CHAPTER 1

Psychiatry

Defense mechanisms

- Defense mechanisms are a concept born out of Freudian psychology.

- Recall that the Freudian psyche consists of:

- Id: animalistic, instinctive urges, sex, aggression, and other primary processes (Impulses from self).

- Ego: rational and language-based executors linking to reality (Problem-solving).

- Super-ego: the conscience, the moral compass insisting on socially acceptable behavior (Values from others).

- Defense mechanisms are means of protecting oneself from awareness of uncomfortable feelings. They can be classified as immature or mature:

- Immature defense mechanisms are maladaptive and generally seen in children and in psychopathologic states.

- Mature defense mechanisms are more often used by adults and allow for a healthy adaptive response to emotional distress.

- Psychopathology is an issue of intensity and extent. Psychopathology = too much all at once, or for too extended a period of time.

- All defenses are unconscious, with one exception: suppression.

Immature Defense Mechanisms

A. Projection:

- Seeing what is within self as part of the outside world, either the general environment or a particular person "Self, seen in others"

- What is in self is projected onto others the way a movie projector puts the movie on the screen.

- Examples:

- Man accuses his wife of having an affair, when he is attracted to his new work colleague.

B. Identification:

- Identification refers to modeling one's behavior after someone who is perceived to be more powerful or prestigious (unconscious imitation).
- Reverse process of projection.
- Examples:

- A resident starts putting his stethoscope in his pocket like his favorite attending, instead of wearing it around his neck like before.

- When conscious, we call this imitation.

C. Denial:

- Avoiding the awareness of some painful reality.
- First stage of grief.
- Often seen in substance-use disorders.
- Examples:

- "Those tests may say I have cancer, but they are wrong".
- "The bank statement says I'm out of money, but that just can't be right!".

D. Splitting:

- The world seen in terms of extremes.
- Things seen as "all good" or "all bad". Can rapidly shift from one to the other.
- Splitting is commonly seen in borderline personality disorder and can contribute to the unstable relationships and mood instability that characterize this disorder.
- Examples:

- "You are the best doctor in the world. My old doctor was a malpractice nightmare"

E. Idealization:

- Expressing extremely positive thoughts of self and others while ignoring negative thoughts.
- Examples:

- A patient boasts about his physician and his accomplishments while ignoring any flaws.

F. Repression:

- Involuntarily withholding an idea or feeling from conscious awareness.
- Involves "unconscious forgetting, with retrieval essentially impossible".
- Examples:

- A person who was a prisoner of war cannot recall a period in captivity.
- A boy who was sexually abused cannot recall time spent with his uncle.

- Contrast with suppression.

G. Displacement:

- Redirecting emotion or behavior to a different target. Usually impulses are redirected to a less threatening, lower status target.
- Person is not aware of doing this (unconscious).
- Examples:

- A person who is angry at the boss yells at the spouse instead.
- The resident was shamed and angered by being reprimanded by the attending and instead of acknowledging his feelings, he displaces his negative emotions onto a "safer" target by making sarcastic, shaming comments to a junior member of the team.

H. Acting Out:

- Subconsciously coping with stressors or emotional conflict using actions rather than reflections or feelings.
- Emotional outburst is not what the person actually feels, but a covering up of actual feelings.
- Common covering behaviors: Getting drunk, driving fast, overeating, having sex, playing music loudly, getting into fights.
- Differentiate from displacement

I. Regression:

- Involuntarily turning back the maturational clock and going back to earlier modes of dealing with the world.
- Regression often happens when people are tired, afraid, hungry, or in pain. Frequently seen in medical settings.
- Children, although young, can still regress.

- Examples:
- An adult act like a child. "Baby talk" between sweethearts.
- A previously toilet-trained child develops enuresis after his baby brother is born.
- A patient breaks down crying hysterically when told bad news.
- A patient began sleeping in his parents' room due to anxiety about being alone, which is more characteristic of an earlier developmental stage.

J. Somatization:

- Real, objective physical symptoms produced by psychological processes.

- Feelings manifest as physical symptoms "Symptom replaces anxiety".

- Examples:
- Woman says she is not sad about her divorce, but complains of headaches and GI upset.
- Getting a headache while taking an exam.

- At the extreme, produces the somatoform disorders.

K. Isolation of Affect:

- Cognitive aspects of experience are retained while emotion is discarded "Facts retained, feelings disposed".

- Examples:
- Woman who was raped discusses the events without any emotion.
- A surgeon tells a patient about negative results without empathy or sensitivity.

L. Intellectualization:

- Emotion removed and replaced by excess cognition.

- Intellectualization is the transformation of an emotionally difficult event into a purely intellectual problem to avoid confronting its uncomfortable emotional components.

- Examples:
- The patient keeps working (another intellectual focus) and discussing details of his medical condition (cancer diagnosis), but not his feelings, with his family interferes with the patient's ability to deal with his feelings and to grieve with his family.

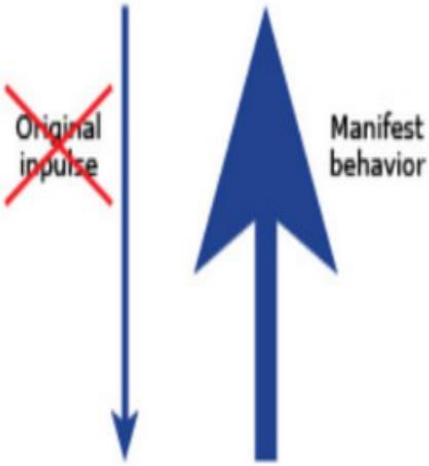
M. Reaction Formation:

- Transforming unacceptable or unattainable emotion into its extreme opposite.

- An exact attitude reversal: Love - hate, joy- despair.

- Examples:

- A mother who does not want her new baby is very solicitous and overprotective.
- A patient with libidinous thoughts enters a monastery.



N. Undoing:

- An action that reverses or fixes the unacceptable or intolerable sense of making things right again; fixing or atoning.

- Examples:

- A man who is sexually aroused by woman he meets immediately leaves and buys his wife flowers.

O. Rationalization:

- Proclaiming logical reasons for actions actually performed for other reasons, usually to avoid self-blame "Unconscious justification".

- Examples:

- After getting fired, claiming that the job was not important anyway.
- "Yes, we killed women and children, but we were at war".
- "If the room were not so dam noisy, I would have done better on the exam."

P. Passive Aggressive:

- Expression of hostility by delaying action or not acting at all.
- Expectation of action followed by inaction.
- Examples:

- A woman makes a date to meet someone at a restaurant but does not show up.
- A professor Ignores questions from a particular student after class but answers questions for others.

Q. Dissociation:

- Splitting off of the brain from conscious awareness.
- Person is having an experience, but is shielded from feeling the full emotional weight of events.
- Example:

- A woman who was raped says that during the rape she felt as if she were floating on the ceiling instead of being within her own body (depersonalization).

Mature Defense Mechanisms

A. Humor:

- Venting of unpleasant feelings by laughter.
- A way to recognize and cope with an unpleasant reality without being overwhelmed by it.
- Examples:

- Joking about failing the board exam.

B. Suppression:

- Suppression is a mature defense mechanism in which an individual intentionally puts aside unpleasant thoughts or feelings to better cope with the present reality. In contrast to repression, the individual is aware of the emotion but decides not to attend to it.
- Person has the ability to access the emotion later and accept it.
- A medical student forgets about his workload while at a party, but then remembers the test he has to study for as he returns to his room.
- Different from repression in that content can be recalled.

C. Altruism:

- Helping others without apparent return to self.

- Person gets unconscious benefit from:

- Making the world a better place.
- Relieving guilt that we have that others do not.
- Storing up credits to balance out future bad behaviors.

- Examples:

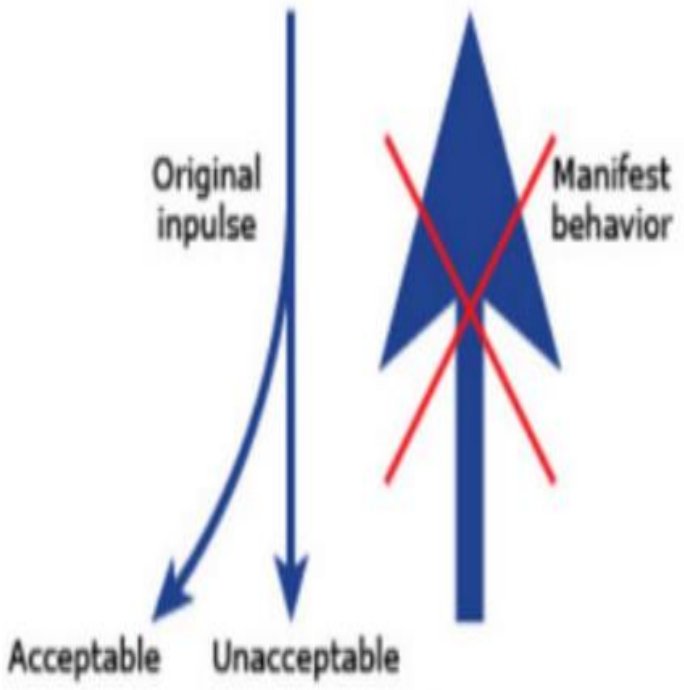
- A man who lost a leg in an accident volunteers at camps for children with physical disabilities.
- Mafia boss makes large donation to charity.
- A wealthy woman volunteers weekly at a soup kitchen for the poor.

D. Sublimation:

- Replacing an unacceptable wish with a course of action that is similar to the wish but socially acceptable (vs reaction formation).

- Examples:

- Intense hostility and anger are redirected by choosing boxing as a sport.
- Professor becomes a helpful mentor for a female student to whom he is attracted.
- Becoming a nutritionist to overcome personal obesity.



Key defense mechanisms	
Immature	• Acting out: Expressing unacceptable feelings through actions • Denial: Behaving as if an aspect of reality does not exist • Displacement: Transferring feelings to less threatening object/person • Intellectualization: Focusing on nonemotional aspects to avoid distressing feelings • Passive aggression: Avoiding conflict by expressing hostility covertly • Projection: Attributing one's own feelings to others • Rationalization: Justifying behavior to avoid difficult truths • Reaction formation: Transforming unacceptable feelings/impulses into the opposite • Regression: Reverting to earlier developmental stage • Splitting: Experiencing a person/situation as either all positive or all negative
Mature	• Sublimation: Channeling impulses into socially acceptable behaviors • Suppression: Putting unwanted feelings aside to cope with reality

Transference and countertransference

- In transference, emotions and reactions to someone in the past are unconsciously carried forward and applied to someone in the present.
- Patient toward doctor = transference.
- Doctor to patient = countertransference.
- Unconscious process, but not a defense mechanism.
- Can be positive or negative and frequently affect doctor-patient relationships.

Types of Abuse

Child Abuse

	Physical abuse	Sexual abuse
Signs	Fractures, bruises, or burns. Injuries often in different stages of healing or in patterns resembling possible implements of injury. Includes abusive head trauma (shaken baby syndrome), characterized by subdural hematomas or retinal hemorrhages. Caregivers may delay seeking medical attention for the child or provide explanations inconsistent with the child's developmental stage or pattern of injury.	STIs, UTIs, and genital, anal, or oral trauma. Most often, there are no physical signs; sexual abuse should not be excluded from a differential diagnosis in the absence of physical trauma. Children often exhibit sexual knowledge or behavior incongruent with their age.
Epidemiology	40% of deaths related to child abuse or neglect occur in children < 1 year old.	Peak incidence 9-12 years old.

- Child neglect:
  - Failure to provide a child with adequate food, shelter, supervision, education, and/or affection.
  - Most common form of child maltreatment.
  - Deprivation for > 6 months can lead to irreversible changes.
  - Severe deprivation can result in infant death.
  - Evidence: poor hygiene, malnutrition, withdrawal, impaired social/emotional development, failure to thrive.
  - As with child abuse, suspected child neglect must be reported to local child protective services.
- Vulnerable child syndrome:
  - Parents perceive the child as especially susceptible to illness or injury.
  - Usually follows a serious illness or life-threatening event.
  - Can result in missed school or overuse of medical services.

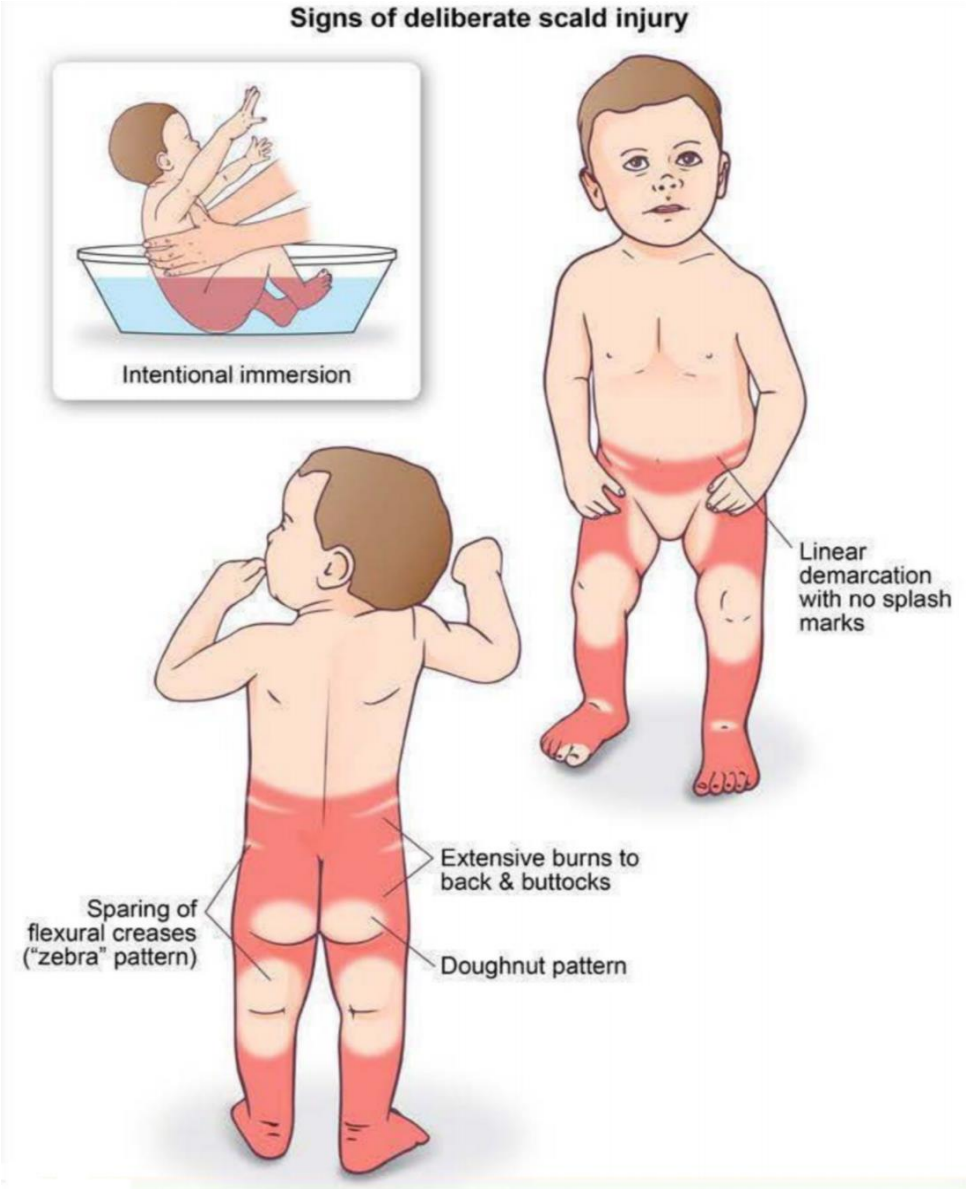
❖ N.B:

1. Child abuse is a mandatory reportable offense up to age 18.

- Failure to do so is criminal offense.
- If case is reported in error, the physician is protected from legal liability.
- Remember your duty to protect the child (separate from the parents), as well as the duty to report.
- Physicians should have a high index of suspicion for physical/sexual abuse in children with sudden behavioral problems, stressful family environments, or parents with active drug/alcohol abuse.

2. Deliberate scald injuries are characterized by sharp lines of demarcation, uniform burn depth, and spared flexor surfaces.

- In contrast, splash marks, poorly defined wound margins, non-uniform burn depth, and immediate presentation after injury are all features of accidents.



Domestic Violence

- Not a mandatory reportable offense in most states.
- Most frequent cause of injury to women in the United States.
- Abusers are typically male with a history of substance abuse, impulsivity, poor anger control, low tolerance for frustration, and poor self-esteem.
- Victims are typically financially and/or emotionally dependent with low self-esteem.
- Reasons victim returns to abuser:
  - Financial dependence on abuser.
  - No plan of escape.
- Physician should:
  - Document the abuse.
  - Ensure the safety of the abused person.
  - Help the abused person develop an emergency escape plan.
  - Encourage the abused person to report to law enforcement officials.

Elder Abuse

- Mandatory reportable offense, age 65 and over.
- Includes: Physical, psychological, financial, neglect (most common).
- Caregiver is most frequent abuser, then spouse.
- Clinicians have ethical and moral obligations to report elder abuse, neglect, and exploitation. If there is reason to suspect abuse or neglect, the patient should be interviewed alone to avoid intimidation by possible abusers.

Human sexuality

Definitions

- Gender identity: established by the age of 3, sense of maleness or femaleness.
- Sexual identity: based on your secondary sexual characteristics.
- Gender role: behavior based on your gender identity.
- Sexual orientation: based on your love objects.
- Gender dysphoria:

- Strong, persistent cross-gender identification that leads to persistent discomfort with sex assigned at birth, causing significant distress and/or impaired functioning and is often associated with comorbid depression and anxiety. Transgender individuals may have gender dysphoric disorder.

- Physicians should provide nonjudgmental support and encourage the involvement of supportive family/friends as early as possible.

- Adolescents with gender dysphoria are at increased risk of depression, anxiety, and bullying, which should be monitored, and they may benefit from mental health evaluation and treatment in addition to medical interventions.

- Transsexualism: desire to live as the opposite sex, often through surgery or hormone treatment.

Gender dysphoria	
Clinical features	• Experiences persistent (≥6 months) incongruence between assigned & felt gender • Desires to be other gender • Dislikes own anatomy, desires sexual traits of other gender • Believes feelings/reactions are of other gender • Feels significant distress/impairment
Initial management (tailored to individual needs)	• Assessment of safety • Support; psychotherapy (individual, family) • Referral to specialist services (medical & mental health multidisciplinary)

Paraphilic disorders

- Pedophilia: sexual urges toward children. Most common paraphilia.
- Exhibitionism: recurrent desire to expose genitals to stranger.
- Voyeurism: sexual pleasure from watching others who are naked, grooming, or having sex. Begins early in childhood.
- Sadism: sexual pleasure derived from others' pain.
- Masochism: sexual pleasure derived from being abused or dominated.
- Fetishism: sexual focus on objects, e.g., shoes, stockings.
- Transvestite fetishism: fantasies or actual dressing by heterosexual men in female clothes for sexual arousal.
- Frotteurism: male rubbing of genitals against fully clothed woman to achieve orgasm; subways and buses.
- Zoophilia: animals preferred in sexual fantasies or practices.
- Coprophilia: combining sex and defecation.
- Urophilia: combining sex and urination.
- Necrophilia: preferred sex with cadavers.

Sexual dysfunction

- Includes sexual desire disorders (hypoactive sexual desire or sexual aversion), sexual arousal disorders (erectile dysfunction), orgasmic disorders (anorgasmia, premature ejaculation), sexual pain disorders (dyspareunia, vaginismus).

- <u>Differential diagnosis includes:</u>

- Drugs (antihypertensives (Beta blockers), neuroleptics, SSRIs, ethanol).
- Diseases (depression, diabetes, STIs).
- Psychological (performance anxiety).
- Genitourinary trauma (prostatectomy).

❖ N.B:

1. Psychogenic causes of ED account for approximately 10% of cases and include performance anxiety, sexual partner dissatisfaction, and marital problems.

- Important clues that point toward psychogenic impotence include sudden onset and the presence of morning erections.

2. Toddlers are normally curious about the human body.

- It is normal for them to touch their own or other young children's genitals, to undress themselves or others, and make masturbatory movements. These behaviors are typically brief, intermittent, and distractible. Simulating the details of sexual acts or using age-inappropriate sexual aknowledge, however, should raise concern for possible abuse.
- These behaviors typically decrease as children approach adolescence, becoming more aware of social norms and expectations and having an increased need for privacy.

Sexuality and aging

- Sexual interest does not decline significantly with aging.

- <u>Changes in men:</u>

- Slower erection.
- More stimulation needed.
- Longer refractory period.

- <u>Changes in women:</u>

- Vaginal dryness.
- Vaginal thinning.
- Can be reduced by estrogen replacement.

Suicide

- Men commit suicide 4 times as often as women. Women attempt suicide 3 times as often as men (Women try more often; men succeed more often).

- Most common method in US is firearms; access to guns ↑ risk of suicide completion.

- The majority of completed suicides occur with the use of a firearm. Access to guns significantly increases the risk of death by suicide. Evaluation of a patient's access to guns is a key part of suicide risk assessment.

- Risk factors for suicide completion:

- Sex (male).
- Age (young adult or elderly).
- Depression.
- Previous attempt (a history of previous suicide attempt is the strongest single risk factor for suicide).
- Ethanol or drug use.
- Rational thinking loss (psychosis).
- Sickness (medical illness).
- Organized plan.
- No spouse or other social support.
- Stated future intent.
- SAD PERSONS are more likely to complete suicide.

❖ N.B:

- Active suicidality is associated with intent and plan for self-harm.
- The first step in the care of patients with active suicidality is to ensure their safety by admitting them to a psychiatric unit (involuntarily, if necessary).
- Although efforts should be made to obtain parental consent, a minor can be hospitalized without it.

Assessment & management of suicidality	
Assessment	**SAD PERSONS** • **S**ex • **A**ge • **D**epression • **P**revious attempt • **E**tOH (or other substance) use • **R**ational thought loss (psychosis) • **S**ocial support lacking • **O**rganized plan • **N**o spouse or significant other • **S**ickness or injury
Management	**High imminent risk** (ideation, **intent & plan**) • Ensure safety: Hospitalize immediately (involuntarily if necessary) • Remove personal belongings & objects in room that may present self-harm risk • Constant observation & security may be required to hold against will **High non-imminent risk** (ideation, intent, but **no plan to act in near future**) • Ensure close follow-up • Treat modifiable risk factors (underlying depression, psychosis, substance abuse, pain) • Recruit family or friends to support patient • Reduce access to potential means (secure firearms, medications)

Sleep and Sleep Disorders

Sleep architecture

- Sleep consists of two distinct states (REM and NREM):

A. REM: Rapid Eye Movement Sleep

- It is an awake brain in a paralyzed body (Brain on; Body off).

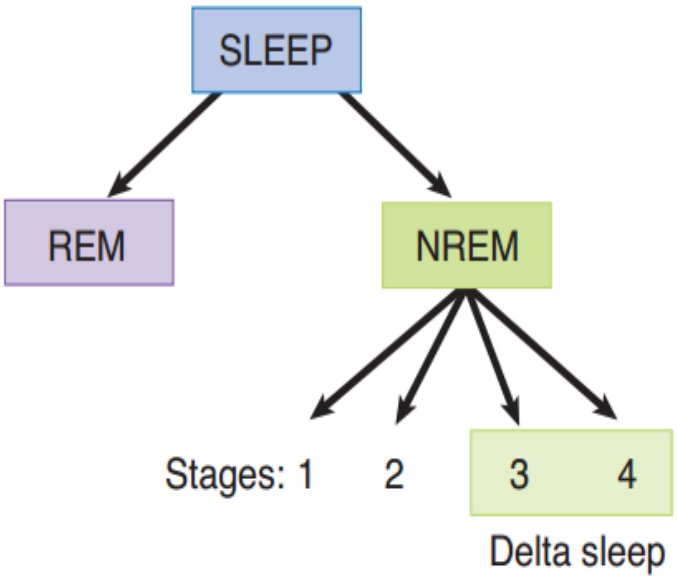
- Characterized by:
  - Saccadic eye movements.
  - An aroused EEG pattern (dreaming).
  - Sexual arousal.
  - Elaborate visual imagery (dreaming).

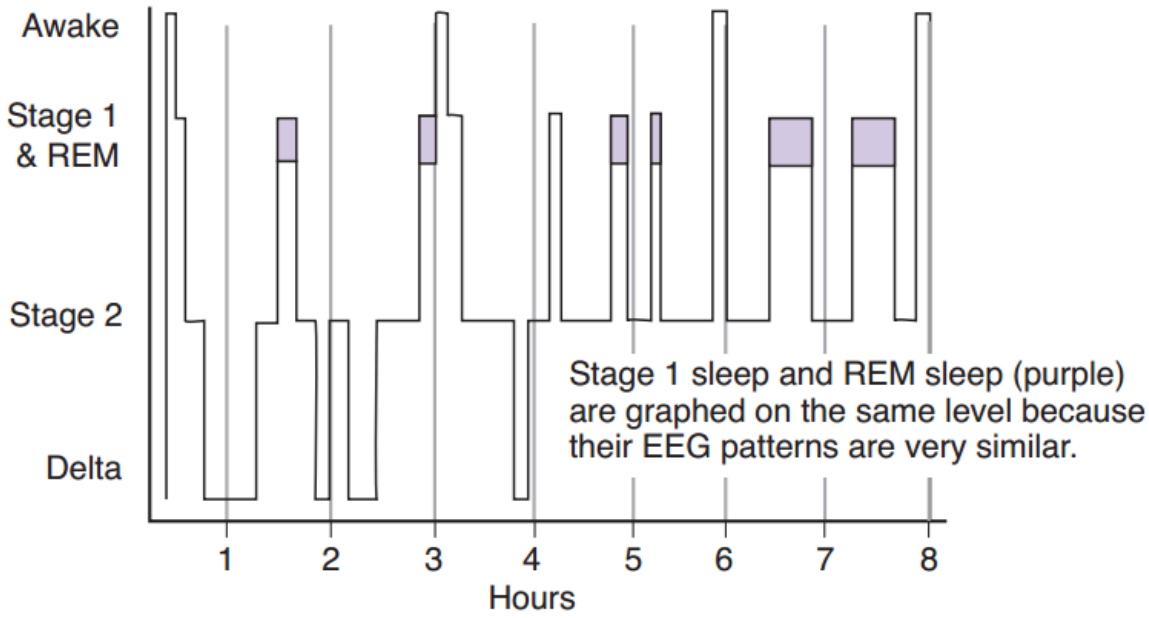
B. NREM: Non-rapid Eye Movement Sleep

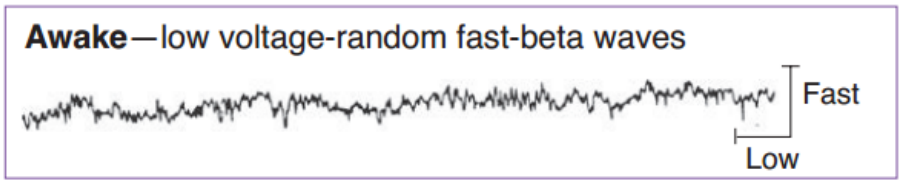
- Divided into 4 stages on the basis of EEG criteria.

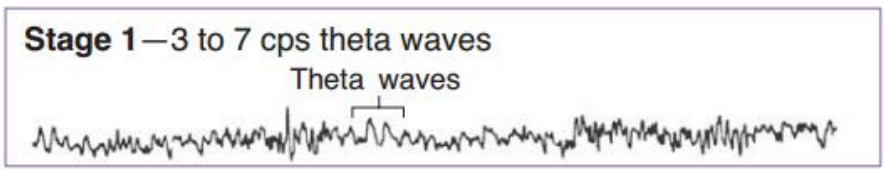
- It is an idling brain in a movable body (Brain off; Body on).

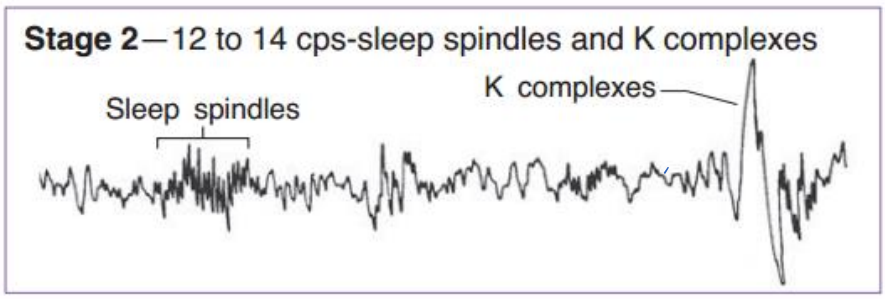
- Alternates with REM sleep throughout the sleep period and is characterized by:
  - Absence of eye movements.
  - Slowing of the EEG rhythms.
  - Higher muscle tone.
  - Absence of "thought-like" mental activity.

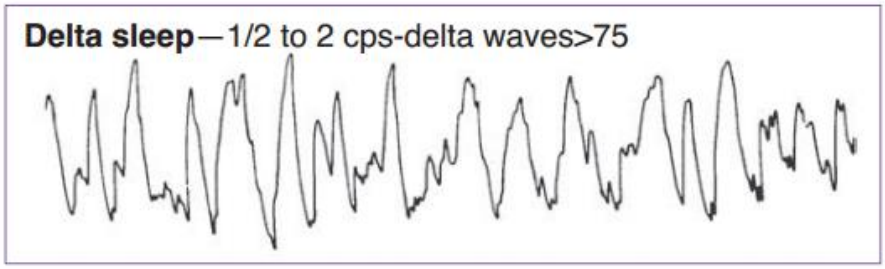


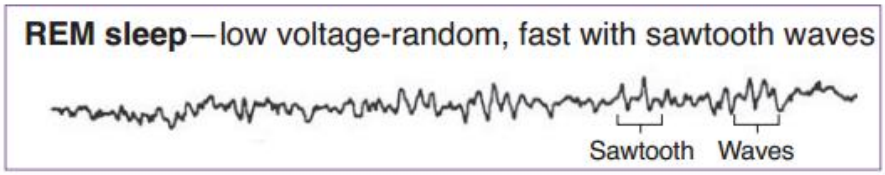

Awake
Stage 1
& REM
Stage 2
Delta
Stage 1 sleep and REM sleep (purple) are graphed on the same level because their EEG patterns are very similar.
1
2
3
4
5
6
7
8
Hours


Awake—low voltage-random fast-beta waves
Fast
Low


Stage 1—3 to 7 cps theta waves
Theta waves


Stage 2—12 to 14 cps-sleep spindles and K complexes
Sleep spindles
K complexes


Delta sleep—1/2 to 2 cps-delta waves>75


REM sleep—low voltage-random, fast with sawtooth waves
Sawtooth
Waves

Sleep disorders

Narcolepsy

- Disordered regulation of sleep-wake cycles; 1° characteristic is excessive daytime sleepiness.

- Caused by ↓ hypocretin (orexin) production in lateral hypothalamus. Loss of hypocretin results in an inability to regulate sleep.

- Strong genetic component.

- Narcolepsy is considered as a disorder of REM sleep.

- Also associated with the narcoleptic tetrad:

1. Sleep attacks and excessive daytime sleepiness.

2. Cataplexy (loss of all muscle tone following strong emotional stimulus, such as laughter) in some patients (pathognomonic sign).

3. Hypnagogic (just before sleep) or hypnopompic (just before awakening) hallucinations:
- Hypnagogic going to sleep.
- Hypnopompic "pompous upon awakening".

4. Sleep paralysis.

- Treatment:

- Treatment includes sleep hygiene, scheduled naps, and avoidance of alcohol and drugs that cause drowsiness.

- When medications are needed to decrease daytime somnolence, wakefulness-promoting agents such as modafinil are preferred.

- Modafinil, a nonamphetamine medication that promotes wakefulness, is considered a first-line pharmacotherapy as it reduces daytime sleepiness, is generally well tolerated, and has less abuse potential compared with traditional stimulants (amphetamines, methylphenidate).

- These older drugs are effective but are generally used as second-line therapies due to a higher risk of adverse effects (hypertension, tachycardia, psychosis, anorexia, abuse).

- Patients with significant cataplexy may also benefit from a REM sleep-suppressing drugs, including antidepressants and sodium oxybate.

Narcolepsy	
DSM-5 diagnostic criteria	• Recurrent lapses into sleep or naps (minimum 3 times per week for 3 months) • At least 1 of the following: o Cataplexy: Brief loss of muscle tone precipitated by strong emotion (eg, laughter, excitement) o Low cerebrospinal fluid levels of hypocretin-1 o Shortened REM sleep latency
Associated features	• Hypnagogic or hypnopompic hallucinations • Sleep paralysis

Insomnia

- Definition:

- A disorder characterized by difficulties in initiating or maintaining sleep.

- Risk Factors/Epidemiology:

- Typically associated with some form of anxiety or anticipatory anxiety.

- Many patients have underlying psychiatric disorders, such as depression, etc.

- Physical and Psychiatric Presenting Symptoms:

- Predominant complaint is difficulty initiating or maintaining sleep.

- Affects the patient's level of functioning.

- Frequent yawning and tiredness during the day.

- Treatment:

- Poor sleep hygiene is a common cause of insomnia. Strategies to improve sleep hygiene include:
  - Maintaining a regular sleep schedule and a quiet, dark, and comfortably cool bedroom.
  - Avoiding late afternoon naps and exposure to electronic devices before bedtime.
  - Avoiding nicotine, caffeine, and heavy meals in the evening.

- If these do not work, consider behavioral modification techniques such as stimulus control. Stimulus control focuses on eliminating stimulating bedroom activities and getting into bed only when sleepy. If the patient cannot fall asleep, he should not look at the clock but go to another room and do something relaxing until he feels drowsy enough to fall asleep.

- If medications are to be used, consider zolpidem, eszopiclone, or zaleplon.

Behavioral treatment of insomnia	
Sleep hygiene	• Maintain regular sleep schedule, avoid naps • Avoid caffeine after lunch • Avoid alcohol, smoking, large meals near bedtime • Adjust bedroom environment to be quiet, dark & cool • Exercise regularly, but not soon before bedtime
Stimulus control	• Use bed only for sleep & sexual activity (no reading, television, eating) • Go to bed only when sleepy • Leave bed when unable to sleep & go to another room • Fixed wake-up time, including weekends
Relaxation	• Progressive muscle relaxation (muscles contracted & relaxed in sequence) • Relaxation response (abdominal breathing, mental focus on peaceful image)
Sleep restriction	• Restrict sleep to time patient is actually sleeping (based on sleep diary) • Increase time in bed in 15- to 30-minute intervals when sleep efficiency is >90%

❖ N.B:

1. Normal age-related sleep changes include decreased total sleep time, Increased nighttime awakenings, sleepiness earlier in the evening with earlier morning awakening, and increased daytime somnolence (napping).

- No further workup is necessary, and patients should be reassured that these changes are normal.

2. Delayed sleep phase syndrome is a circadian rhythm disorder characterized by the inability to fall asleep at "normal" bedtimes, resulting in sleep-onset insomnia and excessive daytime sleepiness.

- Patients sleep normally if allowed to follow their internal circadian rhythm and sleep until late morning (have chronic problems going to sleep at a societally accepted time).

Sleep terror disorder

- Periods of terror with screaming in the middle of the night; occurs during slow-wave/deep sleep.
- Most common in children.
- Occurs during non-REM sleep (no memory of arousal) as opposed to nightmares that occur during REM sleep (memory of a scary dream).
- Cause unknown, but triggers include emotional stress, fever, or lack of sleep.
- Usually self-limited (reassurance).

	Night Terrors	Nightmares
Sleep stage	Stage 4 (delta sleep)	REM
Recall upon waking	No	Yes

❖ N.B:

- Nightmare disorder involves recurrent awakenings from REM sleep associated with full alertness and dream recall. It should be differentiated from non-REM sleep terrors, which are characterized by partial arousals, unresponsiveness, and lack of dream content.

Somnambulism (Sleep-walking)

- Occurs in stage 4 sleep (Delta).
- If wakened, the person is confused and disoriented.
- Treat with benzodiazepines (decreases stage 4 sleep).

Neurotransmitters Associated with Sleep "SANDman"

- Serotonin: helps initiate sleep.
- Acetylcholine (ACh): higher during REM sleep (associated with erections in men)
- Norepinephrine (NE): lower during REM sleep. Ratio of ACh and NE is the biochemical trigger for REM sleep.
- Dopamine: produces arousal and wakefulness. Rises with waking.

Intelligence Quotient (IQ)

- Definition: a general estimate of the functional capacities of the person.
- 70% inherited, recent studies suggest most from mother.
- IQ is not an absolute score but a comparison among people.
- Distribution mean: 100; standard deviation: 15.

- Two methods for generating score from IQ test results:
  - **Mental Age Method**: Compares across ages
    - —Used only for children under age 16
    - —MA/CA x 100 = IQ
    - —MA = mental age, CA = chronological age

An 8-year-old boy scores on his IQ test about the level of the average 10 year old. What is his IQ?

MA/CA × 100 = IQ = 10/8 × 100 = 125

  - **Deviation from Norms Method**: Compares within same age group.
    - —Scores derived based on standard deviations above or below the mean.

An 8-year-old boy scored one standard deviation above the mean on the distribution of score for 8 year olds. What is his IQ?

If mean = 100 and standard deviation = 15,
one standard deviation above the mean = IQ of 115

  - By either method, IQ is strongly related to education. People with higher IQs tend to seek and get more education.

Range	Label	Distribution
Less than 69	Intellectual disability	About 2.5% of the population
70 to 79	Borderline	
80 to 89	Low average	
90 to 109	Average	About 50% of the population
110 to 119	High average	
120 to 129	Superior	
over 130	Very superior	About 2.5% of the population

Intellectual Disability

- Global cognitive deficits (vs specific learning disorder) that affect reasoning, memory, abstract, thinking, judgment, language, learning.
- Adaptive functioning is impaired, leading to major difficulties with education, employment, communication, socialization, independence.
- Treatment: psychotherapy, occupational therapy, special education.

Specific learning disorder

- Onset during school-age years.
- Inability to acquire or use information from a specific subject (math, reading, writing) near age-expected proficiency for ≥ 6 months despite focused intervention.
- General functioning and intelligence are normal (vs intellectual disability).
- Treatment: academic support, counseling, extracurricular activities.

Disorders Usually Diagnosed in Childhood

Autism spectrum disorder

- Autism spectrum disorder is characterized by impaired social communication/interactions and restricted, repetitive interests or behaviors.
- It can occur with or without language and intellectual impairment.
- Must present in early childhood.
- More common in boys. Associated with ↑ head/brain size.
- Early intervention for autism spectrum disorder (ASD) in the preschool and school-age years has been shown to significantly improve outcomes, if there is any concern about ASD, thorough screening and evaluation should be undertaken and educational/behavioral services offered as soon as possible.

Autism spectrum disorder	
Clinical features	• Deficits in social communication & interactions with onset in early development o Sharing of emotions or interests o Nonverbal communication o Developing & understanding relationships • Restricted, repetitive patterns of behavior o Repetitive movements or speech o Insistence on sameness/routines o Intense fixated interests o Adverse responses to sensory input • May occur with or without language & intellectual impairment
Assessment & management principles	• Early diagnosis & intervention • Comprehensive, multimodal treatment (speech, behavioral therapy, educational services) • Adjunctive pharmacotherapy for psychiatric comorbidities

Rett syndrome

- X-linked dominant disorder seen almost exclusively in girls (affected males die in utero or shortly after birth).
- Symptoms usually become apparent around ages 1-4, including regression characterized by loss of development, loss of verbal abilities, intellectual disability, ataxia, stereotyped hand-wringing.

Conduct disorder

- Repetitive and pervasive behavior violating the basic rights of others or societal norms (aggression to people and animals, setting fires, destruction of property, theft) for ≥ 1 year.
- After age 18, many of these patients will meet criteria for diagnosis of antisocial personality disorder.
- Treatment for both: psychotherapy such as CBT (cognitive behavioral therapy).

Conduct disorder	
Clinical features	• Pattern of violating major societal norms & rights of others for ≥1 year • Aggression & cruelty toward people & animals • Destruction of property, setting fires • Serious violation of rules (truancy, running away) • Deceitfulness or theft (lying, stealing)
Treatment	• Cognitive-behavioral therapy, family therapy • Parent management training

Oppositional defiant disorder

- Oppositional defiant disorder is a behavioral disorder of childhood characterized by argumentative and defiant behavior toward authority figures in the absence of serious violations of social norms.
- It does not involve the more severe violations of the basic rights of others seen in conduct disorder.
- Treatment: psychotherapy such as CBT.

