CNS

Doctor 2021

Pharmacology

Modified (5)

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The optimal use of antidepressants requires a clear understanding of their mechanism of action, pharmacokinetics, potential drug interaction, and the deferential diagnosis of psychiatric illnesses.

In most cases, a placebo has more efficacy than the real antidepressant itself

Bipolar disorder, formerly called manic depression, is a mental health condition that causes extreme mood swings that include emotional highs (mania or hypomania) and lows (depression). مرّة بيكون طبيعي وعادي ومبسوط بعدين بيرجع بيكتئب مرة بيزهزه ومرة بيرجع يحزن

Chemical Job

Dopamine : • Attention • Pleasure • Emotions • Reward • Motivation • Movement

Norepinephrine : • alertness • Observance • Daydreaming • Heart/BP rates • Stress

Serotonin : • Regulates mood • sleep • emesis • sexuality • Appetite • impulsiveness/ aggression

Monoamine hypothesis of depression

The monoamine hypothesis grew originally out of associations between the clinical effects of various drugs that cause or alleviate symptoms of depression and their known neurochemical effects on monoaminergic transmission in the brain

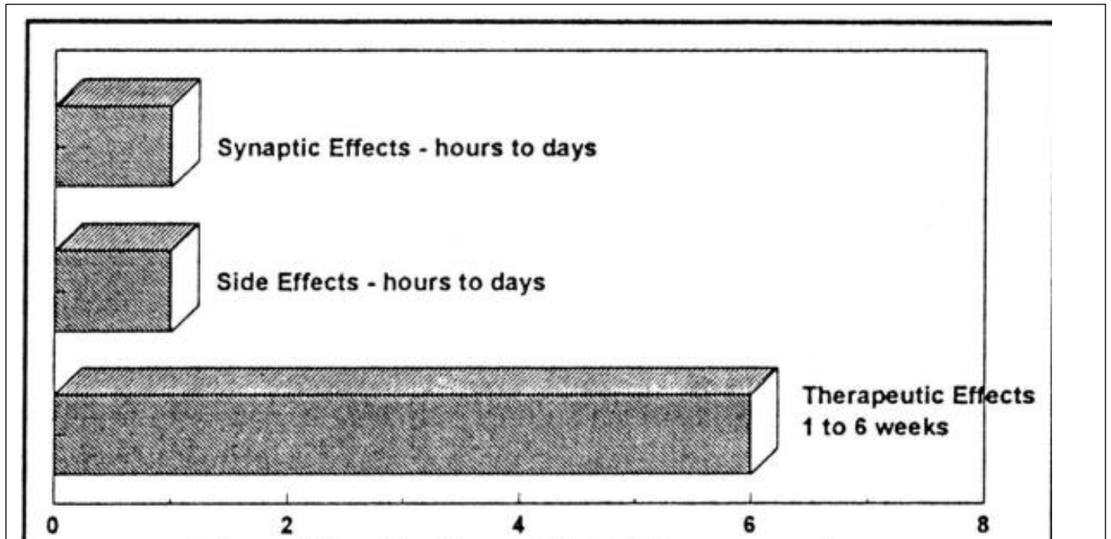
- **The monoamine hypothesis of depression suggests that depression is related to a deficiency in the amount or function of cortical and limbic serotonin (5-HT), norepinephrine (NE), and dopamine (DA)**

The chronic activation of monoamine receptors by antidepressants appears to increase in BDNF transcription

When you give a patient serotonin or dopamine at the same time these drugs have side effect

Pathophysiology of antidepressants is different between patients

The maximum efficacy is achieved after six weeks



Following the initiation of the antidepressant drug treatment there is generally a therapeutic lag lasting for 3-4 weeks.

8-week trial, then you are allowed to switch to another antidepressant.

Partial response then add one another drug from different class.

Neurotrophic Hypothesis

Depression appears to be associated with a drop in brain-derived neurotrophic factor (BDNF) levels in the cerebrospinal fluid and serum as well as with a decrease in tyrosine kinase receptor B activity

BDNF is thought to exert its influence on neuronal survival and growth effects by activating the tyrosine kinase receptor B in both neurons and glia

Animal and human studies indicate that stress and pain are associated with a drop in BDNF levels and that this loss of neurotrophic support contributes to atrophic structural changes in the hippocampus and perhaps other areas such as the medial frontal cortex and anterior cingulate

Studies suggest that major depression is associated with substantial loss of volume in the hippocampus, anterior cingulate, and medial orbital frontal cortex

To increase the efficacy of antidepressants we need to give patients psychotic therapy بنجلس
مع المريض وبنحكي معه انت يا مريض يا عزيزي ما معك اكتئاب لازم يا حلو تلعب رياضة ومن هالحكي

مثل الاكتئاب الي بيصير مع طالبة طب تزوجت وجابت توأم رح تضل تفكر كيف بدها تدبر حالها من دراسة و أطفال و زوج رح تصير تهرب منهم بمرض الاكتئاب

SSRIs (Serotonin-specific reuptake inhibitors)
inhibits the reuptake of serotonin without seriously affecting the reuptake of dopamine & norepinephrine.

