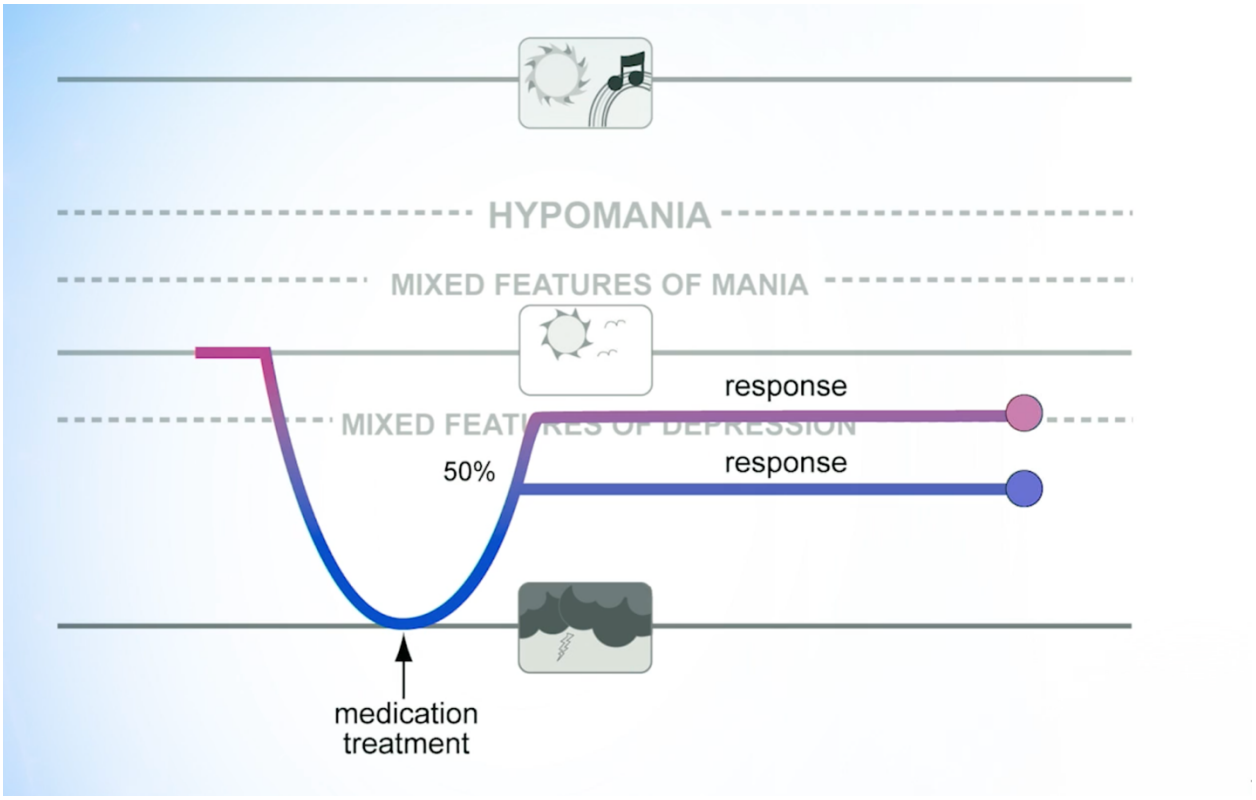
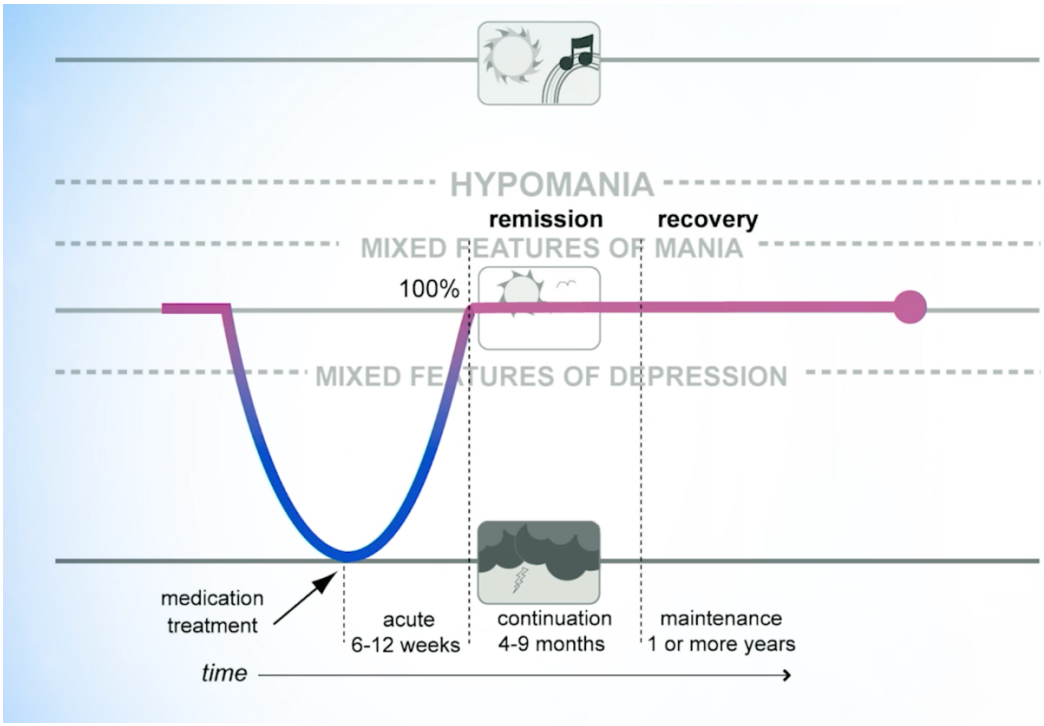
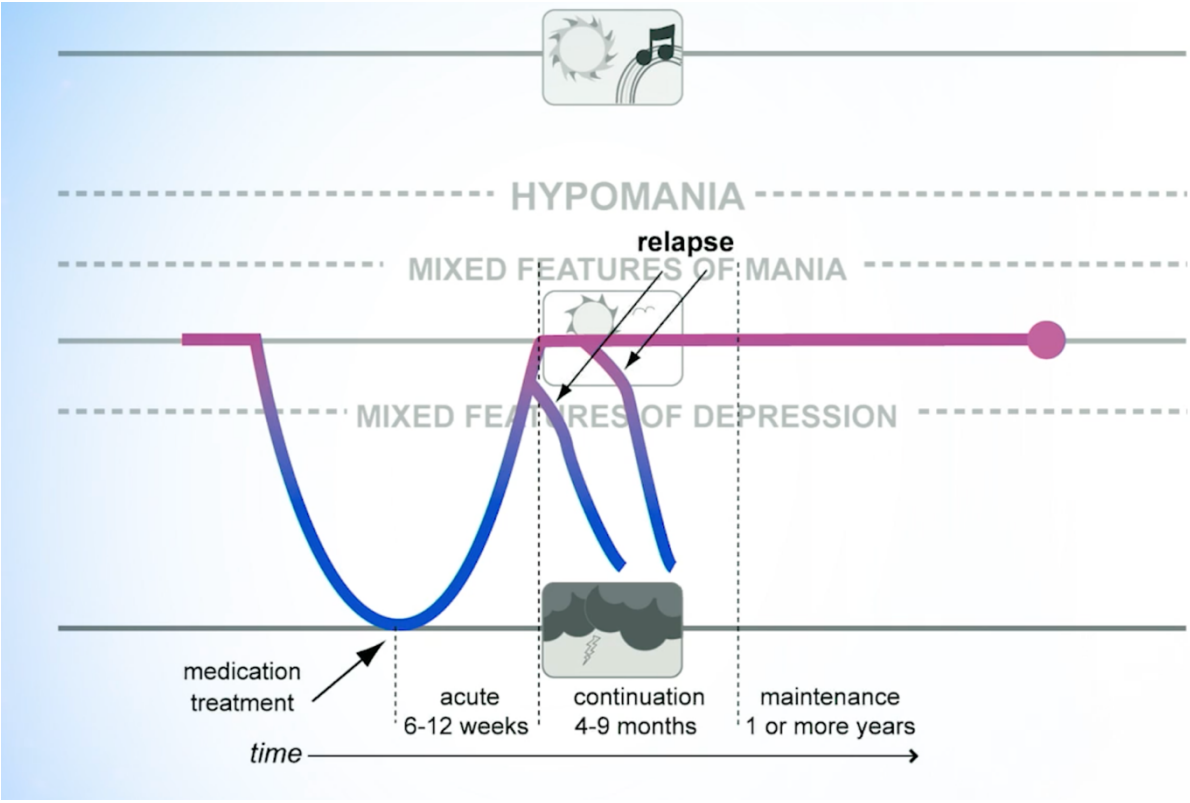
Treatments for Unipolar Depression and Bipolar

