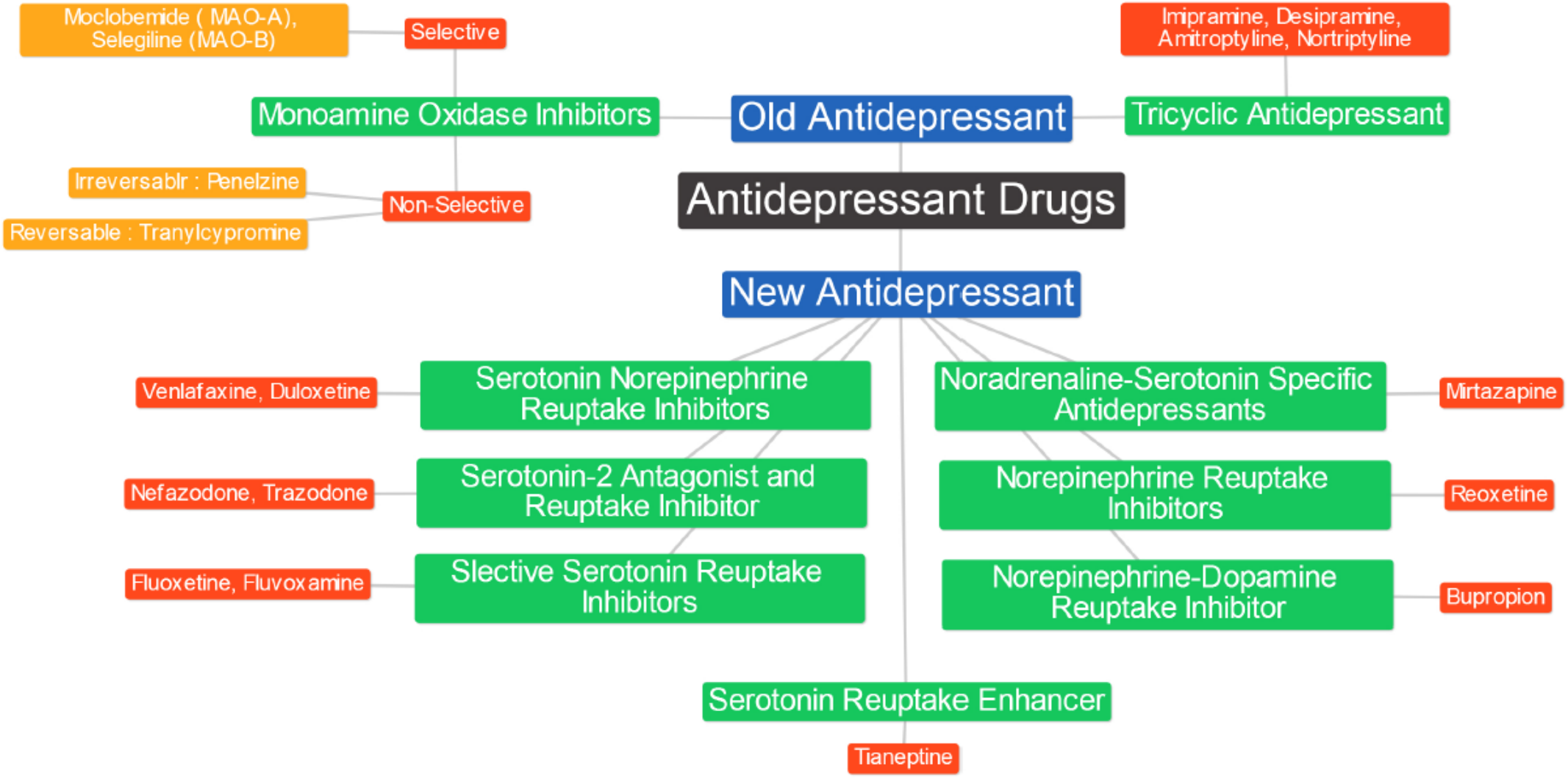
Lecture 8-11

Drugs used in depression Old & New

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.