Separation anxiety disorder

- Common onset at 7-9 years.
- Overwhelming fear of separation from home or loss of attachment figure.
- May lead to factitious physical complaints to avoid going to or staying at school.
- Treatment: CBT, play therapy, family therapy.

Tourette syndrome

- Onset before age 18.
- It occurs more frequently in males.
- Characterized by sudden, rapid, recurrent, nonrhythmic, stereotyped motor and vocal tics that persist for > 1 year.
- Tics are usually preceded by irresistible urges and followed by feelings of relief. Tics are exacerbated by stress and fatigue.
- Motor tics frequently observed include grimacing, eye blinking, nose twitching, head jerking, and shoulder shrugging.
- Vocal tics include barking, grunting, squeaking, coughing, and throat clearing.
- Coprolalia (involuntary obscene speech) found in only 10–20% of patients.
- Patients with Tourette syndrome have high rates of psychiatric comorbidity, with a significantly increased risk for attention-deficit hyperactivity disorder (ADHD) and/or obsessive-compulsive disorder (OCD).
- Treatment:

- Tourette disorder is best treated with antipsychotic medications and habit reversal training. Haloperidol and pimozide are FDA approved, but second-generation antipsychotics such as risperidone are well studied and are increasingly preferred due to their favorable side effect profile.

Tourette disorder	

DSM-5	• Both **multiple motor & one or more vocal tics** (not necessarily concurrent, >1 year)
	  ○ Motor: Facial grimacing, blinking, head/neck jerking, shoulder shrugging, tongue protrusion, sniffing
	  ○ Vocal: Grunts, snorts, throat clearing, barking, yelling, coprolalia (obscenities)
	• Onset before age 18

Treatment	• Antipsychotics • Alpha adrenergic receptor agonists • Behavioral therapy

Attention-deficit hyperactivity disorder

- Onset before age 12.
- Limited attention span and poor impulse control.
- Characterized by hyperactivity, impulsivity, and/or inattention for ≥ 6 months in at least 2 settings (school, home, places of worship, etc).
- Inattentive symptoms include making careless mistakes, forgetfulness, not listening, and avoidance/lack of follow-through with tasks.
- Hyperactive/impulsive symptoms include difficulty staying seated, hyperactivity, talkativeness, impulsivity, difficulty waiting his turn, and interrupting others.
- Normal intelligence, but commonly coexists with difficulties in school.
- Teacher evaluations are an important tool for assessing behavior in the school environment.
- Continues into adulthood in as many as 50% of individuals.
- Treatment:

- Stimulant medications (methyiphenidate, amphetamines) are first-line agents in school-aged children with ADHD. They work by increasing the availability of norepinephrine and dopamine in the prefrontal cortex. They have a rapid onset of action and are generally well tolerated. The most common adverse effect is decreased appetite.

- Monstimulant options include the norepinephrine reuptake inhibitor atomoxetine and alpha-2 adrenergic agonists.

Attention-deficit hyperactivity disorder	
Clinical features	• Inattentive &/or hyperactive/impulsive symptoms for ≥6 months ○ **Inattentive symptoms**: Difficulty focusing, distractible, does not listen or follow instructions, disorganized, forgetful, loses/misplaces objects ○ **Hyperactive/impulsive symptoms**: Fidgety, unable to sit still, "driven by a motor," hyper-talkative, interrupts, blurts out answers • Several symptoms present **before age 12** • Symptoms occur in at least 2 settings (home, school) & cause functional impairment • Subtypes: Predominantly inattentive, predominantly hyperactive/impulsive, combined type
Treatment	• Stimulants (methylphenidate, amphetamines) • Non-stimulants (atomoxetine, alpha-2 adrenergic agonists) • Behavioral therapy

❖ N.B:

- Pyromania is characterized by intentional and repeated fire setting with no obvious motive.
- Individuals with conduct disorder can also have a history of fire setting, but other features (lying, theft, cruelty to others) are also present.

Pyromania
DSM-5 diagnosis • Deliberate fire setting on more than 1 occasion • Tension, arousal prior to act • Fascination with fire & its consequences • Pleasure or relief when setting/witnessing fires • No external gain, revenge, or political motivation; not done to attract attention • Not better explained by conduct disorder, manic episode, psychosis, antisocial personality disorder, or impaired judgment (neurocognitive disorder, substance intoxication)

Psychosis

- Distorted perception of reality characterized by delusions, hallucinations, and/or disorganized thinking. Can occur in patients with medical illness, psychiatric illness, or both.

Delusions

- Unique, false beliefs that persist despite the facts (thinking aliens are communicating with you).

- Delusional disorder is characterized by ≥ 1 delusions lasting ≥ 1 month in the absence of other psychotic symptoms. Behavior is not obviously bizarre and functioning is not significantly impaired apart from the direct impact of the delusions.

- In comparison to schizophrenia, individuals with delusional disorder are typically higher functioning and lack other psychotic symptoms; they do not have prominent hallucinations or grossly disorganized behavior.

- Can be shared by individuals in close relationships (folie à deux). In shared psychotic disorder, the dominant person's delusion is transferred to a more submissive partner. It is important to separate the individuals to determine the degree of impairment in each. Separation can also be used as a therapeutic measure to break the cycle of mutual reinforcement.

Delusional disorder	
Clinical features	• ≥1 delusions for ≥1 months • Other psychotic symptoms absent or not prominent • Ability to function apart from delusion; behavior not obviously bizarre or odd • Subtypes: Erotomanic, grandiose, jealous, persecutory & somatic
Differential diagnosis	• Schizophrenia: Other psychotic symptoms present (eg, hallucinations, disorganization, negative symptoms); greater functional impairment • Personality disorders: Pervasive pattern of suspiciousness (paranoid), grandiosity (narcissistic), or odd beliefs (schizotypal), but no clear delusions
Treatment	• Antipsychotics • Cognitive-behavioral therapy

Disorganized thought

- Speech may be incoherent ("word salad"), tangential, or derailed ("loose associations").

Hallucinations

- Perceptions in the absence of external stimuli (seeing a light that is not actually present).
- Contrast with illusions, misperceptions of real external stimuli.
- Types include:

- Visual: more commonly a feature of medical illness (drug intoxication) than psychiatric illness.
- Auditory: more commonly a feature of psychiatric illness (schizophrenia) than medical illness.
- Tactile: common in alcohol withdrawal and stimulant use (cocaine, amphetamines), delusional parasitosis, "cocaine crawlies".
- Hypnagogic: occurs while going to sleep.
- Hypnopompic: occurs while waking from sleep ("pompous upon awakening"). Sometimes seen in narcolepsy.
- Olfactory: often occur as an aura of temporal lobe epilepsy (burning rubber) and in brain tumors.
- Gustatory: rare, but seen in epilepsy.

Schizophrenia

- Chronic mental disorder with periods of psychosis, disturbed behavior and thought, and decline in functioning lasting > 6 months.

- Associated with ↑ dopaminergic activity in mesolimbic system, Current hypotheses posit ↑ serotonin as a cause of both positive and negative symptoms in schizophrenia.

- Diagnosis requires at least 2 of the following, and at least 1 of these should include 1-3 (first 4 are "positive symptoms"):

1. Delusions.
2. Hallucinations (often auditory).
3. Disorganized speech.
4. Disorganized or catatonic behavior.
5. Negative symptoms (affective flattening, avolition, anhedonia, asociality, alogia).

- Positive symptoms are those symptoms which are present in schizophrenic individuals but are not found in normal people.

- Negative symptoms are those symptoms which are absent in schizophrenic individuals but are found in normal people (five A's).

- Schizophreniform disorder: Schizophreniform disorder is differentiated from schizophrenia by the duration of symptoms. In schizophreniform disorder, symptoms must last for >1 month but <6 months. If symptoms persist beyond 6 months, the diagnosis is changed to schizophrenia.

- Brief psychotic disorder: lasting < 1 month, usually stress related.

- Schizoaffective disorder: Schizoaffective disorder is characterized by a significant mood episode (depressive or manic) with concurrent psychotic symptoms in addition to psychosis without mood symptoms for at least 2 weeks.

- The diagnosis of schizoaffective disorder requires assessing the longitudinal course of the Illness and determining if the patient has had at least 2 weeks of psychotic symptoms in the absence of a mood episode. Schizoaffective disorder is distinguished from schizophrenia by the presence of mood symptoms for a significant portion of the Illness.

- Frequent cannabis use is associated with psychosis/schizophrenia in teens.

- Lifetime prevalence: 1.5% (males = females, African Americans = Caucasians).

- Presents earlier in men (late teens to early 20s vs late 20s to early 30s in women).

- Patients are at ↑ risk for suicide.

- Neuroimaging studies have frequently shown loss of cortical tissue volume with ventricular enlargement in a subset of patients with schizophrenia, with lateral ventricular enlargement being the most widely replicated finding.

- Treatment: atypical antipsychotics (risperidone) are first line.

Differential diagnosis of DSM-5 psychotic disorders	
Brief psychotic disorder	**>1 day & <1 month**, sudden onset, full return to function
Schizophreniform disorder	**>1 month & <6 months**, same symptoms as schizophrenia, functional decline not required
Schizophrenia	**At least 6 months** (includes at least 1 month of active symptoms, can include prodromal & residual periods), requires functional decline
Schizoaffective disorder	Concurrent mood episode, active-phase symptoms of schizophrenia + at least 2-week lifetime history of delusions or hallucinations in the absence of prominent mood symptoms
Delusional disorder	**One or more delusions >1 month, no other psychotic symptoms**, normal functioning apart from direct impact of delusions

❖ N.B:

1. Acutely psychotic patients should be assessed for suicidal/homicidal ideation, command hallucinations to hurt self or others, and ability to care for self.

- Indications for involuntary psychiatric hospitalization include being a danger to self or others and/or grave disability, inability to care for self due to mental illness).

2. Although antipsychotic medication is the primary treatment for schizophrenia, integrating psychosocial interventions into a broader treatment program can improve outcomes.
- Patients with schizophrenia who have critical, hostile or over-involved family members have a higher risk of relapse, while patients have a decreased risk of relapse if the home atmosphere is stable and family stressors are kept to a minimum.

3. Antipsychotic medication nonadherence is a common cause of relapse and rehospitalization in patients with schizophrenia.
- Long-acting injectable antipsychotics are useful in patients who are chronically nonadherent but have responded to oral antipsychotics.
- LAI antipsychotics eliminate the need to take oral medication daily and are administered intramuscularly every 2-4 weeks.

4. The best approach to the psychotic patient with no insight is a nonjudgmental stance that acknowledges the patient's experience and perspective without endorsing specific delusions or hallucinations.
- After a physician-patient relationship is established and the patient's psychosis begins to improve, it may be appropriate to assist the patient in distinguishing psychotic thoughts from reality.

5. Capacity is a patient's ability to understand the illness, treatment options, and consequences and to express a choice reflecting a preference. It is used in medical situations to determine if someone has the ability to give informed consent to receive or refuse a specific intervention.
- Assessing capacity is especially important when someone's cognition may be impaired, such as in neurological conditions (dementia) or severe psychiatric illness.
- Patients with psychiatric diagnoses can give informed consent as long as they have capacity, meaning that their judgment and decision-making abilities are determined to be intact at the time of treatment.

Assessment of decision-making capacity	
Criterion	**Patient task**
Communicates a choice	Patient able to clearly indicate preferred treatment option
Understands information provided	Patient understands condition & treatment options
Appreciates consequences	Patient acknowledges having condition & likely consequences of treatment options, including no treatment
Rationale given for decision	Patient able to weigh risks & benefits & offer reasons for decision

6. The sudden onset of psychosis in a child or adolescent is rare, and it is important to search for potentially reversible conditions such as medical disorders or substance use.
   - Common medical conditions to rule out include systemic lupus erythematosus, thyroiditis, metabolic or electrolyte disorders, central nervous system infection, and epilepsy.

7. Medication-induced psychosis is characterized by delusions and/or hallucinations that are temporally associated with the use of a new medication and rapid onset of symptoms while the medication is being used.
   - Glucocorticoids, particularly at high doses, are often implicated in new-onset psychotic symptoms in patients who may have no current underlying psychiatric illness.

Mood disorder

- Characterized by an abnormal range of moods or internal emotional states and loss of control over them.
- Severity of moods causes distress and impairment in social and occupational functioning.
- Includes major depressive disorder, bipolar disorder, dysthymic disorder, and cyclothymic disorder. Episodic superimposed psychotic features (delusions or hallucinations) may be present.

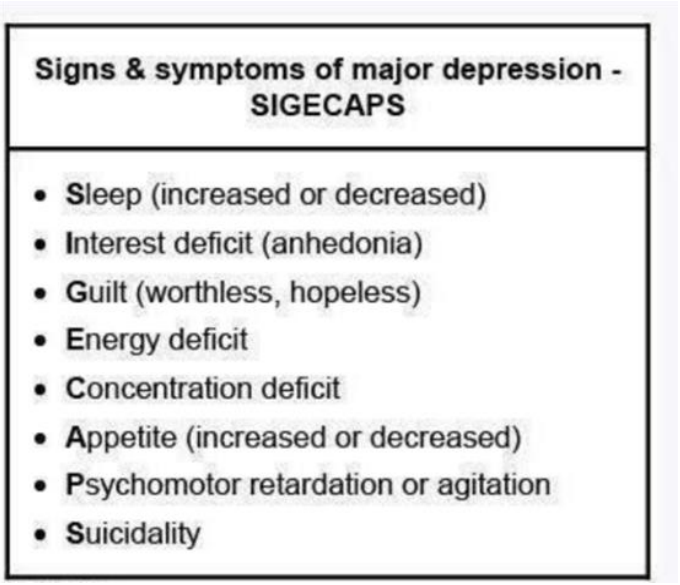
	Mild	Severe
Stable	Persistent Depressive Disorder	Major depression
Alternating	Cyclothymia	Bipolar (manic-depression)

Major depressive disorder

- Episodes characterized by at least 5 of the following 9 symptoms for 2 or more weeks (symptoms must include patient reported depressed mood or anhedonia).
- Persistent depressive disorder (dysthymia): depression, often milder, lasting at least 2 years.
- SIG E CAPS:

- Depressed mood.
- Sleep disturbance.
- Loss of Interest (anhedonia).
- Guilt or feelings of worthlessness.
- Energy loss and fatigue.
- Concentration problems.
- Appetite/weight changes.
- Psychomotor retardation or agitation.
- Suicidal ideations.

- Screen for history of manic or hypomanic episodes to rule out bipolar disorder.



- Patients with depression typically have the following changes in their sleep stages:

- ↓ REM latency (the time from sleep onset until the start of the first REM sleep period).
- ↑ REM early in sleep cycle.
- ↑ total REM sleep.
- Repeated nighttime awakenings.
- Early-morning wakening (terminal insomnia).

- Major depressive disorder is associated with hyperactivity of the hypothalamic-pituitary-adrenal axis, resulting in increased cortisol levels.

- Treatment:

- CBT and SSRIs are first line.
- SNRIs, mirtazapine, bupropion can also be considered.
- Electroconvulsive therapy (ECT) in select patients.

❖ N.B:

1. Periods of sadness are a normal part of human experience and should not be diagnosed as a psychiatric disorder unless criteria are met for severity, duration, and clinically significant distress or impairment.
   - Evaluation of depressive symptoms occurring in response to psychosocial stressors must take into account severity, duration, and degree of functional impairment. Mild or brief sadness without significant interference in psychosocial functioning is consistent with normal sadness.

2. Severe depression, especially in older adults, may present with features similar to dementia and is known as pseudodementia or reversible cognitive impairment.
   - Depression with pseudodementia should be considered in the differential diagnosis of elderly patients with cognitive impairment and depressive symptoms.
   - Antidepressants are the treatment of choice and should result in reversal of cognitive deficits.

Major depressive disorder with psychotic features

- MDD accompanied by hallucinations or delusions.
- Psychotic features are typically mood congruent (depressive themes of inadequacy, guilt, punishment, nihilism, disease, or death).
- Psychotic features occur only in the context of the major depressive episode (vs schizoaffective disorder).
- Treatment: antidepressant with atypical antipsychotic, ECT.

Persistent Depressive Disorder (dysthymia)

- ≥ 2 depressive symptoms lasting ≥ 2 years with no more than 2 months without depressive symptoms.
- Often milder, Patient is functional, but at a suboptimal level.
- Not severe enough for hospitalization.

Depression with Seasonal Pattern (seasonal affective disorder)

- Lasting ≥ 2 years with ≥ 2 major depressive episodes associated with seasonal pattern (usually winter) and absence of nonseasonal depressive episodes.
- Atypical symptoms common (hypersomnia, hyperphagia, leaden paralysis).
- May be related to abnormal melatonin metabolism.
- Treat with bright light therapy (not melatonin tablets).

Depression with atypical features

- Differs from classical forms of depression.
- Characterized by mood reactivity (being able to experience improved mood in response to positive events), "reversed" vegetative symptoms (hypersomnia, hyperphagia), leaden paralysis (heavy feeling in arms and legs), long-standing interpersonal rejection sensitivity.
- Most common subtype of depression.

- Treatment: CBT and SSRIs are first line. MAO inhibitors are effective but not first line because of their risk profile.

Manic episode

- Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently ↑ activity or energy lasting ≥ 1 week. Often disturbing to patient.

- Manic episodes can occur with or without psychotic features (delusions, hallucinations).

- Diagnosis requires hospitalization or marked functional impairment with ≥ 3 of the following (manics DIG FAST):

- Distractibility.
- Irresponsibility: seeks pleasure without regard to consequences (hedonistic).
- Grandiosity: inflated self-esteem.
- Flight of ideas: racing thoughts.
- ↑ in goal-directed Activity/psychomotor Agitation.
- ↓ need for Sleep.
- Talkativeness or pressured speech.

Hypomanic episode

- Like manic episode except mood disturbance is not severe enough to cause marked impairment in social and/or occupational functioning or to necessitate hospitalization.

- No psychotic features.

- Lasts ≥ 4 consecutive days.

Bipolar disorder (manic depression)

- Alternates between depression and mania.

- Subtypes:

- Bipolar I: mania and major depression. Most bipolar I patients will experience both major depressive and manic episodes, but depressive episodes are not required for diagnosis.

- Bipolar II: major depression plus hypomanic episodes.

- Bipolar I disorder includes manic episode(s) with or without a history of major depressive episodes. Bipolar II is distinguished from bipolar I by hypomanic episodes (less severe, less functional Impairment, no psychotic symptoms) and a history of one or more depressive episodes.

- Patient's mood and functioning usually return to normal between episodes.

- Use of antidepressants can precipitate mania.

- High suicide risk.

- Treatment:

- Mood stabilizers (lithium, valproic acid, carbamazepine), atypical antipsychotics.

Cyclothymic disorder

- Milder form of bipolar disorder lasting ≥ 2 years, fluctuating between mild depressive and hypomanic symptoms with symptoms present at least half of the time, with any remission lasting ≤ 2 months.

Electroconvulsive therapy

- Electroconvulsive therapy (ECT) uses a small electric current to produce a generalized seizure for 20-30 seconds under general anesthesia. ECT seems to cause changes in brain chemistry that can quickly reverse symptoms of certain mental health conditions.

- Used mainly for:

- Treatment-refractory depression.
- Depression with psychotic symptoms. Antidepressants typically take up to 6-8 weeks for response and must be combined with an antipsychotic medication to effectively treat major depression with psychotic features.
- Acutely suicidal patients.
- Severely depressed geriatric patients who are not eating or drinking and require a rapid intervention

- Adverse effects include disorientation, temporary headache, partial anterograde/retrograde amnesia usually resolving in 6 months.

- Safe in pregnancy.

Bipolar & related disorders

Manic episode

- Symptoms more **severe**
- **1 week** unless hospitalized
- **Marked impairment** in social or occupational functioning or **hospitalization** necessary
- May have **psychotic features**; makes episode manic by definition

Hypomanic episode

- Symptoms **less severe**
- **≥4 consecutive days**
- Unequivocal, observable change in functioning from patient's baseline
- Symptoms not severe enough to cause marked impairment or necessitate hospitalization
- **No psychotic features**

Bipolar I

- **Manic episode(s)**
- Depressive episodes common, but not required for diagnosis

Bipolar II

- **Hypomanic episode(s)**
- ≥1 major depressive episodes required

Cyclothymic disorder

- At least **2 years** of fluctuating, mild hypomanic & depressive symptoms that do not meet criteria for hypomanic episodes or major depressive episodes

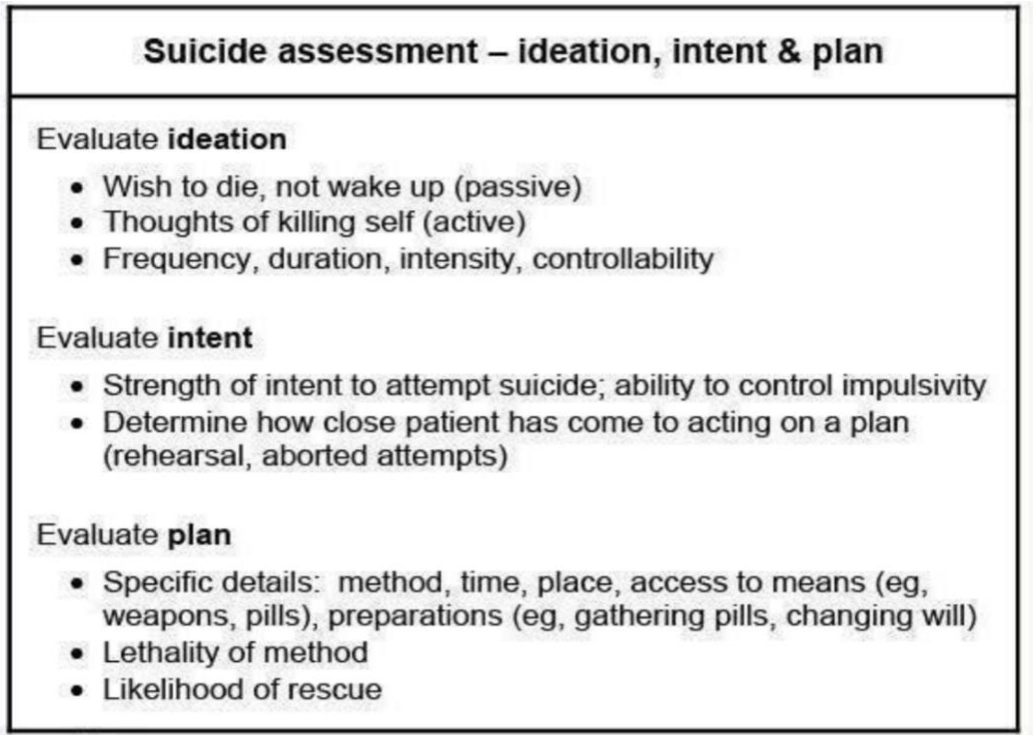
❖ N.B:

1. The US Food and Drug Administration issued a warning in 2007 that patients age 18-24 should be informed about the small risk of becoming suicidal during initial antidepressant treatment. This was based on studies showing a slightly increased risk of suicidal thoughts and behaviors (not completed suicide) among a small group of child and adolescent patients treated with antidepressants compared with placebo. However depression Itself is associated with an increased risk of suicide.

- The consensus among experts and practice guidelines is that the benefits of antidepressants for moderate to severe depression outweigh the risks, and appropriate antidepressant treatment should not be withheld due to this concern.
- Physicians should closely monitor patients for increasing suicidal thoughts and behaviors, especially following initiation of antidepressant treatment.

2. All depressed patients should be screened for suicidal ideation, intent, and plan.

- Actively suicidal patients with intent and plan will often need to be hospitalized for stabilization and to maintain their safety.



Suicide assessment – ideation, intent & plan

Evaluate **ideation**

- Wish to die, not wake up (passive)
- Thoughts of killing self (active)
- Frequency, duration, intensity, controllability

Evaluate **intent**

- Strength of intent to attempt suicide; ability to control impulsivity
- Determine how close patient has come to acting on a plan (rehearsal, aborted attempts)

Evaluate **plan**

- Specific details: method, time, place, access to means (eg, weapons, pills), preparations (eg, gathering pills, changing will)
- Lethality of method
- Likelihood of rescue

3. Cancer patients may have somatic symptoms that overlap those of depression (sleep disturbance, appetite change, poor energy).

- However, if there are additional symptoms such as guilt, loss of interest, feelings of hopelessness, or suicidal thoughts, major depression should be considered, with a low threshold for beginning treatment to provide relief and improve quality of life.

Postpartum mood disturbances

- Postpartum depression has a high incidence and is often underreported.
- Therefore, all women (regardless of prior psychiatric history) require screening for postpartum depression (Edinburgh Postnatal Depression Scale).

Maternal (postpartum) "blues"

- 50–85% incidence rate.
- Characterized by depressed affect, tearfulness, and fatigue starting 2-3 days after delivery.
- Normal physical activity continues, and care of self and baby is seen.
- Usually resolves within 10 days.
- Treatment:
  - Supportive (reassure the patient and encourage her to call if the symptoms do not remit spontaneously). Follow up to assess for possible postpartum depression.
- Women with depressive symptoms persisting beyond 2 weeks should be evaluated for postpartum depression.

MDD with peripartum onset

- 10–15% incidence rate.
- Formerly called postpartum depression.
- Meets MDD criteria with onset no later than 1 year after delivery.
- The patient often does not get out of bed with care of self and baby neglected.
- Treatment: CBT and SSRIs are first line.

Postpartum psychosis

- 0.1–0.2% incidence rate.
- Characterized by mood-congruent delusions, hallucinations, and thoughts of harming the baby or self.
- Risk factors include history of bipolar or psychotic disorder, first pregnancy, family history, recent discontinuation of psychotropic medication.
- Treatment:

- Postpartum psychosis is a medical emergency. Management involves hospitalization to ensure safety (suicide, infanticide) and antipsychotic medication; if insufficient, ECT may be used.

Postpartum blues, depression & psychosis

	Postpartum blues	Postpartum depression	Postpartum psychosis
Prevalence	40%-80%	8%-15%	0.1%-0.2%
Onset	2-3 days (resolves within 14 days)	Within 4 weeks	Variable: Days to weeks
Symptoms	Mild depression, tearfulness, irritability	Moderate to severe depression, sleep or appetite disturbance, low energy, psychomotor changes, guilt, concentration difficulty, suicidal ideation	Delusions, hallucinations, thought disorganization, bizarre behavior
Management	Reassurance & monitoring	Antidepressants, psychotherapy	Antipsychotics, antidepressants, mood stabilizers Hospitalization; do not leave mother alone with infant (risk of infanticide)

Grief

- The five stages of grief per the Kübler-Ross model are denial, anger, bargaining, depression, and acceptance (may occur in any order).

- Other normal grief symptoms include shock, guilt, sadness, anxiety, yearning, and somatic symptoms that usually occur in waves. Hallucinations of the deceased person are common (hearing the deceased speaking). Duration varies widely; usually resolves within 6-12 months.

- Persistent complex bereavement disorder involves obsessive preoccupation with the deceased and causes functional impairment, lasting at least 12 months (6 months in children).

- Can meet criteria for major depressive episode. In normal grief, pervasive anhedonia worthlessness, and suicidality are not present.

Five stages of grief – terminal illness	
Denial	Denies illness, severity, or prognosis
Anger	Directly expressed or may be displaced onto physician or others
Bargaining	Tries to "strike a bargain" in return for surviving illness
Depression	Becomes sad, detached, hopeless
Acceptance	Comes to terms with impending death, "at peace"

❖ N.B:

- Loss of a loved one can trigger the onset of a major depressive episode.
- Bereaved patients who develop major depression should be considered for treatment with both psychotherapy and a trial of antidepressants.
- Major depressive disorder must be differentiated from normal grief (Table).
- In normal grief, feelings of sadness revolve around the deceased, are less pervasive, and typically occur in waves following reminders of the deceased.
- Suicidal Ideation is less common, and self-esteem is preserved. If thoughts of dying are present, these typically involve joining the deceased. Intensity should decrease over time and antidepressant treatment is unnecessary.

Major depressive episode	Grief reaction (bereavement)
• Five of the following 9 symptoms: Sleep disturbances, appetite change, low energy, psychomotor changes, low mood, anhedonia, guilt, focus/concentration difficulty, suicidal ideation • Low mood or anhedonia must be present • May occur in response to a variety of stressors, including loss of loved one • Duration ≥2 weeks • Social & occupational dysfunction • Suicidality related to hopelessness & worthlessness	• Normal reaction to loss • Feelings of loss & emptiness • Symptoms revolve around the deceased • Functional decline less severe • "Waves" of grief at reminders • Worthlessness, self-loathing, guilt & suicidality less common • Sad feelings are more specific to deceased • Thoughts of dying involve joining the deceased • Intensity decreases over time (weeks to months)

Anxiety disorder

- Inappropriate experience of fear/worry and its physical manifestations (anxiety) incongruent with the magnitude of the perceived stressor.
- Symptoms interfere with daily functioning.
- Includes panic disorder, phobias, generalized anxiety disorder, and selective mutism.
- Treatment: CBT, SSRIs, SNRIs.

Generalized anxiety disorder

- Anxiety lasting ≥ 6 months unrelated to a specific person, situation, or event resulting in functional impairment.
- Associated with 3 or more of the following symptoms:

- Restlessness.
- Fatigue.
- Poor concentration.
- Irritability.
- Muscle tension.
- Impaired sleep.

- In GAD, the anxiety is chronic, excessive, difficult to control, and causes significant distress or impairment.
- Treatment:

- Treatment of GAD includes cognitive behavioral psychotherapy, medication, or a combination of both.
- First-line medications for GAD include selective serotonin reuptake inhibitors (SSRIs) such as escitaiopram or serotonin-norepinephrine reuptake inhibitors (SNRIs).
- Buspirone, TCAs, benzodiazepines are second line.

Generalized anxiety disorder	

DSM-5 criteria	• Excessive worry, anxiety (multiple issues) ≥6 months
	• Difficult to control
	• ≥3 of the following symptoms:
	  ○ Restlessness/feeling on edge
	  ○ Fatigue
	  ○ Difficulty concentrating
	  ○ Irritability
	  ○ Muscle tension
	  ○ Sleep disturbance
	• Significant distress or impairment
	• Not due to substances, another mental disorder, or medical condition

Treatment	• Cognitive behavioral therapy • SSRIs or SNRIs

SNRI = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor.

Adjustment disorder

- Emotional symptoms (anxiety, depression) within 3 months of the onset of the stressor causing impairment following an identifiable psychosocial stressor (divorce, illness) and lasting < 6 months.
- If symptoms persist > 6 months after stressor ends, it is GAD.
- Symptoms do not meet criteria for MDD.
- Treatment:

- CBT, SSRIs. The treatment of choice is psychotherapy that focuses on improving coping skills and promoting a return to functioning.

Differential diagnosis of depressed mood	
Major depressive disorder	• ≥2 weeks • **≥5 of 9 symptoms**: depressed mood & SIGECAPS • Significant functional impairment • No lifetime history of mania
Persistent depressive disorder (dysthymia)	• Chronic depressed mood ≥2 years • ≥2 of the following: appetite disturbance, sleep disturbance, low energy, low self-esteem, poor concentration, hopelessness
Adjustment disorder with depressed mood	• Onset within 3 months of identifiable stressor • Marked distress &/or functional impairment • Does not meet criteria for another DSM-5 disorder
Normal stress response	• Not excessive or out of proportion to severity of stressor • No significant functional impairment

Phobias

- Severe, persistent (≥ 6 months) fear or anxiety due to presence or anticipation of a specific object or situation.
- Person recognizes fear is excessive.
- Can be treated with systematic desensitization.

A. Social anxiety disorder (social phobia):

- Exaggerated fear of embarrassment in social situations (public speaking, using public restrooms).

- Treatment:
  - CBT, SSRIs, venlafaxine.
  - For only occasional anxiety-inducing situations, benzodiazepine or β-blocker (propranolol).

B. Agoraphobia:

- Exaggerated fear of open or enclosed places, using public transportation, being in line or in crowds, or leaving home alone.

- Associated with panic disorder.

- Treatment:
  - CBT, SSRIs, MAO inhibitors.
  - Behavioral therapy has been shown to be superior to pharmacologic treatment in specific phobia. Behavioral therapy involves exposure to the phobic stimulus in a gradual manner (systematic desensitization), which results in decreased anxiety overtime through habituation and extinction.

Specific phobia	
History & clinical features	• Marked anxiety about a **specific** object or situation (the phobic stimulus) for >6 months • Common types: Flying, heights, animals, injections, blood • Avoidance behavior (avoiding bridges and elevators, refusing work requiring travel) • Common, 10% of population • Usually develops in childhood; can develop after traumatic event
Treatment	• Cognitive-behavioral therapy with exposure is treatment of choice • Short-acting benzodiazepines may help acutely (therapist unavailable, insufficient time) but have a limited role

Obsessive-compulsive disorder

- Obsessive-compulsive disorder (OCD) is a condition characterized by time-consuming, recurrent, unwanted thoughts (obsessions) and repetitive behaviors that the patient feels compelled to perform (compulsions).

- Recurring intrusive thoughts, feelings, or sensations (obsessions) that cause severe distress; relieved in part by the performance of repetitive actions (compulsions).

- Ego-dystonic: behavior inconsistent with one's own beliefs and attitudes (vs obsessive-compulsive personality disorder).

- Associated with Tourette syndrome.

- Treatment:

- CBT, SSRIs, and clomipramine are first line.
- Exposure and response prevention-based psychotherapy and selective serotonin reuptake inhibitors are first-line treatments for obsessive-compulsive disorder.
- Exposure and response prevention involve repeated exposure to thoughts, images, and situations that provoke obsessional fears followed by prevention of the accompanying compulsion.

Obsessive-compulsive disorder	

Clinical features	• **Obsessions**
	  ○ Recurrent, intrusive, anxiety-provoking thoughts, urges, or images
	• **Compulsions**
	  ○ Response to obsessions with repeated behaviors or mental acts
	  ○ Behaviors not connected realistically with preventing feared event
	• Time-consuming (>1 hr/day) or causing significant distress or impairment

Treatment	• Selective serotonin reuptake inhibitor • Cognitive-behavioral therapy (exposure & response prevention)

Body dysmorphic disorder

- Preoccupation with minor or imagined defect in appearance → significant emotional distress or impaired functioning; patients often repeatedly seek cosmetic treatment.

- Treatment: CBT.

Body dysmorphic disorder	
Clinical features	• Preoccupation with ≥1 perceived physical defects • Defects are not observable or appear slight to others • Repetitive behavior or mental acts performed in response to the preoccupation • Significant distress or impairment • Specific insight (good, poor, absent/delusional beliefs)
Management	• Antidepressants (selective serotonin reuptake inhibitors) • Cognitive-behavioral therapy

Panic disorder

- Defined by recurrent panic attacks (periods of intense fear and discomfort +/− a known trigger, peaking in 10 minutes with ≥ 4 of the following):

- Palpitations.
- Paresthesias.
- dePersonalization or derealization.
- Abdominal distress or Nausea.
- Intense fear of dying.
- Intense fear of losing control or "going crazy".
- light-headedness.
- Chest pain.
- Chills.
- Choking.
- Sweating.
- Shaking.
- Shortness of breath.
- Strong genetic component.

- $P_3AN[ICS]_3$

- Diagnosis requires attack followed by ≥ 1 month of ≥ 1 of the following:

- Persistent concern of additional attacks.
- Worrying about consequences of attack.
- Behavioral change related to attacks.

- Diagnosis requires differentiation from other anxiety disorders that may include triggered panic attacks and ruling out medical and substance-induced causes.

- Treatment:

- Benzodiazepines provide rapid relief of anxiety and are indicated for the management of acutely symptomatic and functionally impaired patients with panic disorder.
- SSRIs, venlafaxine and cognitive-behavioral therapy are preferred for long-term treatment.

Post-traumatic stress disorder

- Exposure to prior trauma (witnessing death, experiencing serious injury or rape) → persistent Hyperarousal, Avoidance of associated stimuli, intrusive Reexperiencing of the event (nightmares, flashbacks), changes in cognition or mood (fear, horror, Distress)

- Having PTSD is HARD.

- Disturbance lasts ≥ 1 month with significant distress or impaired social-occupational functioning.

- Returning combat veterans and survivors of sexual assault are at high risk for developing post-traumatic stress disorder.

- Treatment:

- Trauma-focused cognitive-behavioral therapy and selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors are first-line treatments for post-traumatic stress disorder.

Post-traumatic stress disorder	
Clinical features	• Exposure to life-threatening trauma • Nightmares, flashbacks, intrusive memories • Avoidance of reminders, amnesia for event • Emotional detachment, negative mood, decreased interest in activities • Sleep disturbance, hypervigilance, irritability • Duration ≥1 month
Treatment	• Trauma-focused cognitive-behavioral therapy • Antidepressants (SSRIs, SNRIs)

SNRI = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor.

Acute stress disorder

- Acute stress disorder is a severe anxiety response characterized by re-experiencing of trauma, dissociation, negative mood, avoidance, and hyperarousal lasting >3 days and <1 month after exposure to a traumatic event.

- Treatment:

- CBT; pharmacotherapy is usually not indicated.

Trichotillomania

- Compulsively pulling out one's own hair.
- Causes significant distress and persists despite attempts to stop.
- Presents with areas of thinning hair or baldness on any area of the body.
- Commonly affected sites include the scalp, eyebrows, and eyelids.
- Incidence highest in childhood but spans all ages.
- Treatment:

- Psychotherapy is first line; medications (clomipramine) may be considered.

Trichotillomania (hair pulling disorder)	
DSM-5	• Recurrent hair pulling resulting in hair loss • Repeated attempts to decrease/stop hair pulling • Significant distress or impairment • Not due to a medical/dermatological condition (eg, alopecia areata) • Not due to another mental disorder (eg, body dysmorphic disorder)
Treatment	• Cognitive behavioral therapy (habit reversal training)

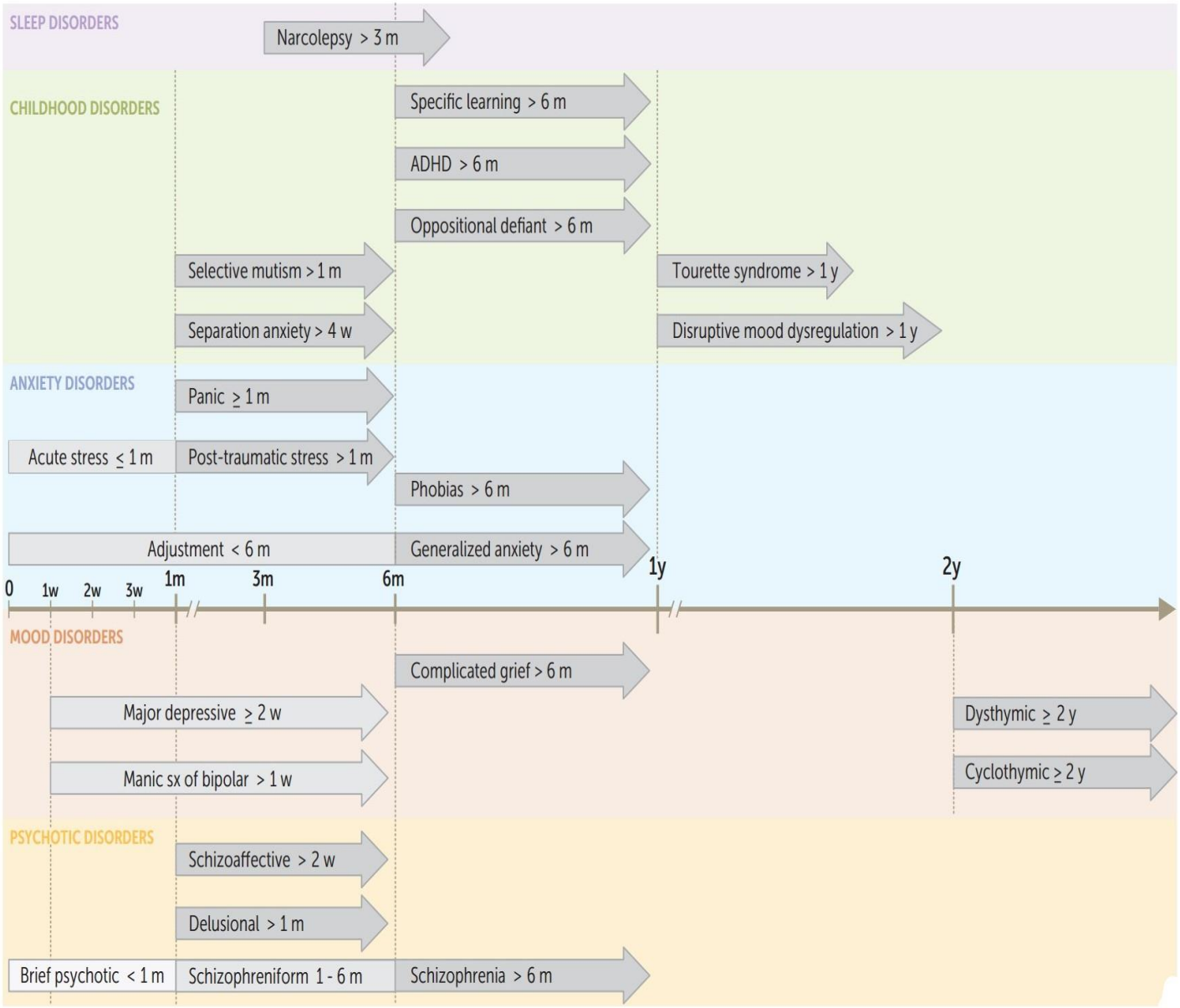
Selective mutism

- Children (Onset before age 5) with selective mutism are verbal and talkative at home but refuse to speak in specific social settings, commonly at school.
- It is considered an anxiety disorder and should be treated early to prevent long-term educational and social impairment.
- This diagnosis requires consistent (≥ 1 month) failure to talk in situations in which it is expected (school) despite speaking in other situations.
- Refusal to speak at school can impair both academic and social development and should not be considered normal shyness.