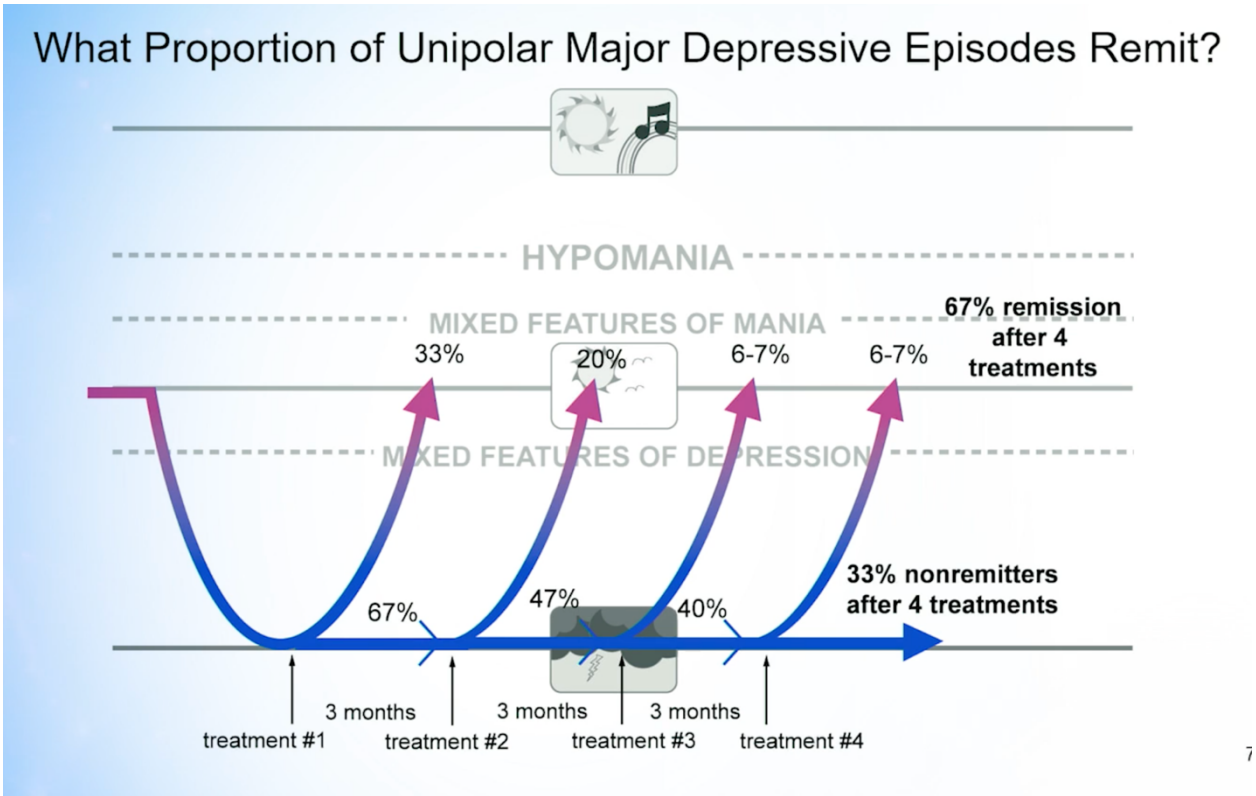


Unipolar Depression

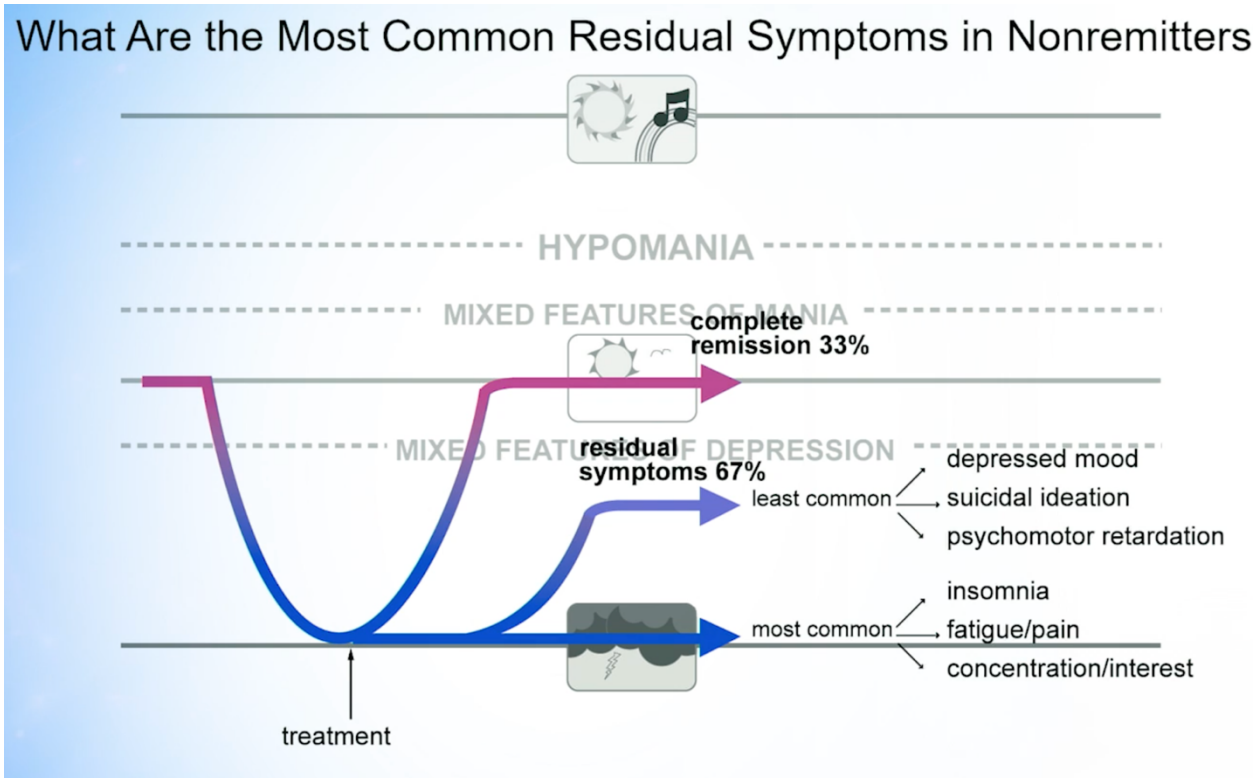
- If medication works at 50% or more it is considered a response.
- 100% better is considered remission
- If 100% for more than a year it is considered recovery



