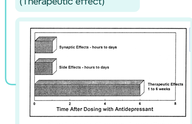
Antidepressants

Features

- The optimal use of antidepressant required a clear understanding of their mechanism of action, pharmacokinetics, potential drug interaction and the deferential diagnosis of psychiatric illnesses.
- chemical jobs
  - In understanding depression, it's essential to look at neurotransmitters in the brain, substances that influence our personality and mood.
  - Three key neurotransmitters are crucial in mood regulation and are particularly relevant to treating depression: Norepinephrine (NE), Dopamine (DA), and Serotonin-
    - Norepinephrine (NE)
      - linked to alterness and energy
      - affects the physical aspects
        - heart rate
        - blood pressure
      - also affects stress and and attentiveness
    - Dopamine (DA)
      - this is the pleasure and motivation chemical
      - helps you feel joy from activities, motivates you and affects emotion and attention
      - also crucial for controlling movement (motor)
    - Serotonin
      - has a broad role
      - keeps your mood steady
      - influences your sleep and appetite
      - control how impulsive or aggressive you might feel
  - When treating depression, which is essentially a mood disorder, balancing these three chemicals is crucial for making someone feel better. They all connect and affect each other (connectivity) in addition to the glutamate and glycin
    - for example
      - dopamine and serotonin both play roles in how we act and feel (personality), but they can also influence each other's levels in our brains
      - Similarly, norepinephrine, while mainly about alertness, can also impact how dopamine and serotonin work (overlapped)
    - In short, getting these chemicals to work together well is key to improving mood in depression.
  -