Hoarding disorder

- Hoarding disorder is characterized by accumulation of a large number of possessions that may clutter living areas to the point that they are unusable.
- Patients experience intense distress when attempting to discard possessions regardless of their actual value.
- Social isolation due to embarrassment (being unable to Invite people to their homes) may also occur.

Diagnostic criteria by symptom duration



Somatic symptom and related disorders

- It is best treated with cognitive-behavioral therapy.

- Category of disorders characterized by physical symptoms causing significant distress and impairment.

- Both illness production and motivation are unconscious driven. Symptoms not intentionally produced or feigned.

- More common in women.

A. Somatic symptom disorder:

- ≥ 1 somatic symptoms (pain, fatigue) causing distress and functional impairment for ≥ 6 months duration.

- It involves excessive preoccupation and overestimation of the seriousness of ≥ 1 somatic complaints and is associated with high levels of medical care utilization.

- Associated with excessive, persistent thoughts and anxiety about symptoms.

- Initial management of somatic symptom disorder consists of regularly scheduled visits with the same physician to develop the physician-patient relationship and minimize unnecessary medical testing, interventions, and subspecialty referrals.

- Because symptoms often worsen during periods of stress, patients should be asked about their current emotional stressors and counseled regarding stress reduction.

Somatic symptom disorder	

Clinical features	• ≥1 somatic symptom(s) causing distress & functional impairment
	• Excessive thoughts or behaviors related to somatic symptoms
	  ○ Unwarranted, persistent thoughts about seriousness of symptoms
	  ○ Persistent anxiety about health or symptoms
	  ○ Excessive time & energy devoted to symptoms
	• ≥6 months duration

Management	• Regularly scheduled visits with same provider • Limit unnecessary workup & specialist referrals • Legitimize symptoms but make functional improvement the goal • Focus on stress reduction & improving coping strategies • Mental health referral if patient will accept

B. Conversion disorder (functional neurologic symptom disorder):

- Conversion disorder is characterized by sudden onset of neurological symptoms (paralysis, blindness, mutism) and clinical findings that are incompatible with recognized neurological conditions.

- Conversion disorder is often precipitated by stress (relationship conflicts), and patients can present as hysterical or strangely indifferent ("la belle indifference") to their symptoms.

- First-line treatment includes education, encouragement, and support for patients and family members about the disorder and self-help techniques. If patients do not respond to education, cognitive behavioral therapy is offered as second-line option.

Conversion disorder (functional neurological symptom disorder)	
Common presenting symptoms	• Weakness &/or paralysis • Nonepileptic seizures • Movement disorders • Speech or visual impairment • Swallowing difficulty • Sensory disturbances • Cognitive symptoms
Diagnostic criteria	• Symptoms of altered neurological function - voluntary motor or sensory • Often precipitated by psychological stressor • Not feigned or intentionally produced (as in factitious disorder or malingering) • Findings incompatible with recognized neurological conditions • Symptoms cause significant social or occupational impairment
Stepwise treatment options	• Education & self-help techniques - first-line • Cognitive behavioral therapy - second-line • Physical therapy for motor symptoms

C. Illness anxiety disorder (hypochondriasis):

- Excessive preoccupation with acquiring or having a serious illness, often despite medical evaluation and reassurance; minimal somatic symptoms.

D. Pseudocyesis:

- Pseudocyesis is a rare psychiatric condition in which a woman presents with nearly all signs and symptoms of pregnancy (amenorrhea, enlargement of the breasts and abdomen, morning sickness, weight gain, sensation of fetal movement and reported positive urine pregnancy test per the patient); however, ultrasound reveals a normal endometrial stripe and negative pregnancy test.

Factitious disorders

- Patient consciously creates physical and/or psychological symptoms in order to obtain attention and receive protracted care (to assume the sick role).
- They lack conscious awareness of why they do it.
- Behaviors may include deceptive reporting of symptoms, manipulating laboratory samples, ingesting a substance (insulin), altering medical records, or inducing illness (injecting fecal matter to produce an abscess).

	Somatic Symptom	Factitious	Malingering
Symptom production	Unconscious	Intentional	Intentional
Motivation	Unconscious	Unconscious	Intentional

A. Factitious disorder imposed on self (Munchausen syndrome):

- Chronic factitious disorder with predominantly physical signs and symptoms.
- Characterized by a history of multiple hospital admissions and willingness to undergo invasive procedures.

B. Factitious disorder imposed on another (Munchausen syndrome by proxy):

- Illness in a child or elderly patient is caused or fabricated by the caregiver.
- Motivation is to assume a sick role by proxy.
- Form of child/elder abuse.

Malingering

- Patient consciously fakes, profoundly exaggerates, or claims to have a disorder in order to attain a specific 2° (external) gain (avoiding work, narcotics, obtaining financial compensation).
- Poor compliance with treatment or follow-up of diagnostic tests.
- Complaints cease after gain (vs factitious disorder).

Key features of somatic symptom & related disorders	
Somatic symptom disorder	Excessive anxiety & preoccupation with ≥1 unexplained symptoms
Illness anxiety disorder	Fear of having a serious illness despite few or no symptoms & consistently negative evaluations
Conversion disorder (functional neurologic symptom disorder)	**Neurologic** symptom incompatible with any known neurologic disease; often acute onset associated with stress
Factitious disorder	Intentional falsification or inducement of symptoms with goal to assume **sick role**
Malingering	Falsification or exaggeration of symptoms to obtain external incentives (**secondary gain**)

Dissociative disorders

Depersonalization/derealization

- Episodes of depersonalization are characterized by a feeling of detachment or estrangement from the self or a sense of being an outside observer of the self.
- Derealization is a subjective sense of detachment or unreality regarding surroundings.

Dissociative identity disorder

- Formerly known as multiple personality disorder. Presence of 2 or more distinct identities or personality states.
- More common in women.
- Associated with history of sexual abuse, PTSD, depression, substance abuse, borderline personality, somatoform conditions.

Dissociative amnesia

- Inability to recall important personal information, usually subsequent to severe trauma or stress.

Dissociative disorders	
Depersonalization/ derealization disorder	• Persistent or recurrent experiences of 1 or both: o Depersonalization (feelings of detachment from, or being an outside observer of, one's self) o Derealization (experiencing surroundings as unreal) • Intact reality testing
Dissociative amnesia	• Inability to recall important personal information, usually of a traumatic or stressful nature • Not explained by another disorder (eg, substance use, post-traumatic stress disorder)
Dissociative identity disorder	• Marked discontinuity in identity & loss of personal agency with fragmentation into ≥2 distinct personality states • Associated with severe trauma/abuse

Eating disorders

- Most common in young females.

Anorexia nervosa

- Patents with anorexia nervosa restrict their energy intake to maintain a body weight that is below a minimal level for age and sex (typically a BMI <18.5). As a result, they develop an emaciated body type and signs and symptoms secondary to starvation.

- Anorexia nervosa can be divided into 2 subtypes restricting and binge eating/purging:

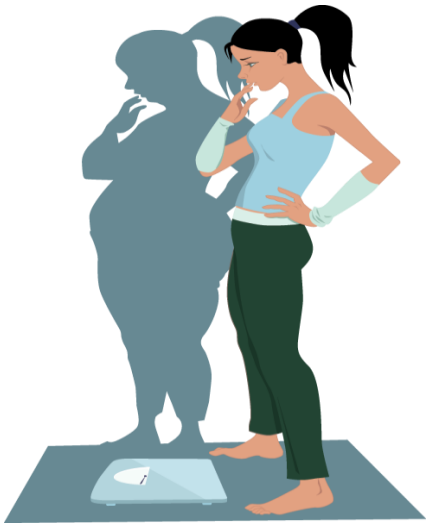
- In the restricting type: weight loss occurs through dieting and/or intensive exercising.
- In the binge eating/purging subtype: the anorectic patient engages in purging behavior (self-induced vomiting, misuse of laxatives, diuretics, enema). Patients who induce vomiting may have parotid gland hypertrophy, dental caries, halitosis, and calluses on the dorsum of their hands (Russell sign).

- Associated with compression fracture (↓ bone density), severe weight loss, metatarsal stress fractures, amenorrhea (due to loss of pulsatile GnRH secretion), lanugo (fine, downy body hair), anemia, electrolyte disturbances (hypokalemia, hypochloremia, metabolic alkalosis) and vital sign derangements (hypotension, hypothermia, bradycardia). Commonly coexists with depression.

- Although amenorrhea is common, not all patients exhibit this finding and it is no longer required for diagnosis in DSM-5.

- Psychotherapy and nutritional rehabilitation are first line. Patients with anorexia nervosa require hospitalization for nutritional rehabilitation when they have unstable vital signs, cardiac dysrhythmias, electrolyte derangements, or severely low body weight.

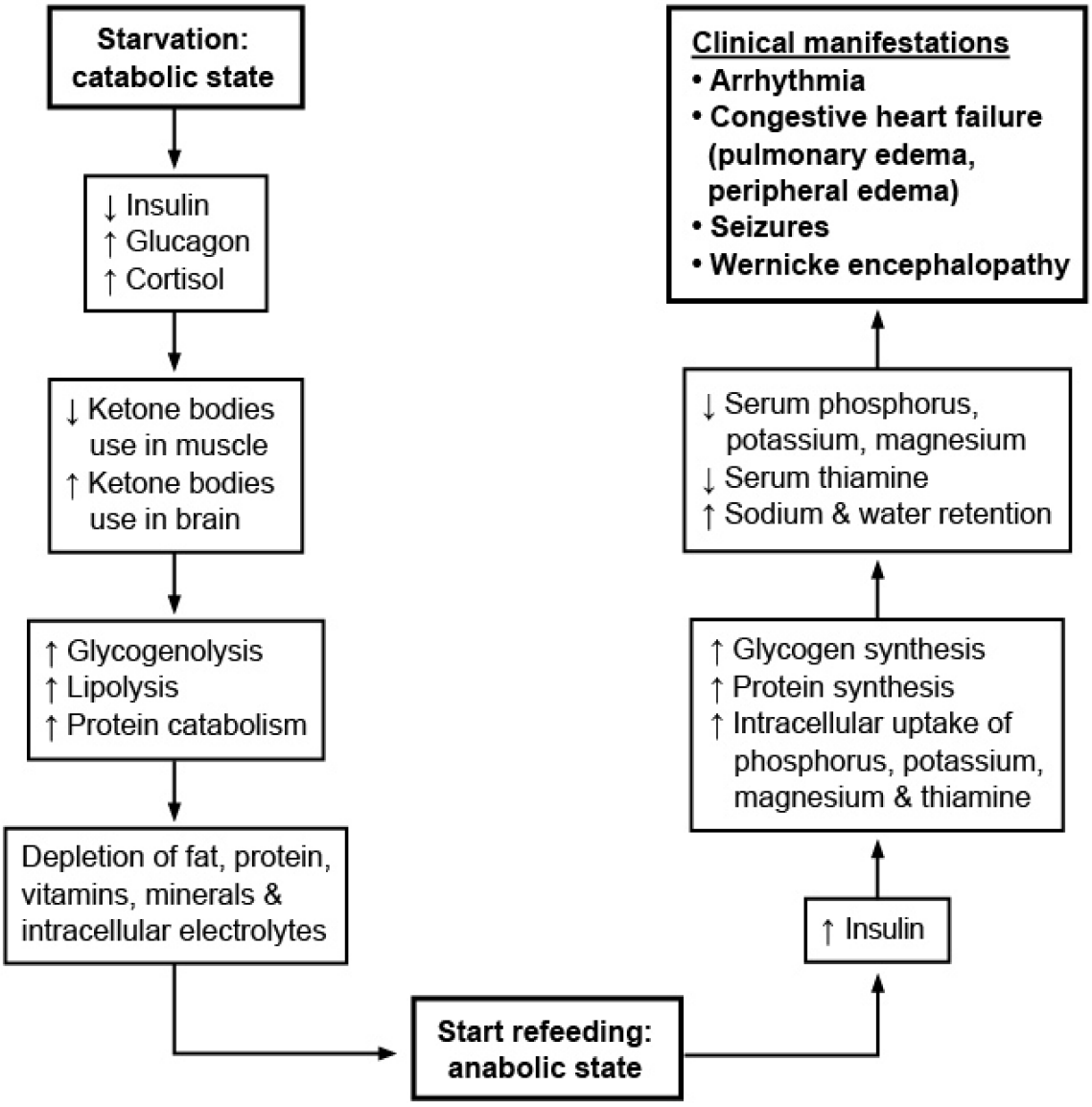
Anorexia nervosa	
Clinical features	• BMI <18.5 • Intense fear of weight gain • Distorted views of body weight & shape
Treatment	• Cognitive-behavioral therapy • Nutritional rehabilitation • Olanzapine for severe cases
Complications	• Hypothermia • Malnutrition • Dehydration • Orthostatic hypotension • Arrhythmia • Refeeding syndrome



❖ N.B:

- Chronic starvation and acute refeeding are potentially life-threatening in patients with anorexia nervosa.
- Refeeding syndrome is the constellation of pathologic derangements resulting from a surge in insulin activity as the body resumes anabolism (Flow chart).
- Carbohydrate ingestion, whether enteral or intravenous, causes pancreatic insulin secretion and cellular uptake of phosphorus, potassium, and magnesium.
- Phosphorus is the primary deficient electrolyte as it is required for energy (adenosine triphosphate).
- Deficiencies in potassium and magnesium potentiate cardiac arrhythmias in a heart that is already atrophic from prolonged malnutrition.
- Therefore, aggressive initiation of nutrition without adequate electrolyte repletion can quickly precipitate arrhythmias and cardiopulmonary failure.

Pathogenesis of refeeding syndrome



Bulimia nervosa

- Binge eating with recurrent inappropriate compensatory behaviors to prevent weight gain (self-induced vomiting, using laxatives or diuretics, fasting, excessive exercise) occurring weekly for at least 3 months and overvaluation of body image.

- Body weight often maintained within normal range to overweight, in contrast to individuals with anorexia nervosa.

- Associated with parotitis, enamel erosion, electrolyte disturbances, alkalosis, dorsal hand calluses from induced vomiting (Russell sign).

- Treatment: psychotherapy, nutritional rehabilitation, antidepressants.

Bulimia nervosa	
Clinical features	• Recurrent episodes of binge eating • Binges followed by compensatory behaviors to prevent weight gain (eg, vomiting, fasting, exercise, laxatives) • Excessive preoccupation with body weight & shape • Body weight within or above normal range
Treatment	• Selective serotonin reuptake inhibitor (fluoxetine) • Nutritional rehabilitation • Cognitive-behavioral therapy

Binge eating disorder

- Regular episodes of excessive, uncontrollable eating without inappropriate compensatory behaviors.

- ↑ risk of diabetes.

- Treatment:

- Psychotherapy such as CBT is first-line; SSRIs.

Pica

- Recurring episodes of eating non-food substances (dirt, hair, paint chips) over ≥ 1 month that are not culturally or developmentally recognized as normal.
- May provide temporary emotional relief.
- Common in children; also common during pregnancy.
- Associated with malnutrition, anemia, developmental disabilities, emotional trauma.
- Treatment:

- Varies by age and suspected cause, but typically includes psychotherapy and nutritional rehabilitation (first line); SSRIs (second line).

Eating disorders	
Diagnosis	**Clinical features**
Anorexia nervosa	• **Significantly low weight** • Intense fear of weight gain • Distorted views of body weight & shape • Subtypes: Binge/purge, restricting
Bulimia nervosa	• Recurrent episodes of binge eating • **Compensatory behavior** (vomiting, exercise, fasting) to prevent weight gain • Excessive worry about body shape & weight • Maintains **normal body weight**
Binge eating disorder	• Recurrent binge eating with lack of control • **No compensatory behaviors**

Orientation

- Patient's ability to know who he or she is, where he or she is, and the date and time.
- Common causes of loss of orientation: alcohol, drugs, fluid/electrolyte imbalance, head trauma, hypoglycemia, infection, nutritional deficiencies.
- Order of loss: 1st: time; 2nd: place; last: person.

Amnesias

A. Retrograde amnesia:
- Inability to remember things that occurred before a CNS insult.

B. Anterograde amnesia:
- Inability to remember things that occurred after a CNS insult (↓ acquisition of new memory).

C. Korsakoff syndrome:
- Amnesia (anterograde > retrograde) caused by vitamin B_1 deficiency and associated destruction of mammillary bodies.
- Seen in alcoholics as a late neuropsychiatric manifestation of Wernicke encephalopathy. Confabulations are characteristic.

D. Dissociative amnesia:
- Inability to recall important personal information (isolated impairment in autobiographical memory), usually subsequent to severe trauma or stress.
- May be accompanied by dissociative fugue (abrupt travel or wandering during a period of dissociative amnesia, associated with traumatic circumstances).

Delirium

- "Waxing and waning" level of consciousness with acute onset; rapid ↓ in attention span and level of arousal.
- Characterized by disorganized thinking, hallucinations (often visual), illusions, misperceptions, disturbance in sleep-wake cycle, cognitive dysfunction.
- Usually 2° to other illness (CNS disease, infection, trauma, substance abuse/withdrawal, metabolic/electrolyte disturbances, hemorrhage, urinary/fecal retention).
- Most common presentation of altered mental status in inpatient setting.
- Commonly, diffuse slowing EEG.
- Treatment is aimed at identifying and addressing underlying condition. Haloperidol may be used as needed. Use benzodiazepines for alcohol withdrawal.
- Delirium = changes in sensorium.
- May be caused by medications (anticholinergics), especially in the elderly.
- Reversible.
- TA-DA approach (Tolerate, Anticipate, Don't Agitate) helpful for management.

❖ N.B:

- Delirium-induced psychosis is differentiated from primary psychotic disorders by fluctuating levels of consciousness, acuity of onset, and association with an underlying condition and/or offending medications. Although antipsychotics can be used to target the psychotic manifestations of delirium, the primary treatment is the identification and treatment of the underlying condition.

Dementia

- ↓ in intellectual function without affecting level of consciousness.
- Characterized by memory deficits, apraxia, aphasia, agnosia, loss of abstract thought, behavioral/personality changes, impaired judgment.
- A patient with dementia can develop delirium (patient with Alzheimer disease who develops pneumonia is at ↑ risk for delirium).
- Irreversible causes: Alzheimer disease, Lewy body dementia, Huntington disease, Pick disease, cerebral infarct, Creutzfeldt-Jakob disease, chronic substance abuse (due to neurotoxicity of drugs).
- Reversible causes: hypothyroidism, depression, vitamin B12 deficiency, normal pressure hydrocephalus, neurosyphilis.
- ↑ incidence with age. EEG usually normal.
- "Dememtia" is characterized by memory loss.
- Usually irreversible.
- In elderly patients, depression and hypothyroidism may present like dementia (pseudodementia). Screen for depression and measure TSH, B12 levels.

❖ N.B:

1. Delirium is a reversible, acute-onset confusional state characterized by a fluctuating level of consciousness with deficits in attention, memory, and executive function. In contrast, dementia is of gradual onset, is irreversible, and does not involve fluctuations in consciousness.

2. Normal age-related cognitive changes include occasional forgetfulness and word-finding difficulty that do not impact activities of daily living.

- Cognitive deficits that interfere with independence in everyday activities are a key feature that distinguishes dementia (major neurocognitive disorder) from normal age-related changes. Patients with dementia have functional impairments that necessitate assistance.

Clinical features of delirium, dementia & depression in the elderly			
	Delirium	**Dementia**	**Depression**
Onset	Acute	Gradual (months to years)	Gradual (months)
Consciousness	Impaired	Intact	Intact
Course	Fluctuating	Progressive	Episodic
Prognosis	Reversible	Irreversible	Reversible
Memory impairment	Global impairment	Remote memory spared	Moderately impaired focus/concentration

	Normal aging	**Dementia (major cognitive disorder)**
Memory loss	• Can provide details about incidents of forgetfulness • Patient is concerned about memory loss • Recent memory for important events & conversations is intact	• Cannot remember specific instances of forgetfulness • Family is more concerned than patient • Has notable decline in memory for recent important events & conversations
Word-finding difficulty	• Occasional (expressive aphasia) • No receptive aphasia	• Frequent, with substitutions • Some receptive aphasia
Independence & functioning	• Maintains independence in ADLs • Is able to operate common appliances • Maintains interpersonal social skills • Does not get lost in familiar territory (may have to pause briefly to reorient)	• Becomes dependent on others for ADLs • Is unable to operate common appliances • Loses interest in social activities • Can get lost for hours in familiar territory while driving or walking

ADL = activities of daily living.

Personality

A. Personality trait:

- An enduring, repetitive pattern of perceiving, relating to, and thinking about the environment and oneself.

B. Personality disorder:

- Inflexible, maladaptive, and rigidly pervasive pattern of behavior causing subjective distress and/or impaired functioning; person is usually not aware of problem (Ego- syntonic).

- Usually presents by early adulthood.

- Three clusters, A, B, and C; remember as Weird, Wild, and Worried based on symptoms.

Cluster A personality disorders

- Odd or eccentric; inability to develop meaningful social relationships. No psychosis; genetic association with schizophrenia.

- "Weird" (Accusatory, Aloof, Awkward).

A. Paranoid:

- Pervasive distrust and suspiciousness; projection is the major defense mechanism.

B. Schizoid:

- Voluntary social withdrawal, limited emotional expression, content with social isolation (vs avoidant).

- Individuals with schizoid personality disorder are socially detached and prefer to be alone.

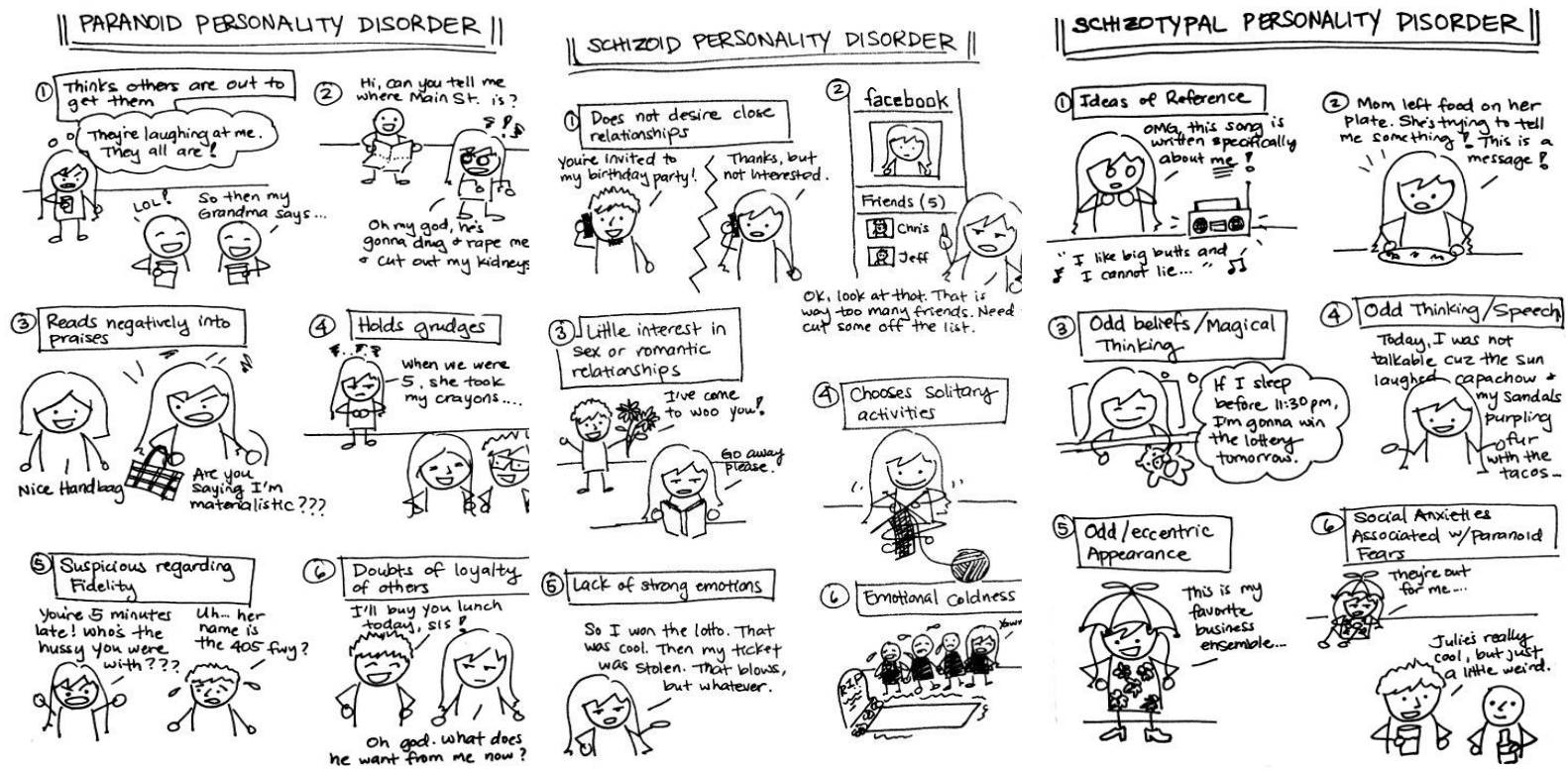
- They can be differentiated from individuals with avoidant personality disorder, who desire relationships but avoid them due to fears of rejection. They also lack the eccentric cognitions and perceptual distortions characteristic of schizotypal personality disorder.

- Schizoid = distant.

C. Schizotypal:

- Eccentric appearance, odd beliefs or magical thinking, idea of reference, interpersonal awkwardness.

- Schizotypal = magical thinking.



Cluster B personality disorders

- Dramatic, emotional, or erratic; genetic association with mood disorders and substance abuse.
- "Wild" (Bad to the Bone).

A. Antisocial:

- Disregard for and violation of rights of others, criminality, impulsivity; males > females; must be ≥ 18 years old and have history of conduct disorder before age 15.
- Conduct disorder if < 18 years old.
- Antisocial = sociopath.

B. Borderline:

- Unstable mood and interpersonal relationships, impulsivity, self-mutilation (cutting, burning), suicidality, sense of emptiness; females > males; splitting is a major defense mechanism.
- They experience extreme mood reactivity to interpersonal stresses and frequently alternate between extremes of idealizing and devaluing others (defense mechanism of splitting).

- A history of childhood trauma (physical and sexual abuse, neglect) is common in patients with BPD. Insecure attachment to the primary caregiver may underlie the unstable relationships and fears of abandonment commonly seen in the disorder.

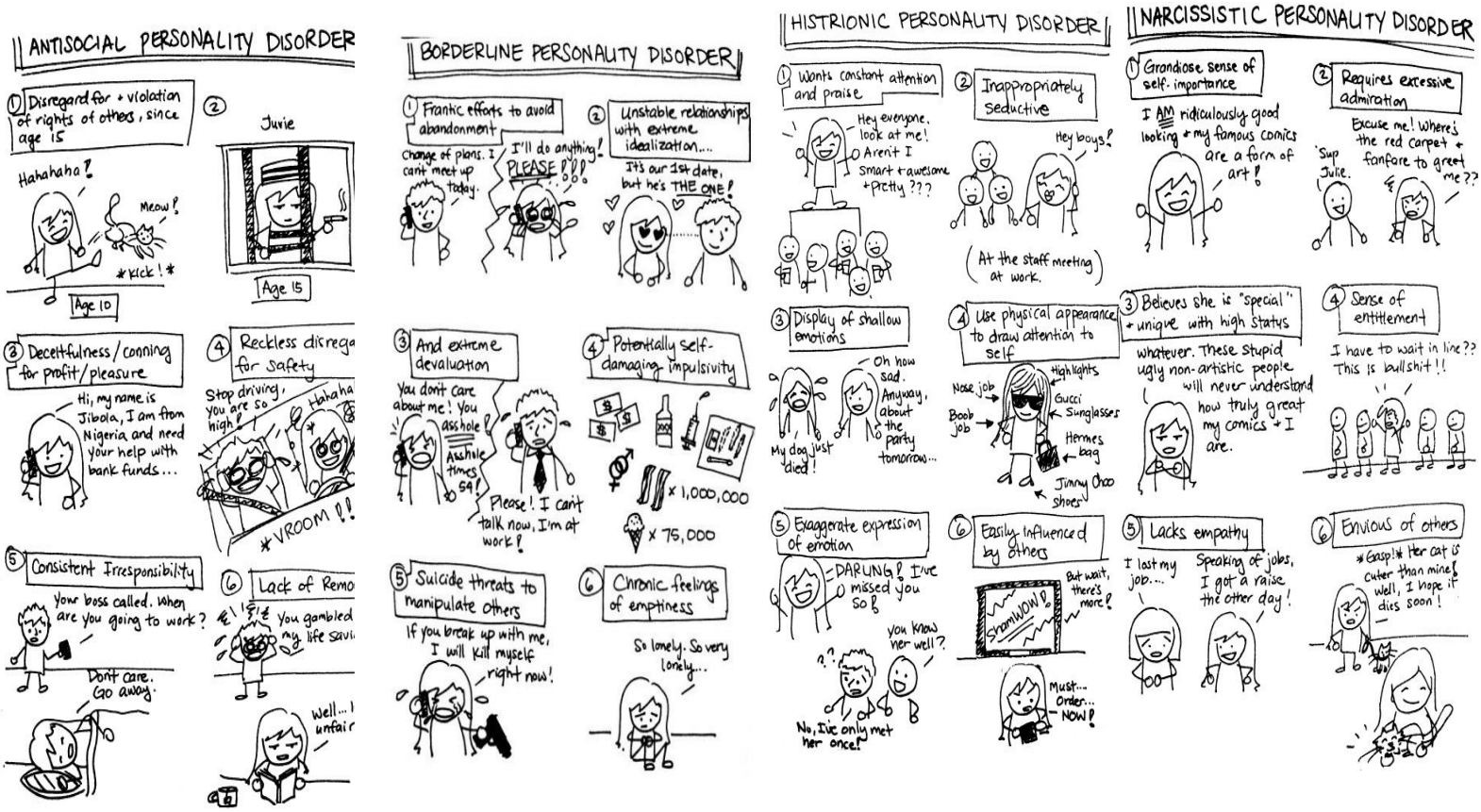
- Psychotherapy is the treatment of choice for BPD, with the best evidence for dialectical behavioral therapy (DBT). DBT is a form of cognitive-behavioral therapy developed specifically for BPD. It integrates techniques of emotion regulation and principles of mindfulness and distress tolerance to target unstable moods, impulsivity. and suicidality. Pharmacological treatments do not treat the core pathology of BPD and are used adjunctively.

C. Histrionic:

- Excessive emotionality and excitability, attention seeking, sexually provocative, overly concerned with appearance.

D. Narcissistic:

- Grandiosity, sense of entitlement; lacks empathy and requires excessive admiration; often demands the "best" and reacts to criticism with rage.



Cluster C personality disorders

- Anxious or fearful; genetic association with anxiety disorders.

- "Worried" (Cowardly, Compulsive, Clingy).

A. Avoidant:

- Hypersensitive to rejection, socially inhibited, timid, feelings of inadequacy, desires relationships with others (vs schizoid).

- Patients with avoidant personality disorder typically have very limited social relationships due to fears of being judged, embarrassed, or rejected. They struggle with feelings of inadequacy and pursue relationships only when they feel assured of uncritical acceptance. Occupational dysfunction due to difficulties interacting with coworkers or turning down promotions due to fear of criticism is common.

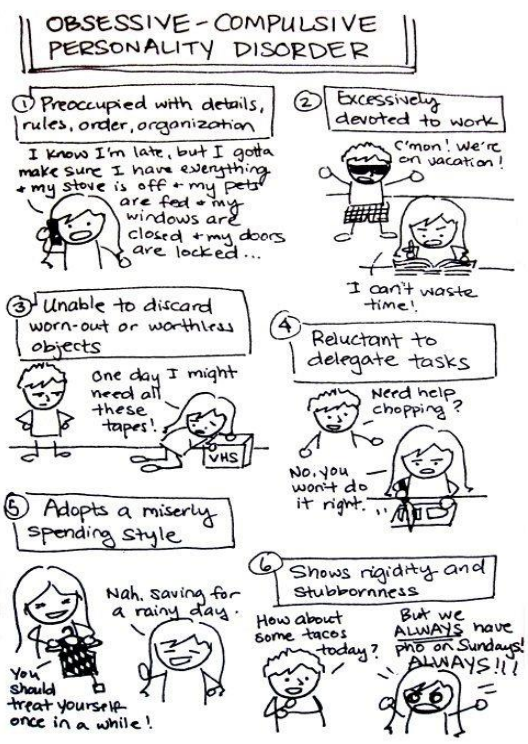
B. Obsessive-compulsive:

- Preoccupation with order, perfectionism, and control; ego-syntonic: behavior consistent with one's own beliefs and attitudes (vs OCD).
- It is differentiated from obsessive-compulsive disorder by the lack of true obsessions and compulsions.

C. Dependent:

- Submissive and clingy, excessive need to be taken care of, low self-confidence.

- Patients often get stuck in abusive relationships.



DSM-5 personality disorders	
Cluster A Odd/eccentric	• **Paranoid:** suspicious, distrustful, hypervigilant • **Schizoid:** prefers to be a loner; detached, unemotional • **Schizotypal:** unusual thoughts, perceptions & behavior
Cluster B Dramatic/erratic	• **Antisocial:** disregard & violation of the rights of others • **Borderline:** chaotic relationships, abandonment fears, labile mood, impulsivity, inner emptiness, self-harm • **Histrionic:** superficial, theatrical, attention-seeking • **Narcissistic:** grandiosity, lack of empathy
Cluster C Anxious/fearful	• **Avoidant:** avoidance due to fears of criticism & rejection • **Dependent:** submissive, clingy, needs to be taken care of • **Obsessive-compulsive:** rigid, controlling, perfectionistic

❖ N.B:

- Kleptomania is an impulse control disorder. These individuals experience impulses to steal objects that are of low monetary value or not needed for personal use. In contrast, stealing by typical shoplifters may be premeditated and for personal gain.
- In kleptomania, overwhelming feelings of tension or anxiety precede impulses and are relieved with the act of theft. Feelings of guilt and shame typically follow these acts, and these individuals may return or give away stolen items.
- Kleptomania can be treated with psychotherapy as well as medications. Psychotherapy involves a cognitive behavioral therapy orientation, focusing on techniques to resist and manage urges and anxiety. Medications that have been used include selective serotonin reuptake inhibitors.

Kleptomania	
Clinical features	• Rare impulse control disorder with typical onset in adolescence • Repetitive failure to resist impulses to steal • Stolen objects have little value • Increasing tension prior to theft; pleasure or relief when committing theft • Stolen objects given away, discarded, or returned; guilt & remorse are common
Differential diagnosis	• Shoplifting: Theft for personal gain; much more common • Antisocial personality disorder: General pattern of antisocial behavior • Bipolar disorder, manic episode: Impulsivity, impaired judgment • Psychotic disorders: Stealing in response to delusions, hallucinations

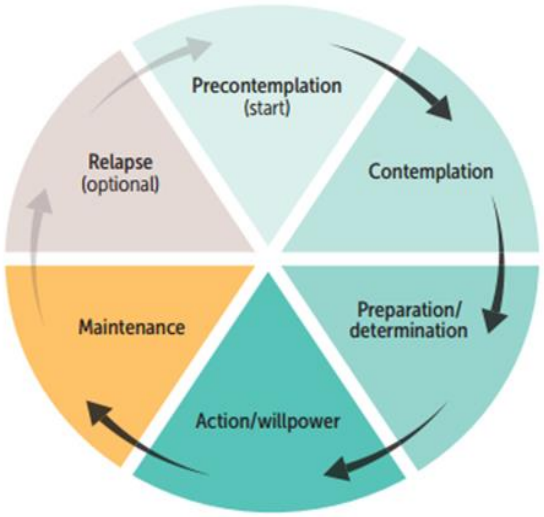
Substance use disorder

- Maladaptive pattern of substance use defined as 2 or more of the following signs in 1 year:

- Tolerance: need more to achieve same effect.
- Withdrawal.
- Substance taken in larger amounts, or over longer time, than desired.
- Persistent desire or unsuccessful attempts to cut down.
- Significant energy spent obtaining, using, or recovering from substance.
- Important social, occupational, or recreational activities reduced because of substance use.
- Continued use despite knowing substance causes physical and/or psychological problems.
- Craving.
- Recurrent use in physically dangerous situations.
- Failure to fulfill major obligations at work, school, or home due to use.
- Social or interpersonal conflicts related to substance use.

Stages of change in overcoming substance addiction

1. Precontemplation: not yet acknowledging that there is a problem.
2. Contemplation: acknowledging that there is a problem, but not yet ready or willing to make a change.
3. Preparation/determination: getting ready to change behaviors.
4. Action/willpower: changing behaviors.
5. Maintenance: maintaining the behavior changes.
6. Relapse: returning to old behaviors and abandoning new changes.



Psychoactive drug intoxication and withdrawal

Depressants

- Intoxication:

- Nonspecific: mood elevation, ↓ anxiety, sedation, behavioral disinhibition, respiratory depression.

- Withdrawal:

- Nonspecific: anxiety, tremor, seizures, insomnia.

A. Alcohol:

- Intoxication:

- Emotional lability, slurred speech, ataxia, coma, blackouts. Serum γ-glutamyltransferase (sensitive indicator of alcohol use).
- AST value is twice ALT value.

- Withdrawal:

- Alcohol withdrawal should be suspected in any hospitalized patient with a history of alcohol abuse:
  - Early symptoms include anxiety, insomnia, tremors, and diaphoresis.
  - Hallucinations and withdrawal seizures can also occur with progression to delirium tremens within 48-96 hours if left untreated.
  - Alcoholic hallucinosis is a type of alcohol withdrawal syndrome that typically develops within 12-24 hours of the last drink and resolves within 24-43 hours. Unlike delirium tremens, sensorium is intact and vital signs are usually stable.
  - Benzodiazepines are the treatment of choice for patients with alcohol withdrawal.

Alcohol withdrawal syndrome		
Manifestations	**Symptoms/signs**	**Onset since last drink (hours)**
Mild withdrawal	Anxiety, insomnia, tremors, diaphoresis, palpitations, gastrointestinal upset, intact orientation	6-24
Seizures	Single or multiple generalized tonic-clonic	12-48
Alcoholic hallucinosis	Visual, auditory, or tactile; intact orientation; stable vital signs	12-48
Delirium tremens	Confusion, agitation, fever, tachycardia, hypertension, diaphoresis, hallucinations	48-96

❖ N.B:

- Alcohol is a central nervous system (CNS) depressant that binds to the GABAA receptor complex, enhancing the inhibitory action of GABA (the major inhibitory neurotransmitter in the brain).
- Chronic alcohol consumption leads to decreased GABA sensitivity, and alcohol tolerance develops (the need to increase the dose to achieve the desirable effect). Abrupt cessation decreases inhibitory tone and results in CNS excitation (withdrawal).
- Alcohol, barbiturates, and benzodiazepines have similar effects on GABA receptors and act by enhancing GABA inhibitory action.
- Benzodiazepines are used as first-line therapy for psychomotor agitation associated with alcohol withdrawal and to prevent progression to seizures and delirium. Diazepam, chlordiazepoxide are preferred in the majority of patients. They have a prolonged half-life and are metabolized by the liver into active metabolites.

B. Opioids:

- Intoxication:

- Euphoria, respiratory and CNS depression, ↓ gag reflex, constipation, pupillary constriction (pinpoint pupils), seizures (overdose).
- Most common cause of drug overdose death.
- Treatment: naloxone.