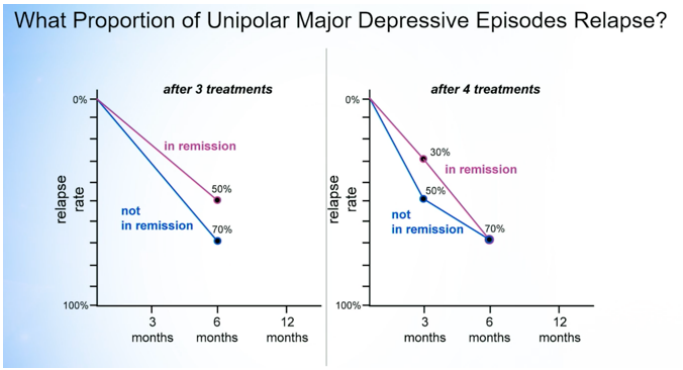


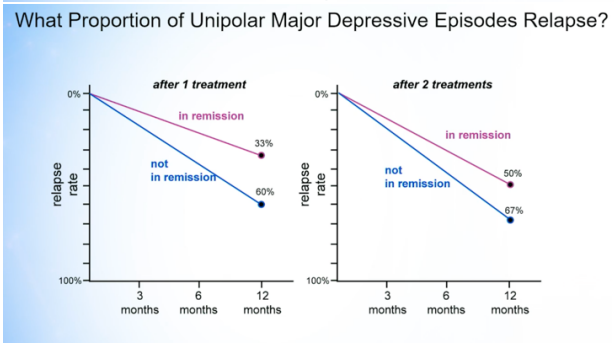


- 1/3 not in remission on monoamines after 4 treatments.



- Nothing works well late, each subsequent treatment works not so well.

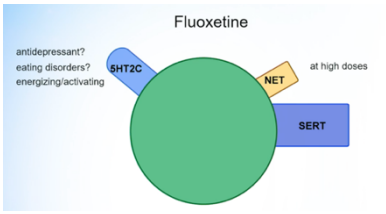




- Don’t wait late to do aggressive treatments or use something different than monoamine inhibitors (SSRI, SNRI)
- When you block reuptake you increase the serotonin in the synapse by serotonin 1 A receptors and reuptake pumps (SERT) on dendrites of the neuron. SSRI blocks the reuptake of serotonin on the axon and dendrite.
    - The increase of 5HT at axon causes the postsynaptic receptors to desensitize and down regulate reducing side effects.

SSRI's

Fluoxetine (Prozac)



- 5HT2C is an antidepressant. Also helps with eating disorders at high doses. Energizing
- Activates NET (norepinephrine transporter) at high doses.
- Disinhibits norepinephrine and dopamine (increases norepinephrine and dopamine in the prefrontal cortex.
- prescribe for patients with hypersomnia, apathy, and fatigue
- You do not prescribe for patients with agitation, insomnia, or anxiety
- Can boost olanzapine in bipolar depression
- Weak norepinephrine reuptake blocking, inhibits CYPd6 and 3A4
- Long half life, 2-3 days. Metabolite 14 days, possibly 21 days
- Decreased withdrawal symptoms, can help withdraw of perotitine or paxil
- Bipolar I depressive episodes: > 7 yrs. 60 mg children & 80 adolescents

	MDD	TRD (Adjunct)	Bipolar Depression	PMDD	GAD	Panic Disorder	Social Anxiety Disorder	PTSD	OCD	Bulimia
Approval	X*	X**	X*,**	X		X			X*	X

*also in children **with olanzapine

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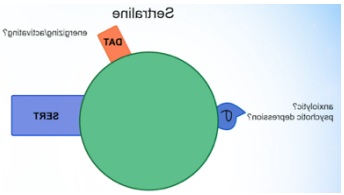
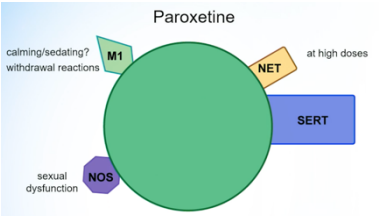
Sertraline (Zoloft)



- DAT is energizing and activating
- Sigma receptor is anxiolytic and helps with psychotic depression
- Improves low energy and hypersomnia
- > 6 YRS: 200 mg children and adolescents

	MDD	TRD (Adjunct)	Bipolar Depression	PMDD	GAD	Panic Disorder	Social Anxiety Disorder	PTSD	OCD	Bulimia
Approval	X			X		X	X	X	X	

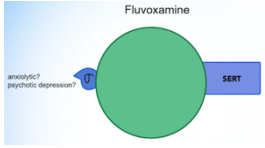
Paroxetine (Paxil)



- M1 is calming/sedating but also mild anticholinergic actions, side effects. Can be sedating. Also cause the withdrawal reactions (GI side effects, restlessness, tingling, restlessness).
- NET at high doses
- NOS (nitric oxide) sexual dysfunction