Depression

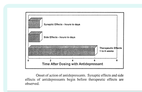
- features
  - its complex
  - common condition that doctors across all specialties encounter
    - , While drugs are commonly prescribed and often effective, they're not always necessary, so the question is, when should they be used?
  - research has shown that in people with depression, the hippocampus, a part of the brain important for memory and mood, can be smaller
    - This raises a question: Does depression cause the hippocampus to shrink, or do people with a smaller hippocampus tend to get depressed?
  - It's influenced by both our physical body and mental state
  - Depression varies widely from person to person. It has many factors and forms, making it a unique experience for everyone. This diversity makes it a challenging condition to understand and treat.
  - In summary, depression is a multifaceted condition that requires careful consideration when it comes to treatment, especially regarding the use of antidepressants.
- WHO predictiON
  - Depression is currently the FOURTH most significant cause of suffering and disability worldwide
  - and, sadly, It will be the SECOND most debilitating human condition by the year 2020
  - its a lady disease (2:1)
- types of depression
  - monopolar depression - Major Depressive Disorder MDD
    - this type is all about the lows
    - people with it feel sad, hopeless and uninterested in almost everything , without mood swings to highs seen in other types of depression
    - when most ppl talk about depression theyre usually referring to MDD
    - characterized by
      - consistent, flat mood state WITHOUT the highs
  - bipolar disorder - Bilateral Depression
    - known for mood swings
    - ppl with bipolar disorder experience both the lows of depression and the highs of mania or hypomania
      - its a different kind of depression because of these intense emotional highs, leading to a rollercoaster of feelings rather than justa. flow, low mood
  - To summarize it, while monopolar depression focuses solely on depressive episodes, bipolar disorder includes both depressive and manic episodes, making the experiences of these conditions quite distinct.
- symptoms
  - cognitive
    - thoughts of hoplessness, poor confidence and negative thoughts
  - emotional
    - feeling sad
    - unable to feel pleasure
    - irritability
  - pyschoootor/physical
    - decreased libido/energy
    - sleep changes (70% less, 30% more)
    - appetite changes (70% less, 30% more)
    - *notice the heterogeneity (depression varies between patients)
- treatment
  - antidepressant medications
    - selective serotonin reuptake inhibitors (SSRIs)
      - first line of treatment
  - psychotherapy
    - usually individual psychotherapy
    - cognitive behavioral therapy has efficacy of most evidence for treatment
    - Psychotherapy alone is effective but may not be enough to prevent a relapse or to achieve the 70% response rate.
  - sometimes exercise or body awareness has been found to be helpful
  - Combining treatments, such as medication with psychotherapy, tends to be the most effective approach.
    - The study found that this combination increased positive outcomes by 70% and decreased the chances of the depression coming back. However, adding psychotherapy to a placebo didn't increase improvement rates beyond the placebo effect alone
- the placebo effect in depression treatment
  - In a study involving 200 people with major depression, patients were divided into two groups. The first group received an actual antidepressant, while the second group received a placebo, which is a substance with no active medication. Surprisingly, the placebo group showed a 5% greater improvement compared to those who took the real medication
  - However, those who took the placebo were also more likely to experience a return of their depression symptoms.This phenomenon demonstrates the power of belief. If patients believe they are receiving an effective depression treatment, their bodies can sometimes respond as if they are getting real medication, potentially increasing their brain's production of mood-boosting chemicals like serotonin, so the question here is Do we really treat or it's the placebo affect only?
  - All antidepressants have an equal effect to a placebo, but real medication tends to lead to fewer relapses.
- monoamine hypothesis of depression
  - We have millions of perscription per year to many types of antidepressants drugs. but why do we have all these drugs of antidepressants?
    - because they haev different mechanism of action
    - because depression is complex to treat
  - what it is
    - idea about what causes depression
    - It suggests that depression might happen because there isn't enough of certain chemicals in the brain, specifically serotonin (5-HT), norepinephrine (NE), and dopamine (DA)
      - Normally, an enzyme called monoamine oxidase breaks these chemicals down, but the idea is that if we inhibit this enzyme with drugs (MAOIs), we can stop the breakdown and increase their levels to improve mood.
      - While MAOIs can make these brain chemicals more available, and therefore potentially ease depression, the full benefit of taking these drugs isn't immediate. It usually takes about 6 to 8 weeks for patients to feel the maximum effects. In the meantime, the increased levels of chemicals like serotonin in the synapses causes side effects, which might include overexcitement, impacting sleep, mood, and sexual desire. These side effects occur before the beneficial effects of the medication are fully realized.
        - The delayed therapeutic effect of antidepressants has led researchers to consider other factors that might contribute to their effectiveness. One area of focus has been on neurotrophic factors such as brain-derived neurotrophic factor (BDNF). These substances support the growth and health of neurons, and their levels appear to increase with chronic activation of monoamine receptors due to long-term antidepressant use. The time needed for the synthesis and action of these neurotrophic factors may partly explain why there's a delay in the antidepressant effect.
        - You're not allowed to switch between drugs until you reach 6-8 weeks (Therapeutic effect)
        - 

          Onset of action of antidepressants. Synaptic effects and side effects of antidepressants begin before therapeutic effects are observed.
- types of antidepressants and the typical order in which they might be tried
  - 1. SSRIs (Selective Serotonin Reputake Inhibitors)
    - often the first type of antidepressants prescribed
  - 2. SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors)
    - if SSRIs dont work the doctors may try SNRIs
  - 3.NDRIs (Norepinephrine-Dopamine Reuptake Inhibitors)
    - if neither SSRIs nor SNRIs helo, NDRIs might be an option
    - they increase both norepinephrine and dopamine levels
  - 4. TCAs (Tricyclic Antidepressants)
    - if others dont work the doctor may prescribe TCAs
    - they work by affecting several brain chemicals (serotonin, norepinephrine, dopamine)
  - 5. other medications like Trazodone
    - If none of the above are effective, doctors might try other drugs like trazodone, which works differently by blocking a specific serotonin receptor and also slows/inhibit the reuptake of serotonin.
  - Each step is tried if the previous one isn't effective after a full trial period, typically around 6 weeks. Its important to give each medication time to work before deciding if its effective or not. If one drug doesnt work we give a drug with different mechanism than the first one. We can inhibit norepinephrine and serotonin reuptake doesnt work--> use drugs that inhibit norepinephrine, dopamine and serotonin