- Withdrawal:

- Heroin withdrawal should be suspected in patients with muscle and joint aches, abdominal cramping, nausea, diarrhea, rhinorrhea, and pupillary dilation. These subjective symptoms are often severe but generally not life-threatening.
- Treatment: long-term support, methadone, buprenorphine.

❖ N.B:

1. Opioids are prescribed for their analgesic properties, but they also have euphoric effects with the potential for tolerance, dependence, and abuse. Both prescription and street drugs can be abused.

- Treatment of addiction includes the use of alternative opioid agonists with less euphoric effect and less potential for acute withdrawal and craving, thereby allowing patients to function more productively on a daily basis.
- Methadone is a drug of choice for maintenance treatment of opioid abuse. It is a potent, long-acting opioid agonist with good bioavailability and can be given in once- daily oral dosing. Its prolonged effects suppress withdrawal symptoms and cravings, allowing for more productive patient functioning. It is a potent opioid agonist with high affinity for the opioid receptor, which blocks the euphoric effects of other opioids and also accounts for its potent analgesic effects.

2. Neonatal abstinence syndrome is caused by infant withdrawal to opiates and usually presents in the first few days of life. It is characterized by irritability, a high-pitched cry, poor sleeping, tremors, seizures, sweating, sneezing, tachypnea, poor feeding, vomiting, and diarrhea.

C. Barbiturates:

- Intoxication:

- Low safety margin, marked respiratory depression.
- Treatment: symptom management (assist respiration, ↑ BP).

- Withdrawal:

- Delirium, life-threatening cardiovascular collapse.

D. Benzodiazepines:

- Intoxication:

- Greater safety margin.
- Ataxia, minor respiratory depression.
- When vital sign derangements or respiratory depression are seen, co-ingestion with other sedative-hypnotics should be suspected.
- Treatment: flumazenil (benzodiazepine receptor antagonist).

- Withdrawal: Sleep disturbance, depression, rebound anxiety, seizure.

Stimulants

- Intoxication:

- Nonspecific: mood elevation, psychomotor agitation, insomnia, cardiac arrhythmias, tachycardia, anxiety.

- Withdrawal:

- Nonspecific: post-use "crash," including depression, lethargy, ↑ appetite, sleep disturbance, vivid nightmares.

A. Amphetamines:

- Intoxication:

- Amphetamine intoxication can present with psychiatric symptoms, including irritability, agitation, and psychosis.

- Common physical signs Include tachycardia, hypertension, hyperthermia, diaphoresis, and mydriasis.

- Severe: cardiac arrest, seizures.

- Treatment: benzodiazepines for agitation and seizures.

❖ N.B:

- "Bath salts" are synthetic cathinones, which consist of a large family of amphetamine analogs. As such: they may increase the release, or inhibit the reuptake, of norepinephrine, dopamine, and serotonin.
- "Bath salts" have amphetamine properties that can cause severe agitation, combativeness, delirium, and psychosis. In contrast to other stimulants and hallucinogens, which have a much shorter duration of effect, the effects of bath salt intoxication may take several days or weeks to subside.

B. Cocaine:

- Intoxication:

- Impaired judgment, pupillary dilation, hallucinations (including tactile), paranoid ideations, angina, sudden cardiac death. Chronic use may lead to perforated nasal septum due to vasoconstriction and resulting ischemic necrosis.
- Cocaine abuse should be suspected in an individual with weight loss, behavioral changes, and erythema of the turbinates and nasal septum.

- Withdrawal:

- Cocaine withdrawal is characterized by the development of acute depression accompanied by fatigue, vivid dreams, hypersomnia, and hyperphagia.
- Treatment: α-blockers, benzodiazepines. β-blockers not recommended.

C. Caffeine:

- Intoxication:

- Restlessness, ↑ diuresis, muscle twitching.

- Withdrawal:

- Headache, difficulty concentrating, flu-like symptoms.

D. Nicotine:

- Intoxication: Restlessness.

- Withdrawal:

- Irritability, anxiety, restlessness, difficulty concentrating.
- Treatment: Nicotine replacement therapy (nicotine patch, gum), bupropion or varenicline are first-line treatments for smoking cessation. They should be used in conjunction with counseling and supportive therapy.

Hallucinogens

A. Phencyclidine (PCP):

- Intoxication:

- Violence, impulsivity, psychomotor agitation, horizontal and vertical nystagmus, tachycardia, hypertension, analgesia, psychosis, delirium, seizures.

- Fatalities are often associated not with direct PCP intoxication but with related trauma due to combative behavior.

- Treatment: benzodiazepines, rapid-acting antipsychotic.

B. Lysergic acid diethylamide (LSD):

- Intoxication:

- Perceptual distortion (visual, auditory), depersonalization, anxiety, paranoia, psychosis, possible flashbacks.

❖ N.B:

1. Phencyclidine (PCP) and lysergic acid diethylamide (LSD) intoxication present similarly, but agitation, aggression, and nystagmus occur more often in patients using PCP. Visual hallucinations and intensified perceptions are hallmarks of LSD use.

2. The commonly used over-the- counter cough suppressant dextromethorphan may cause a false-positive result for phencyclidine (PCP) in Standard urine drug screens (UDS).

C. Marijuana (cannabinoid):

- Marijuana (cannabis) is one of the most commonly used drugs in the United States. It is a cannabinoid that contains the active ingredient tetrahydrocannabinol (THC).

- Intoxication:

- Euphoria, anxiety, paranoid delusions, perception of slowed time, impaired judgment, social withdrawal, ↑ appetite, dry mouth, conjunctival injection, tachycardia, hallucinations.

- Pharmaceutical form is dronabinol: used as antiemetic (chemotherapy) and appetite stimulant (in AIDS).

- Marijuana is metabolized in the liver, distributed and stored in lipophilic tissues, and slowly released. It remains in the body for a long time; depending on the amount and frequency of use, it can be detected in the urine up to 30 days after daily use has ceased.

- Withdrawal:

- Irritability, anxiety, depression, insomnia, restlessness, ↓ appetite.

D. MDMA (ecstasy):

- MDMA (3,4-methylenedioxy-methamphetamine) is a synthetic amphetamine with hallucinogenic properties.

- Intoxication:

- Hallucinogenic stimulant: euphoria, disinhibition, increased sexual desire, hyperactivity, distorted sensory and time perception, teeth clenching.

- Life-threatening effects include hypertension, tachycardia, hyperthermia, hyponatremia, serotonin syndrome.

- Withdrawal:

- Depression, fatigue, change in appetite, difficulty concentrating, anxiety.

Heroin addiction

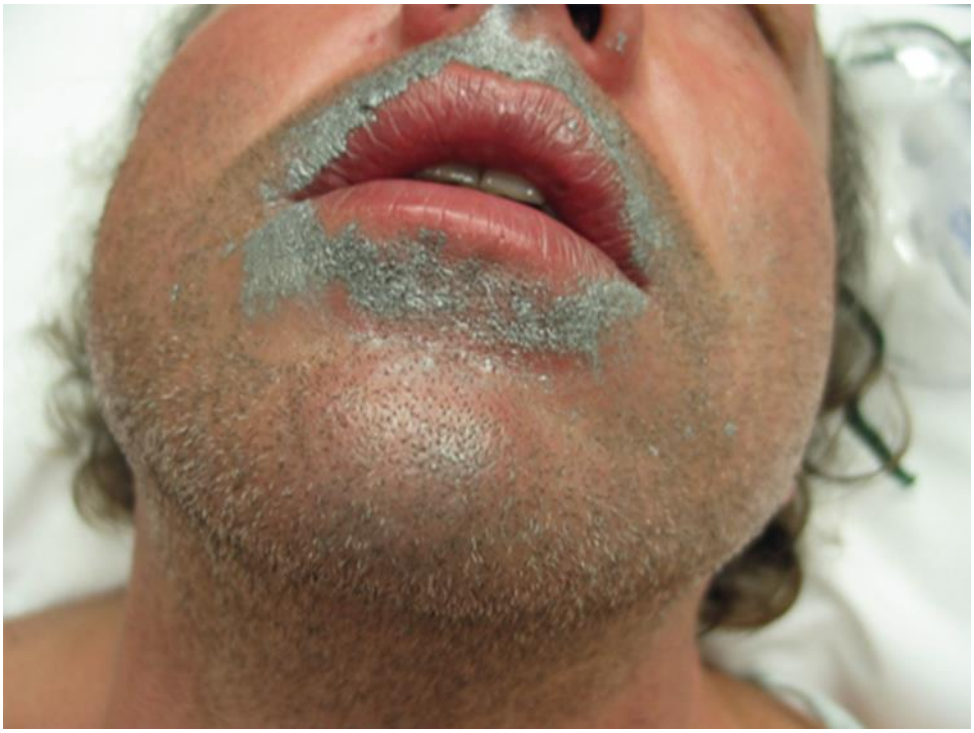
- Users at ↑ risk for hepatitis, HIV, abscesses, bacteremia, right-heart endocarditis.

- <u>Heroin detoxification medications:</u>

- Methadone: Long-acting oral opiate used for heroin detoxification or long-term maintenance therapy.
- Buprenorphine + naloxone (Suboxone): Sublingually, buprenorphine (partial agonist) is absorbed and used for maintenance therapy. Naloxone (antagonist, not orally bioavailable) is added to lower IV abuse potential.
- Naltrexone Long-acting opioid antagonist used for relapse prevention once detoxified.

❖ N.B:

- Inhalant abuse usually occurs in boys age 14-17 and may involve multiple common household chemicals.
- Commonly abused inhalants include glue, toluene, nitrous oxide ("whippets"), amyl nitrite ("poppers"), and spray paints.
- The effects are often rapid and transient but can be life-threatening. Inhalants are highly lipid soluble and produce immediate effects that typically last 15-45 minutes. They act as central nervous system depressants and may cause death.
- Users may also display characteristic perioral skin changes (glue sniffer's rash).



CHAPTER 2

Psychopharmacology

Psychopharmacology

Typical Antipsychotics (first-generation antipsychotics)

- Drugs:

- Haloperidol, trifluoperazine, fluphenazine, thioridazine, chlorpromazine (haloperidol + "-azines").

- Clinical Use:

- Schizophrenia (primarily positive symptoms), psychosis, bipolar disorder, delirium, Tourette syndrome, Huntington disease, OCD.

- Mechanism of action:

- All typical antipsychotics block dopamine D_2 receptors (↑ [cAMP]).

- Potency:

- High potency:

  - Trifluoperazine, Fluphenazine, Haloperidol (Try to Fly High) → neurologic side effects (extrapyramidal symptoms [EPS]) and drug-induced parkinsonism.

- Low potency:

  - Chlorpromazine, Thioridazine (Cheating Thieves are low) → non-neurologic side effects (anticholinergic, antihistamine, and α_1-blockade effects).

First-generation antipsychotics side effects

Type	Side effects	Examples
Low-potency (non-neurological)	• Sedation (histaminergic blockade) • Anticholinergic side effects (cholinergic blockade) • Orthostatic hypotension (alpha-1 adrenergic blockade)	• Chlorpromazine • Thioridazine
High-potency (neurological)	Extrapyramidal symptoms: • Acute dystonia • Akathisia • Parkinsonism	• Haloperidol • Fluphenazine

- Adverse effects:

- Lipid soluble → stored in body fat → slow to be removed from body.

- Endocrine:
  - Dopamine receptor antagonism → hyperprolactinemia → galactorrhea, oligomenorrhea, gynecomastia.

- Metabolic:
  - Dyslipidemia, weight gain, hyperglycemia.

- Antimuscarinic:
  - Dry mouth, constipation.

- Antihistamine:
  - Sedation.

- α_1-blockade:
  - Orthostatic hypotension.

- Cardiac:
  - QT prolongation.

- Ophthalmologic:
  - Chlorpromazine: Corneal deposits.
  - Thioridazine → reTinal deposits.

- Extrapyramidal system side effects:
  - Onset of EPS → ADAPT.
  - Hours to days: Acute Dystonia (muscle spasm, stiffness, oculogyric crisis).
  - Days to months: Akathisia (inner restlessness) and Parkinsonism (bradykinesia). Akathisia is frequently misdiagnosed because the restlessness is misinterpreted as worsening psychotic agitation. The patient's antipsychotic dose is often increased rather than decreased, exacerbating the akathisia. Treatment of akathisia includes antipsychotic dose reduction and treatment with beta blocker (propranolol) or a benzodiazepine (lorazepam).
  - Months to years: Tardive dyskinesia [it typically occurs after prolonged (>6 months) antipsychotic exposure and is characterized by dyskinetic movements that typically involve the mouth/face/trunk/extremities (lip smacking, grimacing, choreoathetoid movements)].

❖ N.B:

- Acute dystonia can develop abruptly any time between 4 hours and 4 days after receiving an antipsychotic medication. The condition is characterized by a sudden involuntary contraction of a major muscle group.
- Examples of acute dystonia include spasmodic torticollis, oculogyric crisis (a forced, sustained elevation of the eyes in an upward position), opisthotonus (arching of the back and head thrown backward), and, rarely, laryngospasm.
- Acute dystonic reactions are theorized to result from the antipsychotic property of D_2 antagonism in the nigrostriatal pathway. In the striatum, the inhibitory effects of dopaminergic neurons (D_2) are normally balanced by the excitatory actions of muscarinic cholinergic neurons (M).
- Strong dopaminergic blockade causes an excess of cholinergic activity, resulting in extrapyramidal side effects (acute dystonic reactions, akathisia, parkinsonism).
- Medications with Muscarinic receptor antagonist properties, such as benztropine or the antihistamine diphenhydramine, help re-establish the dopaminergic-cholinergic balance and effectively treat acute dystonia.
- Tardive dyskinesia (TD) develops in the setting of prolonged exposure to dopamine-blocking agents, which is thought to result in the upregulation and supersensitivity of dopamine receptors. TD is characterized by abnormal involuntary movements of the mouth, tongue, trunk, and extremities and can first appear during treatment or following antipsychotic dose reduction or discontinuation. When discontinuing the antipsychotic is not feasible, switching to clozapine is preferred.

Antipsychotic extrapyramidal effects		Pharmacotherapy*
Acute dystonia	• Sudden, sustained contraction of the neck, mouth, tongue & eye muscles	• Benztropine • Diphenhydramine
Akathisia	• Subjective restlessness, inability to sit still	• Beta blocker (propranolol) • Benzodiazepine (lorazepam) • Benztropine
Parkinsonism	• Gradual-onset tremor, rigidity, bradykinesia	• Benztropine • Amantadine
Tardive dyskinesia	• Gradual onset after prolonged therapy (>6 months): Dyskinesia of the mouth, face, trunk & extremities	• Valbenazine

*Management may include reducing the dose or switching to another antipsychotic, depending on the clinical scenario.

- Other toxicities (Neuroleptic malignant syndrome):

- Neuroleptic malignant syndrome is a rare, idiosyncratic, and potentially life-threatening condition that can occur after administration of antipsychotic medications.

- Although it is more commonly associated with the use of high-potency, first-generation antipsychotics (haloperidol), it can occur with every class of antipsychotics, including second-generation drugs (olanzapine).

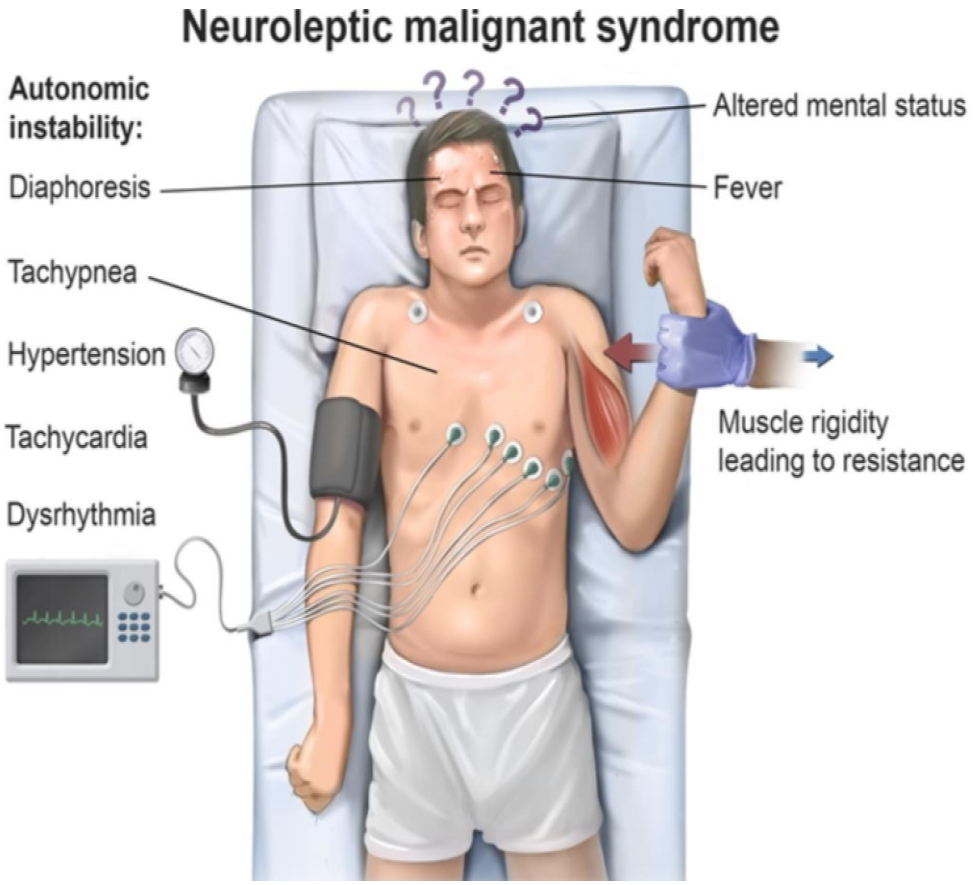
- It may occur at any time but usually develops within the first 2 weeks of treatment.

- For NMS, think FEVER: Fever, Encephalopathy, Vitals unstable, ↑ Enzymes (CK), Rigidity of muscles.

- Symptoms include high fevers, lead-pipe rigidity, altered mental status, and autonomic instability. Creatine kinase level and white blood cell count may be elevated.

- Rhabdomyolysis followed by myoglobinuria that can cause acute renal failure, is a known complication.

- Treatment: Treatment includes discontinuation of all antipsychotics, supportive intensive care (aggressive cooling, antipyretics, fluid and electrolyte repletion), and possible use of dantrolene (a skeletal muscle relaxant) or dopaminergic agents (Bromocriptine).



Atypical antipsychotics (second-generation antipsychotics)

- Drugs:

- Aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone.

- Mechanism of action:

- Not completely understood.
- Most are D_2 antagonists; aripiprazole is D_2 partial agonist.
- Varied effects on 5-HT2, dopamine, and α- and H_1-receptors.

- Clinical Use:

- Schizophrenia (both positive and negative symptoms). Also used for bipolar disorder, OCD, anxiety disorder, depression, mania, Tourette syndrome.

- Clozapine is a uniquely effective antipsychotic medication. Clozapine is unique in that it has shown superiority in treatment-resistant schizophrenia and schizophrenia associated with persistent suicidality. Clozapine has affinity for multiple dopamine and serotonin receptors, but the precise pharmacological mechanism responsible for its superiority is unknown.

- Clozapine: balancing safety with superior antipsychotic efficacy.

- Adverse effects:

- All of them cause prolonged QT interval, fewer EPS and anticholinergic side effects than typical antipsychotics.

- "-pines"—metabolic syndrome (weight gain, diabetes, hyperlipidemia). Olanzapine → Obesity.

- Clozapine: agranulocytosis (monitor WBC weekly) and seizures (dose related). Must watch bone marrow clozely with clozapine.

- Clozapine and olanzapine carry a high risk of metabolic effects, whereas ziprasidone, aripiprazole, and lurasidone are associated with the lowest risk.

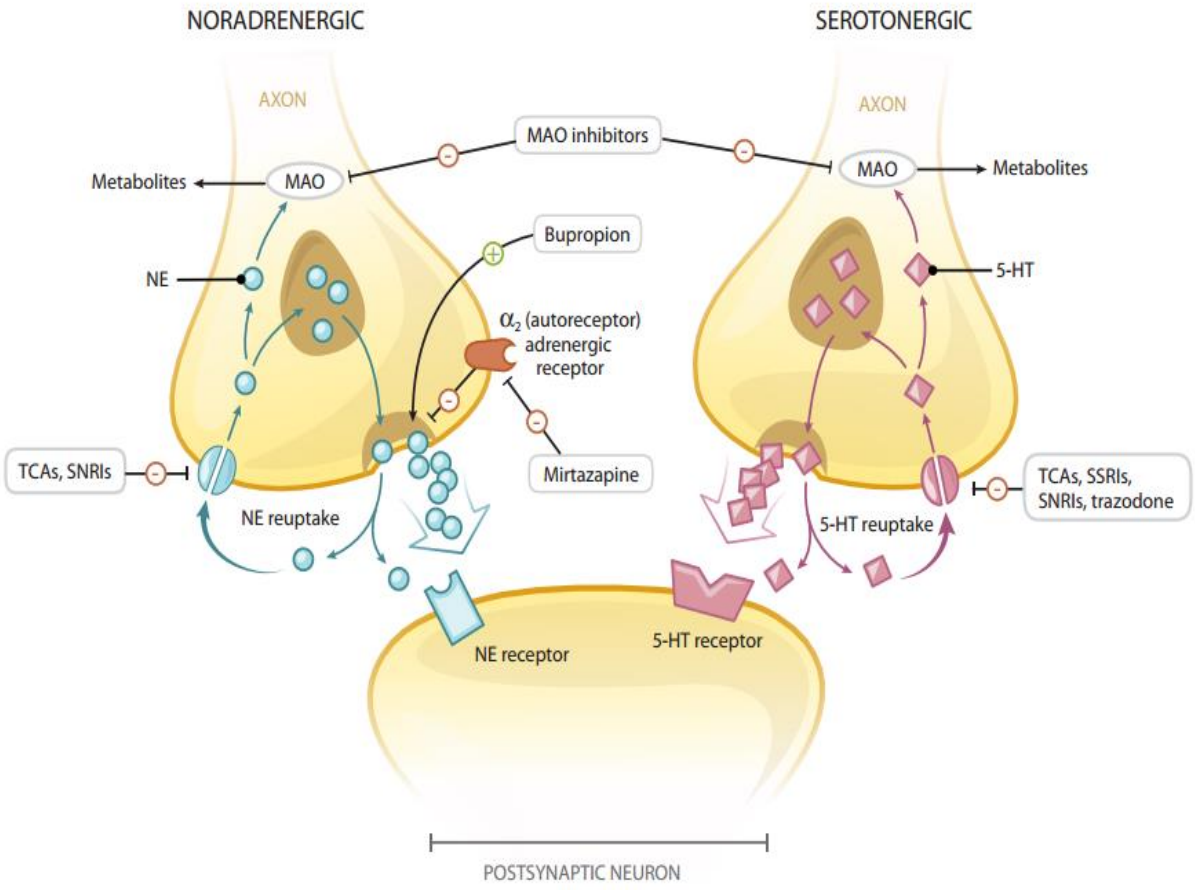
- Antipsychotic medications exert their antipsychotic effects through dopamine antagonism. The blocking of dopamine results in hyperprolactinemia, which can lead to galactorrhea, amenorrhea, and infertility. The second-generation antipsychotic risperidone is most likely to increase prolactin.

Metabolic effects of second-generation antipsychotics	
Metabolic syndrome	• Weight gain • Dyslipidemia • Hyperglycemia (including new-onset diabetes)
Highest risk drugs	• Clozapine • Olanzapine
Monitoring guidelines	Baseline & regular follow-up • Body mass index • Fasting glucose & lipids • Blood pressure • Waist circumference

❖ N.B:

- Antipsychotic medications are first-line treatment for psychosis.
- Second-generation antipsychotics are often chosen due to a comparatively lower risk of extrapyramidal side effects and tardive dyskinesia.
- Due to the risk of agranulocytosis, clozapine is reserved for patients who have failed at least 2 antipsychotic trials.
- If further evaluation indicates a pattern of repeated medication nonadherence, switching to a long-acting injectable antipsychotic could be considered. However, this should be done only after the patient's ability to tolerate the oral formulation is established, making long-acting injectable antipsychotics inappropriate choices as initial agents.

Antidepressants



- The major neurotransmitters involved in the pathophysiology of depression are serotonin and norepinephrine (and dopamine to a lesser extent). Most available antidepressant medications affect serotonin or both serotonin and norepinephrine at the synapse.

- Antidepressants can induce mania in susceptible patients, especially those with unrecognized bipolar disorder. Patients treated with antidepressants should be monitored for mood elevation and symptoms suggestive of mania that require emergency treatment. Management consists of discontinuing the antidepressant and treating the patient with a mood stabilizer if manic symptoms persist.

- Patients with a single episode of major depressive disorder should continue antidepressants for an additional 6 months following acute response to reduce the risk of relapse. Patients with recurrent, chronic, or severe episodes should be considered for maintenance treatment (1-3 years or indefinitely).

- Patients who fail to respond to an initial antidepressant trial should be considered for a switch to another first-line antidepressant. Other options include augmenting with a second agent or switching to or adding psychotherapy.

Selective serotonin reuptake inhibitors (SSRIs)

- Drugs:

- Fluoxetine, paroxetine, sertraline, citalopram. Flashbacks paralyze senior citizens.

- Mechanism of action:

- Selective serotonin reuptake inhibitors are commonly used first-line antidepressants that work by blocking the serotonin transporter. This prevents the normal reuptake of serotonin into the presynaptic neuron, resulting in increased availability of serotonin in the synaptic space. It normally takes 4–8 weeks for antidepressants to have an effect.

- Clinical Use:

- Depression, generalized anxiety disorder, panic disorder (Pharmacotherapy of panic disorder includes selective serotonin reuptake inhibitors and benzodiazepines).

- SSRIs are often preferred to benzodiazepines due to the lack of physiological dependence and abuse potential), OCD, bulimia, social anxiety disorder, PTSD, premature ejaculation, premenstrual dysphoric disorder.

- Adverse effects:

- Fewer than TCAs. GI distress, SIADH, sexual dysfunction (anorgasmia, ↓ libido).

- Bupropion, a norepinephrine dopamine reuptake inhibitor, is a first-line treatment for major depressive disorder that does not cause sexual dysfunction.

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

- Drugs:

- Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran, milnacipran.

- Mechanism of action:

- Inhibit 5-HT and norepinephrine reuptake.

- Clinical Use:

- Depression, general anxiety disorder, diabetic neuropathy. Venlafaxine is also indicated for social anxiety disorder, panic disorder, PTSD, OCD.

- Adverse effects:

- ↑ BP most common; also, stimulant effects, sedation, nausea.

❖ Serotonin syndrome:

- Can occur with any drug that ↑ 5-HT (MAO inhibitors, SNRIs, TCAs).

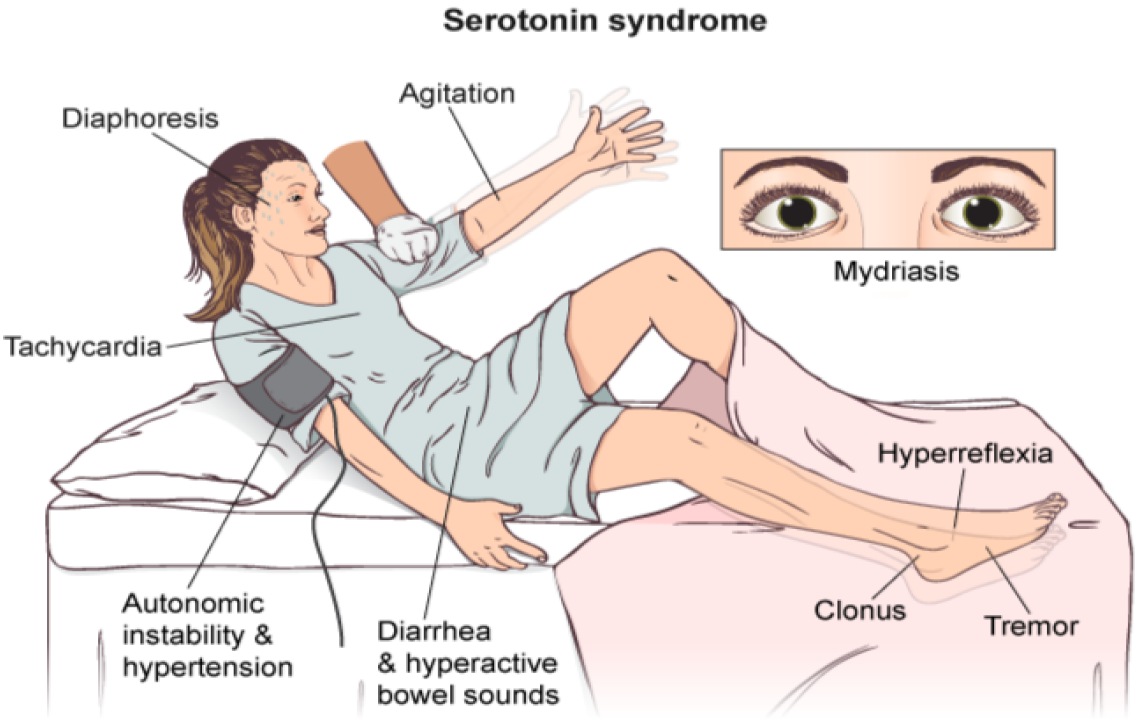
- Serotonin syndrome most commonly occurs when SSRIs are given in conjunction with other serotonergic agents such as monoamine oxidase inhibitors (MAOIs) or triptans. It may also occur with a single agent if an excess dose is taken. However, a multitude of other medications have been implicated in precipitating serotonin syndrome, and it may be difficult to obtain an adequate medication history in patients with altered mental status. Therefore, it is important to maintain a high index of suspicion.

- Characterized by 3 A's: neuromuscular Activity (clonus, hyperreflexia, hypertonia, tremor, seizure), Autonomic stimulation (hyperthermia, diaphoresis, diarrhea), and Agitation.

- Symptoms of NMS overlap and can be confused with serotonin syndrome. Although serotonin syndrome can also present with mental status changes, hyperthermia, and autonomic instability, it typically presents with neuromuscular hyperactivity (shivering, clonus, and hyperreflexia) as opposed to the diffuse rigidity and bradyreflexia seen in NMS. Nausea, vomiting, and diarrhea are more common in serotonin syndrome; hyperthermia and rigidity, when present, are less severe than in patients with NMS.

- Treatment:

- Pharmacologic therapy for severe cases involves treatment with serotonin receptor antagonists such as cyproheptadine which is a first-generation histamine antagonist with nonspecific serotonin receptor antagonistic properties.



Tricyclic antidepressants (TCAs)

- Drugs:

- Amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin, amoxapine.

- Mechanism of action:

- Block reuptake of norepinephrine and 5-HT.

- Clinical Use:

- Major depression, OCD (clomipramine), peripheral neuropathy, chronic pain, migraine prophylaxis.

- TCAs are commonly used for the treatment of painful diabetic neuropathy and are thought to be more effective for short-term pain relief than many newer generation anticonvulsants, also used for neuropathy.

- Adverse effects:

- Sedation, α_1-blocking effects including postural hypotension, and atropine-like (anticholinergic) side effects (tachycardia, urinary retention, dry mouth).

- 3° TCAs (amitriptyline) have more anticholinergic effects than 2° TCAs (nortriptyline).

- Should be used with caution in patients with benign prostatic hyperplasia (BPH), as they may cause urinary retention.

- Can prolong QT interval.

- Tri-C's: Convulsions, Coma, Cardiotoxicity (Tricyclic antidepressants inhibit fast sodium channel conduction, resulting in arrhythmias - the most common cause of death in patients with antidepressant intoxication); also, respiratory depression, hyperpyrexia.

- Confusion and hallucinations in elderly due to anticholinergic side effects (use nortriptyline).

- Treatment:

- Fluid resuscitation with normal saline and hypertonic sodium bicarbonate administration are crucial in these patients.

Monoamine oxidase inhibitors (MOAIs)

- Drugs:

- Tranylcypromine, Phenelzine, Isocarboxazid, Selegiline (selective MAO-B inhibitor). (MAO Takes Pride In Shanghai).

- Mechanism of action:

- Monoamine oxidase (MAO) is an enzyme located in presynaptic nerve terminals that is responsible for the breakdown of monoamine neurotransmitters (serotonin, norepinephrine, dopamine).

- Monoamine oxidase inhibitor work by irreversibly binding and inhibiting MAO A and B. This results in increased availability of monoamine neurotransmitters, thereby increasing their release into the synaptic cleft. Because it irreversibly inhibits MAO, it may take up to 2 weeks following discontinuation of the drug before the enzyme is resynthesized to levels adequate for normal monoamine degradation.

- Clinical Use:

- Atypical depression, anxiety.

- Adverse effects:

- Hypertensive crisis (most notably with ingestion of tyramine, which is found in many foods such as aged cheese and wine); CNS stimulation. Contraindicated with SSRIs, TCAs, St. John's wort, meperidine, dextromethorphan (to prevent serotonin syndrome).

- Wait 2 weeks after stopping MAO inhibitors before starting serotonergic drugs or stopping dietary restrictions.

❖ N.B:

- The acute onset of headache following a meal in a patient treated with phenelzine raises concern for hypertensive crisis.
- MAOIs inhibit the metabolism of the monoamines epinephrine, dopamine, and serotonin, and are typically not used as first-line therapy due to drug-drug interactions and dietary restrictions involving foods containing tyramine.
- Tyramine may be present in aged cheeses, aged or cured meats, aged or fermented soy products, overripe fruits, and some alcoholic beverages.
- Tyramine is a sympathomimetic monoamine that can facilitate the release of other sympathomimetic monoamines, such as adrenaline.
- Tyramine metabolism is inhibited in the presence of MAOIs which causes an increased sympathomimetic (adrenergic) effect that can result in a severe "hypertensive crisis." This commonly presents first as a headache but can lead to intracranial bleeding, stroke, and death.

Bupropion

- Mechanism of action:
- ↑ norepinephrine and dopamine via unknown mechanism.

- Clinical uses:
- Bupropion is an antidepressant with mild stimulant properties that can be particularly helpful for depressed patients with low energy, impaired concentration and hypersomnia.

- Bupropion has a favorable side effect profile (no weight gain or sexual side effects) and activating effects, making it a good choice for patients with weight gain or SSRI-related sexual side effects.

- Also used for smoking cessation.

- Toxicity:
- Stimulant effects (tachycardia, insomnia), headache.

- It is associated with an increased seizure risk at high doses. Bupropion is contraindicated in patients with seizure disorders, anorexia, and bulimia nervosa.

Lithium

- Mechanism of action:
- Not established; possibly related to inhibition of phosphoinositol cascade.

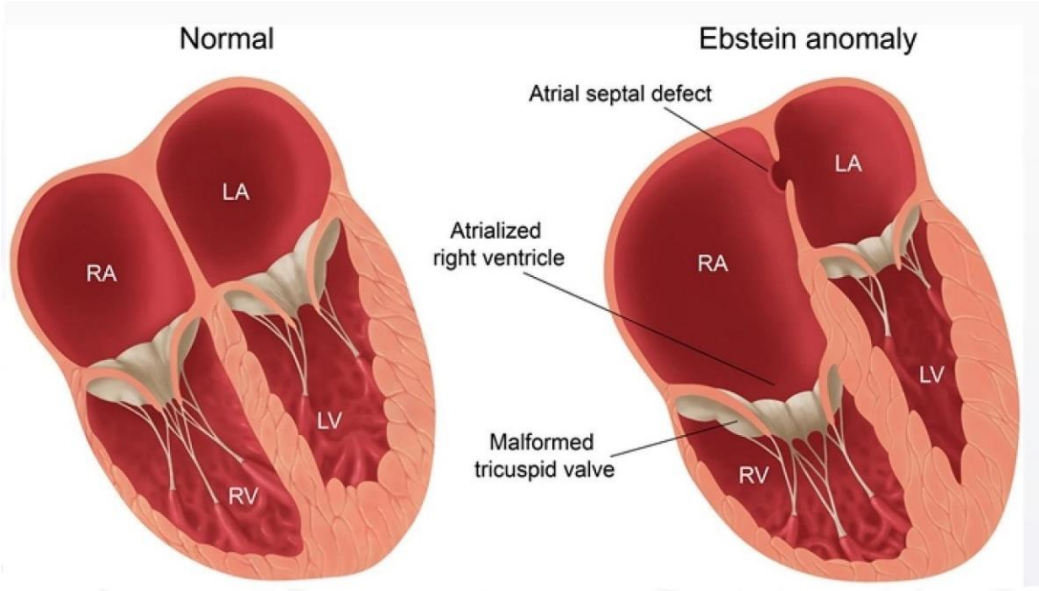
- Clinical Use:
- Mood stabilizer for bipolar disorder; blocks relapse and acute manic events.

- Adverse effects:
- Tremor, hypothyroidism, polyuria (causes nephrogenic diabetes insipidus), hyperparathyroidism with hypercalcemia, teratogenesis.

- Causes Ebstein anomaly in newborn if taken by pregnant mother.

- Narrow therapeutic window requires close monitoring of serum levels. Almost exclusively excreted by kidneys; most is reabsorbed at PCT with Na. Thiazide use is implicated in lithium toxicity in bipolar patients.

- Calcium, renal function, and thyroid function should be monitored prior to starting lithium and periodically during therapy. When hypothyroidism develops, it can be treated with T4 and does not necessarily require lithium discontinuation.



- LiTHIUM:

- Low Thyroid (hypothyroidism).
- Heart (Ebstein anomaly).
- Insipidus (nephrogenic diabetes insipidus).
- Unwanted Movements (tremor).

❖ N.B:

- Bipolar disorder is a highly recurrent illness requiring maintenance treatment with mood stabilizers to decrease the risk of recurrent mood episodes.
- First-line medications for bipolar maintenance treatment include lithium, the anticonvulsant valproate and the second-generation antipsychotic quetiapine, Lamotrigine, another anticonvulsant used in maintenance treatment, has been found to be more effective in preventing depression than mania.
- A mild rash may develop in up to 10% of those treated with lamotrigine. whereas life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis may occur in 0.1%. Any occurrence of rash during the treatment of lamotrigine requires immediate discontinuation of the drug.
- The anticonvulsant mood stabilizer valproate can cause elevated aminotransferases and in rare cases hepatic failure, most commonly in the first 6 months of treatment.
- Antidepressant monotherapy should be avoided in bipolar maintenance treatment due to the risk of mood destabilization.
- Patients with inadequate response to monotherapy and/or severe episodes (psychotic features, aggression, high risk of suicide, frequent episodes with marked impairment requiring hospitalization) often require combination therapy. Lithium or valproate combined with a second-generation antipsychotic (quetiapine) is recommended as first-line treatment.

Mood stabilizers in bipolar disorder		
Drug	**Indications**	**Side effects**
Lithium	• Manic & depressive episodes, maintenance	• Diabetes insipidus • Hypothyroidism • Tremor • Ebstein anomaly
Valproate	• Manic episodes, maintenance • **Absence, generalized tonic-clonic, myoclonic seizures**	• **Hepatotoxicity** • Neural tube defects
Carbamazepine	• Manic episodes, maintenance • Partial & generalized seizures • **Trigeminal neuralgia**	• **Agranulocytosis** • Hyponatremia (syndrome of inappropriate antidiuretic hormone) • Neural tube defects
Lamotrigine	• Depressive episodes, maintenance • Focal seizures	• Benign rash • **Stevens-Johnson syndrome**

CNS stimulants

- Drugs:

- Methylphenidate, dextroamphetamine, methamphetamine.

- Mechanism of action:

- ↑ catecholamines in the synaptic cleft, especially norepinephrine and dopamine.

- Clinical Use:

- ADHD, narcolepsy, appetite control.

- Side effects:

- Common side effects include decreased appetite, weight loss and insomnia.

❖ N.B:

- The etiology of narcolepsy is believed to be due to low levels of the stimulatory neurotransmitter orexin (hypocretin), which is involved in maintaining wakefulness and suppressing REM sleep-related phenomena.
- Treatment is with agents that promote wakefulness (psychostimulants). Modafinil, a non-amphetamine stimulant, has become the first line agent because it is effective, well tolerated, and drug abuse is rare. Its mechanism of action is not well described, but it is thought to enhance dopaminergic signaling. Amphetamines are second line agents due to their sympathomimetic side effects (HTN, arrhythmia, psychosis) and risk for dependency.

