PHARMACOLOGY TEAM

Lecture:8

Antidepressents (New)

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OBJECTIVES

- Realize neurotransmitter defects in different types of depression .
- Elaborate on how antidepressants generally act .
- Classify the existing antidepressant into elder (TCAs & MAO Is) and newer groups (SSRIs, SNRIs, NRIs, NAASs, NDRIs, SARIs) .
- Expand on pharmacology of each group; setting examples, discussing pharmacodynamic potentials, pharmacokinetic differences, varied indications, contraindications and side effects .
- Enumerate augmenter drugs used in depression .

New antidepressents

You don't have To memorize these

Selective Serotonin Reuptake Inhibitors SSRIs	Fluoxetine Fluvoxamine Citalopram Sertraline Paroxetine
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	Venalafaxine
Norepinephrine Reuptake Inhibitors (NRIs)	Reboxetine
Noradrenergic & Specific Serotonergic Antidepressants (NaSSAs)	Mirtazapine
Norepinephrine Dopamine Reuptake Inhibitors (NDRIs)	Bupropion
Serotonin Antagonists & Reuptake Inhibitors (SARIs)	Trazodone Nefazodone

But you have to study these

Fluoxetine Fluvoxamine Citalopram Sertraline Paroxetine)) :- 1-SSRIs

MOA	**Binds to SERT ⇩ 5-HT levels in synapse** you will find that one of the ADRs is sedation and weight gain , don't be confused Nothing is absolute in medicine **No effect on NET No block to mAch, H, or a1 Adrenoceptor ⇨ so no antimuscarinic nor sedative effects** **They are nearly of comparable efficacy but of preferential response in each individual**
Pharmacokinetics	**1- t1/2 :** **A-Too long (3-11 days): Fluoxetine** (Prozac) ,it has a metabolite with long t1?2 also B- **Moderate length (~24hr)**: Sertraline, Paroxetine, Citalopram. باخد بالي وانا بديه اللل strong inhibitors مع دوا ثاني **2- Metabolism: P450 then conjugation They are enzyme inhibitors** **A-Weak inhibitors < Sertraline, Citalopram ⇨⇩** interaction **B-Strong inhibitors > Fluoxetine, Paroxetine ⇨⇩** metabolism of TCA, neuroleptic, some antiarrhythmic, β-blockers. 3- Primarily excreted through kidney; not paroxetine & sertraline undergo partially fecal excretion.**(it is not important)** **Fluoxetine differs from others members of this class in :** **1- It has a longer t1/2 (50hrs).** **2- Available ⇨ as sustained release preparations ⇨ once weekly.** **3- Metabolite norfluoxetine = potent as parent drug t1/2 10 days.**

1-SSRIs .cont

Fluoxetine Fluvoxamine Citalopram Sertraline Paroxetine)) :- 1-SSRIs	
Clinical Indications	First choice for most depression. Comparable efficacy as TCAs but much safer < sedation & antimuscarinic side effects < toxicity in over doses Fluoxetine is approved in children, adolescence, elderly males with prostatic hypertrophy & relatively safe in pregnancy. Used in : 1-Anxiety and panic disorders 2-Obsessive-compulsive disorders 3-Some eating disorders (bulimia) 4-pain associated with diabetic neuropathy 5-premature ejaculation 6-premenstrual syndrome. 7-alcohol abuse. 8-Anorexia nervosa. 9-Generalized anxiety disorder (GAD). ""anorexia nervosa have extreme weight loss as a result of very strict dieting. In spite of this, they believe they are fat "bulimia:An eating disorder characterized by binge eating and inappropriate compensatory behavior, such as vomiting
ADRs	1-insomnia, anxiety, agitation, nervousness > fluoxetine > citalopram useful in fatigued patients 1- 2-sedation & lassitude > paroxetine, sertraline useful in patients with difficult sleep . 3-GIT upset (nausea, vomiting, diarrhea) (indirect stimulation of 5-HT3 receptors in the enteric nervous system) 4-Anorexia & weight loss 5-Impotence & sexual dysfunction; loss libido, delayed ejaculation (Indirect CNS stimulation of 5-HT2) useful in patients who have premature ejaculation. 6-Mild CV & minimal antimuscarinc side effects unlike TCAs (not important) 7-Withdrawal manifestation < intensity than TCAs
Interactions	1-Serotonin Syndrome :- if combined with MAOIs > other ADDs [Autonomic instability (changes in BP, pulse, hyperthermia), muscle rigidity, respiratory depression, mental confusion, shivering, sweating and diarrhea] 2-Enzyme inhibitors :- ↓metabolism = ↑toxicity of TCA, neuroleptic, some antiarrhythmic, β-blockers.

