors of Schizophrenia

- Precise cause of schizophrenia is unknown
- Multiple causes hypothesized:
  - Perinatal insults (hypoxia, fetal distress, influenza, famine)
  - Infectious and autoimmune causes
  - Excessive pruning of synapses because of greater complement activity (i.e. C4)
  - Use of cannabis, methamphetamine
    - Stronger association with cannabis → especially earlier age of cannabis use, increased amount/frequency of use, THC potency
- Genetics: ~10% risk in first-degree relatives



Jauhar S, et al. *Lancet.* 2022;399:473-86
Stilo SA, et al. *Curr Psychiatry Rep.* 2019; 21:100

10

Pathophysiology of Schizophrenia

- **Anatomical structure changes:**
  - Ex: Reduced total brain volume, gray matter, hippocampus
- **Neurotransmitter changes:**
  - Dopamine (DA) hyperactivity in limbic system → positive symptoms
  - **DA** hypofunction in prefrontal cortex → negative symptoms
  - Increased **5-HT** transmission and 5-HT transporter density in subcortical regions
  - **Glutamate, GABA** dysfunction
  - **Acetylcholine** (ACh)**:** Increased expression of specific nicotinic ACh receptors

Yang AC, et al. *Int J Mol Sci.* 2017;18:1689

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Schizophrenia Prevalence & Clinical Course

- **Lifetime prevalence:** 0.3-0.7%
- **Clinical course:**
  - **Onset:** Abrupt or more subtle
  - **Prodromal phase:** Negative and cognitive symptoms likely to occur
  - **Age of onset:** Late teens to mid-30s
    - Females have later onset vs. males
- **Chronic illness** → gradual loss of gray matter
- **Recovery and remission:**
  - Fluctuations between moderate and severe disability
  - Periods of recovery may last several years
  - Adherence to guidelines can improve overall patient functioning and outcomes

Jauhar S, et al. *Lancet.* 2022;399:473-86. Stilo SA, et al. *Curr Psychiatry Rep.* 2019; 21:100 . McGrath J, et al. *Epidemiol Rev.* 2008;30:67-76

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Audience Question 1

A patient with schizophrenia is being managed with an antipsychotic medication. She reports that she is still having trouble motivating herself to go to work every day and have called out several times this month. The patient has also skipped several family events including her cousin's wedding. Which negative symptoms of schizophrenia is this patient experiencing?

A. Avolition & anhedonia
B. Amotivation & avolition
C. Anhedonia & disorganized thinking
D. Blunted affect & depression

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Bipolar Disorder

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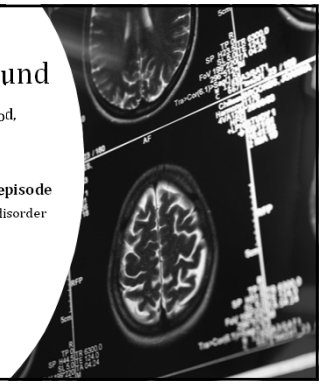
Bipolar Disorder Background

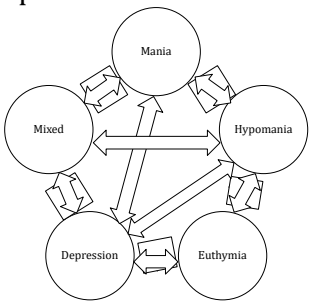
- Mood disorder characterized by changes in mood, sleep, energy, and cognition
- Diagnosis may be delayed **6-8 years**
- **Patients often present first with depressive episode**
  - 40% initially diagnosed with major depressive disorder (MDD)
  - 70% initially misdiagnosed overall
- **Higher morbidity and mortality** than MDD



Lublóy Á, et al. *BMC Psychiatry.* 2020;20:75; Shen H, et al. *Shanghai Arch Psychiatry.* 2018;30:93-101

16

Phases of Bipolar Disorder



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DSM-5 Criteria: Manic Episode

A. ≥ 1 week (or any period if hospitalized) of abnormal mood that is **elevated, expansive, or irritable**. Significant increase in goal-directed activity or energy.