Preferred medications for selected psychiatric conditions

PSYCHIATRIC CONDITION	PREFERRED DRUGS
ADHD	Stimulants (methylphenidate, amphetamines)
Alcohol withdrawal	Benzodiazepines (eg, chlordiazepoxide, lorazepam, diazepam)
Bipolar disorder	Lithium, valproic acid, atypical antipsychotics
Bulimia nervosa	SSRIs
Depression	SSRIs
Generalized anxiety disorder	SSRIs, SNRIs
Obsessive-compulsive disorder	SSRIs, venlafaxine, clomipramine
Panic disorder	SSRIs, venlafaxine, benzodiazepines
PTSD	SSRIs, venlafaxine
Schizophrenia	Atypical antipsychotics
Social anxiety disorder	SSRIs, venlafaxine Performance only: β-blockers, benzodiazepines
Tourette syndrome	Antipsychotics (eg, fluphenazine, pimozide), tetrabenazine

CHAPTER 3

Ethics

Physician-Patient Relationship

- The physician-patient relationship is a potent healing partnership based on trust.

General rules

1. Patient is number one; always place the interests of the patient first:
- Choose the patient's comfort and safety over yours or anyone else's.
- Make it a point to ask about and know the patient's wishes.

2. Nothing should be between you and patient (no barriers):
- Get rid of tables and computers. If you must have a table, pick the smallest one.
- Ask family members to leave the room. If patient says that he or she wants them to stay, then that is okay.
- In situations in which a parent's presence may interfere with obtaining honest answers from an adolescent patient, physicians should politely ask the parent to wait outside and interview the patient privately. This is also important when discussing drugs, alcohol, tobacco, and sexual activity with teenagers.

3. Tell the patient everything, even if he or she does not ask:
- Answer any question that is asked.
- Patient should know what you know and as soon as you know it.
- Do not force a patient to hear bad news if he does not want it at that moment, but do try to discuss it with him or her as soon as possible.
- If you have only partial information, say that it is partial and tell what you know.
- We tell them so they tell us. Make reciprocity the norm.
- Information should flow through the patient to the family, not the reverse.
- Patients' misunderstanding of medication use can result in medication errors, including potential overdose, toxicity, and withdrawal. Physicians must assess the patient's understanding and provide targeted education to address misconceptions.

4. Work on long-term relationships with patients, not just short-term problems:
- Make eye contact.
- Defined touch: tell him or her what you are doing.
- Both patient and physician should both be sitting at the same eye level if at all possible.

5. Listening is better than talking:
- Be an "information sponge". You know what matters, but they don't.
- Getting the patient to talk is generally better than having the physician talk.
- Ask what the patient knows before explaining.
- End encounter by asking, "Is there anything else?"
- Listen without interrupting.
- Allow silences while patients search for words.

6. Negotiate rather than order:
- Treatment choices are the result of agreement, not commands by the physician.
- Remember, the patient makes medical decisions from the choices provided by the physician.
- Relationship and agreement support adherence.

7. Admit to the patient when you make a mistake:
- Everything is your responsibility.
- Take responsibility. Don't blame it on the nursing staff or on a medical student.
- Admit the mistake even if it was corrected and the patient is fine.

8. Never "pass off" your patient to someone else:
- Refer to psychiatrist or other specialist when beyond your expertise (usually the wrong answer).

9. Express empathy, then give control: "I'm sorry, what would you like to do?"
- Important when faced with a patient who is grieving or is angry.
- Important when faced with angry or upset family members.

- When interacting with difficult patients, it is best to try to calm them, explain your position and inquire more about what troubles them by using open-ended questions.

10. Agree on problem before moving to solution:
- Discuss diagnosis fully before moving to treatment options.
- Ask what patient knows about diagnosis before explaining it.
- Tell the patient your perceptions and conclusions about the condition before moving to treatment recommendations.
- Informed consent requires the patient to fully understand what is wrong.
- Offering a correct treatment before the patient understands his or her condition is wrong.

11. Patients do not get to select inappropriate treatments:
- Patients select treatments, but only from presented, appropriate choices.
- If a patient asks for an inappropriate medication that he heard advertised, explain why it is not indicated.
- Make conversations positive. Talk about options that are available; don't just say no to a patient's request.

12. Never lie:
- There is no such thing as a "white lie".
- Do not lie to patients, their families, or insurance companies.
- Do not deceive to protect a colleague.

13. Accept the health beliefs of patients:
- Be accepting of benign folk medicine practices. Expect them.
- Diagnoses need to be explained in the way patients can understand, even if not technically precise.

14. Accept patients' religious beliefs and participate if possible:
- Your goal is to make the patient comfortable. Religion is a source of comfort to many.
- When an ill patient requests your prayers in an acute setting, it is appropriate to offer your personal support without interjecting your personal beliefs into the interaction. The overriding goal in these situations is to "do no harm". This can be achieved by not disagreeing with the patient, not entering

into a religious debate with them, and not displacing responsibility for the care of the patient onto others

- Of course, you are not expected to do anything against your own religious or moral beliefs, or anything which risks patient's health.

15. Anything that increases communication is good:

- Take the time to talk with patients, even if others are waiting.
- Ask "why?"
- Ask about the patient beyond the disease: job, family, children, etc.
- Be available. Take calls. Answer emails.

Types of Questions and Statements

A. Open-ended question:

- Open-ended questions and statements are the most effective way to begin the interview "Please tell me more about your pain".
- Once the patient provides an initial history, the physician can use closed-ended and follow-up questions to clarify certain points and fill gaps in the history.

B. Closed-ended question: limits answer (yes or no questions).

C. Leading question: suggests or indicates preferred answer.

D. Confrontation: brings to the patient's attention some aspect of appearance or demeanor.

E. Facilitation: gets the patient to continue a thought, talk more, "tell me about that...".

Legal issues related to medical practice

1. Patients have the sole right to determine what treatments they shall and shall not accept (Autonomy):

- Autonomy, ethically, is more important than beneficence. Beneficence, trying to do good for others, is generally a good thing-but trying to help someone is not as important as following her wishes.

- Every individual has autonomy over his/her own body, including all reproductive health decisions (sterilization, abortion, contraception). Consent is obtained from the patient alone. Although the physician can encourage the patient to share and discuss her decision to undergo the procedure with her partner, consent from a spouse (or unmarried partner) is not required.

- When a patient refuses potentially life-saving treatment, it is important to fully discuss the specific reasons for the decision before honoring it.

2. Competent patients have the right to refuse medical treatment:

- Patients have control over their own bodies. These are not exceptions:

- Preserving life.
- It's like a suicide.
- Professional ethics.

3. Assume that the patient is competent (unless clear behavioral evidence indicates otherwise):

- The patient does not have to prove to you that he is competent. You have to have clear evidence to assume that he is not.

- Competence is a legal, not a medical issue.

- Clear behavioral evidence would be:

- Gross psychosis.
- Cognitive capacity prevents communication (Dementia).
- Suicide attempt.

4. When surrogates make decisions for a patient, they should use the following criteria and in this order:

A. Subjective standard:

- Actual intent, advance directive.
- What did the patient say in the past?

B. Substituted judgment:

- Who best represents the patient?
- What would patient say if he or she could?

C. Best-interest standard:

- Burdens versus benefits.
- Interests of patient, not preferences of the decision-maker.

5. If patient is incompetent to make decisions, physician may rely on advance directives:

- Advance directives Instructions given by a patient in anticipation of the need for a medical decision. Details vary per state law.

- Order of Decision Making:

A. A patient with capacity supersedes all else.

B. Medical power of attorney:

- Patient designates an agent to make medical decisions in the event that he/she loses decision-making capacity. The proxy overrules all other possible surrogate decision makers, including family members.

C. Living will:

- The living will is a document outlining a patient's wishes.

- A document clearly stating, "I never want dialysis" is more valid than a family member or friend saying, "From what I know about him, he would not want dialysis," or "He told me he never wants dialysis."

- Advance directives are a matter of documentation. A written living will that makes concrete statements such as "I never want blood transfusion or chemotherapy" is valid.

D. Persons clearly familiar with the patient's wishes:

- The problem with this is one of documentation. If the patient loses capacity, it is difficult for a friend to document that she knew the patient's wishes better than the family.
- If the case clearly states that a friend knows and can prove that she knew the patient's wishes, then this is the plan of care that is followed.

E. Family:

- In general, the order of decision making starts with a spouse.

- If there is no spouse, then it goes to adult children, then parents, then siblings.

F. Ethics Committee:

- The ethics committee is important when a patient has lost capacity to make decisions and the advance directive is missing or unclear.

- The ethics committee is also important on issues of medical futility. This is when the healthcare proxy is asking for tests and treatments that may have no benefit.

G. Court Order:

- The court order is important when the patient has no capacity to understand and the family is in disagreement. It is like a house being left equally to four children who cannot agree what to do with it. Examples of when court order is the right answer:
  - A patient has no capacity and no proxy; his family is split about whether to continue care.
  - Caregivers want to withdraw care and the ethics committee cannot reach a conclusion.

6. Feeding tube is a medical treatment and can be withdrawn at the patient's request:

- Not considered killing the patient, but stopping treatment at patient's request.

- A competent person can refuse even lifesaving hydration and nutrition.

7. Do nothing to actively assist the patient to die sooner:

- Physician-Assisted Suicide:

- Physician-assisted suicide is always a wrong answer.

- Physician assisted suicide is administered by the patient, but this is still unethical for the physician.

- Euthanasia:

- Euthanasia is the physician administering treatment intended to end or shorten the life of the patient.

- It is always wrong answer.

- Terminal Sedation and Law of Double Effect:

- It is acceptable to administer pain medication even if there is the possibility of the treatment shortening the patient's life.

- For example, it is acceptable to give pain medications to a person with COPD who has metastatic cancer even if the only way to relieve pain is to give enough opiates that breathing may be impaired, causing the patient to die earlier.

- The question is one of intent: If the medications are given with the intent to relieve pain, and as an adverse effect they shorten life, it is ethical. If the primary intent is to shorten life, it is unethical.

8. Brain death is considered death in U.S legal system:

- If the patient is brain dead, you do not need consent to stop therapy such as mechanical ventilation or antibiotics.

- Court order and ethics committee are not correct answers.

9. The physician decides when the patient is dead:

- If the physician thinks continued treatment is futile (the patient has shown no improvement), but the surrogate insists on continued treatment, the treatment should continue.

- If there are no more treatment options (the patient is brain dead), and the family insists on treatment, there is nothing the physician can do; treatment must stop (futile care).

10. Never abandon a patient:

- Lack of financial resources or lack of results are never reasons to stop treatment of a patient.

- An annoying or difficult patient is still your patient.

- You cannot ever threaten abandonment.

- All patients who present to the emergency department must receive an appropriate screening medical exam and stabilization of their condition, regardless of ability to pay.

- Conscientious refusal of treatment occurs when a provider refuses to provide care due to moral conflict. Providers who cannot, in good conscience, provide treatment that a patient requests, are obligated to refer the patient in a timely fashion to another provider who can.

11. Keep the physician - patient relationship within bounds:

- Intimate social contact with anyone who is or has been a patient is prohibited. AMA guidelines say, "for at least 2 years".

- Do not date parents of pediatric patients or children of geriatric patients.

- Do not treat friends or family.

- If patients are inappropriate, gently but clearly let them know what acceptable behavior would be.

- Any gift from a patient beyond a small token (cards, photographs, cookies) should be declined.

12. Stop harm from happening:

- Beyond "do no harm", you must stop anyone from hurting himself or others.

- Take whatever action is required to prevent harm.

- Harm can be spreading disease, physical assault, psychological abuse, neglect, infliction of pain or anything which produces notable distress.

- You must also protect your patient, or anyone not your patient, from being hurt by another.

13. Always obtain informed consent:

- Full, informed consent requires that the patient has received and understood five pieces of information:

- Nature of procedure.
- Purpose or rationale.
- Benefits.
- Risks.
- Availability of alternatives.

- Exceptions to informed consent:

- Emergency (Implied consent in an emergency).

- Waiver by patient (patient explicitly waives the right of informed consent).

- Patient is incompetent (Patient lacks decision-making capacity or is legally incompetent).

- Therapeutic privilege: withholding information when disclosure would severely harm the patient or undermine informed decision-making capacity.

- Consent can be oral.

- A signed paper the patient has not read or does not understand does NOT constitute informed consent.

- Patient must be informed that he or she can revoke written consent at any time, even orally.

- Physicians must ensure the appropriate use of medical interpreters to promote adequate patent understanding and participation in the decision-making process. This is particularly important during the informed consent process.

- Patients who are temporarily incapacitated should not be allowed to make important health care decisions. Health care decisions should instead be made by surrogate decision makers, such as close family members or the patient's personal physician. When an incapacitated patient presents alone in an emergent setting, however, consent to treatment is presumed.

❖ N.B:

- Physicians must respect parents' medical decisions for their children, with the exception of refusal of life-saving treatment. Physicians must counsel parents about the health risks of refusing vaccination and document the discussion in the medical chart. In addition, physicians should be aware of the vaccination exemption laws in their state.
- Currently, all states allow medical exemption from vaccination (allergy to vaccine components). Some states also allow for exemption based on a parent's religious and/or personal beliefs. If a child is unvaccinated and is not exempt, he/she may not be able to enroll in day care or school, depending on the state.

- The physician must respect the mother's decision but is obligated to inform her about the health-associated risks and benefits as well as the potential consequences (school enrollment). The discussion should be fully documented in the medical record.

14. Special rules apply with children:

- Children younger than 18 years are minors and are legally incompetent.

- Exceptions:

A. Emancipated minors:

- If older than 13 years and taking care of self (living alone) treat as an adult.
- Marriage makes a child emancipated, as does serving in the military.

B. Partial emancipation:

- Many states have special ages of consent, generally, age 14 and older for certain issues only (confidentiality should be also maintained in this exceptions):
  - Substance drug treatment.
  - Prenatal care.
  - Sexually transmitted disease treatment.
  - Birth control (contraception).

❖ N.B:

- Unemancipated minors normally cannot consent to their own medical treatment. Parents or legal guardians must provide consent on the minor's behalf before the physician can proceed, although there are exceptions in emergencies and other situations.

Circumstances in which minors do not require consent	
Medical circumstances	• Emergency care • Sexually transmitted infections • Substance abuse (most states) • Prenatal care (most states)
Emancipated minor	• Homeless • Parent • Married • Military • Financially independent • High school graduate

16. Parents cannot withhold life- or limb-saving treatment from their children:

- If parents refuse permission to treat child: If immediate emergency→ go ahead and treat.

- If parents refuse to consent to treatment of their child for a non-emergency but fatal medical condition → the physician should seek a court order mandating treatment.

- If not life- or limb-threatening (child needs minor stitches) → listen to the parents

- Note that the child cannot give permission. A child's refusal of treatment is irrelevant.

17. For the purposes of the USMLE, issues governed by laws that vary widely across states cannot be tested. This includes elective abortions (minor and spousal rights differ by locality) and legal age for drinking alcohol (vary by state).

18. Good Samaritan Laws limit liability in nonmedical settings:

- Not required to stop to help.

- If help offered, shielded from liability provided:

- Actions are within physician's competence.
- Only accepted procedures are performed.
- Physician remains at scene after starting therapy until relieved by competent personnel.
- No compensation changes hands.

19. Confidentiality is absolute:

- Physicians cannot tell anyone anything about their patient without the patient's permission.

- Physician must strive to ensure that others cannot access patient information.

- Confidential patient information should be disclosed only to fellow health care workers who are directly involved in the patient's care. Physicians should avoid discussing a patient's medical condition in public areas where comments might be overheard, inappropriate Inquiries from colleagues curious about a patient's medical condition should be politely but firmly rebuffed.

- If you receive a court subpoena, show up in court but do not divulge information about your patient.

- General principles for exceptions to confidentiality:

- Potential physical harm to others is serious and imminent.
- Likelihood of harm to self is great.
- No alternative means exist to warn or to protect those at risk.
- Physicians can take steps to prevent harm.

- Patient confidentiality should not be maintained if it endangers the health and welfare of others. In cases of HIV, public health laws require reporting of the patient's positive test results to the local health department. The health department (and not the physician) typically makes contact with all of the

patient's sexual partners and informs them of being at risk for the disease, without giving any identifying information about the partner who placed them at risk.

- Examples of exceptions to patient confidentiality (many are state-specific) include the following ("The physician's good judgment SAVED the day"):

- Suicidal/homicidal patients.
- Abuse (children, elderly, and/or prisoners).
- Duty to protect: State-specific laws that sometimes allow physician to inform or somehow protect potential Victim from harm.
- Epileptic patients and other impaired automobile drivers.
- Reportable Diseases (STIs, hepatitis, food poisoning); physicians may have a duty to warn public officials, who will then notify people at risk. Dangerous communicable diseases, such as TB or Ebola, may require involuntary treatment.

20. Patients should be given the chance to state DNR (Do Not Resuscitate) orders, and physicians should follow them:

- DNR refers only to cardiopulmonary resuscitation.

- Continue with ongoing treatments.

- DNR decisions are made by the patient or surrogate.

21. Detain patients to protect them or others: if they harm to self or to others.

22. Remove from patient contact health care professionals who pose risk to patients:

- Types of risks:

- Infectious disease (TB).
- Substance-related disorders.
- Depression (or other psychological issues).
- Incompetence.

- Actions:

- Insist that they take time off.
- Contact their supervisors if necessary.

❖ N.B:

1. As part of the admission process, patients should be asked whether they have advance directives and informed about options for creating them if they do not. Some physicians may be reluctant to discuss these issues, but studies have shown that most patients prefer to have end-of-life discussions with their caregivers.

- Advance directives consist of 2 main components (a living will and a health care proxy):

A. A living will specify the patient's end-of-life wishes and often includes specific directives regarding intubation, cardiopulmonary resuscitation, enteral feeding, and other life-prolonging interventions. A living will communicate the patient's own wishes if he or she becomes incapacitated, and it overrules the wishes of the family.

B. A health care proxy document allows the patient to designate a specific individual to make health care decisions should the patient become incapacitated. The proxy decision maker must always make these decisions in accordance with the patient's wishes as outlined in the living will.

- Advance directives take precedence over the wishes of family members, Physicians should respect patient autonomy and adhere to patients' wishes as outlined in advance directives.

2. When treating patients who have been referred for specialty care or a second opinion, it is imperative to not undermine the patient's relationship with the primary physician.

- A physician should avoid making negative comments about the quality of care rendered by that practitioner unless practices are imminently dangerous or far outside acceptable standards of care.

3. Abortion is a legal medical procedure in the United States and is performed routinely in specialty clinics and doctors' offices. Although first-trimester abortions are unrestricted, states have different restrictions on second-trimester abortions, including mandatory waiting periods, parental consent for pregnant minors, and mandatory discussion of options.

- Physicians are not required to provide medical services that are against their personal beliefs. In such cases, the physician should provide referral to providers who will perform the requested procedure.

4. When delivering bad news, a face-to-face visit in a comfortable private setting is preferred as it allows the physician to respond to nonverbal aspects of communication and provide empathy and emotional support as needed.

- It is also important to assess the patient's understanding of the condition and how much the patient actually wants to know. Other steps include gaining an understanding of cultural/educational/religious issues, making medical information understandable to the patient, and formulating a collaborative treatment plan.

5. Hospice is a palliative, interdisciplinary model of care for patients with a prognosis of ≤6 months.

- The focus is on symptom control; quality of life; and psychosocial, spiritual, and bereavement care.

6. The ethical dilemma of using newly deceased patients for training purposes involves weighing the conflicting considerations of respect for patient integrity with the need to train health care providers to perform lifesaving procedures.

- According to ethical guidelines, permission must be obtained from the family (or from the patient prior to death) before procedures can be performed on a newly deceased patient for training purposes.

7. Communication failures between physicians during patient handoffs are a large contributor to medical errors and adverse patient outcomes.
- Medical errors resulting from communication failures between medical providers are most effectively addressed by implementing a systematic signout process that includes checklists to Improve efficacy and accuracy.
- Checklists are an important tool to prevent undesired medical outcomes that result from physician communication failures during the patient handoff process.

8. A pregnant woman who has capacity has the right to refuse treatment, even if it places her unborn child at risk.
- In the United States, the mother is considered to have ultimate rights over her unborn child, assuming she has capacity. When a mother refuses a procedure or treatment that is in the best interest of the fetus, the physician should provide counseling and education as to why the procedure is necessary.
- If the mother continues to refuse a procedure that would prevent irreversible harm to the fetus, the hospital ethics committee should be consulted, but the mother should not be coerced or otherwise forced into accepting any form of treatment she does not want.

9. The Health Insurance Portability and Accountability Act protects health information by requiring verbal or written authorization for release of information.
- Hospitals and physicians' offices frequently have additional policies requiring written forms for release of information and procedures to verify the identity of phone callers.
- It is important that health care providers be familiar with these rules and disclose only the minimum necessary information.

10. In general, a patient has the right to know a diagnosis.
- If family members ask for information to be withheld, it is imperative for the physician to understand their reasoning.
- Occasionally, it is in the patient's best interest to withhold especially distressing news (if a severely depressed patient might become suicidal). Therefore, it is best to clarify the situation with the concerned family members first before deciding how best to proceed.

11. It's important to maintain professional conduct when dealing with patients of all types, ranging from hostile to seductive. Several actions suggest that the patient could have boundary issues. These include:

A. Arrival at unscheduled times and/or at closing time (when others are less likely to be available).
B. Insistence on seeing the same physician for each visit (for mild conditions) and in private.
C. Frequent return visits for nonspecific complaints.
D. Health complaints that necessitate examination of private areas or undressing, despite recent normal findings.

- Physicians should respond politely but firmly to inappropriate patient requests. Maintaining professional boundaries is an important component of the physician-patient relationship.

12. When dealing with an angry patient, the most appropriate response is to remain non-defensive, acknowledge that the patient is upset, and begin the discussion with an open-ended question.

13. Accepting gifts from Interested third parties can Influence a physician's practice in subtle or subconscious ways.

- Only nonmonetary gifts that are of minimal value and that directly benefit the patient, such as unbiased educational material or drug samples, should be considered.

14. In the absence of an advance directive, a life-saving blood transfusion can be given to a Jehovah's Witness who lacks decision-making capacity.

Ethical situations

SITUATION	APPROPRIATE RESPONSE
Patient is not adherent.	Attempt to identify the reason for nonadherence and determine his/her willingness to change; do not coerce the patient into adhering and do not refer him/her to another physician.
Patient desires an unnecessary procedure.	Attempt to understand why the patient wants the procedure and address underlying concerns. Do not refuse to see the patient and do not refer him/her to another physician. Avoid performing unnecessary procedures.
Patient has difficulty taking medications.	Provide written instructions; attempt to simplify treatment regimens; use teach-back method (ask patient to repeat regimen back to physician) to ensure comprehension.
Family members ask for information about patient's prognosis.	Avoid discussing issues with relatives without the patient's permission.
A patient's family member asks you not to disclose the results of a test if the prognosis is poor because the patient will be "unable to handle it."	Attempt to identify why the family member believes such information would be detrimental to the patient's condition. Explain that as long as the patient has decision-making capacity and does not indicate otherwise, communication of information concerning his/her care will not be withheld. However, if you believe the patient might seriously harm himself/herself or others if informed, then you may invoke therapeutic privilege and withhold the information.
A 17-year-old girl is pregnant and requests an abortion.	Many states require parental notification or consent for minors for an abortion. Unless there are specific medical risks associated with pregnancy, a physician should not sway the patient's decision for, or against, an elective abortion (regardless of maternal age or fetal condition).
A 15-year-old girl is pregnant and wants to keep the child. Her parents want you to tell her to give the child up for adoption.	The patient retains the right to make decisions regarding her child, even if her parents disagree. Provide information to the teenager about the practical issues of caring for a baby. Discuss the options, if requested. Encourage discussion between the teenager and her parents to reach the best decision.
A terminally ill patient requests physician assistance in ending his/her own life.	Overwhelming majority of states refuse involvement in any form of physician-assisted death. Physicians may, however, prescribe medically appropriate analgesics even if they shorten the patient's life.
Patient is suicidal.	Assess the seriousness of the threat. If it is serious, suggest that the patient remain in the hospital voluntarily; patient can be hospitalized involuntarily if he/she refuses.
Patient states that he/she finds you attractive.	Ask direct, closed-ended questions and use a chaperone if necessary. Romantic relationships with patients are never appropriate. It may be necessary to transition care to another physician.
A woman who had a mastectomy says she now feels "ugly."	Find out why the patient feels this way. Do not offer falsely reassuring statements (eg, "You still look good").
Patient is angry about the long time he/she spent in the waiting room.	Acknowledge the patient's anger, but do not take a patient's anger personally. Apologize for any inconvenience. Stay away from efforts to explain the delay.
Patient is upset with the way he/she was treated by another doctor.	Suggest that the patient speak directly to that physician regarding his/her concerns. If the problem is with a member of the office staff, tell the patient you will speak to that person.
An invasive test is performed on the wrong patient.	Regardless of the outcome, a physician is ethically obligated to inform a patient that a mistake has been made.

Ethical situations *(continued)*

SITUATION	APPROPRIATE RESPONSE
A patient requires a treatment not covered by his/her insurance.	Never limit or deny care because of the expense in time or money. Discuss all treatment options with patients, even if some are not covered by their insurance companies.
A 7-year-old boy loses a sister to cancer and now feels responsible.	At ages 5–7, children begin to understand that death is permanent, that all life functions end completely at death, and that everything that is alive eventually dies. Provide a direct, concrete description of his sister's death. Avoid clichés and euphemisms. Reassure the boy that he is not responsible. Identify and normalize fears and feelings. Encourage play and healthy coping behaviors (eg, remembering her in his own way).
Patient is victim of intimate partner violence.	Ask if patient is safe and has an emergency plan. Do not necessarily pressure patient to leave his or her partner, or disclose the incident to the authorities (unless required by state law).
Patient wants to try alternative or holistic medicine.	Explore any underlying reasons with the patient in a supportive, nonjudgmental manner. Advise the patient of known benefits and risks of treatment, including adverse effects, contraindications, and medication interactions.
Physician colleague presents to work impaired.	If impaired or incompetent, colleague is a threat to patient safety. Report the situation to local supervisory personnel. Should the organization fail to take action, alert the state licensing board.
Patient is officially determined to suffer brain death. Patient's family insists on maintaining life support indefinitely because patient is still moving when touched.	Gently explain to family that there is no chance of recovery, and that brain death is equivalent to death. Movement is due to spinal arc reflex and is not voluntary. Bring case to appropriate ethics board regarding futility of care and withdrawal of life support.
A pharmaceutical company offers you a sponsorship in exchange for advertising its new drug.	Reject this offer. Generally, decline gifts and sponsorships to avoid any appearance of conflict of interest. The AMA Code of Ethics does make exceptions for gifts directly benefitting patients; gifts of minimal value; special funding for medical education of students, residents, fellows; grants whose recipients are chosen by independent institutional criteria; and funds that are distributed without attribution to sponsors.
Patient requests a nonemergent procedure that is against your personal or religious beliefs.	Provide accurate and unbiased information so patients can make an informed decision. Explain to the patient that you do not perform the procedure but offer to refer him/her to another physician.
Mother and 15-year-old daughter are unresponsive following a car accident and are bleeding internally. Father says do not transfuse because they are Jehovah's Witnesses.	Transfuse daughter, but do not transfuse mother. Emergent care can be refused by the healthcare proxy for an adult, particularly when patient preferences are known or reasonably inferred, but not for a minor based solely on faith.
A child presents with injuries inconsistent with parental story.	Contact child protective services and ensure child is in a safe location. Physicians are required by law to report any reasonable suspicion of child abuse or endangerment.

CHAPTER 4

Epidemiology

Epidemiology

Epidemiologic measures

- Epidemiology is the study of the distribution and determinants of health-related states within a population.
- Epidemiology sees disease as distributed within a group, not as a property of an individual.
- The tools of epidemiology are numbers.
- Numbers in epidemiology are ratios converted into rates.
- The denominator is key: who is "at risk" for a particular event or disease state.
- Compare the number of actual cases with the number of potential cases to determine the rate.
- Rates are generally, but not always, per 100,000 persons by the Centers for Disease Control and Prevention (CDC), but can be per any multiplier (Vital statistics are usually per 1,000 persons).

$$\frac{\text{Actual cases}}{\text{Potential cases}} = \frac{\text{Numerator}}{\text{Denominator}} = \textbf{RATE}$$

Incidence and Prevalence

1. Incidence rate (IR):

- The rate at which new events occur in a population.

- The numerator is the number of NEW events that occur in a defined period; the denominator is the population at risk of experiencing this new event during the same period.

- Remember, IR:

- Should include only new cases of the disease that occurred during the specified period.
- Should not include old cases or dead cases in the denominator.

- Primary prevention: Stopping someone from getting the disease = preventing incidence.

$$\frac{\text{Number of new cases}}{\text{Number "at risk" to be a new case}} = \text{incidence}$$

- Mnemonic: Incidence is the rate at which new cases coming in.

❖ Attack rate:

- It is the cumulative incidence of infection in a group of people observed over a period of time during an epidemic, usually in relation to foodborne illness.

- It is the number of exposed people infected with the disease divided by the total number of exposed people.

- It is measured from the beginning of an outbreak to the end of the outbreak. It is often referred to as an attack ratio.

2. Prevalence rate:

- All persons who experience an event in a population.

- The numerator is ALL individuals who have an attribute or disease at a particular point in time (or during a particular period of time); the denominator is the population at risk of having the attribute or disease at this point in time (dead cases are not at risk!).

- The numerator includes not only new cases, but also old cases (people who remained ill during the specified point or period in time).

- A case is counted in prevalence until death or recovery occurs.

- Prevalence is most useful for measuring the burden of chronic diseases such as tuberculosis, malaria and HIV in a population.

$$\frac{\text{Total number of cases}}{\text{Number in population "at risk" to be a case}} = \text{prevalence}$$

- Point vs. Period Prevalence:

A. Point prevalence: prevalence during a particular "point in time".

B. Period prevalence: prevalence during a specified period or span of time.

- Secondary prevention: Reducing the cases of the disease = preventing prevalence.

- Tertiary prevention: Decreasing negative effects of the disease "improve Quality of life"

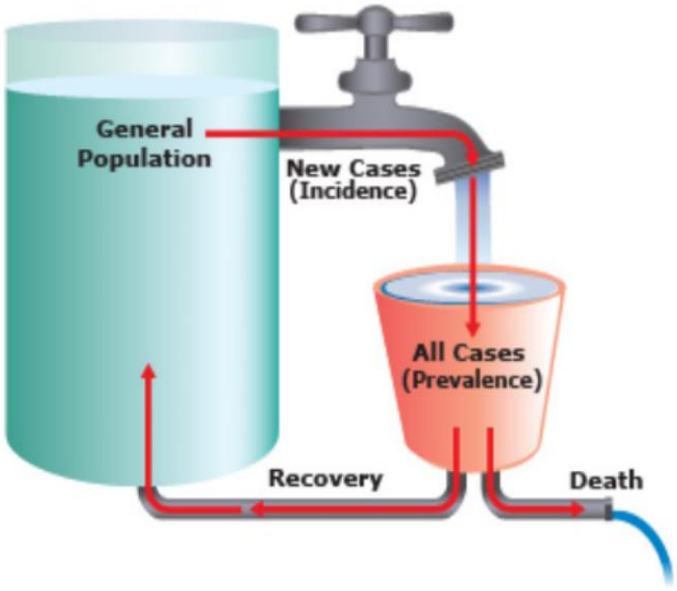
❖ Understanding the relationship between incidence and prevalence:

Prevalence = Incidence × Duration (P = I × D)

- Prevalence ≈ incidence for short duration disease (common cold). Prevalence > incidence for chronic diseases, due to large # of existing cases (diabetes).

- Prevalence pot:

- Incident cases or new cases are monitored over time.
- New cases join pre-existing cases to make up total prevalence.
- Prevalent cases leave the prevalence pot in one of two ways → recovery or death.



❖ Practice:

Qs. How do prevalence and incidence change if:

1. A cure is discovered?

- A Prevalence will go down. New cases may occur at the same rate (incidence), but fewer people are living with it because it can be cured (decreased prevalence).

2. An effective prevention, such as a vaccine, is discovered?

- Both incidence and prevalence will go down. If the disease is chronic and incurable such as hepatitis B, the prevalence may decrease very slowly, but the number of new cases (incidence) may drop dramatically.

3. An effective therapy prolongs life, but does not cure?

- Prevalence increases as more people are living longer with the disease.

4. Person-to-person transmission is decreased?

- Incidence will go down, and over time, prevalence will follow.

What happens to incidence and prevalence if:	Incidence	Prevalence
New effective treatment is initiated?	N	↓
New effective vaccine gains widespread use?	↓	↓
Number of persons dying from the condition increases?	N	↓
Additional Federal research dollars are targeted to a specific condition?	N	N
Behavioral risk factors are reduced in the population at large?	↓	↓
Contacts between infected persons and noninfected persons are reduced: For airborne infectious disease? For noninfectious disease?	 ↓ N	 ↓ N
Recovery from the disease is more rapid than it was 1 year ago?	N	↓
Long-term survival rates for the disease are increasing?	N	↑

❖ N = no change; ↓ = decrease; ↑ = increase.

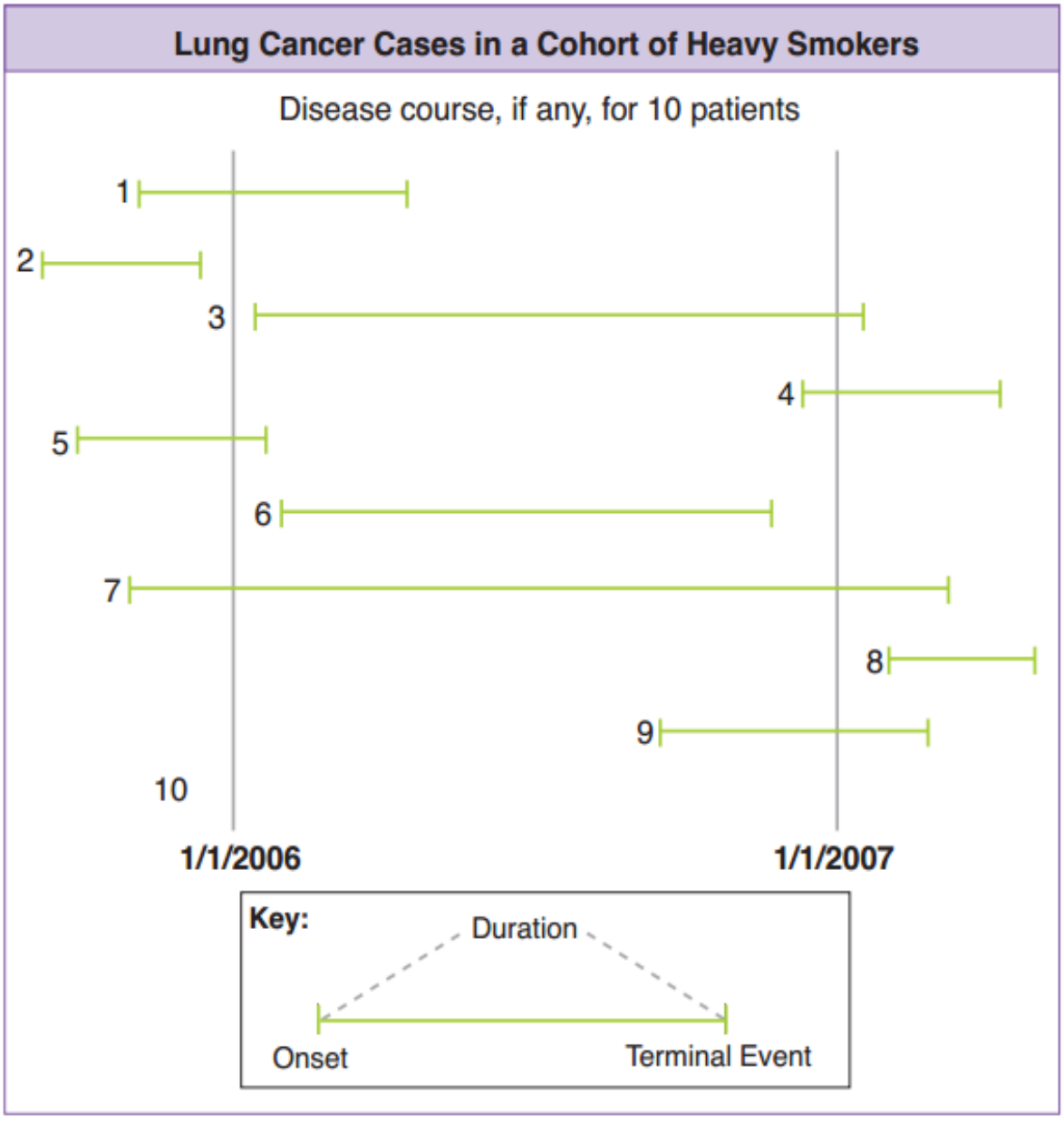
❖ N.B:

- Incidence answers the question: how many new cases of the disease were diagnosed in a population during a particular period of time?
- Prevalence answers the question: how many cases of the disease, both new and old, exist in a population at a particular point in time? The relationship between prevalence and incidence can be expressed as the following equation:

$$\text{Prevalence} = (\text{Incidence}) \times (\text{Time})$$

- Incidence of a disease is not changed by any kind of treatment, because the disease has already developed when the treatment is started.
- Any treatment that prolongs survival but does not cure the disease will increase prevalence due to an increase in the number of afflicted (but still alive) individuals overtime.
- An increasing prevalence and stable incidence can be attributed to factors which prolong the duration of a disease (improved quality of care).

❖ Counting for Incidence and Prevalence:



- Incidence (form 1/1/2006 to 1/1/2007) = $\frac{4}{6}$ (2 is dead, 1&5&7 are old cases).
- Period prevalence (form 1/1/2006 to 1/1/2007) = $\frac{7}{9}$ (2 is dead).
- Point prevalence (1/1/2007) = $\frac{4}{6}$ (1&2&5&6 are dead).

Crude, Specific, and Standardized Rates

A. Crude rate: Numerator/denominator for total population.

B. Specific rate: Numerator/denominator for sub-groups within population. Ex: "age-specific" or "sex-specific" rate.

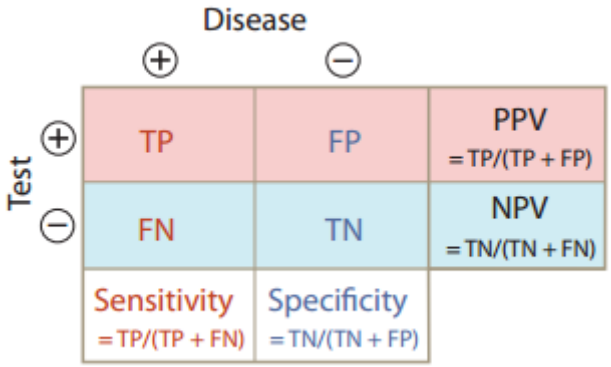
C. Standardized rate (or adjusted rate): Removing effects of demographic variables when comparing two or more populations

- Types of mortality rates:

Crude mortality rate	$\frac{\text{Deaths}}{\text{Population}}$
Cause-specific mortality rate	$\frac{\text{Deaths from cause}}{\text{Population}}$
Case-fatality rate	$\frac{\text{Deaths from cause}}{\text{Number of persons with the disease/cause}}$
Proportionate mortality rate (PMR)	$\frac{\text{Deaths from cause}}{\text{All deaths}}$

Interpreting Diagnostic and Screening Tests

- Uses 2 × 2 table comparing test results with the actual presence of disease.
- TP = true positive; FP = false positive; FN = false negative; TN = true negative.



"Trues on Top divide by everything"

Pre-test Probabilities

A. Sensitivity:

- The probability of correctly identifying a case of disease.
- Sensitivity is the proportion of truly diseased persons in the screened population who are identified as diseased by the screening test. This is also known as the "true positive rate".
- Everyone in the calculation is a diseased person.
- Sensitivity = TP/(TP + FN) = true positives/(true positives + false negatives)
- SEN = 750/(750 + 250) = 750/1,000 = 75%
- 1 - SEN = False Negative Rate.

	Yes	No
Positive	750	50
Negative	250	950

B. Specificity:

- The probability of correctly identifying disease-free persons.
- Specificity is the proportion of truly non-diseased persons who are identified as non-diseased by the screening test. This is also known as the "true negative rate".
- Everyone in the calculation is a healthy person.
- Specificity = TN/(TN + FP) = true negatives/(true negatives + false positives).
- SPEC = 950/(950 + 50) = 950/1,000 = 95%.
- Measures only the distribution of persons who are disease-free.
- 1-specificity = false positive rate.