- Additional Notes
- Important


Antidepressant Drugs
Old Antidepressant
Monoamine Oxidase Inhibitors
Moclobemide (MAO-A), Selegiline (MAO-B)
Selective
Non-Selective
Irreversablr : Penelzine
Reversable : Tranylcypromine
Tricyclic Antidepressant
Imipramine, Desipramine, Amitroptyline, Nortriptyline
New Antidepressant
Serotonin Norepinephrine Reuptake Inhibitors
Venlafaxine, Duloxetine
Serotonin-2 Antagonist and Reuptake Inhibitor
Nefazodone, Trazodone
Slective Serotonin Reuptake Inhibitors
Fluoxetine, Fluvoxamine
Noradrenaline-Serotonin Specific Antidepressants
Mirtazapine
Norepinephrine Reuptake Inhibitors
Reoxetine
Norepinephrine-Dopamine Reuptake Inhibitor
Bupropion
Serotonin Reuptake Enhancer
Tianeptine

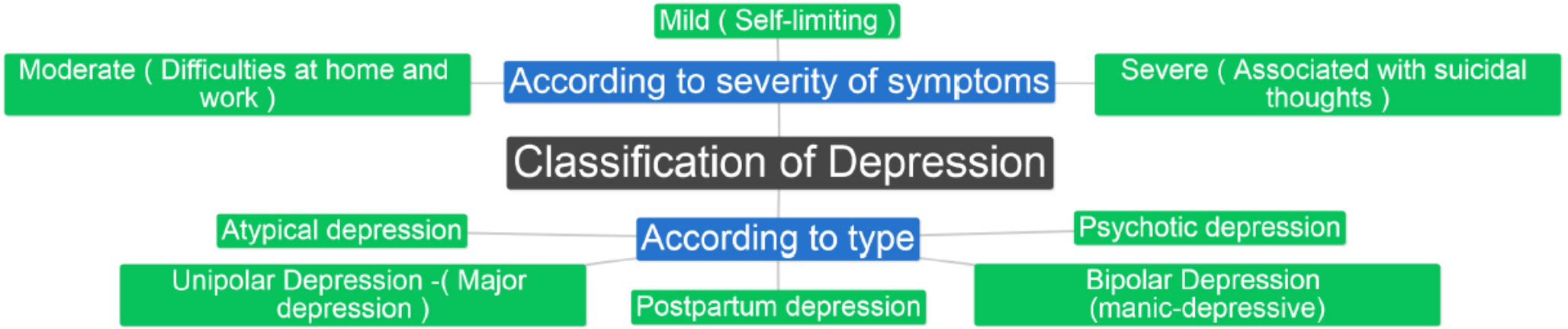
Mind Map

Depression

Depression : is a very common psychiatric disorder that is related to the mood

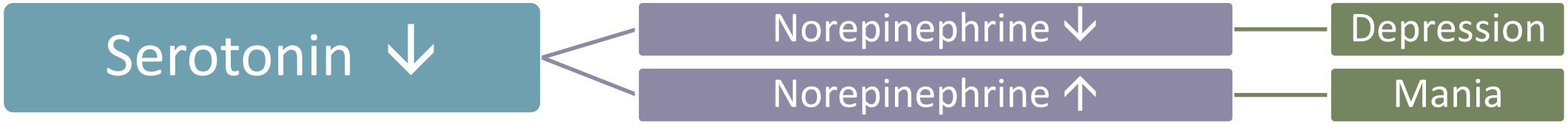
Changes in mood are associated with depression and/or mania. (disturbance of mood)

Incidence of depression : affect at least 20% of the population at some period in their lifetime.



Symptoms of Depression	Symptoms of mania
Loss of energy and interest	A high energy level with decreased need for sleep
Decreased or increased sleeping or appetite.	Extreme irritability
Feelings of worthlessness.	Rapid, unpredictable emotional changes
Recurring thoughts about death and suicide.	Unwarranted or exaggerated belief in one's own ability

Biochemical theory affective disorder



What is the evidence to support this theory ?

Amphetamine Ass with mania while reserpine and methyldopa produce depression.

Pathophysiology of depression

Neurotransmitter Imbalances & Dysregulation → Creates a state of deficiency in monoamines

- **5-HT deficiency** may cause the sleep problems, irritability and anxiety associated with depression.
- **Decreased level of NE,** which regulates mood. alertness, arousal, appetite, reward & drives, may contribute to the fatigue and depressed mood of the illness.
- **Dopamine** is important for pleasure, sex & psychomotor activity.