Tricyclic antidepressants - Amitriptyline

- MOA
  - inhibit serotonin, norepinephrine and dopamine transporters, slowing reputake with a resulatant increase in activity
  - muscarinic acetylcholine receptors, alpha adrenoreceptors and certain histamine (H1) receptors are blocked
- side effects
  - drug induced sedation
  - orthostatic hypotension
  - cardiac effects
  - anticholinergic effects
    - dry mouth
    - constipation
    - blurred vision
    - urinary retention

NDRI (Norepinpherine/Dopamine Reuptake Inhibitor)

- features
  - good for use as an augmenting agent
  - no weight gain, sexual side effects, sedation or caridac interactions
  - low induction of mania
  - does NOT treat anxiety unlike many other antidepressants
    - can actually cause anxitery, agitation and insomnia
  - Following the initiation of the antidepressant drug treatment there is generally a therapuetic lag lasting for 3-4 weeks.
    - 8 weeks trial, then you allow to switch to another antidepressant.
    - partial response then add one another drug from different class
  - if the initial treatment was successful then 6- 12 maintenance periods.
  - If the patient has experience two episodes of major depression, then it is advisable to give an anti depressant life long.
  - 

    Onset of action of antidepressants. Synaptic effects and side effects of antidepressants begin before therapeutic effects are observed.
- drug
  - Buproprion
- MOA
  - likely reuptake inhibition of dopamine and norepinephrine
- side effects
  - anxiety
  - agitation
  - insomnia

Monoamine Oxidase (MAO) and Depression

- features
  - MAO catalyze deamination of intracellular monoamines
    - – MAO-A oxidizes epinephrine, norepinephrine,serotonin
    - – MAO-B oxidizes phenylethylamine
    - – Both oxidize dopamine nonpreferentially
  - MAO transporters reuptake extracellular monamine
- Monoamine Oxidase Inhibitors - MAOIs
  - MOA
    - Inhibition of intra-neuronal degradation of serotonin and norepinephrine causes an increase in extracellular amine levels.
  - drugs
    - Phenelzine
      - non selective
    - Moclobemide
      - reversible
      - selective inhibitor of MAO-A
    - Selegiline
      - selective for MAO-B
  - side effects
    - blood pressure problems
    - dietary requirements
    - weight gain
    - insomnia
    - edema

5-HT2 Antagonists

- drugs
  - Nefazodone
    - weak inhibitor of both SERT (serotonin reuptake) and NET (norepinephrine re-uptake)
  - Trazodone
    - also weak but selective inhibitor of SERT
  - Mirtazapine
- MOA
  - reuptake inhibition of serotonin and inhibition of 2HT2a receptors
    - Inhibition of 5-HT2A receptors in both animal and human studies is associated with substantial antianxiety, antipsychotic, and antidepressant effects
- clinical uses
  - depression
    - Mirtazapine
      - can be advantagous in pts with depression having sleep difficulties
  - insomnia
    - Trazadone
      - low doses of it (50-100mg) have been used widely both alone and concurrently with SSRIs and SNRIs to treat insomnia
- causes
  - sedation
    - necessitates dosing at bedtime
  - dose related GIT SEs
  - weight gain (Mirtazapine)

SNRIs (Serotonin/Norepinephrine reuptake inhibitors)