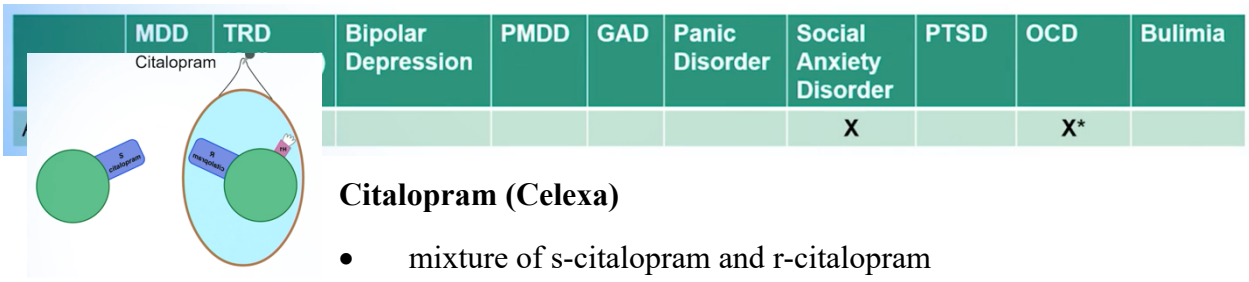
	MDD	TRD (Adjunct)	Bipolar Depression	PMDD	GAD	Panic Disorder	Social Anxiety Disorder	PTSD	OCD	Bulimia
Approval	X			X	X	X	X	X	X	

Fluvoxamine (Luvox)



- sigma helps as an anxiolytic and with psychotic depression

- Approved for MDD in Europe not US. Helps with OCD



	MDD	TRD	Bipolar Depression	PMDD	GAD	Panic Disorder	Social Anxiety Disorder	PTSD	OCD	Bulimia
							X		X*	

Citalopram (Celexa)

- mixture of s-citalopram and r-citalopram
- weak antihistamine properties
- Favored for the elderly
- Took the S out to improve side effects (escitalopram)
- 40 mg children and adolescents

	MDD	TRD (Adjunct)	Bipolar Depression	PMDD	GAD	Panic Disorder	Social Anxiety Disorder	PTSD	OCD	Bulimia
Approval	X									

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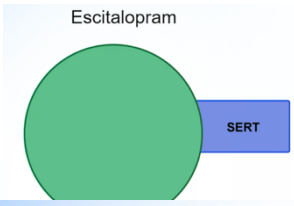
Escitalopram (Lexapro)



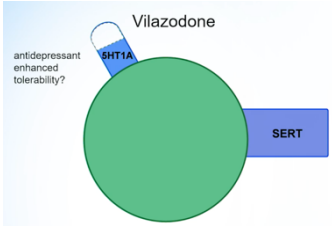
- approved in children for depression
- most selective of the Serotonin reuptake inhibitors
- less Gi affect, no antihistamine affect
- Adolescent 20mg

	MDD	TRD (Adjunct)	Bipolar Depression	PMDD	GAD	Panic Disorder	Social Anxiety Disorder	PTSD	OCD	Bulimia
Approval	X*				X					

*also in children

7-21

Vilazodone



- 5HT1A is an antidepressant with enhanced tolerability
- Off label use in anxiety disorder
- Can cause nausea
- Titrate slow
- Less sexual dysfunction

Mechanism of action:

SPARI (serotonin partial agonist reuptake inhibitor):

1. First about half of SERTs and half of 5HT1A receptors are occupied immediately
2. Second 5HT increases at 5HT1A somatodendritic receptors
3. Third, 5HT actions on the left cause 5HT actions on the somatodendritic cause 5HT1A auto receptors to desensitize/downregulate
4. Fourth, neuronal firing and serotonin release are disinhibited at the synapse on the right

5. Finally, antidepressant action begins, and downstream enhancement of DA release may mitigate sexual dysfunction

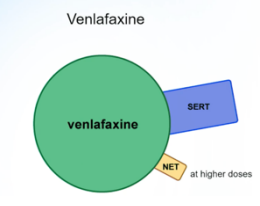
	MDD	TRD (Adjunct)	Bipolar Depression	PMDD	GAD	Panic Disorder	Social Anxiety Disorder	PTSD	OCD	Bulimia
Approval	X									

- Data suggests SSRI induced indifference, (ex. someone cant cry) it is dose dependent, if you reduce the dose it should alleviate this.

SNRI

Action: for patients that need an extra boost. Higher efficacy. Dual reuptake inhibitors serotonin and norepinephrine reuptake inhibitor

Venlafaxine (Effexor)



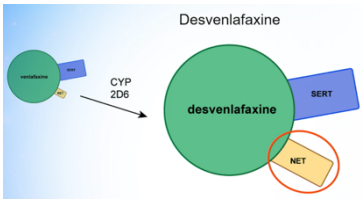
- Serotonin actions are present at low doses
- Norepinephrine actions are enhaced at increased doses
- Using XR dosing once a day reduces nausea
- Increase BP
- 225 mg for adolescents

	MDD	TRD (Adjunct)	Bipolar Depression	PMDD	GAD	Panic Disorder	Social Anxiety Disorder	PTSD	OCD	Bulimia
Approval	X				X	X	X			

Also approved in separation anxiety disorder

7-28

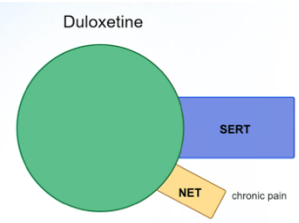
Desvenlafaxine



- Metabolite of venlafaxine
- More predictable plasma levels because no variability of CYP 2D6
- More norepinephrine reuptake inhibition
- More potent than venlafaxine at the serotonin transporter
- Decreased in vasomotor symptoms (BP)

	MDD	TRD (Adjunct)	Bipolar Depression	PMDD	GAD	Panic Disorder	Social Anxiety Disorder	PTSD	OCD	Bulimia
Approval	X									

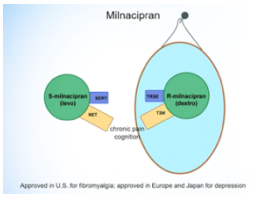
Duloxetine (Cymbalta)

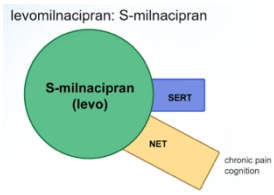


- adrenergic actions contribute to the efficacy of pain reduction
- Lower incidence of HTN than venlafaxine

	MDD	TRD (Adjunct)	Bipolar Depression	PMDD	GAD	Panic Disorder	Social Anxiety Disorder	PTSD	OCD	Bulimia
Approval	X				X					

Milnacipran **Levomilnacipran**





- No QTc prolongation
- Recommended dose: 40 mg to 120 mg once daily with or without food
- Initiate dose at 20 mg once daily for 2 days and then increase to 40 mg once daily
- Based on efficacy and tolerability, increase dose in increments of 40 mg at intervals of 2 or more days.
- The maximum recommended dose is 120 mg once daily.
- Take capsules whole; do not open, chew or crush
- Renal Impairment: Do not exceed 80 mg once daily for moderate impairment.
- Do not exceed 40 mg once daily for severe renal impairment
- Discontinuation: Reduce dose gradually whenever possible
- Dose should not exceed 80mg once daily when used with a strong CYP3A4 inhibitors (eg. Ketoconazole, clarithromycin, ritonavir)
- Monitor for suicidal thoughts and behaviors. Not approved for pediatric patients.