The most common side effects include GI upset buzz serotonin activates nausea, vomiting and diarrhea, sexual dysfunction (30%+!), anxiety, restlessness, nervousness, insomnia, fatigue or sedation, dizziness

Serotonin increasing leads to inhibit dopamine effect which leads to decreased sexual activity

Can develop a discontinuation syndrome with agitation, nausea, disequilibrium, and dysphoria

I need to increase serotonin with norepinephrine or increase serotonin, norepinephrine, and dopamine all to gather

an develop a discontinuation syndrome with agitation, nausea, disequilibrium, and dysphoria

sSRI/SNRI Discontinuation Syndrome in Adults

- Flu-like symptoms: fatigue, muscle aches, headache, diarrhea
- Insomnia: vivid or disturbing dreams
- Nausea • Imbalance: gait instability, dizziness, lightheadedness,
- Sensory disturbance: paresthesia, “electric shock” sensation, visual disturbance
- Hyperarousal: anxiety, agitation

- Onset: 24-72 hours + Resolution: 1-14 days
- Incidence: ~ 20 - 40 % (who have been treated for at least 6 weeks)

Paroxetine: Sedating properties (dose at night) offer good initial relief from anxiety and insomnia
Significant CYP2D6 inhibition

Sertraline: Increased number of GI adverse drug reactions (if the patient has GI problems we don’t give this drug to them)

Fluoxetine Secondary to long half-life, less Discontinuation Syndrome.
Significant P450 interactions so this may not be a good choice in pts already on several meds

Serotonin/Norepinephrine reuptake inhibitors (SNRIs)

If the patient doesn't respond to the previous drugs we need to go to this choice

- **Slightly greater efficacy than SSRIs**
- **Slightly fewer adverse effects than SSRIs**

– Venlafaxine
– Duloxetine

1. Can cause a 10-15 mmHG dose-dependent increase in diastolic BP.
2. May cause significant nausea,
3. Can cause a bad discontinuation syndrome, and taper recommended after 2 weeks of administration

5-HT2 antagonists

- **Agents: Nefazodone, Trazodone, mirtazapine.**
- **Inhibition of 5-HT2A receptors in both animal and human studies is associated with substantial antianxiety, antipsychotic, and antidepressant effects**
- **Nefazodone is a weak inhibitor of both SERT and NET, whereas trazodone is also a weak but selective inhibitor of SERT**

A 48-year-old man with schizophrenia on thyroidzine for 20 years develops bilateral facial and jaw movements and rhythmic motions of his tongue. Physical examination of the heart, lungs, and abdomen are unremarkable. What is the most likely aberration on a neurotransmitter level?

(A) Acetylcholine

(B) Dopamine

(C) Epinephrine

(D) Norepinephrine

(E) Serotonin

The answer is B: Dopamine. Long-term treatment with antipsychotics can cause this motor disorder. Patients display involuntary movements, including bilateral and facial jaw movements and "fly-catching" motions of the tongue. A prolonged holiday from antipsychotics may cause the symptoms to diminish or disappear within a few months. However, in many individuals, tardive dyskinesia is irreversible and persists after discontinuation of therapy. Tardive dyskinesia is postulated to result from an increased number of dopamine receptors that are synthesized as a compensatory response to long-term dopamine receptor blockade. (A) Tardive dyskinesia is caused by overload of dopamine receptors. (C) Epinephrine receptors are not a component of the pathophysiology of tardive dyskinesia. (D) Norepinephrine receptors are not involved in tardive dyskinesia. (E) Serotonin receptors are uninvolved in this disease process.