- Drugs used to treat depression increase the level of these neurotransmitters

Antidepressants

Antidepressants do not act immediately (show clinical effects after 3 weeks) indicating that secondary adaptive changes. The most consistent adaptive change seen with antidepressant drugs is the down regulation of beta, alpa-2 and 5-HT2 receptors.

ANTI-DEPRESSANTS GROUPS

Old Antidepressants	
Tricyclics (TCAs)	Imipramine, Desipramine, Clomipramine, Amitriptyline, Nortriptyline, Protriptyline , Doxepin, Trimipramine
Tetracyclics	Amoxapine, Maprotiline.
Monoamine Oxidase Inhibitors (MAOIs)	Tranylcypramine, Phenelzine, Moclobemide
New Antidepressants	
Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine, Fluvoxamine, Citalopram, Sertraline, Paroxetine, Escitralopram
Serotonin and Norepinephrine Reuptake Inhibitor (SNRI)	Venlafaxine, Duloxetine
Serotonin-2 Antagonist and Reuptake Inhibitors (SARIs)	Nefazodone, Trazodone
Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)	Bupropion
Noradrenergic and Specific Serotonergic Antidepressant (NaSSAs)	Mirtazapine
Noradrenaline Reuptake Inhibitor (NRI)	Reboxetine
Serotonin Reuptake Enhancer	Tianeptine

Old antidepressants

TRICYCLIC ANTIDEPRESSANTS (TCAs) the oldest class of antidepressant drugs with three- ring nucleus

Name	imipramine	amitryptyline	clomipramine	desipramine	nortriptyline
	More potent on 5-TH reuptake pump			more potent on NE reuptake pump	
MOA	• block reuptake pumps for both 5HT and NE in nerve terminals by competing for binding site of the transport protein. So ↑ conc. of NE & serotonin in the synaptic cleft & at the receptor site				
PA	Elevate mood, Improve mental alertness, Increase physical activity, In non-depressed patients sedation, confusion & motor incoordination				
PK	**Peak levels:** 2-6 hours. Are "lipophilic" in nature, well absorbed in GIT & cross the BBB. **Elimination**: hepatic oxidation. Metabolized in the liver by demethylation (Imipramine to Desipramine, Amitriptyline to Nortriptyline) & by hydroxylation >metabolites that retain the biological activity of the parent compounds.				
ADEs	TCAs block: (α1 adrenergic receptors , H1 histamines receptors , M1 cholinergic receptors , 5HT2 receptors) 1. Anti-histamine: Sedation, confusion 2. Anti-Adrenergic: Cardiovascular effects (Tachycardia and hypotension) 3. Anti-cholinergic: Dry mouth, constipation, urinary retention 4. Weight gain 5. Seizure 6. Hypomania 7. sexual dysfunction & impotence • TCAs have narrow therapeutic index >toxicity can develop; excitement, delirium , convulsions, respiratory depression, coma, atropine like- effects, cardiac arrhythmias, sudden death • TCAs are highly protein bound and have a large volume of distribution therefore hemodialysis is not effective for Rx of TCA toxicity.				