	Yes	No
Positive	750	50
Negative	250	950

Post-test Probabilities

A. Positive predictive value:

- The probability of disease in a person who receives a positive test result.
- The probability that a person with a positive test is a true positive (has the disease) is referred to as the "predictive value of a positive test".
- Everyone in the calculation got a positive on the test.
- Positive predictive value = TP/(TP + FP) = true positives/(true positives + false positives)
- PPV = 750/(750 + 50) = 750/800 = 93.8%
- Measures only the distribution of persons who receive a positive test result

	Yes	No
Positive	750	50
Negative	250	950

B. Negative predictive value:

- The probability of no disease in a person who receives a negative test result.
- The probability that a person with a negative test is a true negative (does not have the disease) is referred to as the "predictive value of a negative test".
- Everyone in the calculation got a negative on the test.
- Negative predictive value = TN/(TN + FN) = true negatives/(true negatives + false negatives).
- NPV = 950/(950 + 250) = 950/1,200 = 79.2%.
- Measures only the distribution of persons who receive a negative test result.

	Yes	No
Positive	750	50
Negative	250	950

C. Accuracy (ACC):

- Overall correctness of the test.
- Everyone is included in this calculation.
- ACC = ((TP +TN) / (TP + TN + FP + FN)).
- ACC = ((750 + 950) / (75O + 95O + 5O + 25O)) = 1,700 / 2,000 = 85%.

	Yes	No
Positive	750	50
Negative	250	950

❖ Practice Questions:

1. What is the effect of increased incidence on sensitivity? On positive predictive value?

- (None; screening does not assess incidence).

2. What is the effect of increased prevalence on sensitivity? On positive predictive value?

- (Sensitivity stays the same, positive predictive value increases).

❖ N.B:

1. It is important to remember that the NPV will vary with the pretest probability of a disease.

- A patient with a high probability of having a disease will have a low NPV if a negative test, whereas a patient with a low probability of having a disease will have a high NPV with a negative test.
- Specific examples are given below:

A. Thyroid cancer and FNA test results:

- A patient with a high pre-test probability for having thyroid cancer (young age, radiation exposure) has a low NPV.

B. HIV and ELISA test results:

- A patient who belongs to a high-risk group (multiple sexual partners, admits to not using condoms, IV drug user) has a high pre-test probability; consequently, this patient will have a low NPV. On the other hand, a patient who belongs to a low-risk group (one monogamous sexual partner, consistent condom use, no history of IV drug use) has a low pre-test probability; consequently, this patient will have a high NPV.

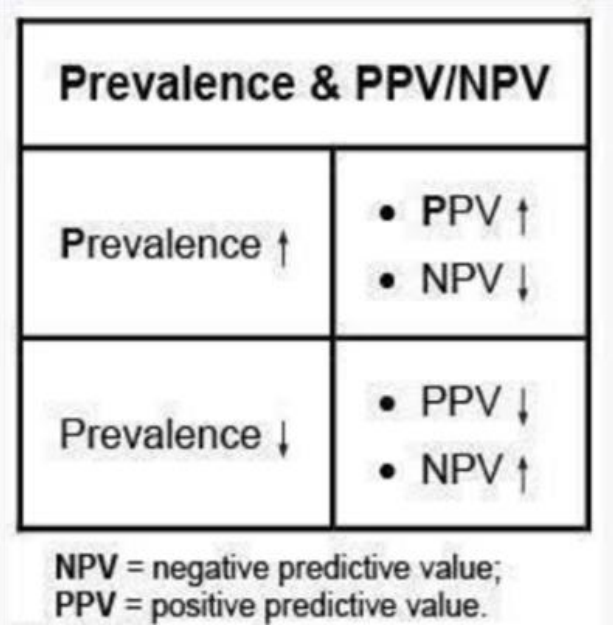
- The prevalence of a disease is directly related to the pre-test probability of having the disease and, thus, also affects the NPV.

- In a nutshell:

- Remember that the NPV will vary with the pretest probability of a disease. A patient with a high probability of having a disease will have a low NPV with a negative test but a patient with a low probability of having a disease will have a high NPV with a negative test.

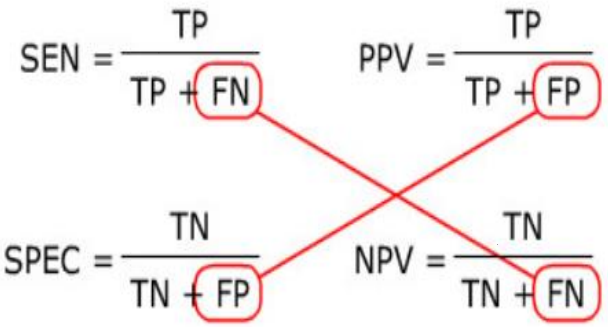
2. Both the positive predictive value (PPV) and negative predictive value (NPV) of a test depend on the prevalence of the disease of interest in the population in which the test is applied. PPV Increases and NPV decreases with an Increase in prevalence.

- The more common the disease is in the population, the more likely a patient with a positive test result actually is diseased (a "true positive"). If the disease is relatively common - as gastric cancer is in China - the probability is reasonably high that a patient who tests positive actually has the disease. If the disease is relatively uncommon - as gastric cancer is in the United States - the probability is far lower that a patient who tests positive actually has the disease.



❖ <u>The relationship between the screening test probability</u>:

- The key links are in the denominators:



Remember SNOUT and SPIN!

- If a test has a high sensitivity, then a negative result would indicate the absence of the disease:

- Take for example temporal arteritis (TA), a large vessel vasculitis involving predominantly branches of the external carotid artery which occurs in patients age >50, has elevated ESR in every case. So, 100% of patients with TA have elevated ESR. The sensitivity of an abnormal ESR for TA is 100%. If a patient you suspect of having TA has a normal ESR, then the patient does not have TA.

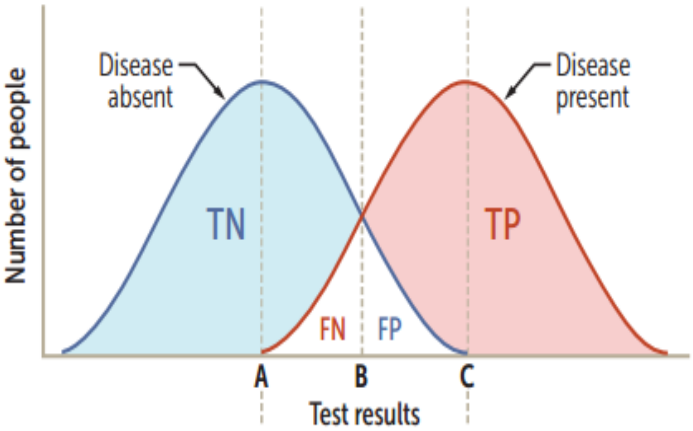
- Mnemonic for the clinical use of sensitivity: SN-N-OUT (SeNsitive test- Negative-rules out disease).

- If a test has a high specificity, then a positive result would indicate the existence of the disease.

- Example:
  - CT angiogram has a very high specificity for pulmonary embolism (97%). A CT scan read as positive for pulmonary embolism is likely true.

- Mnemonic for the clinical use of specificity: S-P-IN (Specific test- Positive-rules in disease).

Selecting Screening Test Cutoff Values



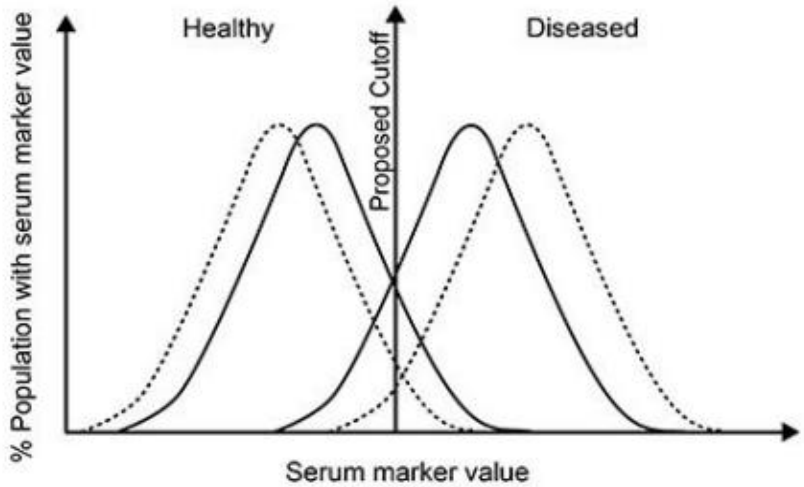
POSSIBLE CUTOFF VALUES
A = 100% sensitivity cutoff value
B = practical compromise between specificity and sensitivity
C = 100% specificity cutoff value

Lowering the cutoff point: B → A (↑ FP ↓ FN)	↑ Sensitivity ↑ NPV ↓ Specificity ↓ PPV
Raising the cutoff point: B → C (↑ FN ↓ FP)	↑ Specificity ↑ PPV ↓ Sensitivity ↓ NPV

- Point of optimum seNsitivty = point of optimum Negative predictive value.
- Point of optimum sPecificity = point of optimum Positive predictive value.

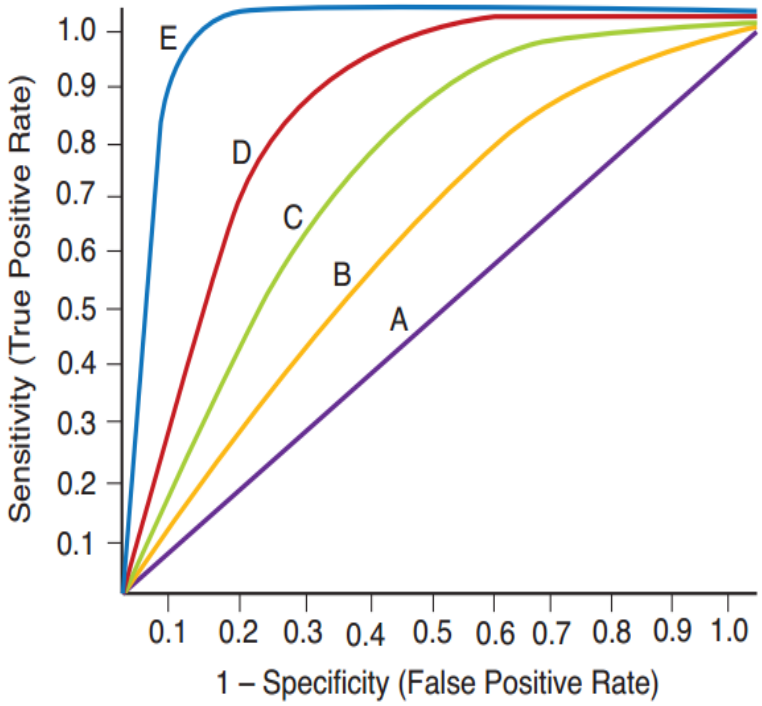
❖ N.B:

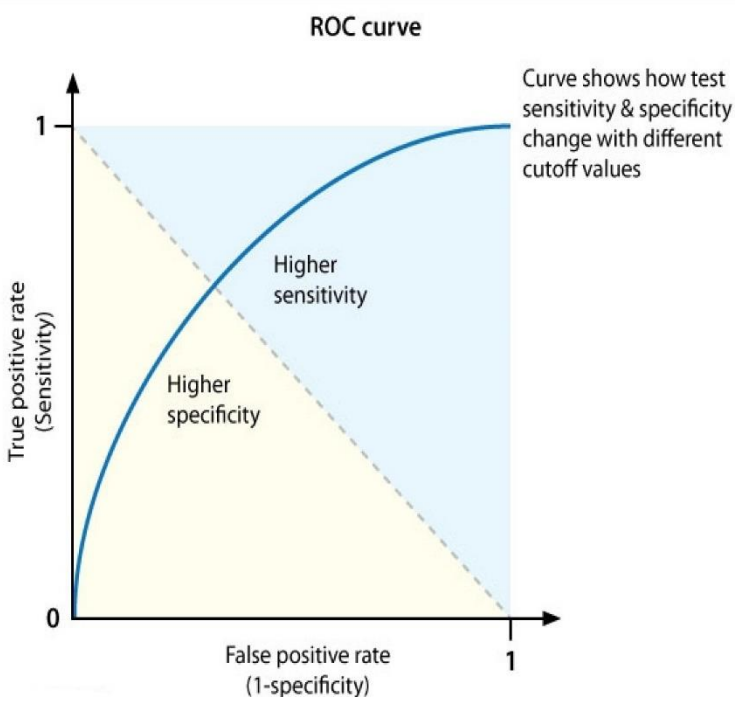
- The degree of overlap between the healthy and diseased population curves limits the maximum combined sensitivity and specificity of a test.
- In this example, the cutoff value is optimally placed to maximize both sensitivity and specificity.
- Sensitivity represents the ability of a test to identify those with a given disease.
- It is calculated as TP divided by the number of people with the disease (TP + FN).
- Specificity represents the ability of a test to exclude those from having a given disease.
- It is calculated as TN divided by the number of people without the disease (TN + FP).
- In this specific instance, decreased overlap between the healthy and diseased population curves decreases both the number of FP and FN, and thus allow for a test with both higher sensitivity and specificity.
- Therefore, the dashed curves are associated with higher sensitivity and specificity.



Receiver Operating Characteristic (ROC)

- Used to compare with available alternative diagnostic test.
- Used to help to set test cutoff values.
- In this example, test E is the best test.
- Screening tests need high sensitivity; confirmatory tests need high specificity.
- The better performing test will have a higher area under the curve (AUC), with the curve closer to the upper left corner.





Understanding Types of Research Studies

A. Observational Studies:

- Recording without intervention.
- Looking at information available in the natural world.

B. Experimental Studies (Clinical Trials):

- Assessing the Effects of an intervention.
- Generates new information by assessing effects of intervention(s).

Types of Observational Studies

A. Cross-sectional study:

- In a cross-sectional study, exposure and outcome are measured simultaneously at a particular point in time ("snapshot study"). In other study designs, a certain time period separates the exposure from the outcome.
- Asks, "What is happening?"
- Prevalence study.
- Cannot provide incidence.
- Assesses who has or does not have a disease in a defined population.
- Conducted at (essentially) a single point in time.
- Also, records occurrence of risk factors that may be related to disease.
- Analysis assesses only the association between disease and risk factors, not causation.

B. Case-Control Study:

- A case-control study is designed by selecting individuals with a particular disease (cases), individuals without that disease (controls), and then evaluating previous exposure status.
- Asks, "What happened?"
- Key comparison: Diseased vs. non-diseased.
- Looks backward in time for the presence or absence of risk factors (Retrospective).

- Analysis looks for risk factors in the history of the diseased group that are not found in the history of the non-diseased group.
- Can give evidence for causality.
- No assessment of prevalence or incidence.
- Allows focus on persons with the disease, with non-disease only included for comparative purposes.

C. Cohort Study:

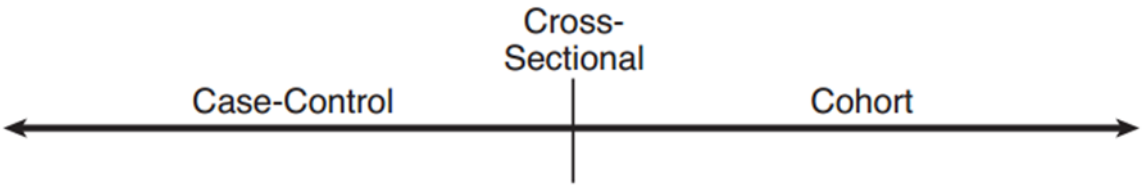
- Identifies people with risk factors and compares disease incidence to incidence rate in another group of people without those risk factors.
- Key comparison: Risk factor vs. no-risk factor.
- Analysis compares incidence rates in those who have and do not have risk factor.
- Can be prospective or retrospective.
- Usually prospective, following people forward in time.
- The critical distinction between case control and retrospective cohort studies is the order in which outcomes and risk factors are assessed. Case control studies determine the outcome first and then look for associated risk factors: retrospective cohort studies first ascertain risk factor exposure and then determine the outcome.
- Gives assessment of incidence and causality.
- No estimate of prevalence.

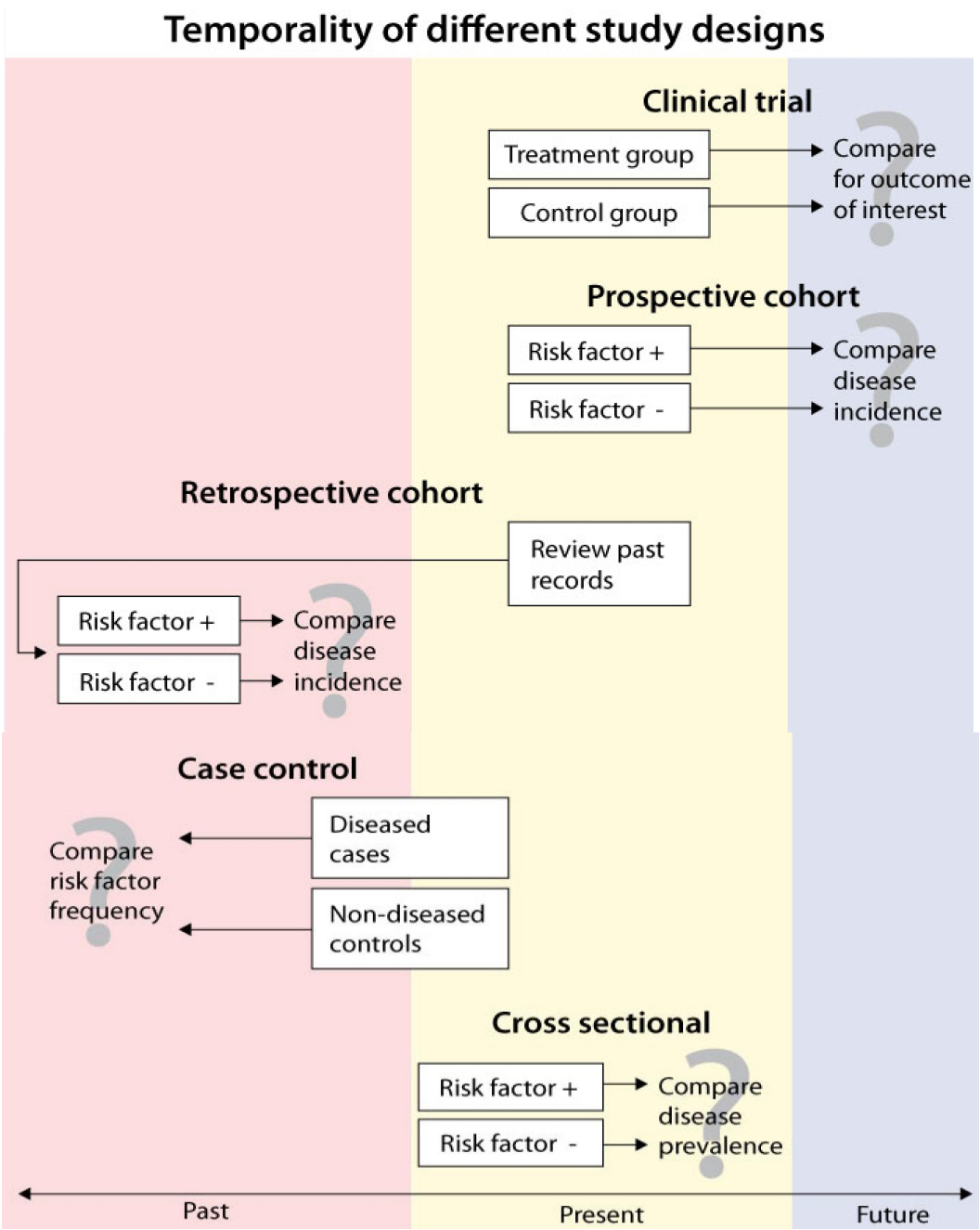
D. Twin concordance study:

- Compares the frequency with which both monozygotic twins vs both dizygotic twins develop the same disease.
- Measures heritability and influence of environmental factors ("nature vs nurture").

E. Adoption study:

- Compares siblings raised by biological vs adoptive parents.
- Measures heritability and influence of environmental factors.


Cross-
Sectional
Case-Control
Cohort


Temporality of different study designs
Clinical trial
Treatment group
Control group
Compare for outcome of interest
Prospective cohort
Risk factor +
Risk factor -
Compare disease incidence
Retrospective cohort
Review past records
Risk factor +
Risk factor -
Compare disease incidence
Case control
Diseased cases
Non-diseased controls
Compare risk factor frequency
Cross sectional
Risk factor +
Risk factor -
Compare disease prevalence
Past
Present
Future

How We Analyze Cohort and Case-Control Studies

A. Cohort and clinical trial studies:

1. Relative Risk (Relative Risk Ratio) (RR):

- Compares incidence rates in groups with and without risk factor by division (Risk of developing disease in the exposed group divided by risk in the unexposed group).

- Relative risk (RR) is used in cohort studies to determine how strongly a risk factor (exposure) is associated with an outcome.

- Answers question: "How much more (or less) likely?"

Relative Risk Calculation

$$RR = \frac{\text{Incidence in exposed}}{\text{Incidence in unexposed}}$$

Relative risk calculation

Risk status	Disease status	
	Present	Absent
Exposed	a	b
Non-exposed	c	d

$$\text{Relative risk (RR)} = \frac{a/(a+b)}{c/(c+d)}$$

- RR = 1 → no association between exposure and disease.

- RR > 1 → exposure associated with ↑ disease occurrence.

- RR < 1 → exposure associated with ↓ disease occurrence.

B. Relative risk reduction:

- The proportion of risk reduction attributable to the intervention as compared to a control.

- If 2% of patients who receive a flu shot develop the flu, while 8% of unvaccinated patients develop the flu, then RR = 2/8 = 0.25, and RRR = 0.75.

$$RRR = 1 - RR$$

2. Attributable Risk (AR):

- Compares incidence rates in groups with and without risk by subtraction (excess risk that is attributable to the exposure).

- Answers question: "How many more cases?"

- If risk of lung cancer in smokers is 21% and risk in nonsmokers is 1%, then the attributable risk is 20%.

Attributable Risk Calculation

AR = Incidence rate in exposed − Incidence rate in unexposed

Infant Mortality for City	
South side = $\frac{8}{1{,}000}$ live births	North side = $\frac{16}{1{,}000}$ live births
1. Relative Risk Calculation	**How much more likely?**
$RR = \frac{\frac{16}{1{,}000}}{\frac{8}{1{,}000}} = 2.0$	**Twice as likely**
$RR = \frac{\frac{8}{1{,}000}}{\frac{16}{1{,}000}} = 0.5$	**Half as likely**
2. Attributable Risk Calculation	**How many more cases?**
$AR = \frac{16}{1{,}000} - \frac{8}{1{,}000} = \frac{8}{1{,}000}$	For every 1,000, 8 more cases

	Disease	No Disease	
Exposed	80 **A**	**B** *720*	800 $I_E = \frac{80}{800} = 10\%$
Unexposed	80 **C**	**D** 1,520	1,600 $I_U = \frac{80}{1{,}600} = 5\%$
	$RR = \frac{10\%}{5\%} = 2.0$		
	$AR = \frac{160}{1{,}600} - \frac{80}{1{,}600} = \frac{80}{1{,}600}$		

3. Attributable Risk Percent (AR%):

- Attributable risk percent (ARP) or etiologic fraction is an important measure of the impact of a risk factor being studied.

- ARP represents the excess risk in the exposed population that can be attributed to the risk factor in percentage.

- Calculation uses RR.

$$AR\% = \frac{RR - 1}{RR}$$

If RR = 4.0

$$AR\% = \frac{4.0 - 1.0}{4.0} = \frac{3}{4} = 75\%$$

4. Absolute risk reduction:

- The difference in risk (not the proportion) attributable to the intervention as compared to a control.

- If 8% of people who receive a placebo vaccine develop the flu vs 2% of people who receive a flu vaccine, then ARR = 8%–2% = 6% = 0.06.

$$ARR = \frac{c}{c+d} - \frac{a}{a+b}$$

5. Number Needed to Treat (NNT):

- Really about prevention, not treatment.

- How many do you have to do something to prevent one case of disease?

- Calculated as inverse of Absolute risk reduction (ARR).

- Lower number = better treatment.

NNT = 1/ARR

6. Number needed to harm (NNH):

- Number of patients who need to be exposed to a risk factor for 1 patient to be harmed.

- Higher number = safer exposure.

NNH = 1/AR

C. Case-Control Studies:

❖ Odds Ratio:

- A case-control study is used to compare the exposure of people with the disease (cases) to the exposure of people without the disease (controls).

- The main measure of association is the exposure odds ratio (Cross calculation).

Risk	Disease: Yes	Disease: No
Yes	A	B
No	C	D

Computing an Odds Ratio

$$OR = \frac{A/C}{B/D} = \frac{AD}{BC}$$

❖ N.B:

1. If the disease is rare (low disease prevalence), disease incidence (number of new cases) is typically low, and the OR generally approximates the RR. This is called the "rare disease assumption".

- Mathematically: given standard contingency tables, RR = [a / (a + b)] / [c / (c + d)] and OR = AD/BC. When the disease is rare, A and C represent small quantities. Therefore, A is negligible compared to B, and C is negligible compared to D; this results in a reasonable mathematical approximation of RR, where RR becomes approximately AD/BC, which equals OR.

2. Hazard ratios are the ratio of an event rate occurring in the treatment group versus the non-treatment group.

- Ratios <1 indicate that the treatment group had a lower event rate and ratios >1 indicate that the treatment group had a higher event rate.

Experimental Studies (Clinical Trials, Intervention Studies)

❖ Phases of Clinical Trials:

A. Phase 1: Safety Trial

- Drug is tested on healthy individuals.
- Conducted on small numbers of subjects.
- Assesses any unknown dangers or negative effects.

B. Phase 2: First Use on Patients

- Drug is given in different doses, timings, and delivery mechanisms.
- Goal: to determine dosage levels and proper protocols for use.
- Moderate sample size.
- Some hints at efficacy.

C. Phase 3: Main Event

- Assesses efficacy and side effects.
- Large number of patients involved.
- Evidence used for FDA approval.

D. Phase 4: Post-Marketing Survey

- Monitoring of reports from physician and patients after drug is in common usage.
- Looking for issues that were missed in previous studies.
- Focus on identifying as yet undetected "rare but serious" side effects.
- If adverse effects found:
  - Black box warning, or
  - Drug removed from usage.

E. Phase 4 continues for as long as the compound is in use.

Features of Randomized Controlled Clinical Trials

❖ **Baseline for Comparison is Control Group:**

A. Placebo Group:

- Research subjects given everything treatment group is given except the actual drug being tested.
- Usually given inert substance, "sugar pill".
- Ethical if not withholding known effective treatment.
- Many patients get better in placebo group (often 35% or more).
- Question: "Does this drug work better than no drug?"

B. Standard of Care Group:

- Used when another treatment of some benefit already exists, as in looking for a better cancer treatment.
- Question: "Does this new drug work better than the old drug?"

C. Random Assignment:

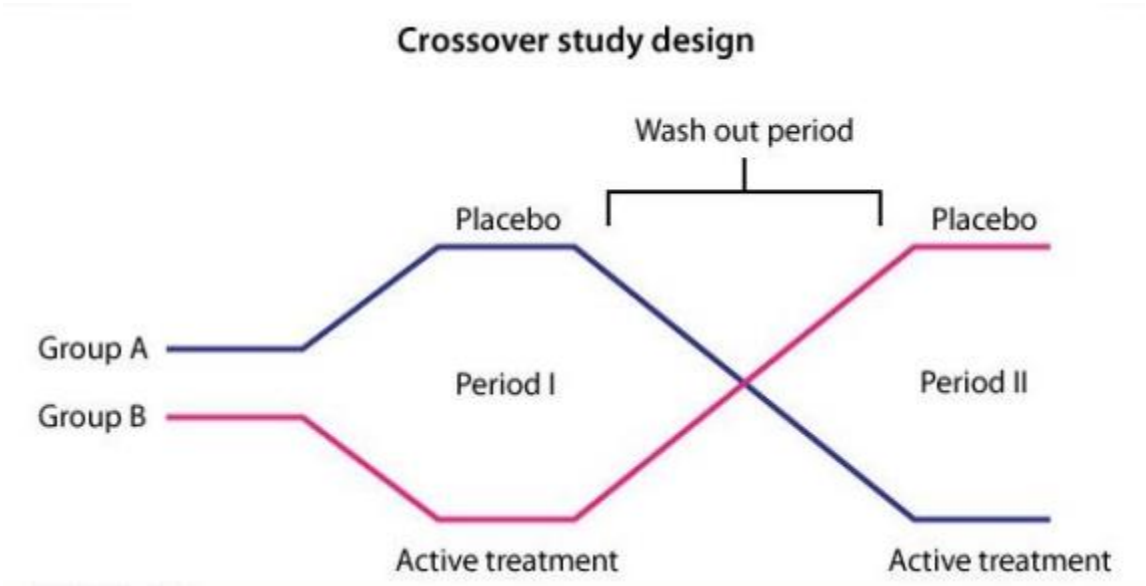
- Research subjects put into treatment or control groups by a random process.
- Random number generator may be used.
- Helps to ensure same kind of people in both groups.
- "Individually we are all different, but in the aggregate, we are all the same."

D. Double-Blind Design:

- Blinding technique is commonly used in clinical trials.
- The blinding can involve patients exclusively or both patients and physicians (double blinding). The main purpose of blinding is to prevent patient or researcher expectancy from interfering with the determination of an outcome.
- For example, a researcher's belief in a positive outcome in treated patients can potentially result in observer bias.

E. Crossover Design:

- If you need comparison group, but want everyone in the study to get the drug being tested.
- At start of study, one group gets drug while other group gets placebo.
- Then, at a set time point, group getting placebo is switched to drug, and group getting drug is switched to placebo.
- Must be double-blind.
- The principal drawback of crossover trials is that the effects of one treatment may “carry over' and alter the response to subsequent treatments. To limit this disadvantage, a washout (no treatment) period is often added between consecutive treatments. The washout period is designed to be long enough to allow the effects of prior treatment to wear off.



Ways Research Can be Misleading (Understanding the Bias)

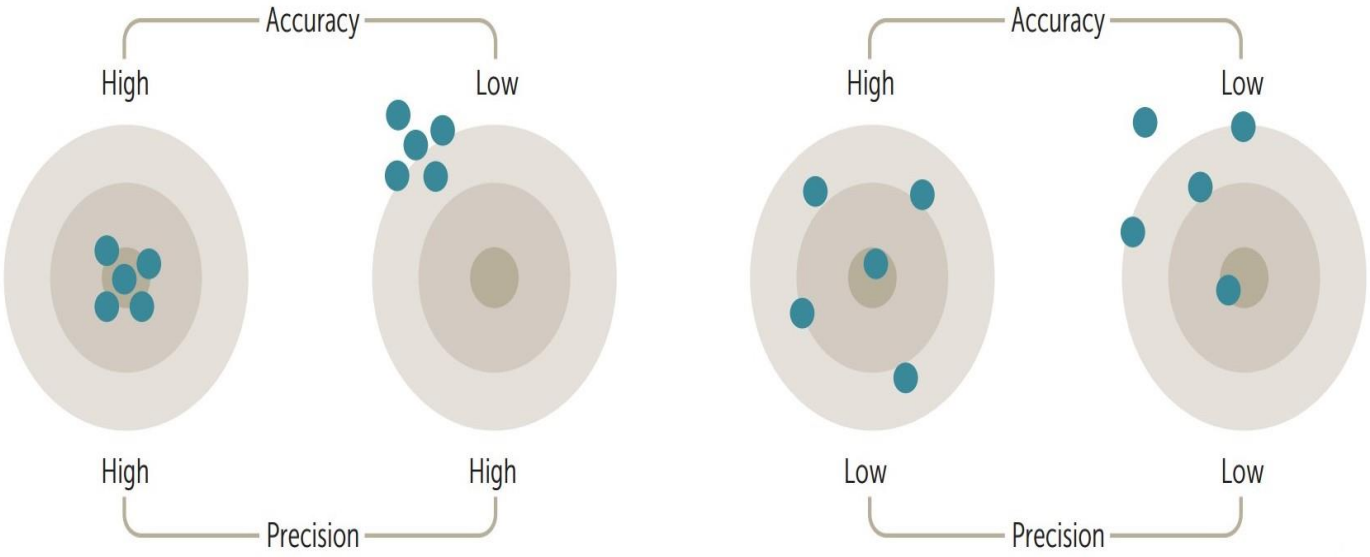
- Bias Occurs When Research Generates a Distorted Picture of Reality.

- Precision:

- The consistency and reproducibility of a test (reliability).
- A reliable test gives similar results on repeat measurements.
- Random error ↓ precision in a test. Reliability is maximal when random error is minimal.
- ↑ Precision → ↓ standard deviation.
- ↑ precision → ↑ statistical power (1 – β).

- Accuracy:

- The trueness of test measurements (validity).
- The absence of systematic error or bias in a test.
- Systematic error ↓ accuracy in a test.



Bias and study errors

- Bias in research is a deviation from the truth of inferred results. It can be done intentionally or unintentionally.

1. Selection bias:

- Problem: Sample does not reflect the population.

- Those in the study sample are not a good reflection of the population we want to say something about: "Who is in does not match who is out".

A. Ascertainment (sampling) bias: Study population differs from target population due to nonrandom selection methods.

B. Non-respondent bias:

- Participating subjects differ from non-respondents in meaningful ways.

- Generally speaking, the lower the response rate, the greater the likelihood of a non-response bias.

C. Berkson's bias: study population selected from hospital is less healthy than general population.

D. Healthy worker effect: The working population is healthier on average than the general population → Any sample consisting of only working individuals does not represent the general population (This effect occurs because severely ill individuals do not usually work).

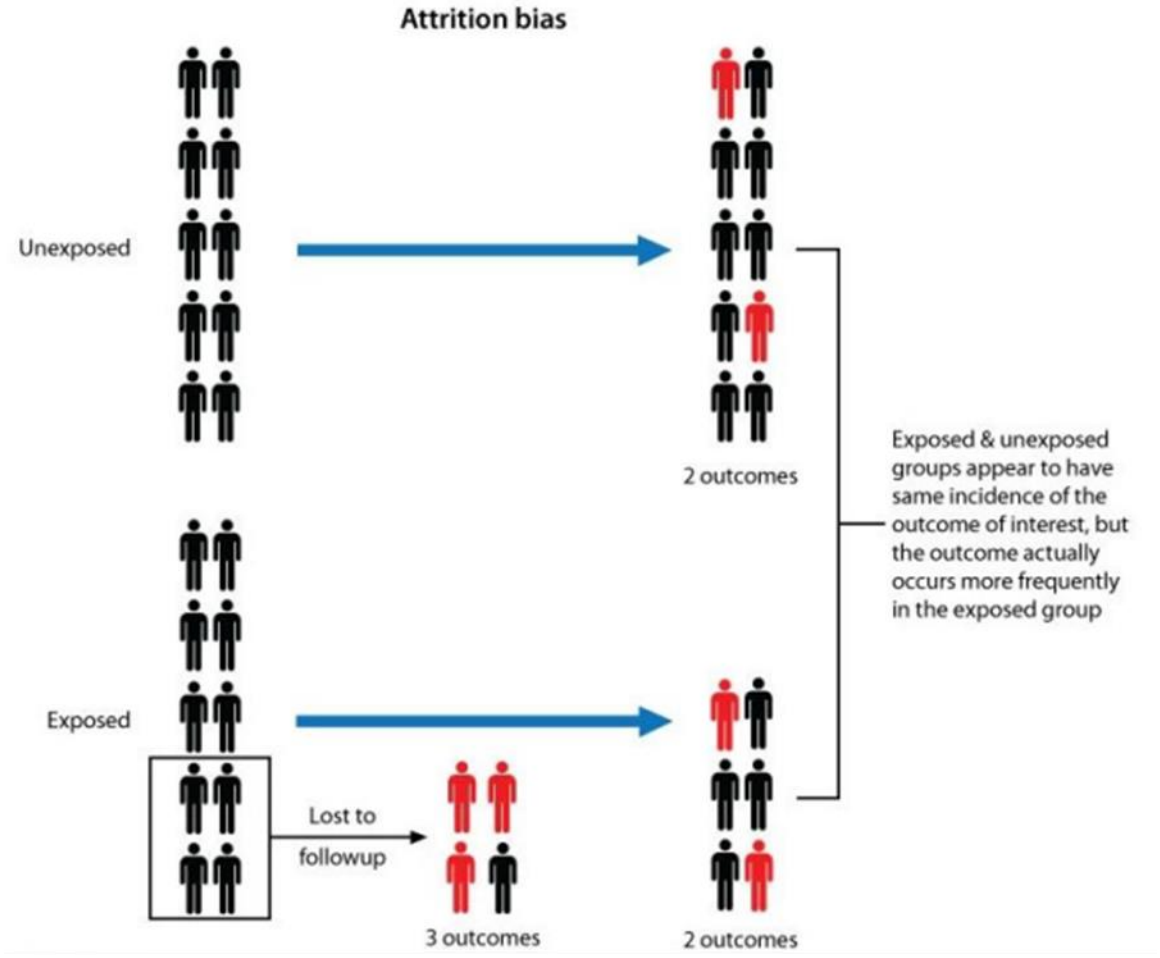
E. Prevalence (Neyman) bias:

- Occurs when individuals with severe or mild disease are excluded, resulting in an error in the estimated association between an exposure and an outcome.

- If you were studying risk factors for myocardial infarction among patients admitted to a cardiac ward, you could get a skewed result if you failed to include healthier patients (perhaps those who has “silent MIs”) or sicker patients, such as those who have already died from a cardiac arrest before reaching the emergency department.

F. Attrition bias (loss of follow up bias):

- In prospective studies, disproportionate loss to follow-up between the exposed and unexposed groups creates the potential for attrition bias, which is a form of selection bias. As a result, investigators generally try to achieve high patient follow-up rates in prospective studies.



- Solution to selection biases:

- Random assignment. An ideal randomization process minimizes selection bias, results in near-equal treatment and control group sizes and achieves a low probability of confounding variables.

2. Measurement Bias:

- Problem: How the data is collected affects the data that is obtained.

A. Leading questions:

- Suggesting in word choice, nonverbal behavior, or tone, what answer is preferred.

B. Hawthorne effect:

- The Hawthorne effect is defined as the tendency of a study population to affect an outcome due to the knowledge of being studied.

- This awareness leads to a change in behavior while under observation, thereby seriously affecting the validity of the study.

C. Recall bias:

- People do not remember clearly what happened in the past.

- Recall bias results from inaccurate recall of past exposure by people in the study and applies mostly to retrospective studies such as case-control studies.

- Sometimes, they simply make things up.

D. Reporting bias:

- Reporting bias may occur if subjects over- or under-report exposure history due to perceived social stigmatization (smoking, sexual experiences).

E. Observer-Expectancy Bias (Pygmalion effect):

- Observer bias occurs when the investigator's decision is adversely affected by knowledge of the exposure status.

- Person making assessment perceives things in a certain way based on prior knowledge or experience.

F. Procedure bias:

- Subjects in different groups are not treated the same.

- Patients in treatment group spend more time in highly specialized hospital units.

▪ Solution to measurement bias:

- Use a control group.

- Double-blind design: If the researchers do not have the knowledge, it cannot influence how they deal with research subjects.

3. Lead-Time Bias:

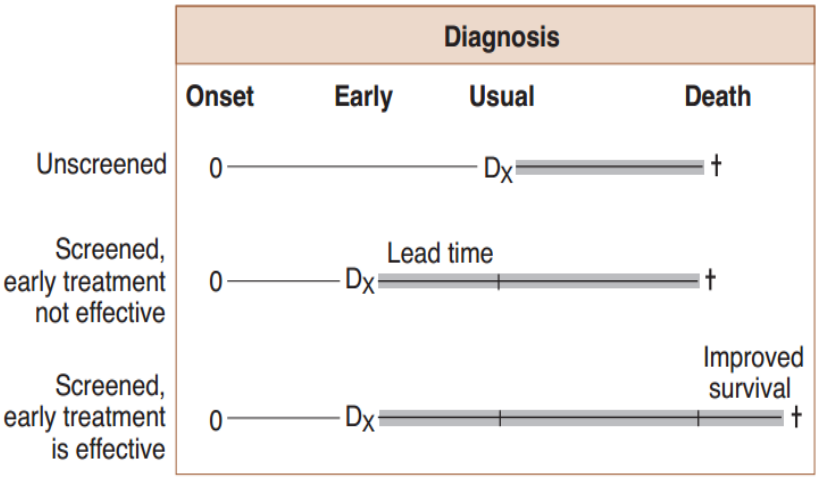
▪ Problem: False estimate of the benefits of an intervention.

▪ The prospect of lead-time bias should always be considered when evaluating any screening test. Lead-time bias is defined as an artificial increase in survival time among tested patients who actually have an unchanged prognosis.