محل أسألة أي واحد اعطيه المريض بالليل واي واحد اعطيه المريض بالصبح

How does SSRIs decrease the appetite ?
By acting on 5-ht2

She might ask here
Patient came with muscle rigidity and hyperthermia
Which one of the following drugs could be the cause

Slides Important Doctor's Notes Explanation

Reuptake Inhibitors& Mixed Action Novel Adds

Serotonin Norepinephrine Reuptake Inhibitors [SNRIs] (Venalafaxine)	Norepinephrine Reuptake Inhibitors [NRIs] (Reboxetine)	Noradrenergic & Specific Serotonergic Antidepressants [NaSSAs] (Mirtazapine)	Norepinephrine Dopamine Reuptake Inhibitors (NDRIs) (Bupropion)
Restore the levels of NE & 5HT in the synaptic cleft by binding to NET & SERT Has mild antimuscarinic effect Short t1/2 =increase HR & BP Side effects similar to SSRI drugs but may be withdrawal manifestations on discontin-uation = may need dosage tapering	Block only NET No affinity for 5HT, DA, ADR, H, mAch receptors So, has positive effects on the concentration and motivation in particular. Safe to combine with SSRIs Minimal side effects only related to activation of ADR system as tremor, tachycardia, and urinary hesitancy	Blocks presynaptic a2 adrenoceptors + 5HT3 > 5HT2 receptors Preferred in cancer patients because: 1. Improves appetite 2- decrease nausea & vomiting (5-HT3 blocking) 3- increase body weight 4- Sedation (potent antihistaminic) 5- Less sexual dysfunction (5-HT2 blocking) 6- Has no anti-muscarinic effect . Side effects; drowsiness, gain appetite, and weight gain. 1-Ideal drug for cancer patient Important 2-it is not uptake inhibitor	Is unique in possessing significant potency as NE and DA reuptake inhibitor, with no direct action on 5HT. Acts as a nAch antagonist Therapeutic uses: 1- Treatment of major depression and bipolar depression. 2- Can be used for smoking cessation. As it reduces the severity of nicotine craving & withdrawal symptoms Advantages: No sexual dysfunction =given in young No weight gain [No 5HT effect] No orthostatic hypotension. Side effects: Seizures; it ☐ threshold of neuronal firing Ideal drug for Young patient Important DA=dopamine

Serotonin Antagonists & Reuptake Inhibitors (SARIs)

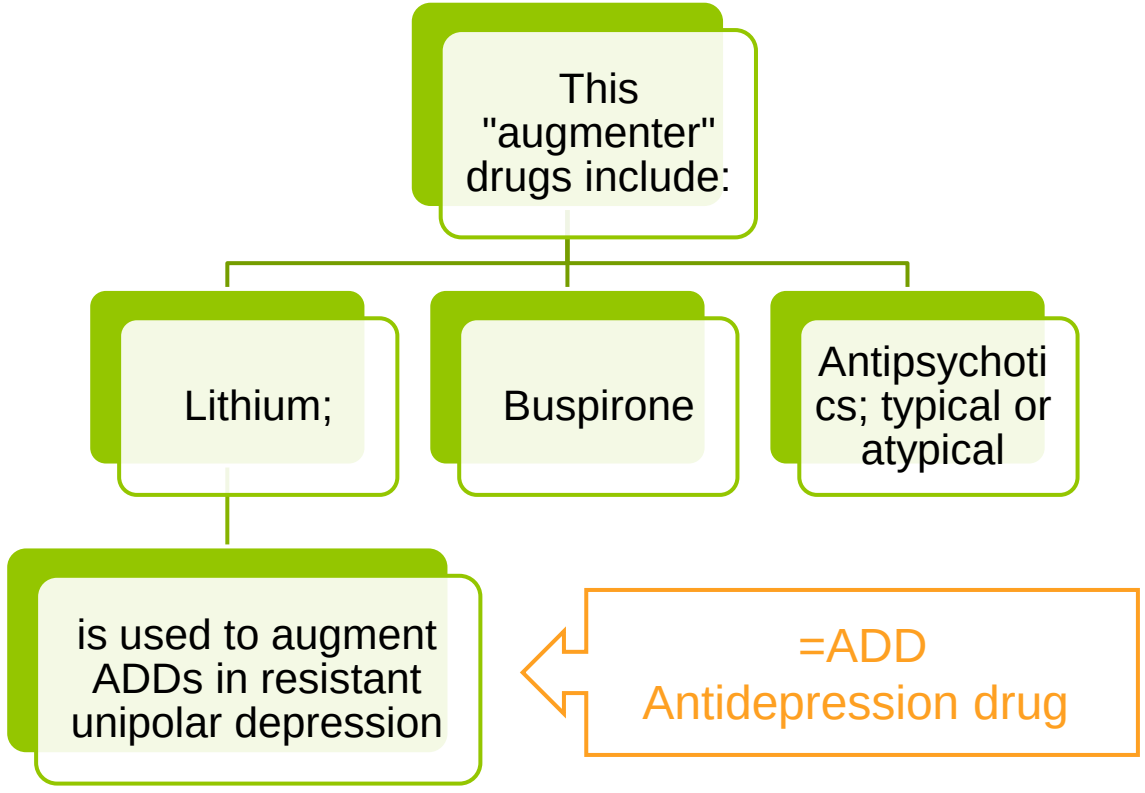
Trazodone	Nafazodone
Psychtropic drug	**Trazodone is its precursor**
Weak block of SERT > NE Block 5-HT2	
α- blocking effect (hypotension)	No
Potent H1- blocker(sedation)	**No**
High protein bound Extensive hepatic metab	**Inhibit Cyt450**
Urine excretion Cause **priapism** (a antagonisim) **Arrythmogenic**	**"Hepatic failure**

Nothing here is imortant exept priapism

Priapism: is a potentially painful medical condition, in which the erect penis does not return to its flaccid state, despite the absence of both physical and psychological stimulation
Potential complications include ischemia
ischemia may result in gangrene, which could necessitate penis removal.

