

OVERVIEW OF ANTI-DEPRESSANTS:

- Antidepressant drugs are drugs used to treat the mental condition of depression
- Antidepressants do not reverse the effects of depressant drugs (ex// alcohol, barbiturates and narcotics)
- Antidepressant drugs act on monoaminergic synaptic transmission in the brain

OVERVIEW OF PRESYNAPTIC AND POSTSYNAPTIC MONOAMINERGIC RECEPTORS:

NORADRENERGIC NEURONS:

- NE receptors:
 - Presynaptic α_2 autoreceptor
 - Terminal or somatodendritic
 - Inhibits NE release = protective brake for NE neuron from excessive NT release
 - Postsynaptic $\alpha_1, \alpha_2, \beta_1$ adrenergic receptors
- NE inactivation occurs in:
 - Synaptic cleft via:
 - NE re-uptake transporter pump
 - Enzymatic degradation via COMT
 - Presynaptic terminal via:
 - Monoamine oxidase (MOA)

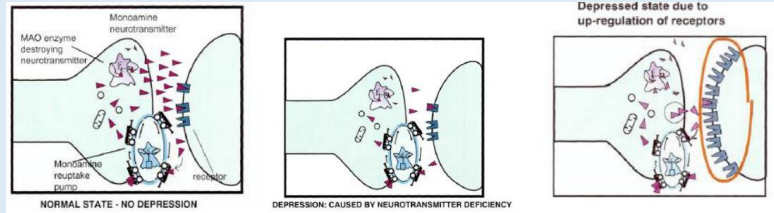
SEROTINERGIC NEURONS:

- >25 5-HT receptors; following are important for MOA of anti-depressants:
 - **5HT_{1D}** and **5HT_{1B}** autoreceptors on presynaptic axon terminal
 - Inhibits NT release when agonized
 - **5-HT_{1A}** autoreceptors located on somatodendritic sites
 - Inhibits spike genesis and transmission
 - **5-HT_{2A}** receptors located postsynaptically
 - Produces APs & postsynaptic excitation (via G-proteins and 2nd msgers)
- 5-HT inactivation occurs in:
 - Synaptic cleft via presynaptic transport pump selective for 5-HT
 - Presynaptic terminal via MAO which metabolizes 5-HT to an inactive metabolite

DOPAMINERGIC NEURONS:

- DA receptors: at least 5 subtypes
 - **D₂** receptor is stimulated by DA agonists for treatment of PD and blocked by dopamine antagonists for treatment of schizophrenia
- DA inactivation occurs in:
 - Synaptic cleft via:
 - DA reuptake transporter pump
 - COMT
 - Presynaptic terminal via:
 - Monoamine oxidase (MOA)

BIOGENIC AMINE THEORY OF DEPRESSION: more described in Lecture 1



- Normal state: releases a neurotransmitter (NE or 5-HT) at a normal rate
 - Regulatory elements of neuron is also normal:
 - Functioning of enzyme MOA (destroys NE or 5-HT)
 - NE reuptake pump(s) which terminate action of NE (or 5-HT)
 - Receptors which react to release of NE (or 5-HT)
- Monoamine Hypothesis: neurotransmitter NE (or 5-HT) is depleted → NT deficiency
 - “Depressed” monoaminergic synapse up-regulates postsynaptic receptors

TRICYCLIC ANTIDEPRESSANTS:

MECHANISM OF ACTION:

1. Blocks the neuronal uptake of the biogenic amines 5-HT and/or NA:

Tertiary amines	Secondary amines
Preferentially block uptake of 5-HT	Preferentially block uptake of NA
Imipramine (Tofranil)	-----> Desipramine (Pertofrane)
Amitriptyline (Elavil)	-----> Nortriptyline (Aventyl)
Trimipramine (Surmontil)	-----> Protrityline (Triptil)
Clomipramine (Anafranil)	
Doxepine (Sinequan)	

DOUBTS ON THIS MECHANISM :