Old antidepressants

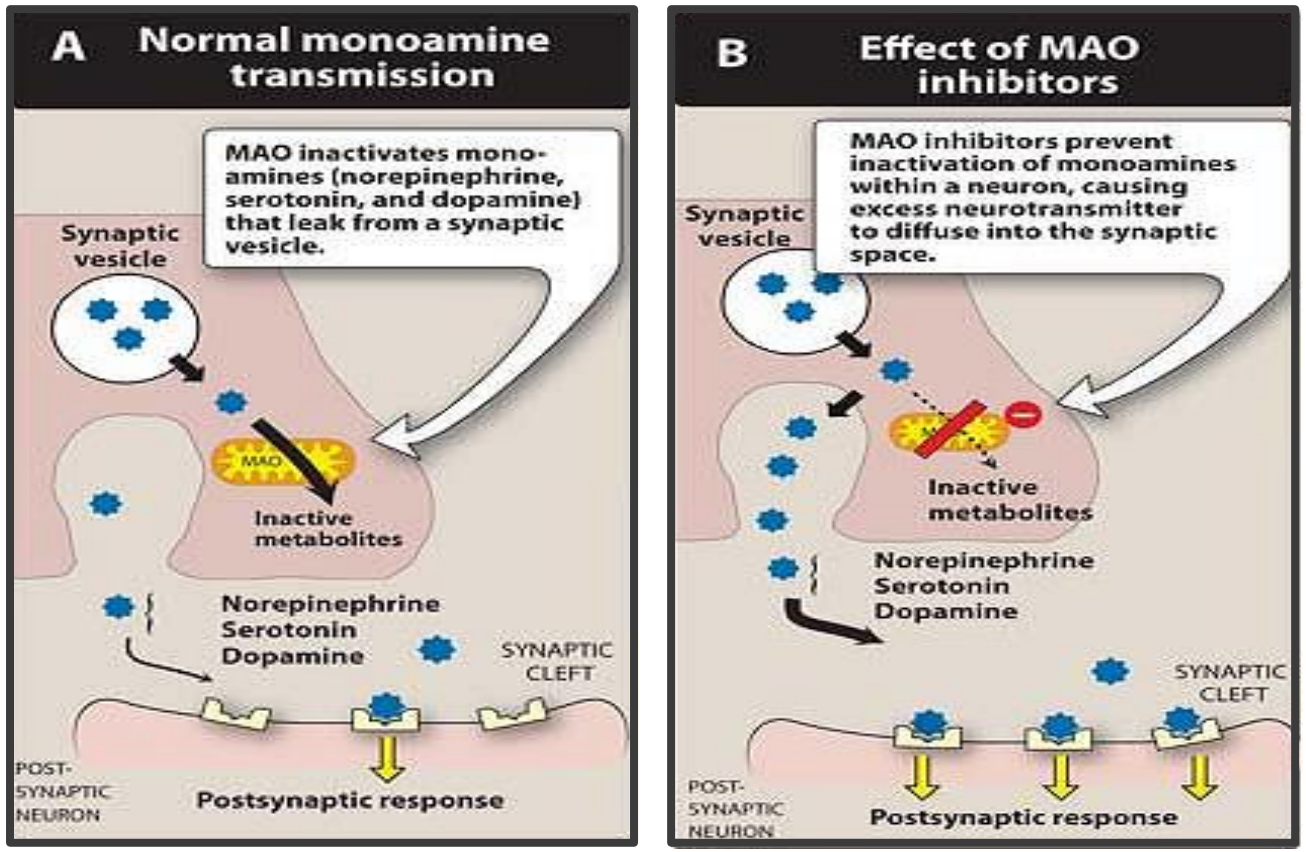
TRICYCLIC ANTIDEPRESSANTS (TCAs) the oldest class of antidepressant drugs with three- ring nucleus

D.I	• because the are strongly bound to plasma protein their effect can be increased by drugs that compete for their plasma protein binding site like (Aspirin and Phenylbutazone). • They are metabolized by liver microsomal enzymes, therefore their effect can be reduced by inducers of liver microsomal enzymes (Barbiturates), or potentiated by inhibitors of liver microsomal enzymes (Oral contraceptives, Antipsychotics, and SSRIs).
Uses	• Endogenous (Major) Depression moderate to severe. • Panic attack /acute episode of anxiety. • Imipramine is used for treatment of nocturnal enuresis in children and geriatric patients as it constricts internal urethral sphincter (anti-muscarinic effect). • Generalized Anxiety Disorder (GAD). • Obsessive Compulsive Disorder (OCD) • Attention Deficit Hyperkinetic Disorder (ADHD). • Chronic neuropathic pains or unexplained body pains.
C.I	• TCAs should not be used in patients with Glaucoma or with enlarged prostate because of their atropine-like action. • TCAs (given alone) are contraindicated in manic-depressive illness, because they tend to "switch" the depressed patient to the "manic" phase, therefore, they should be combined with "lithium salts". • -Seizure disorders

What is monoamine oxidase?

MAO is a mitochondrial enzyme found in nearly all tissues and they exist in two forms :

1. MAO-A responsible for NE, 5-HT metabolism. It also metabolizes tyramine of ingested food.
2. MAO-B is more selective for dopamine metabolism



Important

- cheese reaction This occurs when Tyramine rich foods are taken with MAOIs.
- Tyramine in food is normally degraded in the in the gut by MAO-A.
- Since the enzyme is inhibited by MAOIs, tyramine from ingested food is absorbed, and then taken up into adrenergic neurons where it is converted into octopamine - a false transmitter which causes massive release of NE and may result in hypertensive crisis ; severe hypertension, severe headache and fatal intracranial haemorrhage
- Note : Moclobemide has No cheese reaction occurs with its use.