▪ Patients screened with more sensitive tests appear to live longer only because the disease was detected earlier than it would have been if diagnosed clinically. The overall length of time from disease onset to death actually remains the same in both groups.

▪ Solution to lead-time bias:

- Use life-expectancy, not time since diagnosis.



4. Proficiency Bias:

- Problem: Interventions or treatments are not applied with equal skill to all research subjects.
- Who does the procedure may matter more than what procedure is done.
- New surgical procedures are often first done by the most expert surgeons, yielding an inflated estimate of the benefits and outcomes from the surgery.
- Solution to proficiency bias:

- Be sure that treatment providers are selected at random.

5. Confounding:

- Problem: Some additional variable, not the subject of research interest, produces the observed results.
- Often about the "hidden cause".
- No study is entirely free of confounding.
- Alcoholics have higher rates of lung cancer than non-alcoholics, suggesting that alcohol use causes lung cancer. Confounding issue: Alcoholics are more likely to be smokers.
- Solution to confounding:

- Do multiple studies (meta-analysis).
- Matching is a method generally used in the design stage of case-control studies to control confounding (when a perceived association between an exposure and an outcome is actually explained by a confounding variable associated with both the exposure and the outcome). The initial step in matching involves selecting variables that could be confounders (age, race). Cases and controls are then selected based on the matching variables so that both groups have a similar distribution in accordance with the variables.

❖ N.B:

1. Effect modification results when an external variable positively or negatively impacts the effect of a risk factor on the disease of interest. It can be distinguished from confounding by performing a stratified analysis centered on the variable of interest. Effect modification is not a bias, but rather is a natural phenomenon that is important to recognize.

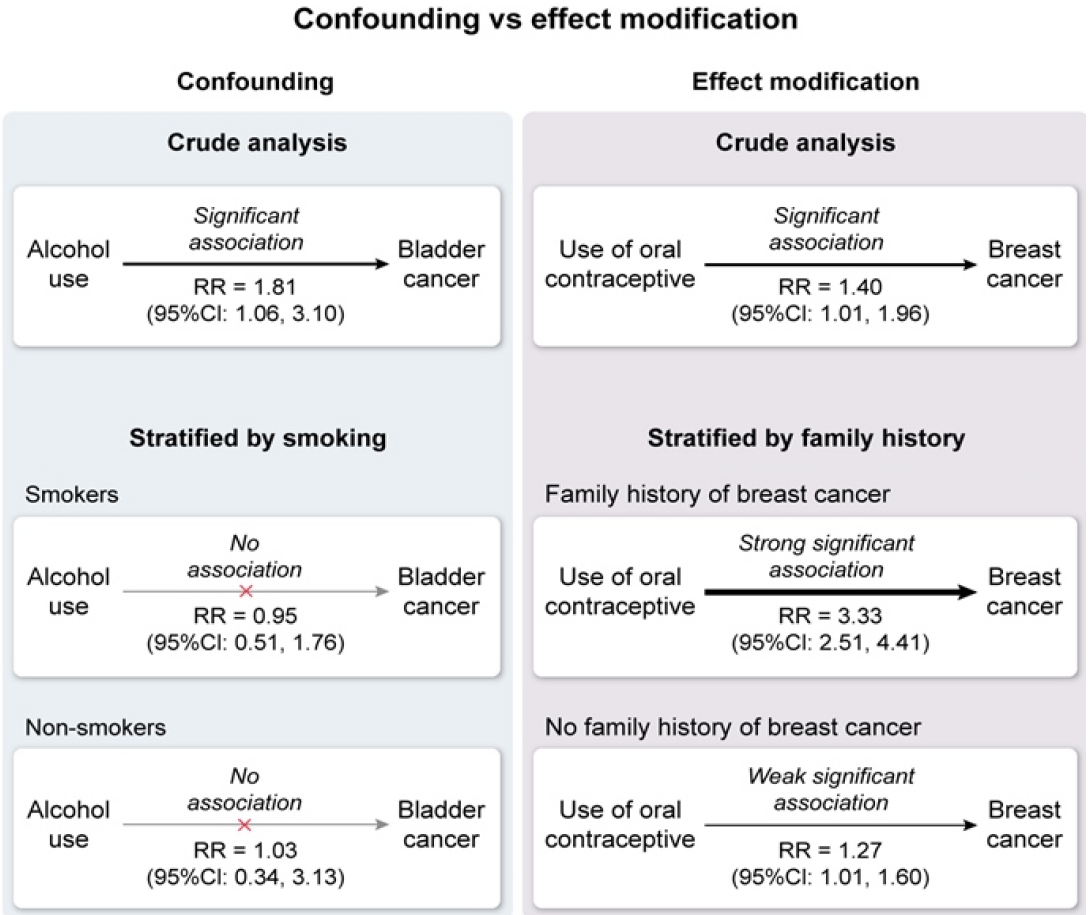
▪ The difference between confounding, effect modification:

A. Confounding bias:

- Alcohol (exposure) Oral cancer (outcome). Smoking is a confounding bias here, Why?
  - Because smoking is related to BOTH the exposure and the outcome. People who smoke will more often drink alcohol, and people who have oral cancer, were probably smokers (smoking is a known risk factor for oral cancer).

B. Effect modification:

- OCPs (exposure) Breast cancer (outcome). Family history of breast cancer is an effect modification here.
- Asbestos (exposure) Lung cancer(outcome). Smoking is an effect modification
- Estrogens (exposure) DVT (outcome). Smoking is an effect modification.
  - The effect modification is ONLY related to the outcome, but NOT to the exposure. Smoking does not affect neither asbestos exposure nor estrogen levels or intake, BUT definitely is a risk for lung cancer and DVT!
  - Family history of breast cancer has nothing to do with choosing to use OCPs, but definitely has a factor in increasing risk of breast cancer!



2. Latent period (Latency) is a very important issue to consider when studying disease epidemiology.

- In most infectious diseases, the latent period (the time elapsed from initial exposure to clinically apparent disease) is relatively short. On the other hand, the pathogenesis of some disease processes (cancer or heart disease) may demonstrate a very long latent period before clinical manifestations develop.
- The concept of a latency period can also be extended to risk factors and risk reducers. Sometimes, a significant amount of time must pass before exposure to a risk modifier has a clinically evident effect on the disease process. In addition, exposure to a risk modifier may need to occur continuously over a certain period before the disease outcome is affected. For example, at least 1 year of high-dose statin therapy was required to show a significant protective advantage over moderate-dose therapy.

CHAPTER 5

Biostatistics

Biostatistics

Answering Probability Questions

A. Combining Independent Events:

- Independent means that knowing one probability tells you nothing about the occurrence of another.

- Key idea: Multiply probabilities (A x B).

- Example:

- If the chance of having blond hair is 0.3 and the chance of having a cold is 0.2, the chance of meeting a blond-haired person with a cold is: 0.3 × 0.2 = 0.06 (or 6%)

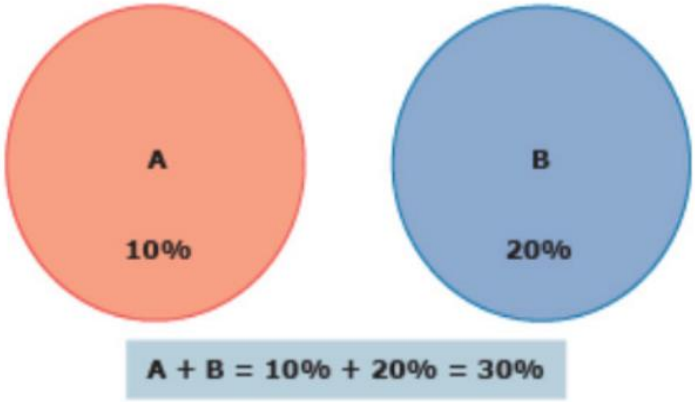
B. Combining Mutually Exclusive Events:

- Mutually exclusive means events cannot occur at the same time.

- Key idea: Add probabilities together = (A + B).

- Example:

- If a coin lands on heads, it cannot be tails; the two are mutually exclusive. If a coin is flipped, the chance that it will be either heads or tails is: 0.5 + 0.5 = 1.0 (or 100%)



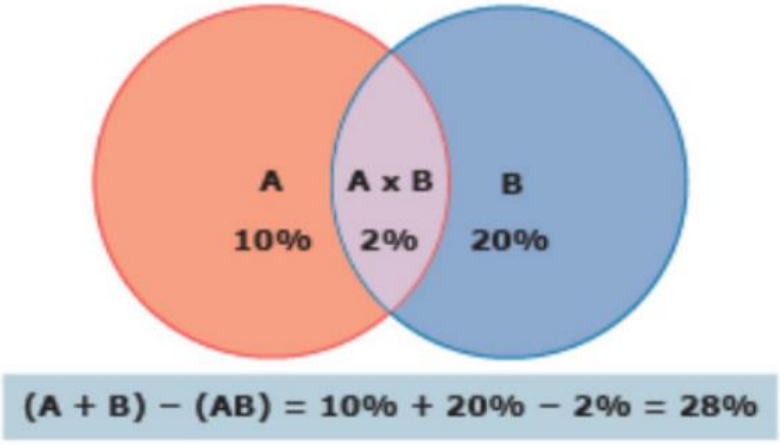
C. Non-mutually Exclusive Events= (A+ B) - (AB)

- Non-mutually exclusive means events can occur at the same time.

- Key idea: add probabilities together, then subtract the overlap.

- Example:

- If the chance of having diabetes is 10% and the chance of being obese is 20%, the chance of meeting someone who is obese or has diabetes or both is: 0.1 + 0.2 – (0.1 × 0.2) = 0.28 (or 28%)



Descriptive Statistics

- Summarizing the data you have to make it understandable and easier to manage.
- Representing the world as a distribution.

Central tendency

A. Mean:

- Mathematical average.
- Add together all values and divide by number of observations.
- Most affected by outliers (extreme values).
- Example:
  - The average (or mean) of a dataset is the sum of the values divided by the total number of values. In this example, the average number of UTI episodes per child is the sum (total number) of UTIs divided by the total sample size (total number of children). The total sample size is: 50 + 30 + 10 + 10 = 100 children.
  - The total number of UTIs is: (0 X 50) + (1 X 30) + (2 X 10) + (3 X 10) = 0 + 30 + 20 + 30 = 80 UTIs. The average is obtained by dividing the total number of UTIs (80) by the total sample size (100). Therefore, the average number of UTI episodes per year = 80/100 = 0.8 UTIs for a child in this sample

B. Median:

- 50th percentile, middle number.
- The median of an ordered dataset is the number that separates the right half of the data from the left half.
- If even number of observations; add middle 2 numbers and divide by 2.
- Example:
  - If the ordered dataset is (75, 75, 80, 90, 110, 110). There are 6 observations, which is an even number of observations. The median value splits the dataset in half; it lies between 80 and 90 (3 values on the left and 3 values on the right). The median is (80 + 90) / 2 = 85 mm Hg.
  - Now, assume one of the values is missing and the ordered dataset includes the following 5 observations (odd number of observations): (75, 80, 90, 110, 110). In this case, the median value would be 90 mm Hg, which splits the dataset in half (2 values on the left and 2 values on the right).

C. Mode:

- Highest frequency.

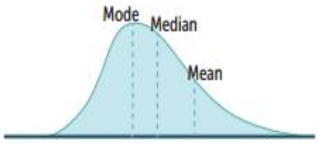
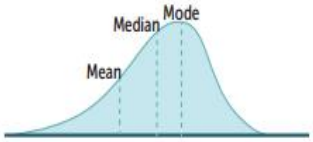
- Most common value.

- Least affected by outliers.

❖ N.B:

1. In normal distribution curve, also called bell-shaped curve: Mean = median = mode.

2. An outlier is defined as an extreme and unusual observed value in a dataset. It may be the result of a recording error, a measurement error, or a natural phenomenon. It can affect measures of central tendency (mean, median, mode) as well as measures of dispersion (standard deviation, variance). Modes tend to be resistant to outliers.

Nonnormal distributions		
Bimodal	Suggests two different populations (eg, metabolic polymorphism such as fast vs slow acetylators; age at onset of Hodgkin lymphoma; suicide rate by age).	
Positive skew	Typically, mean > median > mode. Asymmetry with longer tail on right.	
Negative skew	Typically, mean < median < mode. Asymmetry with longer tail on left.	

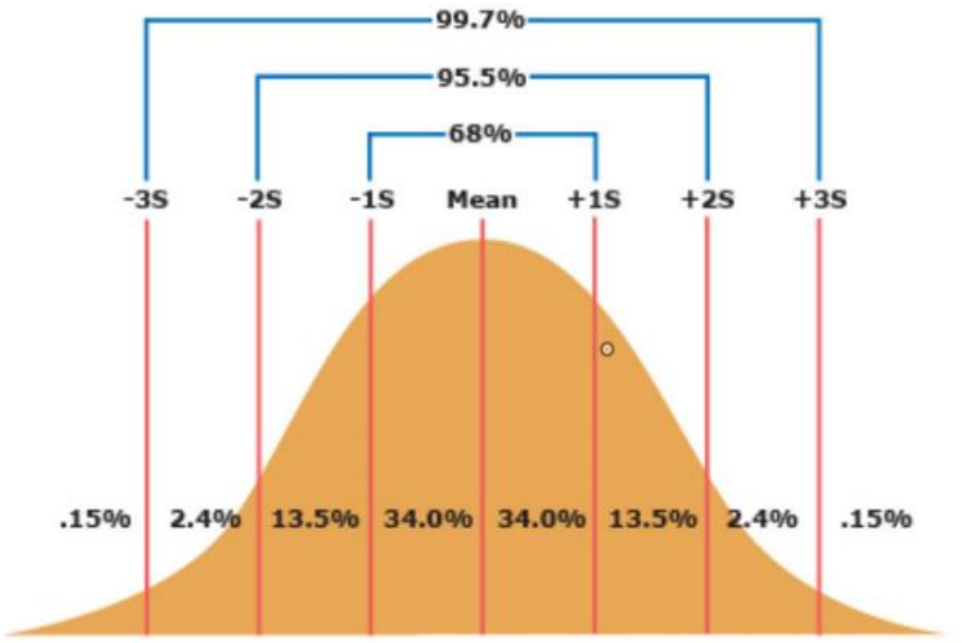
Measures of Variation

❖ Standard Deviation:

- Standard deviation = how much variability exists from the mean in a set of values.
- Standard error of the mean = an estimate of how much variability exists between the sample mean and the true population mean.
- Assessing spread around the mean.
- For example, 68% of all the values lie within 1 standard deviation from the mean. The remaining 32% of the values are therefore outside of one standard deviation, with 16% of these above and 16% below one standard deviation from the mean. In addition, 95.5% of values are within 2 standard deviations from the mean and 99.7 % are within 3 standard deviations.
- Think about it as the "average deviation".
- Concept, not calculation is what is needed for the exam.

$$S = \sqrt{\frac{\sum(x-\bar{x})^2}{n-1}}$$

s = standard deviation (s^2 = variar
x = each observation
$\bar{x}$ = mean
n = sample size



IQ $\bar{x}$ = 100 s = 15	55	70	85	100	115	130	145
USMLE $\bar{x}$ = 220 s = 20	160	180	200	220	240	260	280

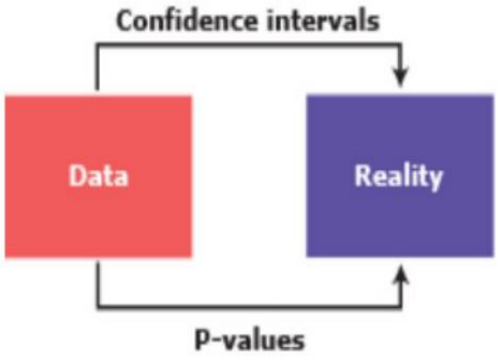
Inferential statistics

- Making an inference from the Sample to the population; or Data to reality.

- Inferential statistics would not be necessary if investigators studied all members of a population. However, because we can rarely observe and study entire populations, we try to select samples that are representative of the entire population so that we can generalize the results from the sample to the population.

- Two types of inferential statistics:

1. Confidence intervals.
2. P-values.



Confidence Intervals

- Measured value is understood as an approximation.

- Reality is seen as very likely "around" that measured value.

- A 95% confidence interval (CI) is the range of values in which one can be 95% confident that the true mean of the underlying population falls. The 95% CI (corresponding to p = .05) is often used.

- For the 95% CI, Z = 1.96.

- For the 99% CI, Z = 2.58.

$$\bar{x} \pm z\left(s/\sqrt{n}\right)$$

- $\bar{x}$ = mean
- z = z-score (standard score)
- $\left(s/\sqrt{n}\right)$ = standard error

Computing Confidence Interval of The Mean

If on a test:

Mean = 81% $\quad \bar{x} \pm Z\left(S/\sqrt{n}\right)$

S = 9% $\quad 81 \pm 2\left(9/\sqrt{36}\right)$

N = 36 $\quad 81 \pm 3$

Compute 95% CI.

Conclusion: The *real mean* likely falls somewhere between 78 and 84

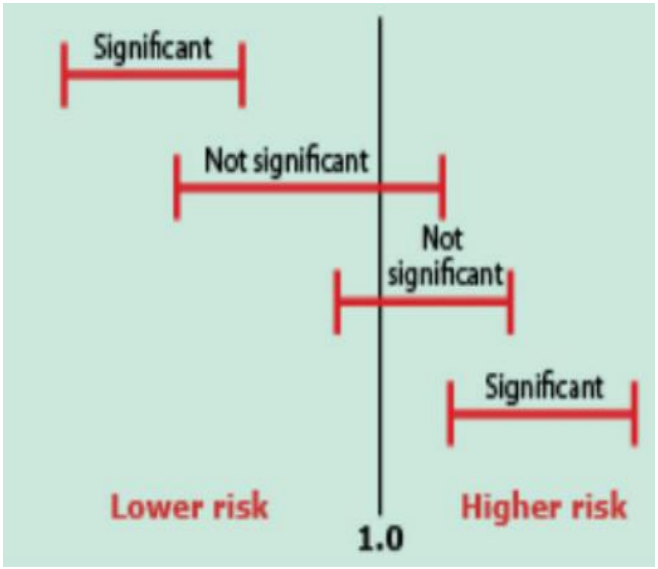
Note: CI does NOT mean:

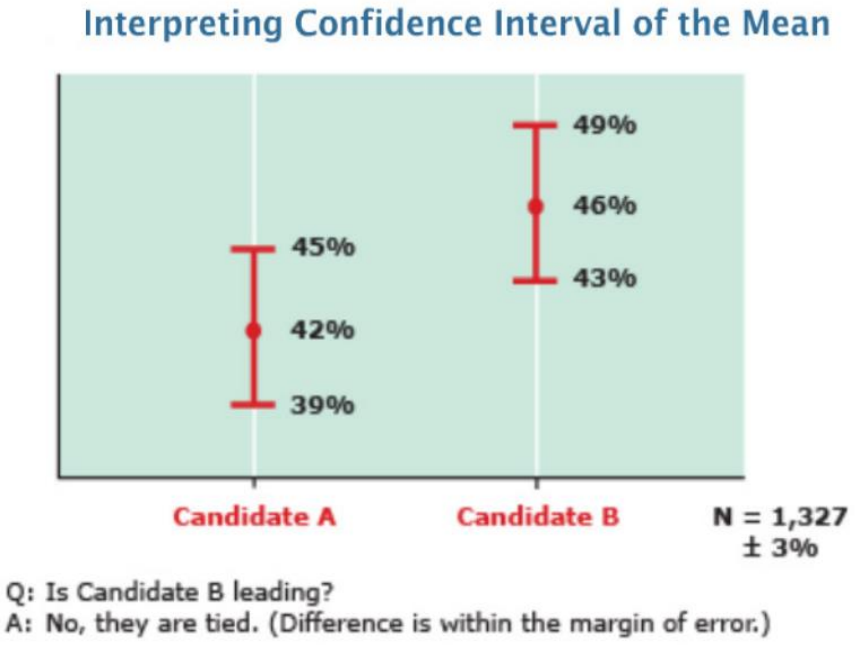
- 95% of class falls within 78 to 84
- the real mean is most likely 81

Interpreting Confidence Intervals for Relative Risks and Odds Ratios

- Use the rule for interpreting relative risks (from cohort studies) or odds ratios (from case-control studies).
- If the 95% CI for odds ratio or relative risk includes 1 → then there is no significant difference and H_0 is not rejected.
- If the 95% CI for a mean difference between 2 variables includes 0 →then there is no significant difference and H_0 is not rejected.
- If the CIs between 2 groups do not overlap → statistically significant difference exists.
- If the CIs between 2 groups overlap → usually no significant difference exists.

	RR	CI	Meaning
Comparison A	2.34	(1.67–2.95)	significant, increased risk
Comparison B	1.97	(0.89–2.88)	not significant
Comparison C	0.64	(0.31–1.14)	not significant
Comparison D	0.73	(.51–.92)	significant, decreased risk





P-Values and Hypothesis Testing

1. Null (H0):

- Hypothesis of no difference or relationship (there is no association between the disease and the risk factor in the population).
- Start with the Null Hypothesis (The opposite of what you are trying to show).
- "Null" is a statement of no effect.
- If you want to show "The drug works," the null hypothesis is stated as "The drug does not work"
- In other words, any difference observed in the study is due to chance or random factors, not the action of the drug.

- We do not prove the null hypothesis, but hope to reject it. If I reject "The drug does not work," I am left with the alternative, "The drug works."

- The logic is such that we do not get to prove something. Rather, we accumulate evidence to disprove something.

- The p-value is the probability of observing a given (or more extreme) result due to chance alone, assuming the null hypothesis is true. A result is generally considered statistically significant when p <0.05.

2. Alternative (H1):

- Hypothesis of some difference or relationship (there is some association between the disease and the risk factor in the population).

Outcomes of statistical hypothesis testing

- Correct result:

- Stating that there is an effect or difference when one exists (null hypothesis rejected in favor of alternative hypothesis).

- Stating that there is no effect or difference when none exists (null hypothesis not rejected).

- Types of Errors in Statistical Decision Making:

A. Type I (alpha error):

- Reject the null hypothesis when it is really true.

- Stating that there is an effect or difference when none exists (null hypothesis incorrectly rejected in favor of alternative hypothesis).

- Also called false-positive error.

- α = you accused an innocent man.

- Computed p-value estimates chance of Type I error. If $p < 0.05$ for a study outcome, the probability of obtaining that result purely by chance is < 5%.

B. Type II (beta error):

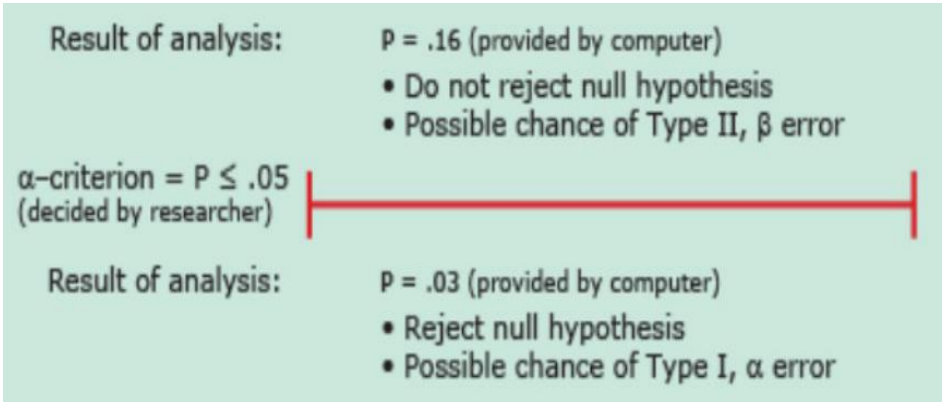
- Not reject the null hypothesis when it is really false.

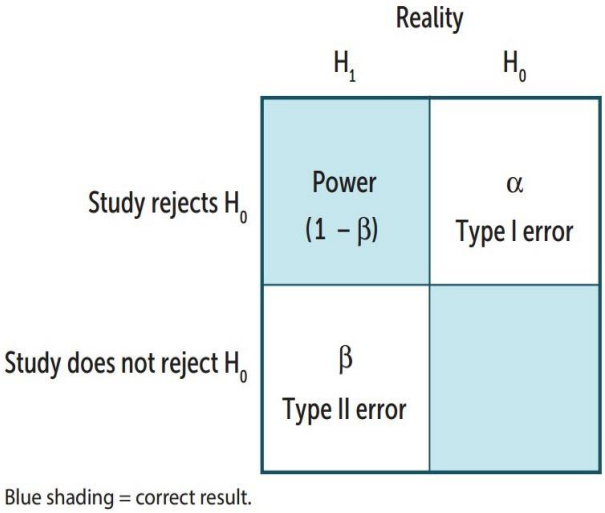
- Stating that there is not an effect or difference when one exists (null hypothesis is not rejected when it is in fact false).

- Also called false-negative error.

- β = you blindly let the guilty man go free.

- β is related to statistical power (1 – β), which is the probability of rejecting the null hypothesis when it is false.





❖ N.B:

- Statistical significance can be expressed with either p values or confidence intervals, but both are interrelated. For instance, p < 0.05 corresponds to a 95% confidence interval that does not contain the null value. Likewise p < 0.01 is equivalent to a 99% confidence interval that does not contain the null value. Conversely, if the null value is within a given confidence interval, then the p value is > the equivalent confidence interval.

Statistical Power (1- β)

- Definition:

- It is the probability of rejecting the null hypothesis when it is truly false.

- 1-Power = Type II error.

- Three things increase power:

- Larger sample size (more information). There is power in numbers.
- Larger effect size (looking for something bigger).
- ↑ precision of measurement.

- If you reject the null hypothesis, you must have had enough power. You were able to make a decision.

Statistical Significance vs. Clinical Significance

1. Statistical Significance Occurs When Computed P Value Is Low Enough:

- Answers the question: "Is there a difference?"

- Reject null hypothesis.

- Chance of Type I error.

2. Clinical Significance Occurs When the Difference We Detect Has Real-World Consequence:

- P-value does not tell you this.

- Answers the question: "Is this a difference that matters?"

- Decide clinical significance based on common sense assessment.

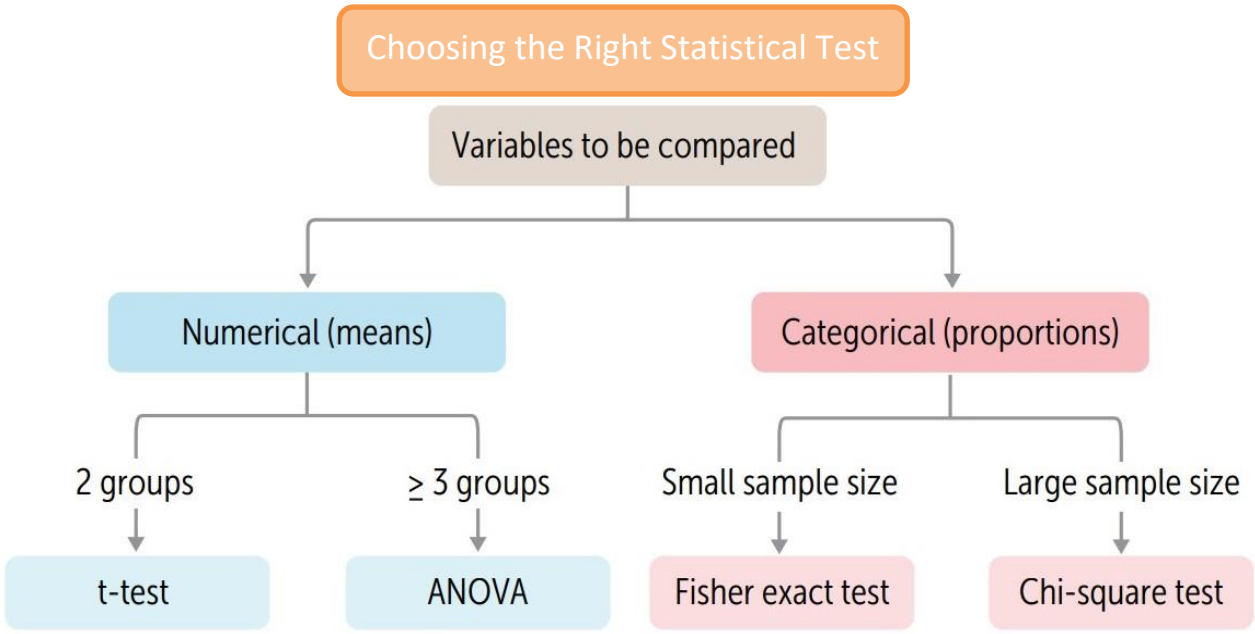
- Decide based on what seems right to you.

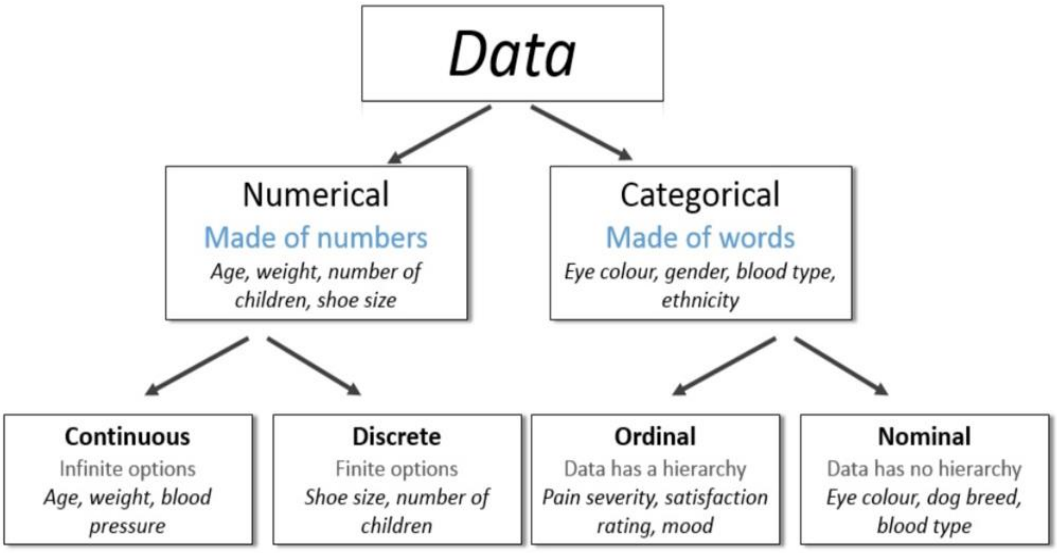
- Example:

- Drug A lowers blood pressure (BP) more than Drug B. This difference is statistically significant at p = .001. However, Drug A lowers BP only 1% more than Drug B. The actual difference is small.

- Likely conclusion → Strong statistical significance. No real clinical significance.

- Common reason for this outcome is very large sample size (N).





T-Test

- T-Test → Checks differences between means of 2 groups. Tea is meant for 2.
- Example: comparing the mean blood pressure between men and women.
- Compares the means and standard deviations of two groups. Limited to comparing only two groups.

ANOVA

- Checks differences between means of 3 or more groups.
- 3 words: ANalysis Of VAriance.
- Example: comparing the mean blood pressure between members of 3 different ethnic groups.

❖ N.B:

- A t-test is used to compare the difference between the means of 2 groups. Analysis of variance (ANOVA) compares the difference between the means of 2 or more groups.

Chi-Square

- Checks differences between 2 or more percentages or proportions of categorical outcomes (not mean values).
- Pronounce Chi-tegorical.
- Example: comparing the percentage of members of 3 different ethnic groups who have essential hypertension.

Fisher's exact test

- Checks differences between 2 percentages or proportions of categorical, nominal outcomes.
- Use instead of chi-square test with small populations.
- Example: comparing the percentage of 20 men and 20 women with hypertension.

Pearson Correlation coefficient

- For two interval variables, use Pearson correlation (r).

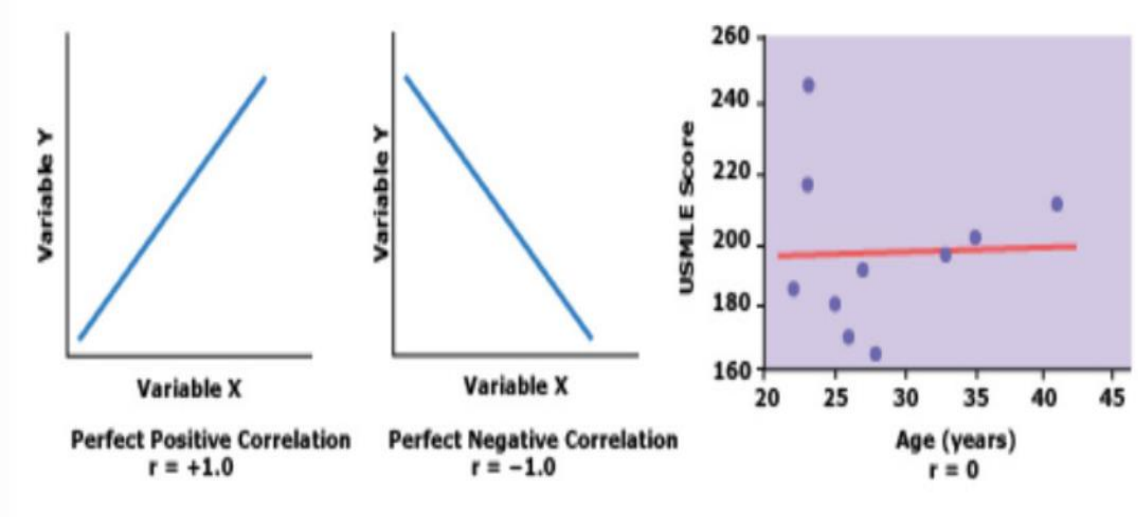
- Ranges from -1.0 to +1.0:

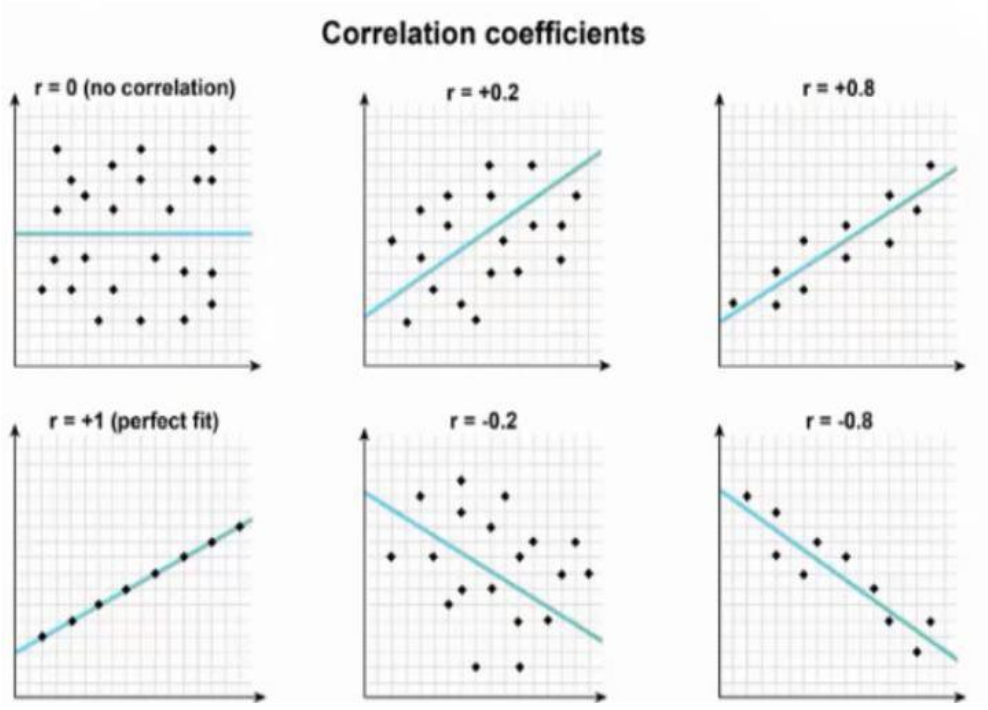
- Positive number → proportional relationship (as one variable ↑, the other variable ↑).

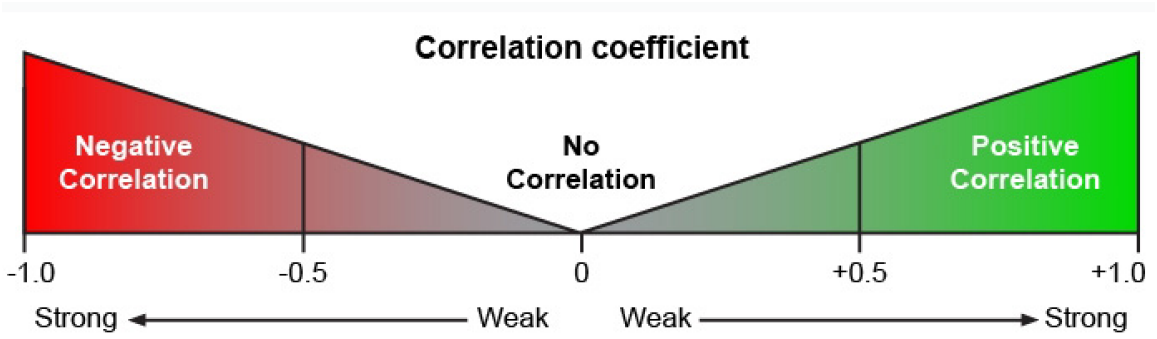
- Negative number → inverse relationship (as one variable ↑, the other variable ↓).

- The closer the absolute value of r is to 1, the stronger the linear correlation between the 2 variables, either positive or negative.

- A correlation coefficient of 0 → there is no association (a random distribution).





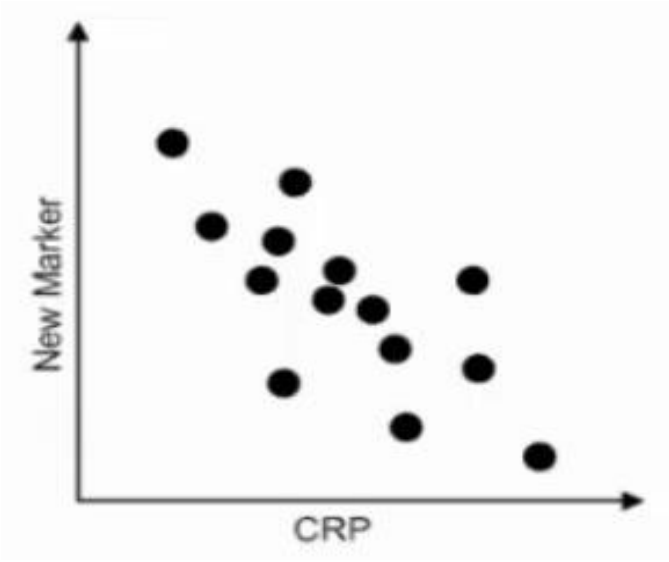


- Based on the plot below, the correlation coefficient between the 2 variables is closest to which of the following values?

- In this case, the scatter plot shows a linear association between the blood level of the new marker and that of CRP, so we know that the correlation coefficient is not 0.

- The scatter plot above shows that an increase in CRP level is associated with a decrease in the new marker's level. Therefore, you should expect the correlation coefficient to be negative.

- That leaves only the two negative values, -0.2 and -0.8. Although the scatter plot does not demonstrate a perfect linear arrangement of measurements, the plot appears to demonstrate a reasonably strong linear association. Thus, a correlation coefficient value of -0.8 is the most appropriate answer among the options given.



Interpretation of Medical Literature

- The purpose is to provide you with an approach to reading and understanding research articles and pharmaceutical advertisements. It is based on principles of epidemiology.

- Check for:

1. Fair balance.
2. Misleading statements in the text.
3. Misleading graphs and tables.
4. Misleading images.
5. Safety information.
6. Efficacy supported by data.
7. Information on appropriate population.
8. Information on side effects or contraindications.
9. Statistical significance and clinical significance.

Pharmaceutical Ad 1

Tazofect

(tanzopanib 10 and 20 mg capsules)

For newly diagnosed and treatment-resistant EGFR-mutated NSCLC, an effective treatment is now available to improve progression-free survival (PFS)!