- TCAs rapidly block the uptake (latency to effect : hours) yet the drugs must generally be administered for 2 weeks or more for a clinical improvement in depressed mood to be seen
- Atypical antidepressants (trazodone, iprin/dole, mianserin) , which don't block biogenic amine uptake, are effective clinically as antidepressants

2. Down-regulation of 5-HT receptors in the brain:

- Consequence of long-lasting blockade of reuptake pump by a TCA is to cause the previously up-regulated postsynaptic NT receptors to become desensitized or down-regulated
 - Same outcome as with long-lasting blockade of MAO with MAOIs
- Down-regulation seems to correlate better in time with the clinical antidepressant effects of TCA, MAOI, atypical ADs and electroconvulsive therapy (ECT)

SIDE EFFECTS OF TCAs:

Anticholinergic, muscarinic receptor blockade	<ul style="list-style-type: none"> • Constipation • Blurred vision • Dry mouth • Drowsiness
Most common: amitriptyline > imipramine > doxepin >> desipramine	
α_1 receptor blockade	<ul style="list-style-type: none"> • Dizziness • Orthostatic hypotension • Reflex tachycardia • Drowsiness
H₁ histamine receptor blockade	<ul style="list-style-type: none"> • Weight gain • Drowsiness
Overdose (blocks Na channels)	<ul style="list-style-type: none"> • Cardiac arrhythmias • Seizures
H₁, Ach & adrenergic antagonism	<ul style="list-style-type: none"> • Sedation <ul style="list-style-type: none"> ○ Take majority of daily dose at bedtime
Most common: amitriptyline > trimipramine > doxepin >> 2° amines	
	<ul style="list-style-type: none"> • Conversion to (hypo)mania

OTHER POINTS:

- TCAs do not elevate mood in normal subjects
 - Tend to produce sedation, unpleasant anti-ACh effects and impair the intellect
 - Not reinforcing and considered drugs of abuse
- Most failures in treatment are due to use of inadequate dose, treatment period too short, or non-compliance due to ADRs

DRUG INTERACTIONS: MAOI, guathenidine, clonidine, adrenergics, CNS depressants, agents which bind to plasma protein

ACUTE TOXICITY: OD characterized by hyperpyrexia, arrhythmias, hypertension, delirium, seizures and coma

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)**MECHANISM OF ACTION:**

- Selective in blocking the neuronal uptake of 5-HT = fewer SEs than TCAs
 - **Fluoxetine (Prozac)**, Fluvoxamine (Luvox), Paroxetine (Paxil), Sertraline (Zoloft), Citalopram (Celexa), Escitalopram (Cipralex)
 - Vortioxetine (Trintellix) blocks 5-HT uptake, but is also:
 - Antagonist at 5-HT_{2A}, 5-HT_{1D} and 5-HT₇ receptors
 - Agonist at 5-HT_{1A}
 - Partial agonist at 5-HT_{1B} receptor
- In depression, 5-HT neurons are thought to up-regulate 5-HT pre- & post-synaptic receptors due to deficiency of 5-HT transmission → 5-HT_{1A} autoreceptors are upregulated
 - SSRIs acutely block the 5-HT reuptake pumps increasing 5-HT levels **preferentially in the somatodendritic area** of the serotonin neuron (as opposed to the axon terminals)
- Increased 5-HT in the somatodendritic area of the 5-HT neuron following SSRI administration leads to 5-HT_{1A} receptor down-regulation → **more** 5-HT neuron impulses (spike activity) → more 5-HT release from axon terminals
 - There is a delay in the time for “somatodendritic down-regulation” to occur = SSRI therapy has to be maintained

SIDE EFFECTS:

- Generally, SSRIs are better tolerated than TCAs
 - << anticholinergic, sedation and dizziness
 - >> insomnia, anxiety, agitation
- GI distress: constipation, diarrhea
- Sexual dysfunction

OTHER POINTS:

- 25-30% of depressed patients treated with TCA do not respond
 - Of these, 60-65% respond to SSRI
 - Converse is true
- Dosing can be difficult for certain agents
 - Ex// fluoxetine has an active metabolite (norfluoxetine) with a long t_{1/2} (up to 15 days) → long time to reach steady state making titration of the dose more difficult

DRUG INTERACTIONS:

- MAOI
- CNS depressants (BZDs, opioids, alcohol)
- Other antidepressants → serotonin syndrome

5-HT, NA (and DA) REUPTAKE BLOCKERS (SNRIs):

Desvenlafaxine (Pristiq); venlafaxine (Effexor); duloxetine (Cymbalta); levomilnacipran (Fetzima)*

MECHANISM OF ACTION:

- Inhibits reuptake of 5-HT, NA (dose-dependent)
 - Low doses: SSRI
 - Medium doses: NA uptake blocked
 - Higher doses: similar to bupropion
- Weak, if any, cholinergic or histamine receptor blockade

SIDE EFFECTS:

- Nausea, drowsiness, dizziness, sexual dysfunction, headache, anxiety
- Hypertension (at higher doses)

*** LEVOMILNACIPRAN:**

- Exerts more balanced reuptake inhibitory action of 5-HT and NE
 - This more balanced ratio may = improved effectiveness, but cost of possible increased ADRs
- SEs: nausea, dry mouth, constipation, hyperhidrosis, headache, dizziness, tachycardia, insomnia, erectile dysfunction

NA and DA Reuptake Inhibitors (NDRIs):

Bupropion (Wellbutrin-SR, Zyban)

- Used primarily for the symptoms of DA deficiency in depression (anhedonia, hypersomnia, cognitive slowing, inattention & craving)

MECHANISM OF ACTION:

- Blocks NE and DA re-uptake
 - Blockade of DA uptake > NA uptake
- Metabolite more potent in blocking NE re-uptake than parent compound

SIDE EFFECTS:

- In general, fewer SEs than TCAs or SSRIs
- Insomnia, CNS stimulation, headaches, nausea, seizures
- Less sexual dysfunction compared with SSRIs
- Only marginal weight gain, orthostatic hypotension

RX USES:

- Good substitute for pts with SSRI-induced sexual dysfunction
- Also used in ADHD and treatment of smoking cessation

5-HT_{2A} ANTAGONIST & 5-HT REUPTAKE INHIBITOR (SARIs): Trazodone (Desyrel)**MECHANISM OF ACTION:**

- Potent blocker of 5-HT_{2A} receptors
 - Reduces anxiety, insomnia and myoclonus
- Moderate 5-HT reuptake blocker, but less than TCAs or SSRIs
- Also blocks α receptors & histamine receptors
- Little or no ability to block NE reuptake

SIDE EFFECTS: orthostatic hypotension, sedation

5-HT MODULATOR AND STIMULATOR: Vortioxetine (Brin/Trin -tellix)**MECHANISM OF ACTION:**

- Inhibits 5-HT reuptake
- 5-HT_{1B} partial agonist
- 5-HT₃, 5-HT₇ & 5-HT_{1D} antagonist

METABOLISM: CYP450

(CYP2D6) = use in caution with CYP2D6 inhibitors (bupropion, paroxetine, fluoxetine)

SIDE EFFECTS: nausea, headache, dizziness, dry mouth, ↑nasopharyngitis

NA AND SPECIFIC 5-HT ANTAGONIST (NaSSAs): Mirtazapine**MECHANISM OF ACTION:**

- α₂ antagonism at presynaptic α₂ autoreceptors on NE neurons
 - Enhances NA neurotransmission
- α₂ antagonism at presynaptic α₂ heteroreceptors on 5-HT neurons
 - Enhances 5-HT neurotransmission

MOA → RX & SIDE EFFECTS:

- 5-HT_{2A} antagonism: anxiolytic action, sedation, ↓ sexual dysfxn
- 5-HT_{2C} antagonism: anxiolytic action, weight gain
- 5-HT₃ antagonism: no nausea
- H₁ antagonism: weight gain, sedation

OTHER POINTS:

- May enhance sedative effects of BZDs, alcohol
- Relatively safe drug, few drug interactions
- Does not cause serotonin syndrome
- No significant effects on CV system even at high doses

MONOAMINE OXIDASE INHIBITORS (MAOIs); Tranylcypromine (Parnate), Isocarboxazide (Marplan)**MECHANISM OF ACTION:**

- Irreversible inhibitors of MAO
 - Non-selective = MAO_A & MAO_B of NA, 5-HT, DA
- Two weeks required for enzyme to regenerate
 - Acutely: enhancement of biogenic amine transmission
 - Chronically: also down-regulate 5-HT, NA, DA receptors
- Not as effective as TCA but useful in subsets of depression
- Greater potential for toxicity (DRUG INTERACTIONS!!)

SIDE EFFECTS: agitation, orthostatic hypotension, weight gain, sexual dysfunction

DRUG INTERACTIONS: SEROTONIN SYNDROME

- Any agent which blocks 5-HT uptake → serotonin syndrome
 - TCA, SSRI, meperidine, DM, antihistamines
- Serotonin syndrome = hyperpyrexia, hyperexcitability, motor restlessness, coma, death
- Results when patient concurrently takes two types of drugs that enhance monoaminergic transmission
 - Can take TCA & MAOI but *exercise caution !!!*

DRUG INTERACTIONS: HYPERTENSIVE CRISIS

- Tyramine-containing foods & beverages → hypertensive crisis
 - Aged cheeses, sour cream, beer, soy sauce, canned figs, chocolate, liqueurs, sardines, liver, yogurt, dried salted fish, sauerkraut, anchovies, pickled herring, Chianti wine
- Hypertensive crisis = N, V, HA, palpitations, cerebral hemorrhage, death
 - Irreversible MAO_A inhibition in gut → tyramine concentrations rise → tyramine enters nerve terminal → increase release of NE that will contribute to a pressor response leading to hypertensive crisis

REVERSIBLE MAO_A INHIBITOR (RIMAs): Meclobemide (Mannerix)**MECHANISM OF ACTION:**

1. In presence of RIMA, the accumulation of NE caused by tyramine can displace the binding of RIMA off MAO
2. MAO, now devoid of its inhibitor, can catabolize NE and prevent the dangerous accumulation of NE

- Therapeutically claimed to be as effective as TCAs
- Less potential for "tyramine" interaction
- Less potential for interaction with 5-HT uptake blockers??

NON-SEROTONERGIC AGENTS FOR MDD: Ketamine**USE:**

- Known as an illicit, psychedelic club drug (Special K, horse tranquilizer)
- Used previously as a dissociative anesthetic agent in anesthesiology
- Produces marked analgesia via its NMDA blocking actions
- Produces psychotomimetic effects ("flashbacks")
- Recent studies show usefulness in producing marked antidepressive actions
 - Depressed mood, anhedonia, & suicidal thoughts in refractory uni and bi-polar depressed pts rapidly & robustly improved
 - Subanesthetic doses (0.5 mg/kg IV over 40 mins)
 - Onset of action within 40 mins & lasted up to 14 days

PROPOSED MOA FOR KETAMINE'S RX ACTIONS IN MDD:

- Through NMDA blocking actions, ketamine may also upregulate AMPA receptors (a sub-receptor type of the excitatory glutamate family of receptors)
- Ketamine = partial D₂ agonist = increases dopamine levels in the striatum (caudate & putamen)
- Ketamine metabolite (2R,6R-HNK) produces anti-depressive actions via an acute increase in glutamatergic synaptic transmission → long-term adaptation involving the upregulation of synaptic AMPARs
- Emerging role(s) of glutamate in depression & search for ketamine-like agents may provide novel rapidly acting antidepressants