	MDD	TRD (Adjunct)	Bipolar Depression	PMDD	GAD	Panic Disorder	Social Anxiety Disorder	PTSD	OCD	Bulimia
Approval	X									

- Contraindications:
  - Hypersensitivity to levomilnacipran, milnacipran HCl, or any excipient in the formulation.
  - Serotonin Syndrome and MAOIs:
  - Do not use MAOIs intended to treat psychiatric disorders within 7 days of stopping treatment.
  - Do not use within 14 days of stopping an MAOI intended to treat psychiatric disorders.
  - Do not start in a patient who is being treated with linezolid or intravenous methylene blue.
- Precautions:
  - Elevated BP, HR, and abnormal bleeding
  - Serotonin syndrome
  - SI
  - Angle closure glaucoma
  - Urine hesitation or retention
  - Activation of hypo-mania or mania
  - Discontinuation syndrome
  - Seizure
  - Hyponatremia
  - Common side effects: nausea, constipation, hyperhidrosis, heart rate increase, erectile dysfunction, tachycardia, vomiting, and palpations
  - Pregnancy category c

NDRI

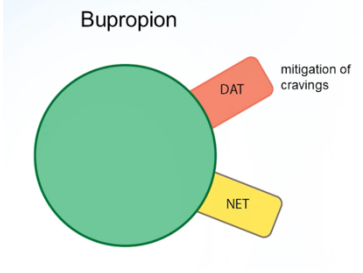
Differences between dopamine and norepinephrine in the PFC:

- Dopamine has a wide diffusion
- Norepinephrine transporter in the prefrontal cortex (no dopamine transporter)
- If the norepinephrine transporter is blocked in the prefrontal cortex it will increase norepinephrine and dopamine

Actions: blocks Norepinephrine and dopamine transporter

- Prefrontal cortex: NET blockade increase NE and DA
- Striatum: DAT blockade increases DA

Bupropion (Wellbutrin)



- mitigate cravings
- Weak DAT and NET inhibition
- No sexual dysfunction side effects
- Less likely to produce hypomania in adolescence: 300 MG children 450 adolescence

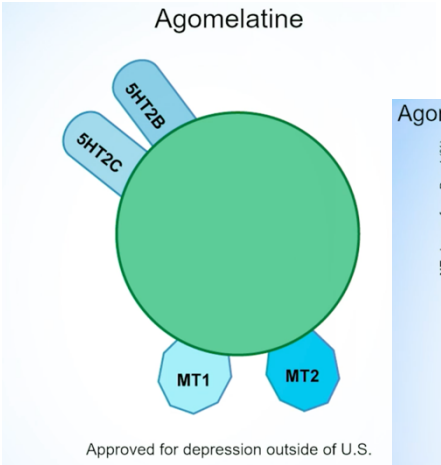
	MDD	TRD (Adjunct)	Bipolar Depression	PMDD	GAD	Panic Disorder	Social Anxiety Disorder	PTSD	OCD	Bulimia
Approval	X									

Also approved in seasonal affective disorder and nicotine addiction

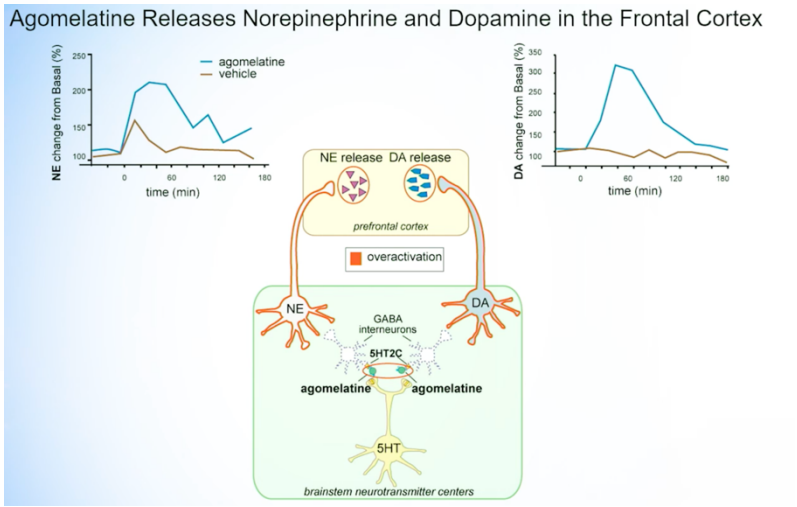
7-29

Treatment for unipolar depression beyond monoamine reuptake

Agomelatine

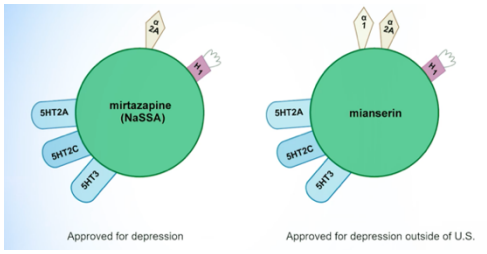


- M1 and M2 like melatonin
- 5HT2b and 5HT2C can change serotonin in the cortex



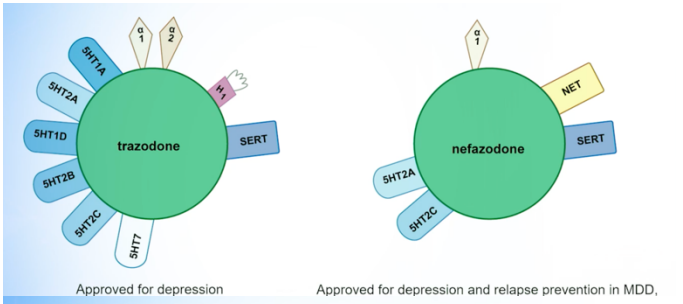
- If you block 5HT with agomelatine it will decrease GABA and increase norepinephrine and dopamine (disinhibition)
- Goes to pineal gland and gives you artificial melatonin circadian rhythm
- Not approved in the US. Used in Europe