Monoamine Oxidase

Old antidepressants

Monoamine Oxidase Inhibitors (MAOIs)

Name	Phenelzine	Tranylcypromine	Moclobemide	Selegiline
	Non Selective Inhibitors		Selective Inhibitors	
type	Irreversible long acting	Reversible	(MAO-A) Short acting	(MAO-B) treatment of Parkinsonism
Uses	Only used for refractory cases and in atypical depression where phobia and anxiety are prominent symptoms. limited uses because: • they have high adverse effect reactions (food and drug interactions.) • low antidepressant efficacy = Low benefit/risk ratio.			
ADRS	Anti-muscarinic effects, Postural hypotension, Sedation, sleep disturbance, Weight gain			
Specific ADRS	• Sexual Dysfunction • Hepatotoxicity	------	------	-----
D.I	1- Pethidine: MAOIs interact with the opioid receptor agonist (pethidine) which may cause severe hyperpyrexia, restlessness, coma, hypotension. The mechanism still unclear – but it is likely that an abnormal pethidine metabolite is produced because of inhibition of normal demethylation pathway. 2- Levodopa: Precursor of dopamine can interact with MAOIs leading to hypertensive crisis. 3- Amphetamine and Ephedrine: Indirectly acting sympathomimetics can interact with MAOIs causing the liberation of accumulated monoamines in neuronal terminals leading to hypertensive crisis. (so much NE) 4-TCAs (inhibitors of monoamine reuptake) can interact with MAOIs (inhibitors of monoamine degradation) leading to hypertensive crisis. (so much NE) 5- MAOIs & SSRIs:Serotonin syndrome			

New antidepressants

Selective Serotonin Reuptake Inhibitors (SSRIs) 1st Choice

Name	Fluoxetine	Fluvoxamine	Citalopram	Escitalopram	Setraline	Paroxetine
MOA	• Binds to SERT → ↑ 5-HT levels in synapse • No effect on NET • No block to mAch, H, or a_1 Adrenoceptor → so no antimuscarinic nor sedative effects Except Paroxetine. • They are nearly of comparable efficacy but of preferential response in each individual					
Advantages	1) The most commonly prescribed antidepressants. 2) lacks of CVS and anticholinergic side effects compared to TCA. 3) They do not have cheese reaction as MAOI . 4) Safer (low risk of overdose) . 5) Acute toxicity is less than MOAI or TCA .					
PK	• **t1/2 :** 1) Too long (3-11 days) → Fluoxetine (Prozac). 2) Moderate length (24hr) → Sertraline, Paroxetine, Citalopram. • **Metabolism :** inhibit cytochrome P450 enzymes then conjugation - weak inhibitors (sertraline, citalopram) → ↓ interaction . - Strong inhibitors (Fluoxetine, parpxetine) → ↓ metabolism of TCA, neuroleptic, some antiarrhythmic ,B-blockers. • **Fluoxetine differs from others members of this class in:** It has a longer t1/2 (50hrs), Available as sustained release preparations → once weekly, Metabolite norfluoxetine = potent as parent drug t1/2 10 days.					
Uses	• Same as for TCA, in addition effective in the following conditions : 1) Depression. 2) Anxiety Disorder. 3) Eating disorders- bulimia nervosa" vomiting food" (fluoxetine), Anorexia nervosa . 4) Post traumatic stress disorder. 5) Premenstrual dysphonic disorder. 6) Attention Deficit Hyperkinetic Disorder. 7) Treatment of premature ejaculation (via stim of 5-HT2A).					

New antidepressants

Selective Serotonin Reuptake Inhibitors (SSRIs) 1st Choice

Side Effects

- GIT symptoms: Nausea vomiting (due to 5-HT3 stimulation) & diarrhea.
- Changes in appetite (5-HT3) - weight loss
- Sleep disturbances: Drowsiness with Fluvoxamine.
- Anxiety & Tremors.
- Sexual dysfunction (The most drugs): Loss of libido, delayed ejaculation (stimulation of 5-HT2A).