B. ≥ 3 of the following (or 4 if mood is only characterized as irritable):
1. Inflated self-esteem or **grandiosity**
2. **Decreased need for sleep** or feeling rested after only a few hours of sleep
3. Increased quantity of speech or **speech that is pressured**
4. **Flight of ideas** or subjective racing thoughts
5. Easily distracted, may be in social situations, work, or school
6. Increased **goal-directed activity or psychomotor agitation**
7. Engaging in activities that can result in detrimental outcomes (spending, sex, drugs)

Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association, 2013

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DSM-5 Criteria: Manic Episode (Cont.)

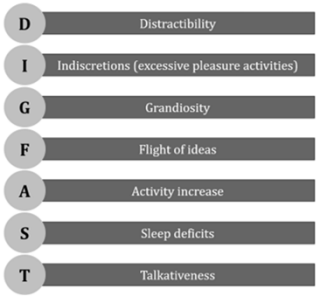
C. **Significant social/occupational functioning, hospitalization** required**,** or **psychotic features** present

D. Not result of a substance or another medical condition

Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association, 2013

19

Clinical Features: Mania



- Typically **begins abruptly** with symptoms escalating over several days
- "DIGFAST"

Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association, 2013; Dailey MW, et al. *StatPearls [Internet].* 2022

20

DSM-5 Criteria: Hypomanic Episode

A. A period of abnormally and continually **elevated, expansive, or irritable mood** with increased activity or energy for **≥ 4 consecutive days**

B. ≥ 3 from criterion B of manic episode (or 4 if mood is only characterized as irritable)

C. Change in functioning from baseline that is evident to others

D. Impairment in social or occupational functioning that is **not severe**. **Hospitalization is not required and there are no psychotic symptoms.***

E. Not attributable to substance, another treatment, etc.

*Delusions or hallucinations present at any time during an episode

Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association, 2013

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Mania vs. Hypomania

Mania	Hypomania
≥ 1 week (unless hospitalized)	≥ 4 consecutive days
May have psychotic features (hallucinations, paranoia, delusions)	No psychotic features
May require hospitalization	Does not require hospitalization
	Functional impairment is less severe

Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association, 2013

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Type I & Type II Bipolar Disorder

Type I	Type II
• At least one **manic** episode • **May** have had previous hypomanic or depressive episodes	• At least one **hypomanic** and one **depressive** episode • No history of manic episode

- Key difference = **severity of mania/hypomania**
- **Depressive episodes may be equally severe** in type I or type II

Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association, 2013

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DSM-5 Criteria: Depressive Episode

- Same criteria as for an episode of major depressive disorder

A. ≥ 5 of the following during 2-week period representing a **change from previous functioning;** at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure

1. **Depressed mood** most of the time on most days
2. Decreased **interest** or **pleasure** in daily activities
3. Significant change in **weight or appetite** (≥5% change)
4. Significant changes in **sleep** nearly every day
5. Psychomotor agitation or retardation, observable by others
6. **Fatigue**/decreased energy
7. Feelings of worthlessness or **guilt**
8. Decreased **concentration** or difficulty making decisions
9. Recurrent thoughts of **death, suicidal ideation** with or without specific plan, or suicide attempt

Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association, 2013

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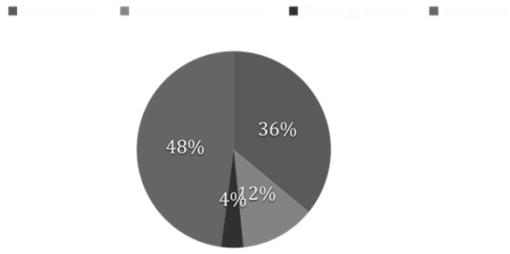
Proportion of Mood Episodes