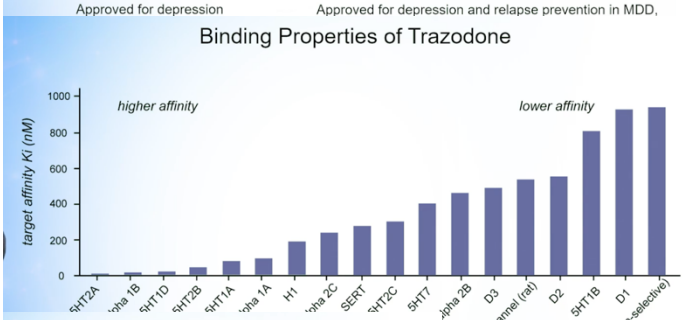
Mirtazapine **Mianserin**



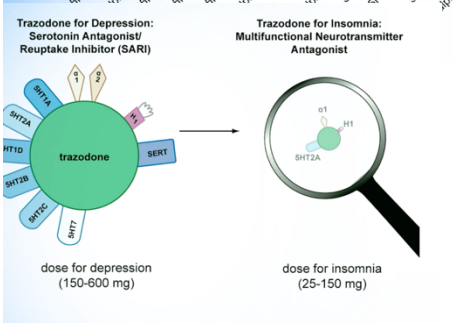
- NASSA (noradrenergic and specific serotonergic antidepressant)
- Primary therapeutic action is alpha 2 antagonist
- 5HT2A, 5HT2C (weight gain), 5HT3 antagonist
- HI: makes you sleepy and sedated, weight gain
- Alpha 1 and Alpha 2a antagonist
- Alpha 2 agonist increases serotonin and norepinephrine
- 5HT has an alpha 2 receptor. If we block it (alpha 2 antagonist) increases serotonin
- 5HT3Antagonists disinhibits glutamate release and enhances the release of downstream neurotransmitters to improve depression. Does this by blocking serotonin's ability to activate GAPBA and this will then stimulate downstream glutamate
- 5HT3: 5HT3 receptors cause inhibition of norepinephrine and acetylcholine release
- Mirtazapine does not induce or inhibit any CYP450 enzymes

Trazadone **Nefazodone**





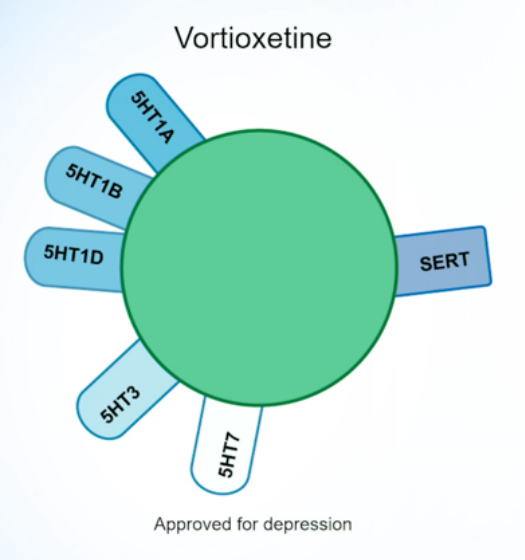
- trazadone at full dose is an antidepressant
- At low doses it is a sleep aid
- Most potent property is 5HT2A
- SARI (serotonin antagonist reuptake inhibitor) blocks serotonin 2A and dose dependent blocking of serotonin 2C
  - at low doses 5HT2A and alpha 1A antihistamine (sleepy)
  - SERT similar to SSRI (at higher does)
  - 5HT7 (at higher doses) antidepressant)



- Short half like and doses have to be so high they have to give you antidepressant affect, not tolerable
- Then they created extended release 300mg

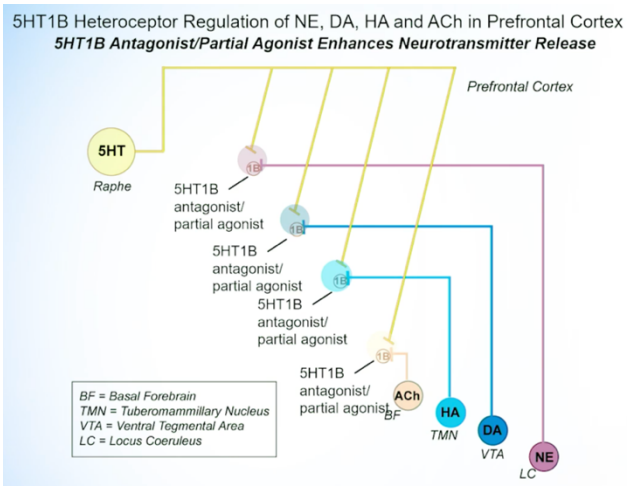
5HT2A and 5HT2C sexual dysfunction, insomnia, and anxiety however at high doses it will stop these side effects, you could add a low or moderate dose of trazadone to SSRI.

Vortioxetine



- 5HT1A agonist
- 5HT1B, 5HT1D partial agonist
- 5HT7 antagonist enhances serotonin release, also regulates glutamate release will increase
- SERT
- The mixture is Pro-cognitive
- Cognition is: attention, executive function, memory, & processing speed
- 5HT3 improve cognition by increasing the downstream release of norepinephrine and acetylcholine

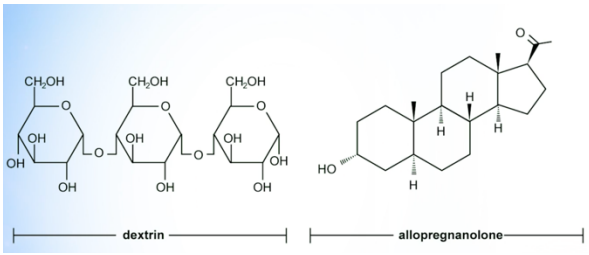
5HT1B heteroreceptor regulation of NE, DA, Histamine, and Ach in prefrontal cortex



- if you block then the neurotransmitters will increase
- Dose: 10mg once per day, then increase to 20mg/day, can be lowered to 5mg per day
- Can be stopped abruptly but recommended to reduce 15/20mg to 10mg one week before stopping
- Max dose for poor metabolizers of CYP2D6 is 10mg/day
- Contraindications
  - MAOIs (need to wait 14 days after stopping MAOIs or 21 days after stopping Vortioxetine)
  - Linezolid or IV methylene blue

- Warning: Serotonin syndrome, Abnormal bleeding, Mania/hypomania, Angle closure glaucoma, Hyponatremia
- Adverse reaction: Nausea, constipation, vomiting
- Reduce dose by 50% when strong inhibitor (bupropion, fluoxetine, paroxetine, quinidine) is coadministered
- Increase dose when a strong inducer is coadministered (carbamazepine, phenytoin, rifampicin)
- Pregnancy C

<u>Neuroactive Steroid</u>



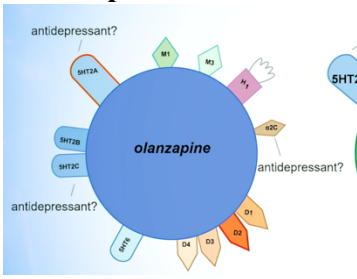
- Allopregnanolone is a steroid in pregnancy. Decreases after birth leads to prost partum depression. Given over infusion and treats postpartum depression.