Discontinuation syndrome:

Symptoms are headache ,malaise & flu like symptoms, agitation , irritability & nervousness.

D.I

- SSRIs are potent inhibitors of liver microsomal enzymes.
  Therefore they should not be used in combination with TCAs
  - because they can inhibit their metabolism increasing their toxicity.

- SSRIs should not be used in combination with MAOIs
  - because of the risk of life-threatening "serotonin syndrome"
    (tremors, hyperthermia, cardiovascular collapse and death).
  - Both drugs require a washout "period without drugs" period of 6 weeks before the administration of the other.

New antidepressants

Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)

Mirtazapine

- Alpha 2 antagonist.
- ↑ NE & 5HT.
- Block 5HT2A & $5HT_3$ → ↓ ADRs of Anxiety & sexual dysfunction.
- Block 5HT2C & H1 receptors → sedation & weight gain.
- Use In cancer patient b/c:-
  1) Improve appetite.
  2) ↓ Nausea & vomiting ($5HT_3$ blockers).
  3) ↑ Body weight.
  4) Sedation. (Potent antihistamine).
  5) Less sexual dysfunction (5HT2A blockers)
  6) No anti-muscarinic effect.

Serotonin-2A Antagonist and Reuptake Inhibitors (SARI)

Trazodone & Nefazodone

- Block 5HT uptake "selective"
- 5HT2A antagonist → stimulate 5HT1A help to reduce depression.
- 5HT2A antagonism ↓ anxiety & sexual dysfunction & sedation.
- Nefazodone → has less sedative effect & doesn't block Alpha receptors.
- Inhibit P450 3A4 isoenzyme. like SSRI

Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

Venlafaxine "Effexor"

- For mainly depression, generalized & social anxiety disorder
- Selective 5HT & NE uptake blockers.
- Similar to TCAs but more selective
- Desyenlafaxine → metabolite of Venalavaxine.

Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)

Bupropion

- NE & DA reuptake inhibitors with no direct action on 5HT.
- use for 1) Depression & bipolar depression 2) Smoking cessation.
- Advantages :-
  1) No sexual dysfunction.
  2) No weight gain.(no 5HT effect).
  3) No orthostatic hypotension.
- ADRs → seizure, by lowering the threshold of neuronal firing.

NE Selective Reuptake Inhibitors (NRIs)

Reboxetine

- Block only NE.
- Safe combination with SSRIs.
- ADRs :-
  1) Tremor.
  2) Tachycardia.
  3) Urinary hesitancy called urinary retention.

Clinical uses of antidepressants

Endogenous depression	SSRIs (1st choice) , Tricyclic
Panic disorder	SSRIs , Imipramine
Obsessive compulsive disorder	SSRIs , Clomipramine , Amitriptyline (chronic pain)
Anorexia nervosa & Bulimia	SSRIs
Schizoaffective disorders	SSRIs , Amoxapine , Haloperidol
Premature ejaculation	SSRIs
Anxiety disorders	Amitriptyline
Migraine & Anxiety & IBS “Irritable bowel syndrome”	Amitriptyline
Nocturnal Enuresis in children “Bedwetting”	Imipramine
Neuropathic pain	NE & 5HT reuptake Blockers

Summary

Old antidepressants

Drugs	TCA's	MAOI
MOA	Block reuptake pumps for 5HT and NE. With variable potency depending on drug.	Inhibits MAO which is responsible for NE, and 5-HT catabolism
Uses	• Endogenous Depression • Panic Attacks • GAD, OCD, ADHD • Chronic neuropathic pain • Imipramine→ Nocturnal Enuresis	Refractory cases Atypical depression
ADEs	Anti-cholinergic effects (M1), Anti-histaminic effects (H1) Anti-adrenergic effects (a1), Weight gain, sexual dysfunction & impotence, Lower seizure threshold	Antimuscarinic effects, Postural hypotension, Sexual dysfunction (phenelzine.), Sedation, sleep disturbance. Weight gain, Hepatotoxicity (phenelzine).
C.I	Glaucoma, Enlarged Prostate, Monotherapy in manic-depressive illness, Seizure disorders	------
D.I	• Aspirin, and Phenylbutazone (compete for plasma protein binding site) • Barbiturates (Reduce effect) • Oral contraceptives, antipsychotics, SSRI (potentiate effect) • MAOI (Hypertensive crisis)	• Pethidine (severe hyperpyrexia, coma, hypotension) • Levodopa, amphetamines, Ephedrine, and TCAs(Hypertensive crisis) • SSRI (serotonin syndrome)
Note	Lipophilic, Narrow therapeutic index	Cheese reaction: (MAOI + food containing tyramine → false neurotransmitter → Hypertensive crisis)