Kupka RW, et al. Bipolar Disord. 2007;9:531-5

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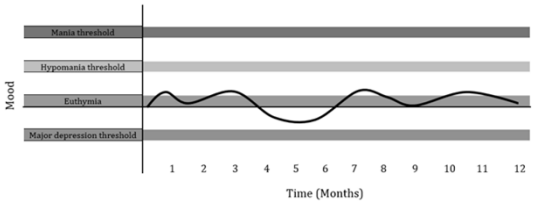
Euthymia



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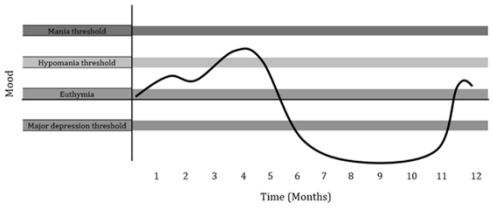
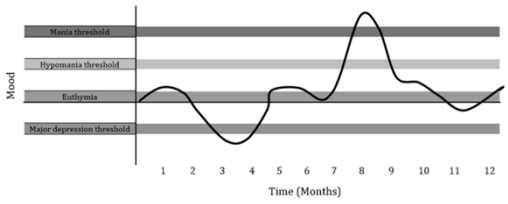
Hypomania + Depression



27

Depression + Mania



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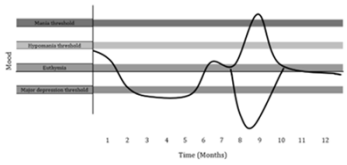
Mixed Episode



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Morbidity & Mortality of Bipolar Disorder

- Misdiagnosis may lead to incorrect treatment, more mood episodes, rapid cycling, decreased quality of life, suicide
- Life expectancy decreased by 9-17 years compared to general population
- **Highest suicide rate of any psychiatric disorder**
  - Up to 30x higher than general population
  - 50% attempt suicide (8-20% complete)
  - Suicide risk factors:
    - Previous psychiatric admission
    - Comorbid substance use, personality disorder, or eating disorder

Dome P, et al. *Medicina (Kaunas).* 2019;55:403

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Bipolar Disorder: Common Comorbidities

Comorbidity	Incidence	Comments
Anxiety	56%	• Worse prognosis: Higher risk of relapse, increased time to recovery, treatment nonresponse, suicidality
Substance Use Disorder	61%	• Alcohol most commonly abused substance • Alcohol use disorder risk higher for women than men
ADHD	20%	• Children with ADHD have 10x increased risk of being diagnosed with bipolar disorder • Worse prognosis: More depressive episodes, significant comorbid anxiety and SUD • Some diagnostic criteria overlap → misdiagnosis
Medical Comorbidities	Variable	Diabetes, dyslipidemia, obesity, cardiovascular disease

ADHD: Attention deficit hyperactivity disorder

Cerullo MA, et al. *Subst Abuse Treat Prev Policy.* 2007;2:29 Grunze H, et al. *Front Psychiatry.* 2021;12:660432
Spoorthy MS, et al. *World J Psychiatry.* 2019;9:7-29 Salvi V, et al. *Medicina (Kaunas).* 2021;57:466 Miller TH. *Prim Care.* 2016;43:269-84

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Etiology and Risk Factors of Bipolar Disorder

- Multifactorial
- **Genetics:**
  - **Heritability:** 70-90%
  - Genetic differences in type I vs. type II → differences in clinical course, treatment response
  - **Epigenetics** may play role → heritable alterations without change in DNA sequencing due to environmental factors (i.e. stressful life events, medication)
- **Kindling hypothesis:** First episode occurs after exposure to stressor --> subsequent episodes may not have identifiable preceding stressor
- Childhood risk factors: Trauma, abuse, anxiety

Carvalho AF, et al. *N Engl J Med.* 2020;2:29 Kerner B. *Appl Clin Genet.* 2014;7:33-42
Marwaha S, et al. *Psychol Med.* 2020;50:2346-54