Recap :

- **The first choice is SSRI if it isn't working effectively, we need to give SNRIs**
- **SSRIs are different on the pharmacokinetic level and slightly on a dynamic level**
- **Sertraline is free from drug-drug interaction and it isn't given to patients who have GI problems**
- **Escitalopram free from drug-drug interaction (Free from drug-drug interaction means it doesn't inhibit cytochrome P450)**
- **Paroxetine Significant CYP2D6 inhibition بنعطيه للست الي ما بتنام (Sedating properties (dose at night) offers good initial relief from anxiety and insomnia)**
- **Significant P450 interactions so this may not be a good choice in pts already on a number of meds**
- **Initial activation may increase anxiety and insomnia More likely to induce mania than some of the other SSRIs**
- **Fluoxetine Secondary to long half-life, less Discontinuation Syndrome بنعطيه للمريض الي مش متعاون**

Serotonin/Norepinephrine reuptake inhibitors (SNRIs) (these drugs increase the level of adrenaline and serotonin)

Slightly greater efficacy than SSRIs (buzz they have a dual effect) (they increase adrenaline and serotonin to gather)

May cause significant nausea
Can cause a bad discontinuation syndrome, and taper recommended after 2 weeks of administration

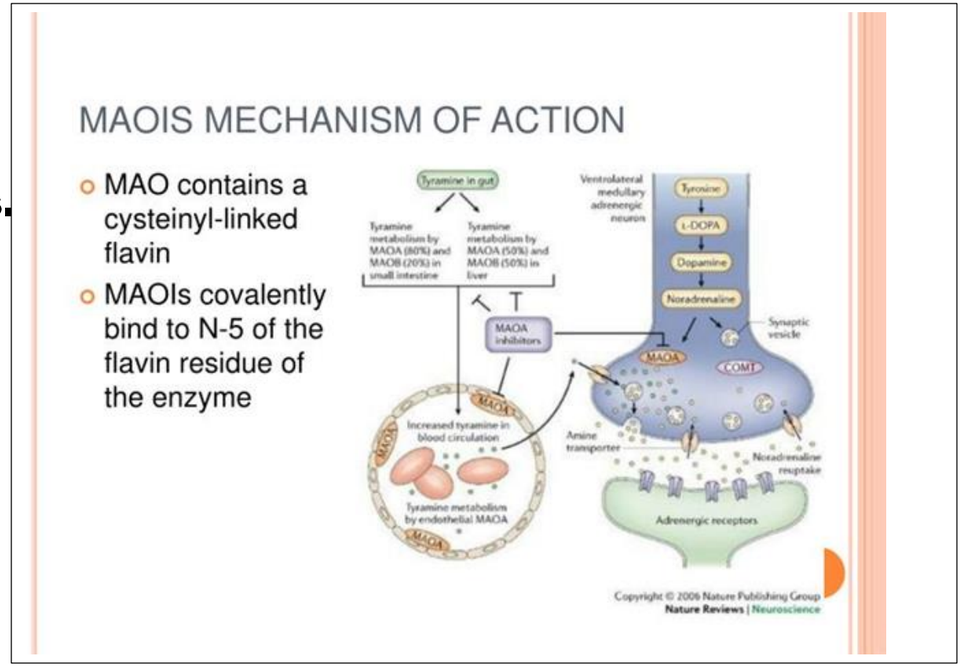
Tricycle antidepressant (Amitriptyline) has the strongest activity
Used for atypical depression

TCAs inhibit serotonin, norepinephrine, and dopamine transporters, slowing reuptake.

Side effects:
(1) drug-induced Sedation (histamine (H1) receptors are blocked)
(2) Orthostatic hypotension (alpha-adrenoceptors)
(2) Cardiac effects (alpha-adrenoceptors)
(3) Anticholinergic effects dry mouth, constipation, blurred vision, urinary retention (Muscarinic acetylcholine receptors)

MONOAMINE OXIDASE (MAO) AND DEPRESSION

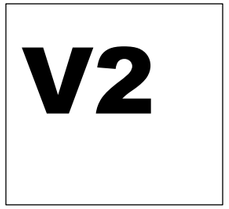
MAO catalyzes the deamination of intracellular monoamines.
– MAO-A oxidizes epinephrine, norepinephrine, serotonin
– MAO-B oxidizes phenylethylamine
– Both oxidize dopamine non preferentially
• MAO transporters reuptake extracellular monoamine



• Side effects: Blood pressure problems, Dietary requirements, Weight gain, Insomnia, Edema.

• Selegiline is selective for MAO-B

• Inhibition of intra-neuronal degradation of serotonin and norepinephrine causes an increase in extracellular amine levels. • Phenelzine is a none selective • Moclobemide is a reversible and selective inhibitor of MAO-A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