Augmenter drugs

- Some antidepressants work better in some patients when used in combination with another drug.



Trazadone, Nafazodone, Bupropion are sometimes included among augmenters but there use as such should be under strict clinical supervision

SUMMARY

1- Antidepressants when block other postsynaptic receptors can confer side effects.
Such receptors include mainly histaminergic [H1], muscarinic, [a1]-adrenergic.

- Histaminergic antagonism has been associated with sedation and drowsiness. Can contribute to increased appetite & weight gain.
- Muscarinic-receptor antagonism is responsible for gastrointestinal disturbances; constipation, dry mouth, tachycardia, blurred vision, urine retention
- Block of the [a1]-adrenergic receptor may be responsible for dizziness and orthostatic hypotension

2- Antidepressants increase variably the availability of 5HT & NE at synapes

- Increased NE transmission tremors, insomnia.
- Increased 5HT transmission sedation, and a decrease in sexual drive.

3- Antidepressants & sexual dysfunction?

Through acting on 5HT2 → sexual dysfunction (loss of sexual desire and impaired sexual response (ejaculatory delay, erectile dysfunction, anorgasmia)

ADDs with 5HT2 blocking action as mirtazipine, has minimal action on sexual dysfunction.

With > NE than 5HT as Bupropion , have minimal sexual side effects

Trazodone, nafazodone, With dual action are better than SSRIs with respect to sexual side effects

SUMMARY

4- Antidepressants & Sedation

- Sedating ADDs are; Amitryptyline, Paroxiteine, Sertraline, Mirtazapine, Trazadone, So better given near bed time
- Less Sedating ADDs are; Bupropion, Venalafoxine , MOAIs, So can be given in the morning as some cause insomnia as side

effect.

5- Antidepressants and appetite???

DA is responsible for eating. 5HT action on 5HT2 halts dopamine release so suppress appetite.

Depression is accompanied more by weight loss.

SSRIs by ↑ 5HT availability to act on 5HT2 could suppress appetite. At least no weight gain with SSRIs.

Most TCAs have dual reuptake inhibition + sedation + antihistaminic effects ↑ weight gain

Mirtazepine blocks 5HT2 so cannot shut off dopamine signals ↑ weight gain

N.B. Antidepressants isn't always a direct cause to cause alteration in weight. Other contributing factors to weight gain during

antidepressant therapy are for example: ↑ day time sleep, ↑ craving for food when mood alleviates,

Nausa & Vomiting by SSRIs ↑ 5HT availability act on 5HT3 nausea & vomiting

SUMMARY

6- Antidepressants safe combinations;

- Bupropion + Desipramine
- SSRIs + Mertazepine, Reboxetine or any other NRIs / SNRIs/
- Antidepressant approved for use in children; fluoxetine
- Antidepressants good for elderly are SSRIs because they can be used at lower dosage giving least side effects in this age group
- SSRIs use is more than TCAs because they are better tolerated by patients
- Antidepressants dangerous combinations;

MAO Is + SSRIs Serotonin syndrome

Paroxetine / Fluoxetine / Nefazodone / + Desipramine, Nortryptiline severe sedation or > toxicity

7- Others:

Enuresis Imipramine

Chronic pain TCAs (Tertiary better than 2ndry amines) Duloxetine(SSRIs not effective)

Bulimia Fluoxetine

Obsessive convulsive disorder SSRIs

Cancer associated depression Mirtazapine

Depression in Adolescence and young adults Bupropion.

Depressive phase of bipolar add? Lamotrigine (anticonvulsant) or lithium.

QUESTIONS

1) Which ONE of the following antidepressant Drug can be given in depressed patient having difficulty to sleep?

a) Fluoxetine

b) Fluvoxamine

c) Citalopram

d) Paroxetine

2) 73-year old Depressed Cachectic suffering from end-stage of cancer, which ONE of the following antidepressants can be

prescribed in his condition?

a) Fluoxetine

b) Paroxetine

c) Imipramine

d) Mirtazapine

3) Which of the Following SSRIs has the longest half-life?

a) Fluoxetine

b) Fluvoxamine

c) Citalopram

d) Paroxetine

4) A 27 year old married male smoker suffers from major depression disorder, he also wants to quit smoking, Which ONE of the

following Anti-depressants is the best for his case:

a) Fluoxetine

b) Buspirone

c) Bupropion

d) Amitriptyline

QUESTIONS

5- Which of the following drugs cause priapism ? (very imp.)

a) Fluoxetine

b) Trazodone

c) Bupropion

d) Amitriptyline

ANSWERS: 1-D , 2-D , 3-A , 4-C , 5-B

THE END

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