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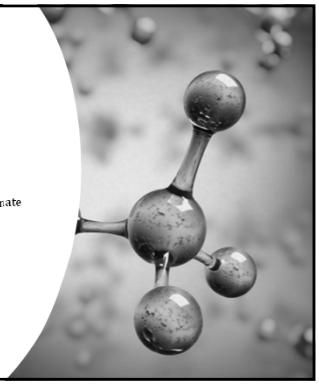
Pathophysiology of Bipolar Disorder

- Complex with many suggested theories
  - Anatomical structure changes
  - Neurochemical changes
    - Possible GABA deficiencies or excessive glutamate
  - Second messenger systems affected:
    - Brain-derived neurotrophic factors (BDNF)
    - B-cell lymphoma 2 (Bcl-2)
    - Glycogen synthase kinase-3 (GSK-3)
    - Protein kinase C
    - Calcium



Harrison PJ, et al. *Trends Neurosci.* 2018;41:18-30

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Bipolar Disorder Prevalence & Clinical Course

- Age of onset 15-24 years but diagnosis may take additional 5-10 years
- **Prevalence:** 2.6% of adults in U.S.
  - Bipolar I: 0.6-1% (female=male)
  - Bipolar II: 0.4-1.1% (female>male)
- Chronic, lifelong illness with frequent recurrences
  - ~80% of patients have > 4 mood episodes per lifetime
- Subsyndromal symptoms may occur even with treatment
- Episodes may become **more frequent and difficult to treat** with each episode

Rowland TA, et al. *Ther Adv Psychopharmacol.* 2018;8:251-69 Poon SH, et al. *Curr Neuropharmacol.* 2015;13:592-604
Peters AT, et al. *J Nerv Ment Dis.* 2016;204:87-94

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Audience Question 2

A patient with bipolar disorder presents to his outpatient provider. He is speaking rapidly and tells you that yesterday he impulsively purchased brand new cars for himself and his significant other. He also tells you that the president of the U.S. has given him orders to take over the presidency in 3 months' time. He is awaiting further instructions from the president but in the meantime intends to write his memoir.

Which type of mood episode is this patient experiencing and which type of bipolar disorder fits their current symptoms?

A. Mania, bipolar disorder type I
B. Hypomania, bipolar disorder type II
C. Hypomania, bipolar disorder type I
D. Mania, bipolar disorder type II

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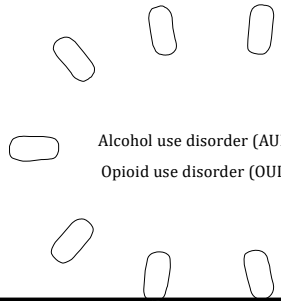
Substance Use Disorders (SUDs)



Alcohol use disorder (AUD)

Opioid use disorder (OUD)

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SUDs: DSM-5 Diagnosis

A cluster of **cognitive, behavioral, and physiological symptoms** indicating that the person continues to use the substance **despite significant substance-related problems** over **≥ 12 months**
≥ 2 of the following symptoms:

1. Takes substance in **larger amounts** or over a **longer period** than was originally intended
2. Expresses a persistent **desire to cut down** or regulate substance use and may report multiple unsuccessful efforts to decrease or stop use
3. Spends a great deal of **time** obtaining the substance, using the substance, or recovering from its effects
4. **Craving**, or strong desire to use the substance
5. Recurrent substance use may impact **ability to perform** work, school, or home
6. Continues substance use despite having persistent or recurrent social or interpersonal **problems**
7. Important social, occupational, or recreational activities may be **given up** or reduced because of substance use
8. May cause situations that are **physically hazardous**
9. Continued substance use despite knowledge of having a persistent or recurrent physical or psychological problem
10. Tolerance
11. Withdrawal

Diagnostic and Statistical Manual of Mental Disorders: DSM-5, 5th ed. American Psychiatric Association. 2013.