Summary

Monoamine Oxidase Inhibitors (MAOIs)

Drugs	Mechanism	Indication	ADR	Extra info.
SSRI	• Inhibits 5-HT reuptake transporter	• Anxiety disorders, • Bulimia nervosa • Anorexia nervosa • PTSD • ADHD • Premenstrual dysphoric disorder • Premature ejaculation	• GIT symptoms (5-HT3 stimulation) • Drowsiness (by fluvoxamine) • Loss of libido, delayed ejaculation. (5-HT2A stimulation)	• Most common antidepressant • TCA (potentiate effect. "increase toxicity') • MAOI (Serotonin syndrome)
NaSSA	• Blocks presynaptic α2 • Blocks 5-HT3>5-HT2A	Preferred in cancer patients because:- a) Improves appetite b) Reduces nausea and vomiting c) Less sexual dysfunction d) No anti-muscarinic effect	• Drowsiness • Weight gain	-
SARI	• 5-HT reuptake inhibitor • 5-HT2A antagonist	-	-	-
SNRIs	• Selective 5-HT and NE reuptake inhibitors	• Depression • Generalized anxiety disorders • Social anxiety disorder	-	Without α1, M1 cholinergic or H receptor blocking properties
NDRI	• NE and DA reuptake inhibitor	• Major depression • Bipolar depression • Smoking cessation	Seizures	• No sexual dysfunction → given in young • No weight gain [No 5HT] • No orthostatic hypotension
NRIs	• NE reuptake inhibitor	-	Limited to ADR system; Seizures, tachycardia, and urinary hesitancy.	Safe to combine with SSRI

1. **Which one of these drugs has height potency for inhabit of NE reuptake pump?**
   A. Clomprine
   B. Imipramine
   C. Desipramie
   D. Amitryptim

2. **Which one of these drug are uesed in case of nocturnal enuresis in childern ?**
   A. Desipramie
   B. Imipramine
   C. Clormpramie
   D. Nortiyine

3. **Which one of these drugs are irrevesbal non-selective MOAI's ?**
   A. Phenezline
   B. Selegiline
   C. Tranlycyrpromine
   D. Mcrolbemide

4. **Which one of these MOAI's lead to hapetoxity ?**
   A. Phenezline.
   B. Selegiline
   C. Mcrolbemide.
   D. Tranlycyrpromine

5. **Epileptic person has done dignoss with moderate depression which one of these drugs is should not give to him?**
   A. Anti-psychotic.
   B. SSRI's
   C. TCA
   D. MOAI

Answers: 1. C 2. B 3. A 4. A 5. C

MCQs

6. **Which one of these drugs doesn't have cheese reaction?**
   A. Mcroblobemide.
   B. Phenezline
   C. Trancypromie.
   D. Isocarboxized

7. **Reaction of L-Dopa with MOAI's result into ?**
   A. Hypertensive Crisis
   B. Hypotension
   C. Hyperpryexia.
   D. Coma

8. **Which one of these compand lead to serotonin syndrome?**
   A. MOAI's – L-Dopa
   B. MOAI's – SSRI.
   C. MOAI's – phthidine.
   D. MOAI's – TCA

9. **Which one of the following drugs is Preferred in cancer patients?**
   A. Mirtazapine
   B. Venlafaxine
   C. Bupropion
   D. Nefazodone

10. **Which one of the following drugs can be used for smoking cessation?**
    A. Mirtazapine
    B. Bupropion
    C. Sertraline
    D. Fluvoxamine

Answers: 6. A 7. A 8. B 9. A 10. B

MCQs

What is the most widely using class of antidepressants in clinical practice currently?

Selective Serotonin Reuptake Inhibitors

1. How its work?
   - They act within the brain to increase the level of serotonin (5-HT) in the synaptic gap by inhibiting its re-uptake.

2. Named two of them?
   - Fluoxetine.
   - Fluvoxamine.

SAQs

Good luck!

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