Action: Works on GABA receptors. (GABA receptors have multiple binding sites) can also bind to non-benzodiazepine sensitive GABA receptors

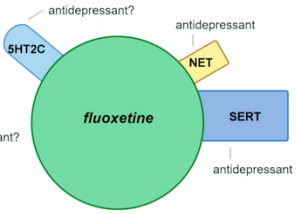
Treatment Resistance and Future Treatments

Serotonin/Dopamine Blockers for treatment-resistant unipolar depression

Olanzapine

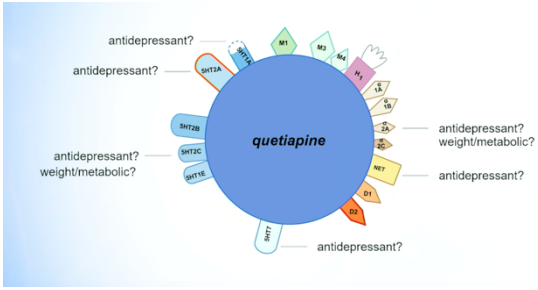


Fluoxetine



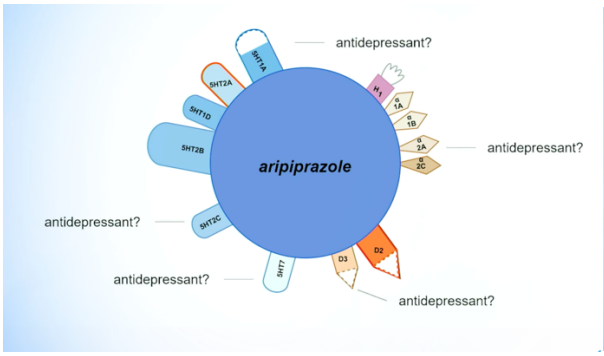
- Side effects:
  - H1 weight gain and metabolic, sleepy
  - 5HT2C weight gain

Quetiapine

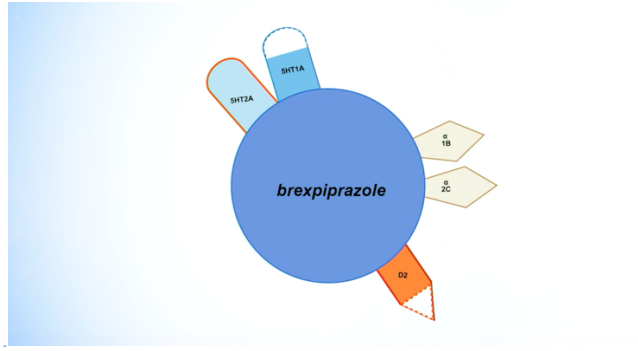


- 5HT2c weight gain metabolic
- M1, H1 and alpha2a sedation

Aripiprazole

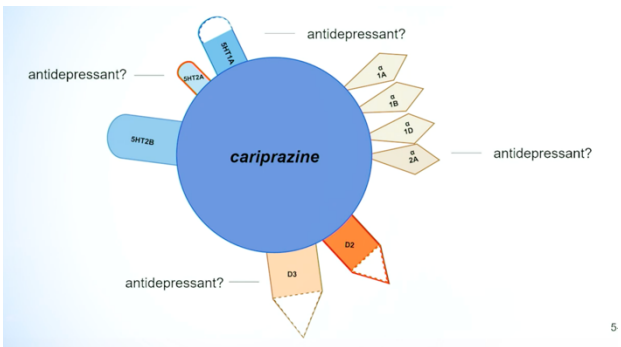


Brexipiprazole



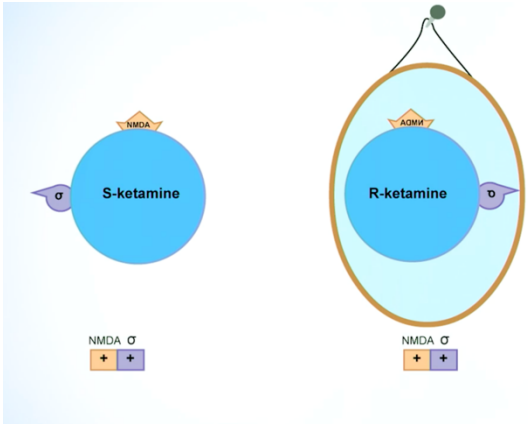
- Being tested for agitation in dementia
- Being tested for PTSD with sertraline
- Reduced drug induced parkinsons
- Can also improve mood

Cariprazine



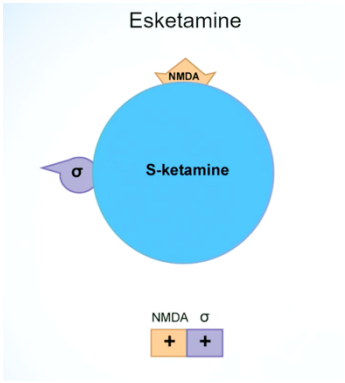
- Alpha 1 and 2 antagonist
- D3 partial agonist properties

Ketamine: R+S Ketamine



- work by a boost of glutamate
- NMDA receptor is blocked by ketamine now glutamate can no longer excite because it is being blocked. Inhibition down stream and there is a burst of glutamate to turn on the neuron downstream
- AMP receptor stimulated which creates stimulation
- This leads to release of mTOR which leads to spine growth and an antidepressant effect.
- Does it fast, and works for people who are monoamine med resistant.