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SUD Risk Factors

- **Multifactorial: biological, psychologic, social factors:**
  - Dysregulation of neurotransmission (dopamine, norepinephrine) or HPA* axis
  - Prefrontal cortex dysfunction
  - Peer group attitudes/expectations
- **Additional risk factors:**
  - Genetic predisposition
  - Co-occurring psychiatric disorders
  - Males, younger adults, single, unemployed
  - Deceased parents
  - Personality traits (i.e. impulsivity)
  - Early exposure to substance
  - Stressful external environment, trauma

*hypothalamic-pituitary-adrenal

Nelson LF, et al. *Med Clin North Am*. 2022;106:153-68

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Alcohol Use Disorder (AUD) Background

- Affects **29.5 million people** in the U.S. (age ≥ 12 years)
  - Males: 16.6 million (12.1%)
  - Females: 13.0 million (9.1%)
- Highest prevalence among:
  - American Indian
  - Alaskan Native
  - Native Hawaiian or other Pacific Islander
  - ≥ 2 races

National Institute on Alcohol Abuse and Alcoholism, Prevalence of past-year alcohol use disorder (AUD), 2021; Available from: https://www.niaaa.nih.gov/alcohols-effects-health/alcohol-topics/alcohol-facts-and-statistics/alcohol-use-disorder-aud-united-states-age-groups-and-demographic-characteristics

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Recommended Drinking Limits

	Daily drinking limit	Weekly drinking limit	Heavy drinking day
Healthy men ≤ 65 years	≤ 4 drinks	≤ 14 drinks	≥ 5 drinks/day
Healthy women and healthy men >65 years	≤ 3 drinks	≤ 7 drinks	≥ 4 drinks/day

1 standard drink = 12 oz beer, 5 oz wine, or 1.5 oz 80-proof spirits

Metz VE, et al. *Addiction*. 2022;117:2847-54
NIAAA Helping patients who drink too much: a clinician's guide, 2005; Available from: www.niaaa.nih.gov

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Sequelae of AUD

GI
Esophagitis, gastritis, pancreatitis, diarrhea, ulcers

Liver
Steatosis, hepatitis, cirrhosis, portal htn, varices

Cancer
Digestive (mouth, esophagus, stomach), hepatocellular, breast

Neuro
Dementia, CNS structural changes, peripheral neuropathy, Wernicke-Korsakoff syndrome, Korsakoff psychosis

CV
Acute: ↓ BP and myocardial contractility, peripheral dilation
Chronic: Htn, cardiomyopathy, arrhythmias, CAD, stroke, intracranial hemorrhage, sudden death

Hematopoietic
Anemia, ↑ MCV, leukopenia, coagulopathy, thiamine and folate deficiencies

GU
Infertility, sexual dysfunction, amenorrhea

Other
Osteopenia/fractures, myopathy, encephalopathy, hormonal changes, acute renal failure

CNS: Central nervous system
CAD: Coronary artery disease
CV: Cardiovascular
GI: Gastrointestinal
Htn: Hypertension
MCV: Mean corpuscular volume

Schuckit MA. *Lancet*. 2009;373:492-501

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Pathophysiology of AUD

- Release of dopamine into nucleus accumbens and prefrontal cortex reinforces drinking behaviors
- **Inhibitory and excitatory neurotransmission:**
  - Alcohol **enhances GABA** by binding GABA receptors: decrease in brain excitability
    - GABA receptors down-regulate with chronic use
  - Alcohol **inhibits glutamate NMDA** receptors
    - Glutamate receptors up-regulate with chronic use
  - **Alcohol withdrawal:** Abrupt cessation causes brain hyper-excitability because there are fewer GABA receptors and excessive glutamate