- Tazofect is indicated for treatment of EGFR-mutated NSCLC
- Tazofect has shown efficacy in PIK3CA, PTEN, and KRAS-mutated NSCLC

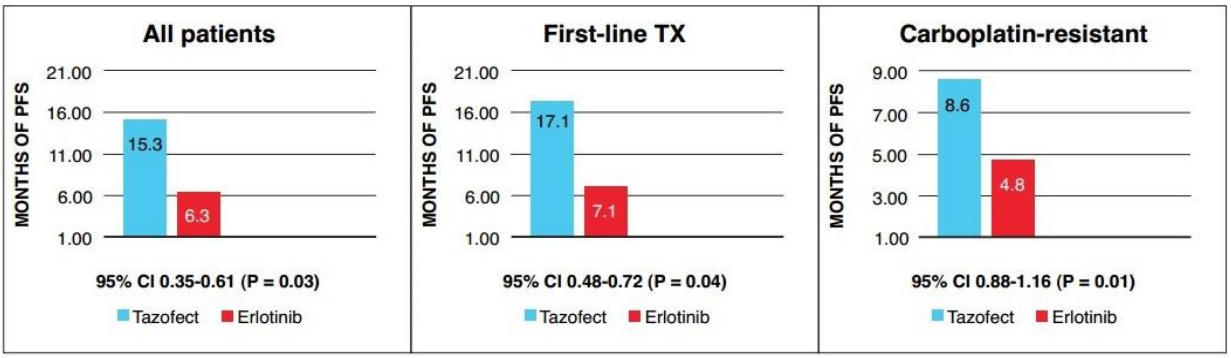
Tazofect is like extra time in a capsule...

...so your patients have more time to do what they want to do!

Tazofect has been proven to:

- Increase PFS by an average of 9 months in all NSCLC study participants (first-line and erlotinib resistant)
- Increase PFS by an average of 10 months in first line NSCLC study participants over those receiving Tarceva® (erlotinib)
- Almost double the PFS in carboplatin resistant NSCLC study participants over those receiving Tarceva® (erlotinib)

The side effect profiles for both Tazofect and erlotinib were similar.



- The effects of Tazofect (10-20 mg qd) and erlotinib (150-200 mg qd) in subjects with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations are presented above. The results were taken from a phase 3, randomized, double blinded multicenter clinical trial. Per protocol, each of these agents was continued until clinically significant disease progression occurred plus an additional 2 months unless mortality occurred. The average follow-up time for patients who completed the study in both Tazofect groups was 17.3 months and 8.3 months in both erlotinib groups.
- Of the 800 initial participants enrolled in the phase 3, randomized, double blinded multicenter trial, 225 (of 398) participants completed the study in the Tazofect group and 388 (of 402) participants completed the study in the erlotinib group.
- Of the original number of study participants, 103 Tazofect patients and 102 erlotinib patients were classified as carboplatin-resistant.

Increased progression-free survival!

Additional product information provided below

SMILE Pharmaceuticals

Smile for life with SMILE Pharmaceuticals

Improved patient outcomes!

HIGHLIGHTS OF PRESCRIBING INFORMATION

Please see Tazofect (tanzopanib) drug package insert for complete prescribing information

Indications and Usage: Tazofect (tanzopanib) is a kinase inhibitor indicated for first-line treatment of NSCLC with EGFR exon 19 deletions and EGFR exon 21 (L858R) substitution mutations in patients age 18 years and older.

Mechanism of Action: Tanzopanib is a kinase inhibitor that acts by inhibiting intracellular tyrosine kinase domain of epidermal growth factor receptor (EGFR) thus resulting in cell cycle arrest and angiogenesis inhibition. Tanzopanib has an elimination half-life of approximately 28 hours in patients with normal hepatic and renal function.

Dosage and Administration: Treatment of NSCLC with EGFR exon 19 deletions and EGFR exon 21 (L858R) substitution mutations in patients aged 18 years and older with normal hepatic and renal function: 10-20 mg daily until clinically significant disease progression.

Contraindications: Hypersensitivity to tanzopanib; use in patients with severe hepatic impairment, active infection and thrombocytopenia.

Warnings and Precautions: May cause reactivation of tuberculosis and hepatitis B. Use caution in patients receiving other chemotherapeutic agents, thyroid disorders, dehydration, mild to moderate renal and hepatic dysfunction

Adverse Reactions:

Common (≥5%): elevated AST & ALT (15%), diarrhea (15%), fatigue (13%), elevated bilirubin (12%), infection (10%), cough (8%), thrombocytopenia (7%)

Less common (<5%): hepatorenal syndrome (2%), hepatotoxicity (2%), toxic epidermal necrolysis (1%), Stevens-Johnson syndrome (1%), acute renal failure (1%), hypothyroidism (1%), hemolytic anemia (<1%)

Practice Questions

1. The data provided in the drug advertisement most strongly supports which of the following conclusions?

   (A) In the treatment of cancer, Tazofect and erlotinib can be used interchangeably.

   (B) Tazofect is not indicated for treatment of EGFR exon 19 insertion in non-small cell lung cancer.

   (C) Tazofect should be considered for use in patients with PIK3CA mutated NSCLC.

   (D) The combination of Tazofect and erlotinib will improve the PFS to a greater extent than either agent alone.

   (E) The dose of Tazofect should be adjusted in patients with hepatic dysfunction.

The correct answer is B. The key to answering this type of question is to first rapidly scan the drug ad and highlights of prescribing information so that you are able to obtain a general sense of how the content is arranged. Then read the question and quickly search for each of the answer choices in the body of the drug ad itself. In the Indications section of the prescribing information, the following is stated. "Tazofect (tanzopanib) is a kinase inhibitor indicated for first-line treatment of NSCLC with EGFR exon 19 deletions and EGFR exon 21 (L858R) substitution mutations in patients aged 18 years and older." There is no mention of "EGFR exon 19 insertions." That is not to say that the drug cannot be used in NSCLC patients with EGFR exon 19 insertions. However, Tazofect is not indicated (FDA approved) for use in these patients by the FDA. Hence this is a true statement and the correct answer.

Both Tazofect and erlotinib are indicated for EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Also both drugs are noted to have similar side effect profiles (as indicated in the primary drug ad). However, erlotinib is also indicated for the treatment of pancreatic cancer. Since erlotinib has a broader range of clinical indications and choice A states "in the treatment of cancer," these agents are not interchangeable. It should also be pointed out that almost half of the Tazofect patients dropped out of the trial. Without knowing the reasons why, it would not be advisable to interchange Tazofect with erlotinib. Choice A is a false statement.

Choice C states that "Tazofect should be considered for use in patients with PIK3CA mutated NSCLC." Although the main drug ad states that "Tazofect has shown efficacy in PIK3CA, PTEN and KRAS Mutated NSCLC," there is no data in the prescribing information or drug ad itself to support this claim. Also what exactly does "shown efficacy" mean? The drug may be marginally effective in a small percentage of PIK3CA patients, for example. In other words, there is no data to support this claim in the drug ad. Choice C is an incorrect statement.

Choice D states that "The combination of Tazofect and erlotinib will improve the PFS to a greater extent than either agent alone." There is no information indicating whether the combination of the 2 agents will provide more benefit, less benefit or the same benefit as either agent used alone. Choice D is an incorrect statement.

Choice E refers to making a dosing adjustment in patients with hepatic dysfunction. In the prescribing information section, there is a contraindication for use in severe hepatic impairment as well as a precaution about use in patients with mild-moderate hepatic dysfunction. However, there is no information provided in the drug ad related to a dosing adjustment in patients with hepatic dysfunction. Choice E is an incorrect statement.

2. Consider the following statement: "Tazofect was proven to provide approximately double the PFS in carboplatin resistant NSCLC study participants over those receiving Tarceva® (erlotinib)." When evaluating the drug ad and highlights of prescribing information, which of the following provides the best evidence that this statement is inaccurate?

   (A) Number of patients treated in the carboplatin resistant group for both drugs
   (B) The calculation of months of PFS for the carboplatin resistant graph
   (C) The confidence interval for the carboplatin resistant graph
   (D) The p value for the carboplatin resistant graph
   (E) The y axis data points for the carboplatin resistant graph

The correct answer is C. You are asked to evaluate a statement found on the main drug ad and then indicate what information provided in the drug ad invalidates this statement. Of all the answer choices, the data provided on the confidence interval for the carboplatin resistant graph provides the best evidence that the statement is inaccurate. A confidence interval gives an estimated range of values which is likely to include an unknown parameter (such as actual PFS), the estimated range being calculated from a given set of sample data. In the original statement, the drug company claimed that their drug (Tazofect) was proven to provide approximately double the PFS in carboplatin resistant NSCLC study participants over those receiving Tarceva® (erlotinib). However, the confidence interval provided with the carboplatin resistant graph contains the number 1. If the 95% confidence interval for a study includes 1.0, then there is >1 in 20 chance that random variation in outcome incidence among the study groups (Tazofect-study and erlotinib-control) is what produced the observed correlation between treatment and outcome. In the instance the p value is also likely to be >0.05. In summary if the confidence interval contains the relative risk of 1.00, the result is not significant. As discussed, this should also lead the reader to believe that the P-value (provided on the same graph, choice D) is also inaccurate. However, without the data seen with the confidence interval, the reader would have no way of suspecting that the provided P-value is also likely inaccurate. Therefore, choice C is the best answer

In the key under the 3 graphs, it is stated that 103 Tazofect patients and 102 erlotinib patients were classified as carboplatin resistant. This is a sufficient number of patients in each group (**choice A**).

The statement makes reference to the number of months of PFS in the Tazofect group being "almost double" the erlotinib group in carboplatin resistant patients. The PFS for Tazofect is 8.6 months and the PFS for erlotinib is 4.8 months. This statement could have been phrased differently, but is not completely inaccurate (**choice B**).

When comparing the data points on the y-axes of the 3 graphs, the y-axis on the carboplatin resistant group was clearly manipulated so that a more "profound graphical representation" of the actual results is evident. Although this should cause the reader to question the integrity of the authors, choice C is still the best answer.

3. Shortly after Tazofect is released for use in the general population, the FDA and drug manufacturer begin to receive numerous reports of complete treatment failure in both carboplatin resistant patients and first line therapy patients as well as higher than expected percentages of adverse events in all patients. Which of the following is the most likely reason for these reports on Tazofect?

   (A) Insufficient follow-up of study participants
   (B) Insufficient information on adverse effects
   (C) Insufficient information on drug indications
   (D) Subject attrition
   (E) Type II error was committed

The correct answer is choice D. In the question stem we are told that shortly after the drug is used in the general population there are reports of treatment failure in both carboplatin resistant patients and first line treatment patients. We are also told that higher-than-expected percentages of adverse events are occurring. The question is asking for the most likely cause of this occurrence. The most likely reason based on the data provided in the drug ad and highlights of prescribing information is subject attrition. Under the 3 graphs it is stated that "Of the 800 initial participants enrolled in the phase 3, randomized, double blinded multicenter trial, 225 (of 398) participants completed the study in the Tazofect group and 388 (of 402) participants completed the study in the erlotinib group." Approximately half (225/398 participants) of the original Tazofect study participants never completed the trial. Furthermore, the authors did not provide an explanation as to why they did not complete the study. Is it likely that they did not complete the trial because of severe adverse effects and/or death?

Without knowing the reasons why the participants never completed the trial, it is difficult to evaluate the safety and efficacy of Tazofect in both first line therapy and carboplatin resistant patients. Also, it is quite possible that only a small percentage of the 103 participants in the carboplatin resistant arm of the study never completed the study. Without more information, it is hard for the reader to make a valid conclusion. In summary, the authors should have indicated why almost half of the study participants never completed the study; hence, the primary reason why these reports are occurring (due to treatment failures and increased adverse effect occurrence) is directly related to the circumstances surrounding the high level of subject attrition in this trial.

The phase 3 trial for Tazofect lasted in each patient until clinically significant disease progression occurred plus an additional 2 months unless mortality occurred. Furthermore, the average follow-up time for patients who completed the study was listed. The length of the study was sufficient to assess the effects it was designed to assess. Choice A is an incorrect response.

At the bottom of the highlights of prescribing information page of the drug ad, there is an extensive list of adverse effects and percentage of occurrence of each of these side effects. Hence, sufficient information on these adverse effects was provided. Choice B is an incorrect response. However, this information was based on the number of patients who completed the clinical trial. Since almost half of the study participants (in the Tazofect arm) never completed the trial, an accurate accounting of side effect appearance was not available. This is directly related to subject attrition.

At the top of the highlights of prescribing information page of the drug ad, it clearly states that "Tazofect (tanzopanib) is a kinase inhibitor indicated for first-line treatment of NSCLC with EGFR exon 19 deletions and EGFR exon 21 (L858R) substitution mutations in patients aged 18 years and older." The drug is NOT indicated for use in carboplatin resistant patients. Although there is a graph on the first page of the drug ad and comments about proven effects, the drug ad never claimed that the drug was "indicated" for use in carboplatin patients. Choice C is an incorrect response.

A type II or beta error is where the researcher fails to reject the null hypothesis when it is really false. In other words, the researcher declared that there was no significant effect on the basis of the sample when there really is one in the population. The likely impact of this type of error is that the drug (Tazofect) would NOT obtain FDA approval and the general population would not receive this medication. Choice E is an incorrect response.

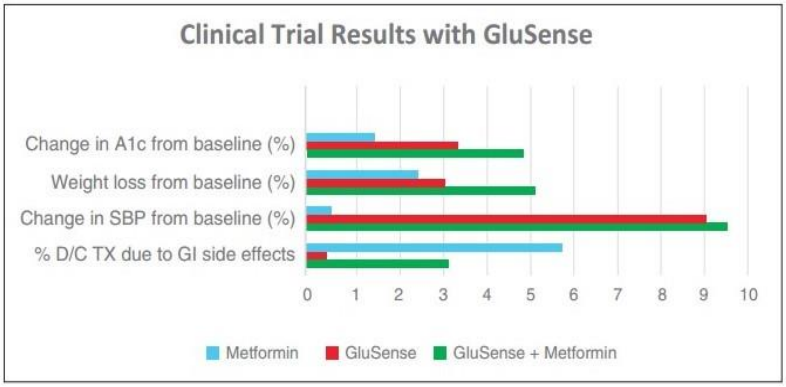
Pharmaceutical Ad 2

GluSense™ ... because it makes sense!

(Glugliflozin 75 mg, 150 mg and 300 mg tablets)

Diabetes is a complex disease ...

GluSense is a simple treatment measure with proven therapeutic outcomes!



- The clinical effects of GluSense (150-mg qd), metformin (1000 mg bid) and combination therapy (GluSense 150 mg qd + metformin 1000 mg bid) in patients with newly diagnosed type 2 diabetes who failed to meet glycemic goals with diet and exercise alone are presented above. The results were taken from a phase 3, randomized, double-blinded multicenter clinical trial.
- Each therapy was administered in conjunction with a structured diet and exercise program.
- A baseline A1c, body weight and systolic blood pressure reading were obtained at the onset of the trial and every 8 weeks during the trial. All participants were enrolled in the study for 12 months.
- Of the 1600 initial participants enrolled in the trial, 462 (of 510) participants in the metformin-only group completed the study, 358 (of 533) of the GluSense-only group completed the study, and 313 (of 577) in the GluSense + metformin group completed the study.
- The primary reason (as stated by the patient) for withdrawing from the study was unwanted side effects.

GluSense demonstrated greater reductions in A1c, weight loss & blood pressure than metformin alone at 52 weeks!

- GluSense is indicated for treatment of T2DM as monotherapy & in combination with metformin.
- GluSense has shown efficacy when used in conjunction with other oral hypoglycemic agents.

The treatment your T2DM patients have always needed is finally here!!

SMILE Pharmaceuticals

Smile for life with SMILE Pharmaceuticals

GluSense has been proven to:

- Reduce A1c in T2DM patients by an average of 3.4% as monotherapy (P<0.001) & in combination with metformin an average of 4.9% (P<0.002) – mean baseline A1c = 8.05%
- Reduce baseline weight in T2DM patients by an average of 3.1% as monotherapy (P<0.02) & in combination with metformin an average of 5.2% (P<0.03) – mean baseline weight = 182 lb (87.3 kg)
- Reduce baseline systolic blood pressure in T2DM patients by an average of 9.1% as monotherapy (P<0.006) & in combination with metformin an average of 9.6% (P<0.001) – mean baseline SBP = 177 mm Hg.

Additional product information provided below

HIGHLIGHTS OF PRESCRIBING INFORMATION

Please see GluSense (glugliflozin) drug package insert for complete prescribing information.

Indications and Usage: GluSense (glugliflozin) is an SGLT2 inhibitor with insulin-sensitizing properties, indicated for the treatment of type 2 diabetes in conjunction with diet and exercise as monotherapy, and in combination with metformin in patients aged 18 years and older.

Mechanism of Action: Glugliflozin is an SGLT2 inhibitor with insulin-sensitizing properties. This agent has a dual mechanism of action. It acts by:

- Inhibiting the sodium-glucose cotransporter 2 (SGLT2), thereby reducing glucose reabsorption and increasing urinary glucose excretion
- Decreasing insulin in the periphery and liver, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Glugliflozin is an agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). Activation of PPARγ nuclear receptors in the liver, skeletal muscle, and adipose tissue modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.
- Other: antagonizes peripheral alpha-1 adrenergic receptors

Pharmacokinetics

- Glugliflozin has an elimination half-life of approximately 16 hours in patients with normal hepatic and renal function.
- Following oral administration of glugliflozin, Tmax occurs within 3 hours.
- Glugliflozin is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates.
- Following oral administration of glugliflozin, approximately 15–20% of the drug dose is recovered in the urine.

Dosage and Administration: Treatment of type 2 diabetes in patients aged 18 years or older who have failed to meet glycemic goals with diet and exercise alone:

- Monotherapy: 150-300 mg PO qd; start at 75 mg PO qd and increase by 75 mg qwk; max dose 450 mg/day
- Combination with metformin: same as monotherapy and standard metformin dose of 2000 mg daily (in divided doses)

Contraindications: Type 1 diabetes mellitus, hypersensitivity to glugliflozin and/or sulfonamides; NYHA class III or IV heart failure, severe hepatic impairment, hyperkalemia, use with medications causing hyperkalemia and diabetic ketoacidosis

Warnings and Precautions: May cause hypoglycemia, hypotension, and AST/ALT elevation. Caution use in elderly patients with poorly controlled diabetes and patients with past history of cardiovascular disease.

Adverse Reactions (for a complete list, see drug package insert)

Common (≥5%):	Less Common (<5%):
Hyperkalemia	Fatigue
Hypoglycemia	Hepatic dysfunction
Orthostatic hypotension	Thirst
Dizziness	Fainting
Tachycardia	Mental impairment
Hyperhidrosis	Pancreatitis

Drug Interactions (see drug package insert)

Practice Questions

1. The data provided in the drug advertisement most strongly supports which of the following conclusions?

   (A) GluSense is a substitute for diet and exercise in type 2 diabetes due to its weight loss properties.

   (B) GluSense is recommended for use in patients with a history of myocardial infarction.

   (C) GluSense is safer to use in patients with type 2 diabetes than metformin.

   (D) The antihypertensive effects of GluSense are comparable to some currently available antihypertensive medications.

   (E) The combination use of GluSense and a sulfonylurea is recommended for those who initially fail sulfonylurea monotherapy.

The correct answer is D. This type of question generally requires a process of elimination. The statement "The antihypertensive effects of GluSense are comparable to some currently available antihypertensive medications" is most strongly supported by the drug ad. Relevant information to support this statement can be found in several places: First in the table, GluSense is associated with 9.1% decrease in average systolic blood pressure. This percentage decrease is comparable to the diuretics, low-moderate doses of ACE inhibitors, alpha antagonists as well as varying doses of other drugs from different drug classes. Second, the mechanism of action section of the highlights of prescribing information states that this drug antagonizes peripheral alpha-1 adrenergic receptors. This is the same mechanism of action as drugs like terazosin and doxazosin. Finally, the side effects of the drug (orthostatic hypotension, dizziness, and tachycardia) also support its antihypertensive properties since these are side effects commonly seen in alpha antagonists. Hence, out of all of the answer choices, this statement is most strongly supported by the drug ad.

There are several places which indicate GluSense is used in conjunction with diet and exercise, such as the key under the chart on the main ad page and in the Indications and Usage section in the highlights of prescribing information. Although the drug promotes weight loss, GluSense is not a substitute for diet and exercise (**choice A**).

The Warnings and Precautions section states that GluSense should be used cautiously in patients with past history of cardiovascular disease. Furthermore, in Contraindications, it is stated that GluSense is contraindicated for use in patients with NYHA Class III or IV heart failure. Since myocardial infarction (**choice B**) is a form of cardiovascular disease and a common precipitating cause of heart failure, GluSense would not be recommended for use in these cases. GluSense may potentially be used "cautiously" in patients with a mild form of cardiovascular disease but is not "recommended."

The drug ad does not have a safety profile comparison between GluSense and metformin (**choice C**). The only related comparison between the drugs is the appearance of severe GI side effects leading to withdrawal from the study.

The only statement relating to the use of GluSense and another drug is found in the main area of the drug ad: "GluSense has shown efficacy when used in conjunction with other oral hypoglycemic agents." It does not specify the names or drug classes of the other agents (**choice E**). Furthermore, it does not provide any data to support this claim.

2. Of the initial trial participants, 175 persons from the GluSense-only group and an even large number from the GluSense and metformin group withdrew from the study. Which of the following is the most likely reason for participant withdrawal?

   (A) Appearance of drug interactions
   (B) Hypersensitivity to sulfonamides
   (C) Severe hypoglycemia
   (D) Severe hypotension
   (E) Severe GI side effects

The correct answer is C. You are asked to determine the most likely reason why participants withdrew from the study. In the key under the graph on page 1, it states "The primary reason (as stated by the patient) for withdrawing from the study was unwanted side effects." However, it is not stated what side effect caused them to withdraw. Therefore, you must determine the most likely reason based on information provided in the drug ad. The Adverse Reactions section of the highlights of prescribing information provides only a "partial" list of side effects with a percent occurrence above and below 5% so this section alone cannot be used to answer the question. The correct answer can be derived from the section on the bottom right of the main drug ad. It states that GluSense has been proven to reduce A1c in type 2 diabetes (T2DM) patients by an average of 3.4% as monotherapy ($P<0.001$) and in combination with metformin an average of 4.9% ($P<0.002$). The mean baseline A1c was 8.05% for study participants. If the mean baseline A1c was 8.05%, that means that some patients likely started with an A1c around 7%. Remember that an A1c 6% is an average daily glucose level of 126 mg/dL. If you lower this A1c by 3.4% (GluSense only) or 4.9% (GluSense + metformin), the resulting A1c levels are 3.6% and 2.1%, respectively. Since the A1c is a long-term average of the daily blood glucose levels, it is likely that this agent caused severe hypoglycemia in participants; hence, the likely reason for withdrawal from the study. Furthermore, it is stated that hypoglycemia is one of the most common adverse effects. Choice C is the best answer choice.

The drug ad does not specifically mention any problems with drug-drug interactions (**choice A**) in the clinical trial and there is a comment indicating that the reader should please see GluSense (glugliflozin) drug package insert for complete prescribing information. Based on this information, it is unlikely that drug-drug interactions are the primary reason for patient withdrawal.

The Contraindications section states that GluSense is contraindicated for use in patients with sulfonamide hypersensitivity (**choice B**). However, there is nothing which would lead the reader to believe this is the primary reason for withdrawal from the study.

The bottom right of the ad states that GluSense has been proven to reduce baseline SBP (systolic blood pressure) in T2DM patients by an average of 9.1% as monotherapy ($P<0.006$) and in combination with metformin an average of 9.6% ($P<0.001$). The mean participant baseline SBP was 177 mm Hg. Even if the starting blood pressure was 100 mm Hg, the patient would still not be hypotensive with a 9.6% drop in blood pressure. Note, too that orthostatic hypotension is listed as a common side effect, but with the information presented it is unlikely that was the primary reason for patient withdrawal (**choice D**).

It is unlikely that severe GI side effects (**choice E**) were the primary reason for participant withdrawal since the table shows that the GluSense-alone arm had almost no withdrawals from study. GluSense also improved the GI side effect withdrawal rate for patients receiving metformin when the 2 medications were combined.

3. A 64-year-old man comes to the physician with complaints of increasing polyuria and polydipsia. His past medical history is significant for type 2 diabetes, hypertension, hyperlipidemia, and a myocardial infarction 4 years ago. Allergy history includes an anaphylactic reaction to levofloxacin. He is currently receiving metformin 1000 mg 2x daily, enalapril 10 mg daily, pravastatin 20 mg daily, and spironolactone 25 mg twice daily. Physical examination shows blood pressure of 126/82 mm Hg, heart rate 62/min, height 172.7 cm (5 feet, 8 inches), weight 88.6 kg (195 lb), and BMI 29.6.

   Laboratory studies show:

   - Blood glucose: 215 mg/dL
   - A1c: 10.5%
   - Albumin: 3.8 g/dL
   - Creatinine: 1.3 mg/dL
   - AST: 20 IU/L
   - ALT: 22 IU/L
   - Sodium: 138 mEq/L
   - Potassium: 4.9 mEq/L
   - Calcium: 9.6 mg/dL
   - Ejection fraction: 66%

   If the attending physician is considering the addition of GluSense to this patient's medication regimen, which of the following is a contraindication for prescribing this medication?

   (A) Allergy contraindication
   (B) Cardiovascular contraindication
   (C) Drug interaction contraindication
   (D) Hepatic contraindication
   (E) Renal contraindication
   (F) There is no contraindication in this patient and the medication can be prescribed

The correct answer is C. You are being asked for the most likely reason to not prescribe this medication to a given patient. Therefore, you need to look for either an absolute or relative contraindication for prescribing this medication in the drug ad. The Contraindications section states that GluSense is contraindicated for "use with medications causing hyperkalemia." The patient is currently receiving enalapril and spironolactone. Both of these medications are associated with the development of hyperkalemia. Furthermore, the patient's potassium level is 4.9 mEq/L, which is at the high level of normal. The patient is likely to become hyperkalemic once starting this medication. Based on this information, a drug-drug interaction (**choice C**) between GluSense and both enalapril and spironolactone is the most likely contraindication for use of this medication in this patient. Choice C is correct and choice F is incorrect.

The patient has a history of anaphylaxis to the fluoroquinolone levofloxacin. Although GluSense is contraindicated for use in patients with a sulfonamide allergy, there is no allergy contraindication for using this medication in patients with a fluoroquinolone allergy (**choice A**).

The only cardiovascular contraindication (**choice B**) listed for GluSense is NYHA Class III or IV heart failure. This patient has a normal ejection fraction of 66% (normal 55-70%) so does not meet the cardiovascular contraindication criteria for this drug. Although the patient's past history of myocardial infarction predisposes him to heart failure, the patient currently does

not have heart failure so there is no contraindication. However, there is a warning for use of GluSense in patients with cardiovascular disease. As indicated, this patient has a past history of a myocardial infarction as well as hyperlipidemia and hypertension. Therefore, this medication should be used cautiously in this patient. If GluSense is prescribed, the patient should be monitored closely but there is no cardiovascular contraindication for the use of this drug in this patient.

The patient has normal hepatic function (AST: 20 IU/L (normal <35 IU/L) and ALT 22 IU/L (normal <35 IU/L)); hence, there is no hepatic contraindication for using GluSense in this patient (**choice D**).

The patient has normal renal function (creatinine: 1.3 mg/dL (normal 0.5-1.4 mg/dL)); hence, there is no renal contraindication for using GluSense in this patient (**choice E**).

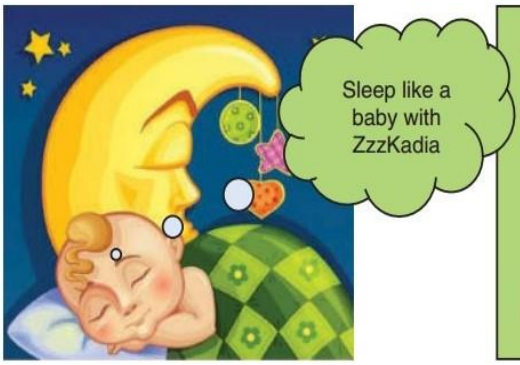
Pharmaceutical Ad 3

Zzzkadia™

(Zlideplon 2.5, 5, 7.5 mg tablets)

The only orexin receptor antagonist with $GABA_BZ$ receptor modulator properties indicated for long-term treatment of insomnia!

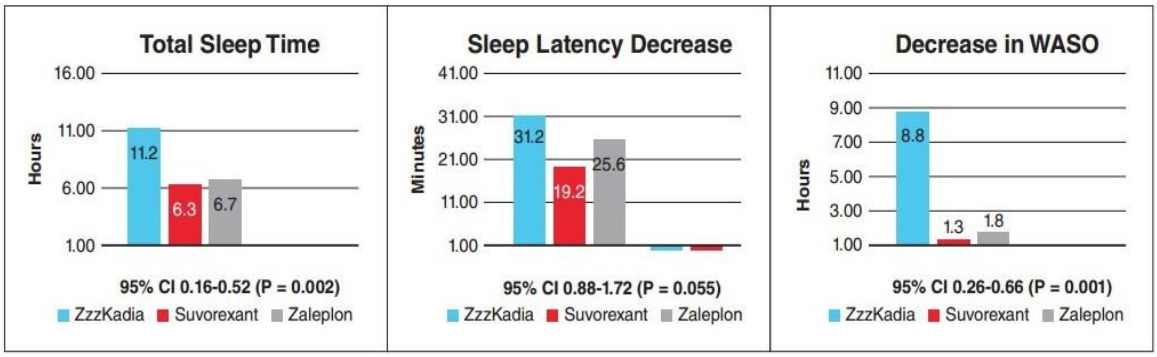
- TIndicated for long-term treatment of insomnia
- Shown to be non-addicting
- The most effective sedative/hypnotic available



ZzzKadia has been proven to:

- Increase mean total sleep times (TST) by 5.7 hours compared to 1.3 hours with suvorexant and 1.1 hours with zaleplon
- Significantly decrease sleep latency (SL) over both suvorexant and zaleplon
- Significantly decrease wake time after sleep onset (WASO) over both suvorexant and zaleplon

Most common side effects: headache, dizziness, lightheadedness, daytime drowsiness, somnolence, and nightmares



- The effects of ZzzKadia (5 mg HS), Suvorexant (10 mg HS) and Zaleplon (5 mg HS) were evaluated in participants age 35-70 with a DSM-5 diagnosis of insomnia disorder who have not previously used prescription sedative/hypnotics. The results were taken from a 16-week phase 3, randomized, double blinded multicenter clinical trial. Per protocol, patients were instructed to take 10 minutes prior to bedtime 5 times per week maximum.
- Of the 651 initial participants enrolled in the study 137 (of 222) ZzzKadia, 198 (of 220) suvorexant and 192 (of 209) zaleplon participants completed the study.
- Following the study, each of the medications was discontinued and 93% of all participants (who completed the trial) requested further treatment due to the reemergence of severe insomnia as well as side effects ranging from autonomic hyperactivity to psychomotor agitation to seizures.

Increased total sleep time!

Additional product information provided below

SMILE Pharmaceuticals

Smile for life with SMILE Pharmaceuticals

Improved daytime function!

HIGHLIGHTS OF PRESCRIBING INFORMATION

Please see ZzzKadia (Zlideplon) drug package insert for complete prescribing information.

Indications and Usage: ZzzKadia (Zlideplon) is an orexin receptor antagonist with $GABA_BZ$ receptor modulator properties indicated for first-line treatment of short-term insomnia and insomnia disorder (according to DSM-5 diagnostic criteria) in patients age 35 years and older.

Mechanism of Action: Zlideplon is an orexin receptor antagonist with $GABA_BZ$ receptor modulator properties. Specifically zildeplon is a selective dual antagonist of orexin receptors OX1R and OX2R that promotes sleep by reducing wakefulness and arousal. It also exerts its action through subunit modulation of the $GABA_BZ$ receptor chloride channel macromolecular complex. Zildeplon also binds to the brain omega-1 receptor located on the alpha subunit of the GABA-A/chloride ion channel receptor complex and potentiates t-butyl-bicyclophosphorothionate (TBPS) binding. Zlideplon has an elimination half-life of approximately 10 hours in patients with normal hepatic function.

Dosage and Administration: Treatment of short-term insomnia and insomnia disorder in patients age 35 years and older with normal hepatic and renal function: 2.5-5 mg PO at bedtime. Maximum dose per day is 7.5 mg.

Contraindications: Hypersensitivity to zlideplon or sulfonylureas; abrupt discontinuation or use in patients with severe hepatic impairment.

Warnings and Precautions: Use caution in the patient who is sensitive to sulfonylureas; has a past history of depression or substance use disorder; drives or operates heavy machinery, or has altered CYP3A4 function (especially CYP3A4 poor metabolizers).

Adverse Reactions:

Common (>5%): orthostatic hypotension (25%), tachycardia (18%), headache (15%), dizziness (13%), lightheadedness (12%), daytime drowsiness (10%), hypotension (9%), somnolence (8%), decreased coordination (7%); memory impairment (5%) and nightmares (5%)

Less common (<5%): hepatotoxicity (2%), toxic epidermal necrolysis (1%), Stevens-Johnson syndrome (1%), diarrhea (1%), paresthesia (1%), and ocular pain (<1%)

Practice Questions

1. The data provided in the drug advertisement most strongly supports which of the following claims?

   (A) The dose of ZzzKadia should be adjusted in patients with hepatic dysfunction.
   (B) Zzzkadia improves daytime function.
   (C) ZzzKadia is indicated for long-term treatment of insomnia.
   (D) ZzzKadia is the most effective sedative/hypnotic.
   (E) ZzzKadia significantly decrease sleep latency (SL) over both suvorexant and zaleplon.

The correct answer is D. Of the 3 medications studied (ZzzKadia, suvorexant, zaleplon), ZzzKadia is significantly more effective than the other 2 agents in terms of total sleep time (TST) and wake time after sleep onset (WASO). These facts are supported by both the confidence intervals and p values provided.

In the prescribing information section, there is a contraindication for use in severe hepatic impairment as well as a precaution about use in patients with altered CYP3A4 function (especially CYP3A4 poor metabolizers). Although a dosage adjustment in patients with renal dysfunction is likely, there is no information provided in the drug ad related to a dosing adjustment in patients with hepatic dysfunction (**choice A**).

The side effects for this drug include headache (15%), dizziness (13%), lightheadedness (12%), daytime drowsiness (10%), somnolence (8%), decreased coordination (7%) and memory impairment (5%). There is no indication that this drug improves daytime function (**choice B**).

In the main drug ad it is stated that "the results were taken from a 16-week phase 3, randomized, double blinded multicenter clinical trial." This timeframe does not constitute long-term efficacy (**choice C**). Furthermore, in the indications section of the prescribing information it is stated that ZzzKadia is indicated for the treatment of short-term insomnia and insomnia disorder (according to DSM-5 diagnostic criteria).

Choice E refers to the stated decrease in sleep latency (SL) over both suvorexant and zaleplon. This statement is false based on the confidence interval provided for SL. If the given confidence interval (for relative risk or odds ratio) contains 1.0 (as seen in the SL graph), then there is no statistically significant effect of exposure. If the confidence interval for an OR does not contain the number "1" then the following rules apply to the odds ratio:

- If OR > 1, the exposure is associated with a higher risk of outcome
- If OR < 1, the exposure is associated with a lower risk of outcome

2. Although not mentioned in the mechanism of action for ZzzKadia, this drug most likely has which of the following pharmacological properties?

   (A) Alpha 1 antagonist
   (B) Beta 1 agonist
   (C) Beta 2 antagonist
   (D) Muscarinic 2 agonist
   (E) Muscarinic 3 antagonist

The correct answer is A. You are being asked to determine the additional pharmacological effects of ZzzKadia, which is currently described as an orexin receptor antagonist with $GABA_BZ$ receptor modulating properties. The best way to answer this question is to review the adverse effects and match several of these effects to the correct answer choice. Since most of the

CNS-related adverse effects are caused by interaction with the orexin and GABA receptors, the focus should be on the non-CNS related effects. The high incidence of orthostatic hypotension (25%), tachycardia (18%) and hypotension (9%) suggests that the drug has some cardiovascular effects. Of the answer choices, only alpha 1 antagonists (such as terazosin) would cause these cardiovascular effects.

Beta 1 agonists (**choice B**) are likely to cause increased heart rate, conduction velocity and force of contraction leading to hypertension (not hypotension).

Beta 2 antagonists (**choice C**) will block the beta-2 receptors found on blood vessels which are responsible for vessel dilation. Hence, blood pressure will not change or may increase.

Muscarinic 2 receptors are primarily located on the heart and when stimulated lead to decreased heart rate. However a muscarinic 2 receptor antagonist (**choice D**) will block these receptors leading to tachycardia and increased blood pressure secondary to the unopposed beta 1 receptor effects.

Muscarinic 3 receptors are non-innervated receptors located on blood vessels. Antagonism (**choice E**) of these receptors would cause not change in blood pressure since stimulation (via nitrous oxide endothelium-derived relaxing factor) leads to dilation.

3. Consider the following statement: "ZzzKadia has been shown to be non-addicting!" When evaluating the drug ad and highlights of prescribing information for ZzzKadia, which of the following provides the best evidence that this statement is inaccurate?

   (A) Long drug half-life
   (B) Presence of euphoric symptoms
   (C) Presence of severe side effects
   (D) Presence of withdrawal symptoms
   (E) This is an accurate statement

The correct answer is D. You are being asked why ZzzKadia is likely an addictive substance with abuse potential. The first step is to understand the definition of abuse potential. According to the FDA, abuse potential refers to a "drug that is used in nonmedical situations, repeatedly or even sporadically, for the positive psychoactive effects it produces. These drugs are characterized by their CNS activity. Examples of the psychoactive effects they produced include sedation, euphoria, perceptual and other cognitive distortions, hallucinations, and mood changes. Drugs with abuse potential often (but not always) produce psychic or physical dependence (leading to withdrawal when substance is removed) and may lead to the disorder of addiction."

In the main drug ad, the following is stated "Following the study, each of the medications was discontinued and 93% of all participants (who completed the trial) requested further treatment due to the reemergence of severe insomnia as well as side effect ranging from autonomic hyperactivity to psychomotor agitation to seizures". Based on this information and the FDA definition of abuse potential, when ZzzKadia is abruptly withdrawn physical side effects (including CNS effects) are seen.

Half-life and the presence of severe side effects (**choices A and C**) have no established impact on abuse potential.

Euphoric symptoms (**choice B**) are probably the most common reason why prescription and illicit drugs are abused. Euphoria is defined as an intense feeling of well-being, elation, happiness, excitement and joy. However, there are no euphoric symptoms listed in the adverse

effects of for this drug. Pharmacologically-induced euphoria is most commonly seen with stimulants, opioids and cannabinoids.

4. A 42-year-old woman comes to the physician because of a persistent inability to fall asleep and/or stay asleep each night (4-5 nights per week) over the past 8-9 months. She states that she is continually exhausted during the day and her work as a pharmacist is "really suffering." She indicates that she normally works 3 shifts, 12 hours each, plus one 8-hour shift per week. She denies using alcohol or illicit drugs. Physical examination is normal. Based on the information presented in the drug ad for ZzzKadia, which of the following is the most appropriate initial statement to the patient?

   (A) "Before I prescribe you a prescription medication for your insomnia, let's try some natural remedies found at a local health and wellness store."

   (B) "I am thinking that ZzzKadia would be perfect for you. Although it does have some serious side effects, you are not likely to experience them due to your relatively young age."

   (C) "I do not recommend prescribing you any medication at this time since you do not have insomnia disorder."

   (D) "I do not recommend ZzzKadia for you; however, suvorexant or zaleplon may be an appropriate treatment option."

   (E) "ZzzKadia is a new drug that will be perfect for you; however, it does have some serious side effects."

The correct answer is D. According to the DSM-5, the diagnostic criteria for insomnia disorder are as follows:

- Predominant complaint of dissatisfaction with sleep quality or quantity associated with 1 or more of the following: difficulty initiating sleep, difficulty maintaining sleep, or early-morning awakening with inability to return to sleep
- Sleep disturbance cause clinically significant distress or impairment in social, occupational or other important areas of functioning
- The sleep difficulty occurs at least 3 nights per week
- The sleep difficulty is present for at least 3 months
- The sleep difficulty occurs despite adequate opportunity for sleep
- The insomnia is not better explained by another disorder or is attributed to effects of a substance (drug abuse, medication).

Based on this information, the patient meets the DSM-5 criteria for insomnia disorder, which is commonly treated with pharmacological therapy. Although ZzzKadia is indicated for treatment of insomnia disorder (as seen in the Indications section), this drug would not be recommended for this patient since she works 12-hour shifts and the average total sleep time with ZzzKadia is 11.2 hours. Furthermore, the drug has a half-life of approximately 10 hours. Assuming that the patient was able to awaken earlier than 11.2 hours, the pharmacological effect (and CNS side effects) would likely be present in the patient while she was working in the pharmacy. However the average total sleep time with both suvorexant and zaleplon are 6.3 and 6.7 hours, respectively. Either of these medications (currently approved for insomnia by the FDA) would likely be an appropriate treatment option.

Choice A is incorrect since you would not see non-FDA approved medications on the exam.