- features
  - if SSRIs has no effect we use SNRIs
  - slightly greater efficacy than SSRIs
  - slightly fewer adverse effects than SSRIs
    - serotonin levels in SSRIs is higher than SNRIs because its specific
- MOA
  - SSRIs effects serotonin levels only, SNRIs increase serotonin and norepinphrine and dopamin so fewer side effects of serotonin
- side effects
  - severe nausea and vomiting
    - especially Venlafaxine
  - can cause a 10-15 mmHG dose dependent increase in diastolic BP (because fo norepinephrine and dopamine)
  - can cause a bad discontinuation syndrome, and taper recommended after 2 weeks of administration
    - Withdrawal symptoms is more severe in SNRI than SSRI because we're dealing with 2 things: serotonin and dopamine
- drugs
  - Venlafaxine
  - Duloxetine

SSRIs (Serotonin specific reuptake inhibitors)

- features
  - goal of SSRIs is reaching motivation
  - serotonin receptors family
    - 5HT1a and 5HT5 which have inhibitory effects on brain
    - while 5-HT (2,3,4,6,7) have excitaatory effects
  - the SSRIs will activate all the receptors of 5-HT
    - most of the antidepressants activity come from activation of
      - 5-HT1a
      - 5-HT1b
      - 5-HT1c
  - have no euphoria so no addiction in SSRI its physical dependence (tolerance)
    - discountinuation sundrome
- uses
  - depression
  - obsessive
  - pain management
  - antistress
  - fibromylagia
    - generalized pain due to depression
- MOA
  - inhibit the reputake of serotonin WITHOUT seriously effecting the reuptake of dopamine and norepinephrine
- side effects
  - GI upset
    - this cause the GIT has a lot of serotonin receptors and their role is motility, nausea and vomiting
      - so increasing the serotonin levels will increase their effects
  - sexual dysfunction (30%+!)
    - reversible
      - dose dependent
    - this is cause serotonin inhibits dopamine activity through GABA activation
  - most common
    - anxiety
    - restlessness
    - nervousness
    - insomnia
    - fatigue
    - sedation
    - diziness
      - due to the excitement activity of serotonin in the brain due to activation of 5HT1b and 5HT1c receptors
  - other side effects
    - these drugs can change the personality and make the person live without feeling because serotonin inhibits dopamine especially in frontal loves, its reversible, this is the rule of cosmo pharmacology
  - side effects
    - can develop a discontinuation syndrome with
      - FINISH
        - Flu like symptoms
          - fatigue
          - muscle aches
          - headaches
          - diarrhea
        - Insomnia
          - vivid or disturbing dreams
        - Nausea
        - Imbalance
          - gait instability
          - dizziness
          - lightheadeness
          - vertigo
        - Sensory disturbances
          - parethesia
          - electric shock sensation
          - visual disturbances
        - Hyperarousal
          - anxiety
          - agitation
      - onset
        - 24-72 hrs
      - resolution
        - 1-14 days
      - incidence
        - approx 20-40 %
          - who have been treated at least 6 weeks
- drugs
  - Paroxetine
    - features
      - sedating properties (dose at night) offers good initial relief from anxiety and insomnia
      - significant CYP2D6 inhibition
    - MOA
      - antagonistic effects on 5-HT1a and 5-HT1b receptors so it has sedative effects (no excitement) so can be used on agitated patients
  - Setraline (zoloft)
    - features
      - most used in the US
      - increased number of GI adverse drug reactions
        - thats why we dont use it in GI disordered pts
  - Fluozetine (prozac)
    - features
      - secondary to long half life
      - less discontinuation syndrome
      - drug of choice in myocardial infarction depression
      - significant P450 interactiosn so this may not be a good choice in pts already on a number of meds
      - initial activation may increase anxitery and insomnia
      - more likely to induce mania than some of the other SSRIs
  - Tamoxifen
    - features
      - pro drug for breast cancer activated by CYP6D6
      - its a CYP2D6 pro drug activatoir

serotonin syndrome

- MOA inhibitors or tricyclic and SSRI increases serotonin level significantly ,if we give them at the same time will cause: hyperthermia, seizures, Gi problems and death(serotonin syndrome). In opiods lec, tramadol, piperidine and mepridine increase serotonin so we don't give them with SSRI

Presented with xmind