Wackernah RC, et al. *Subst Abuse Rehabil.* 2014;5:1-12

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Clinical Course of AUD

- **Clinical Course:**
  - Average age of first drink: 15 years
  - Drinking often moderates in mid-20s (AUD may develop)
  - AUD is chronic with fluctuations over time
  - 20-30% with AUD likely to remain abstinent or in long-term remission **without formal treatment**

Maisto SA, et al. *J Stud Alcohol Drugs.* 2014;75:415-22

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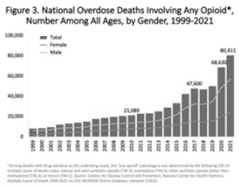
Opioid Use Disorder (OUD) Background

- Affects ~3 million people in the U.S.
- 80% of people who us heroin report prescription opioid pills as their initiation to opioid use
- Highest prevalence:
  - Younger age (<40 years)
  - Severe pain
  - Comorbid mental health disorder
  - White race



Azadfard M, et al. *StatPearls [Internet].* 2023
National Institute on Drug Abuse, Drug overdose death rates, 2023; Available from: https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

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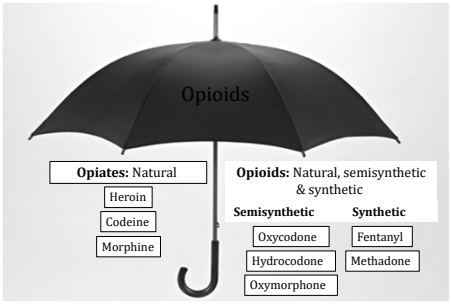
Opioid Terminology



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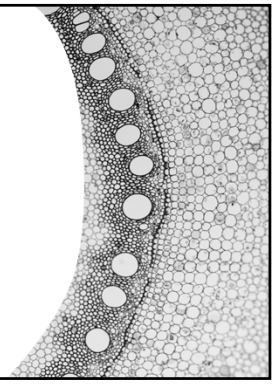
Sequelae of OUD

- Incarceration
- Injuries (traffic, falls, drowning)
- Suicide
- Homicide
- Blood-borne virus infections
- Other infections:
  - Endocarditis
  - Skin and soft tissue
  - Pulmonary



Strang J, et al. *Nat Rev Dis Primers.* 2020;6:3

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Pathophysiology of OUD

- Stimulation of mu-opioid receptors in ventral tegmental area stimulates dopaminergic reward system
  - Other opioid receptors may cause additional responses:
    - Ex: Binding of kappa-opioid receptors may release dynorphine and cause dysphoria
- HPA axis involvement (stress response)
- Overuse of mu-opioid agonists leads to tolerance and withdrawal

Strang J, et al. Nat Rev Dis Primers. 2020;6:3
Brown KG, et al. *Am J Nurs.* 2020;120:38-46

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Clinical Course of OUD

- Likelihood of developing OUD after use of opioids is higher than other drugs
- Chronic, remitting course
  - Periods of use often interspersed with periods of treatment, incarceration, and/or abstinence
- Periods of partial or complete remission

Strang J, et al. *Nat Rev Dis Primers.* 2020;6:3 Nunes EV, et al. *J Subst Abuse Treat.* 2019; 105:64-70
Saddichha S, et al. *Indian J Community Med.* 2010;35:359-61

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Summary

- Schizophrenia and bipolar disorder are serious mental illnesses associated with a significant impact on patient morbidity and mortality
- Substance use disorders such as alcohol use disorder and opioid use disorder affect millions of Americans and are associated with both physical and mental sequelae

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Mental Illness and Substance Use Disorders: Background

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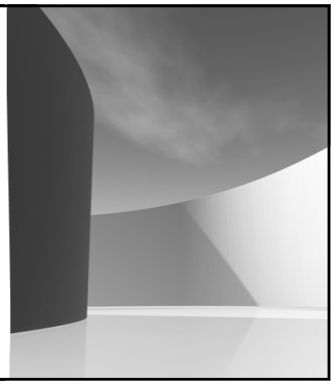

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