

# Antidepressant and Antianxiety Medications

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- What is depression?
- What is anxiety?
- What neurotransmitters are involved in those states?
- What medications are used to treat disorders of anxiety and depression?
- What is the timeline of action?
- What side effects or additional benefits come with different medication choices?

# What is depression?

- A term that is used broadly and loosely in 2025
- Often conflated with “depressive symptoms”
- Requires some digging when the client/patient uses the term themselves
- Not uncommon for the disorder to be confused with a state
- “My depression” or “I was diagnosed with anxiety and depression”
- Pharmacological treatments are studied around identified disorders not just symptoms
- Grief, rejection, failure, loss of identity element, chronic stress may all manifest with “depression” but may not respond to typical treatments for Major Depressive Disorder

# What is depression?

- Most often referring to Major Depressive Disorder or Bipolar Disorder in a depressed state
- Other forms of depressed mood
  - Persistent Depressive Disorder (previously dysthymia, previously neurotic depression)
  - Impact of trauma +/- formal criteria for PTSD
  - Chronic Adjustment Disorders
  - Personality Disorders (i.e., narcissistic injury, chronic rejection)
  - Substance-induced/related states (i.e., amotivational syndrome of cannabis, withdrawal phase from stimulants)

# What is anxiety?

- Similar difference between anxious states and anxiety disorders
- “Anxiety” can be used to mean
  - Insomnia, ruminating thoughts
  - Restlessness
  - Avoidance
  - Somatic symptoms related to panic (tremor, sweating, shortness of breath)
- Medications available for acute relief of anxious states (typically benzodiazepines) versus treatment of the chronic disorder (Generalized Anxiety Disorder, Social Anxiety Disorder)
- Today we will focus on chronic anxiety disorders which are often more persistent than depression

# “A Chemical Imbalance”

- Historically, treatment of clinical depression has focused on the monoamine hypothesis—that there was a relative deficiency in serotonin and norepinephrine
- In 1950s, a blood pressure medication (reserpine) caused acute depression that was reversed by ECT, this medication blocked release of monoamines suggesting a role in depressed mood
- Isoniazid, a tuberculosis drug was found to improve the mood of patients being treated for TB, found to have Monoamine Oxidase inhibiting properties

# “A Chemical Imbalance”

- Taken together, the hypothesis was that deficiencies in serotonin and norepinephrine cause depression and conversely, medications that slowed their metabolism/kept concentrations higher in the synapse were anti-depressants
- Current understanding is far more complex and does not support a simple “don’t have enough chemical” model
- Anatomical studies have found relative shrinkages of brain areas in depression, changes in unilateral functioning, inflammatory markers that may be involved, gut flora that could have implications
- While there is unlikely to be a single mechanism of depression, ideally medications would have a single and specific action

# Neurotransmitters in Depression/Anxiety

- Serotonin

- Likely improves sense of calm, hopefulness, joy
- In post-mortem studies of suicidal victims very low suggesting hopelessness, impulsivity, anhedonia
- Receptors throughout the body including gut, genitals, and vasculature
- OCD circuit very specifically impacted by serotonergic medications

- Norepinephrine

- When “low” —fatigue, poor concentration/focus are implicated
- Receptors throughout vasculature

# Neurotransmitters in Depression/Anxiety

- Dopamine
  - (as in previous lecture)—the meaning chemical
  - Increasing dopamine can have mood altering effect quickly (cocaine)
  - Overlaps with addiction pathway, but some antidepressant treatment use dopamine agonism to boost other medications (aripiprazole, brexpiprazole)
- GABA
  - Predominant inhibitory neurotransmitter in the brain—very diffuse
  - Increasing GABA-ergic transmission decreases anxiety but also causes general slowing of brain functioning (think alcohol)
- Glutamate
  - Predominant activating neurotransmitter of brain
  - Some use of NMDA (one type of receptor) attenuation to treat depression

# First Antidepressants

- Monoamine Oxidase Inhibitors
  - Evolved from monoamine hypothesis and isoniazid observation
  - Used for many years
  - Require a special diet as cheese, cured meats, alcohols could cause dangerously elevated blood pressure and stroke
  - Rarely used now outside refractory depression
- Tricyclic Antidepressants
  - Impacted norepinephrine and serotonin receptors (but also acetylcholine, histamine and other receptors) in different ratios
  - Effective but significant side effects and potentially lethal in overdose
  - Still used by neurology for migraine prophylaxis, sleep or refractory conditions (depression or OCD)

# Selective Serotonin Reuptake Inhibitors (SSRIs)

- Based on the name, the class should suggest that they are all “selective” and therefore do the same thing without side effects beyond the described method of action
- In truth, chemically quite different although all primarily impact Serotonin Reuptake
- Notable that treatment response 4-6 weeks after starting treatment suggests that it is not only the medication’s action that is antidepressant but likely a compensatory/downstream change that rewires the brain out of a depressed state

# Selective Serotonin Reuptake Inhibitors (SSRIs)

- Across the group they are approved for MDD, persistent depressive disorder, OCD, Generalized Anxiety Disorder, Panic Disorder, phobias
- In this way, the drug likely has led to diagnostic vagueness (“I have depression and anxiety”)
- Generally well-tolerated, often self-discontinued
- Withdrawal symptoms are rapid onset (days) and not reflective of the clinical role, brain zaps/spaciness/general malaise are quite common
- As prescription became broader has had large cultural impact with concerns for age of prescribing, encouragement of suicidal ideation or aggression in high-profile cases
- Current climate with a significant focus on the difficulty of discontinuation that is certainly much more intense than 10-20 years ago

# Selective Serotonin Reuptake Inhibitors (SSRIs)

- On initiation, typical side effects are upset stomach/quicker GI transit time and headache
- Can cause fatigue or activation
- Tremors are not uncommon
- Weight gain common (usually ~5 lbs/year)
- Changes to dream quality not uncommon
- Delayed orgasm, erectile dysfunction, decreased libido not uncommon
- Often worsen anxiety (particularly in patients with panic) in first few doses—require dose modification and supportive treatments to initiate
- Concerns for increased suicidal ideation but mixed picture in large data sets
- OCD and highly anxious people often require much higher doses than depression responds to (and often require longer treatment time to achieve improvement)

# Prozac (fluoxetine)

- Released in 1986, reports of “personality changes” likely related to people who had been quite depressed lifelong
- Generally activating, typically started in the morning
- Available as liquid for children or those who can’t swallow pills
- Long half-life—can be dosed weekly, therefore forgetting a few doses is not problematic (teenagers!) and discontinuation will not have withdrawal
- Well studied in comorbid eating disorders and used for bulimia, anorexia nervosa; some evidence that there is less weight gain however
- Large dosing range so useful in OCD
- Around long enough that name can be somewhat stigmatizing or thought to be “too strong” for some patients

# Paxil (paroxetine)

- Released in 1992, still used widely globally but less often in North America
- Felt to have “calming” properties which are likely caused by anticholinergic action—also causes more constipation, urinary hesitancy, dry mouth than other SSRIs
- Not approved in pediatric population and thought to have outsized impact on suicidal thinking in youths
- Similar dosing/dosing range as fluoxetine though less well tolerated

# Zoloft (sertraline)

- Released in 1991
- Remains widely prescribed, about as well tolerated as fluoxetine
- More often causes tiredness so typically started at bedtime
- Wide range of dosing so used for anxiety disorders and OCD
- Short half-life, a medication holiday (skipping a dose) can relieve sexual side-effects if needed

# Luvox (fluvoxamine)

- In the United States, never went for a depression indication, only approved to treat OCD (currently approved from age 8 up)
- In Canada, used to treat depression and OCD
- Hasn't demonstrated better efficacy for OCD compared to other SSRIs but is synonymous with that disorder due to approvals
- Typically dosed twice daily
- Never had significant market share

# Celexa (citalopram)

- Well-tolerated, similar dosing as paroxetine/fluoxetine
- Concerns raised for cardiac conduction changes at higher doses
- Still occasionally prescribed but typically by older physicians
- Because...

# Cipralex (escitalopram)

- A more specific synthesis process of citalopram was able to isolate the S-enantiomer of the molecule which reportedly is the “effective” compound while the R-enantiomer was responsible for side effects
- Known in the US as “Lexapro”
- Well-tolerated with fewer side effects
- Huge market share
- Concerns for cardiac impact limit dosing range, so typically not started for OCD or conditions where higher dosing range is intended/needed

# Selective Norepinephrine-Serotonin Reuptake Inhibitors (SNRIs)

- Medications that are functionally closer to tricyclics than SSRIs
- Impact two neurotransmitters, consequently hypothesized to be more effective for depression
- Still get used for anxiety conditions as have impact at serotonin receptors
  - Effexor – good antidepressant, dual mechanism above 150 mg/day, bad withdrawal
  - Pristiq—pro-drug of Effexor, longer half-life but still bad withdrawal
  - Cymbalta—used frequently in chronic pain or in comorbid pain
  - Fetzima – newest drug

# Other Antidepressants – bupropion (Wellbutrin)

- Functionally a Norepinephrine-reuptake inhibitor, boosting NE and dopamine
- Considered an “activating antidepressant” but poor efficacy when used alone—good in combination with a second agent
- Taken in the morning, often feels like a “strong cup of coffee” but can worsen anxiety in vulnerable individuals
- Can increase libido, weight neutral or negative, also curbs smoking tobacco
- High risk of seizure in overdose, although less in extended-release preparations
- Black box warning for eating disorders especially with purging
- Can get diverted in correctional settings (i.e., snorting)

# Other Antidepressants

- vortioxetine (Trintellix)
  - Functions as an SRI but has various additional actions of both agonism/antagonism and therefore considered a serotonin modulator
  - Significant nausea not uncommon in starting
  - Thought to be better for “brain fog” and cognitive complaints with depression
- trazodone
  - Another serotonin modulator based on multiple interactions at different serotonin receptors
  - Rarely used for treatment of depression, commonly used for sleep but few studies to support its use despite widespread prescription
  - Priapism a concern, especially in younger males

# Other Antidepressants

- mirtazepine (Remeron)
  - Serotonin modulator, also prominent anti-histaminic action
  - Very sedating and increases appetite
  - Often used in geriatric depression
- vilazodone (Viibryd)
  - SRI and serotonin modulation
  - Expected to have SSRI-like action but without sexual side effects as a result

# Antidepressant Use for other conditions

- POTS (postural orthostatic tachycardia syndrome)
- Eating Disorders
- Hypersexual conditions (paraphilias, brain injury, ID)
- Autism Spectrum Disorder
- Premature Ejaculation
- Excoriation Disorder/Skin-Picking

Thank You For Listening!