Esketamine

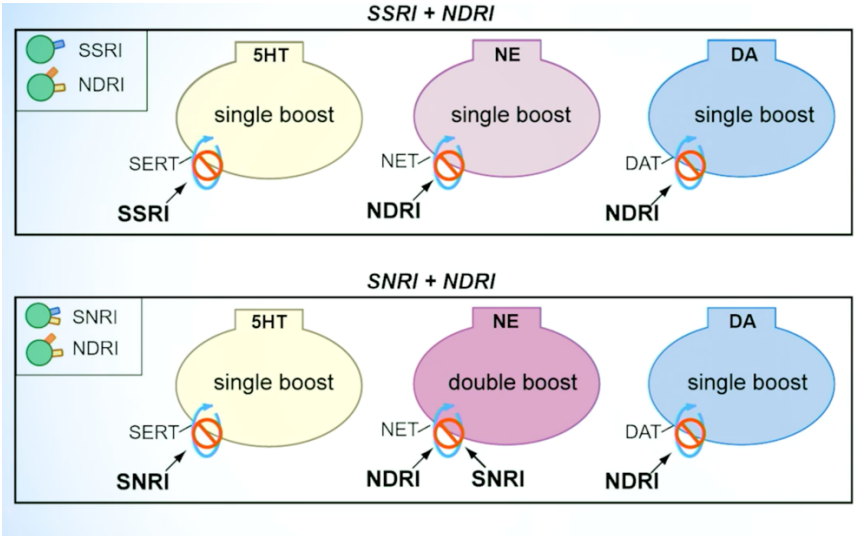


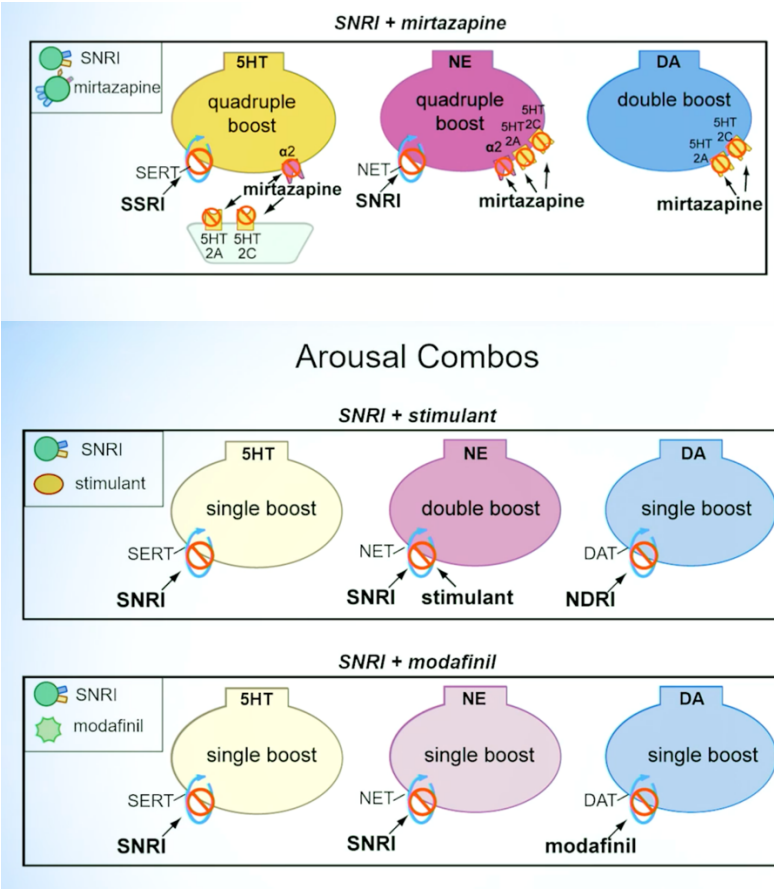
- intranasal

Other drug combinations for treatment-resistant depression

- Lithium
- Buspirone
  - Is a 5HT1A partial agonist
- Thyroid hormone

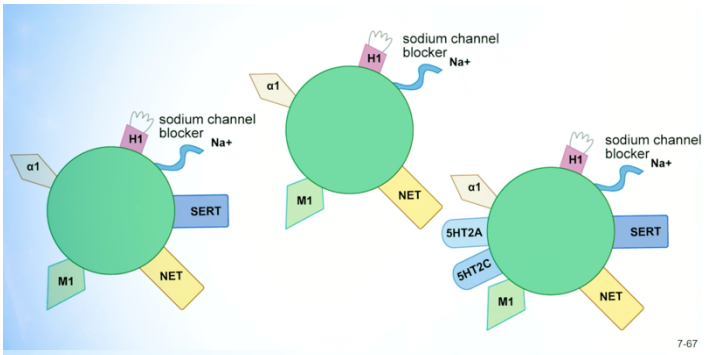
You can have more potent action by combining two drugs:





"California Rocket Fuel"

Second-line monotherapies: Tricyclic Antidepressants (TCA)



- Block reuptake of serotonin and norepinephrine
- Side effects
- alpha 1: cause sedation and antagonism, dizziness, orthostatic
- H1: sedation and weight gain
- M1: anticholinergic, blurred vision, urine retention
    - Used in kids for enuresis
    - Not used often in US.

- A 30 day supply can cause coma, seizures, arrythmia, or death due to blocking sodium channels

Some Tricyclic Antidepressants Still in Use

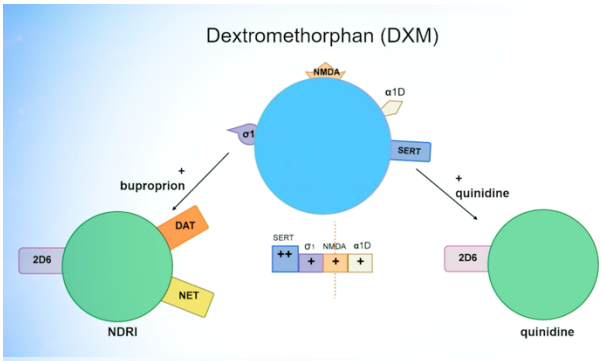
Generic name	Trade name
Clomipramine	Anafranil
Imipramine	Tofranil
Amitriptyline	Elavil; Endep; Tryptizol; Laroxyl
Nortriptyline	Pamelor; Aventyl
Protriptyline	Vivactil
Maprotiline	Ludiomil
Amoxapine	Asendin
Doxepin	Sinequan; Adapin
Desipramine	Norpramin; Pertofran
Trimipramine	Surmontil
Dothiepin	Prothiaden
Lofepramine	Deprimyl; Gamanil
Tianeptine	Coaxil; Stablon

Second line monotherapies: Monoamine Oxidase Inhibitors (MAOI's)

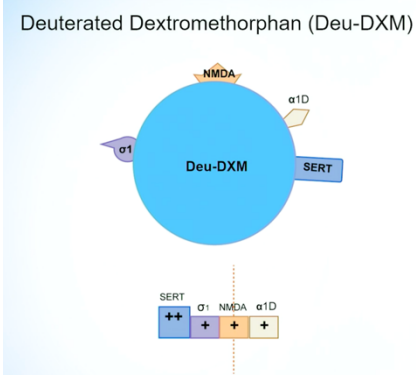
- Two forms of MAO: MAO-A and MAO-B
  - MAO-B is in serotonin neuron
  - MAO-A in norepinephrine and dopamine neurons
  - There is also MAO-A and MAO-B outside the neuron
- MAO inhibitors block both.
  - MAO-A is inhibited is an antidepressant affect.
  - MAO-B inhibited has no antidepressant action
  - Both MAO-A and MAO-B is inhibited there is a robust antidepressant action including dopamine action
- Have to limit drug interaction which limits serotonin uptake because you can have serotonin syndrome.
- There is a tyramine reaction so you have to limit tyramine in the diet.

Future treatments for mood disorders

Dextromethorphan

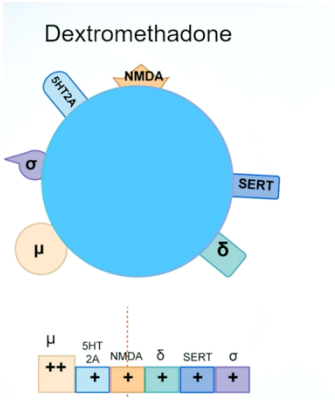


- treatment for pseudobulbar affect
- Agitation in Alzheimer's disease



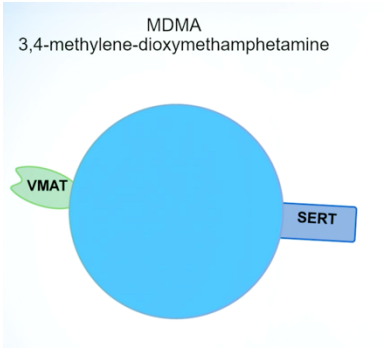
- To further commercial development you can "deuterate" it. Changes the half light and extends it but also resets the patent.

Deutromethadone



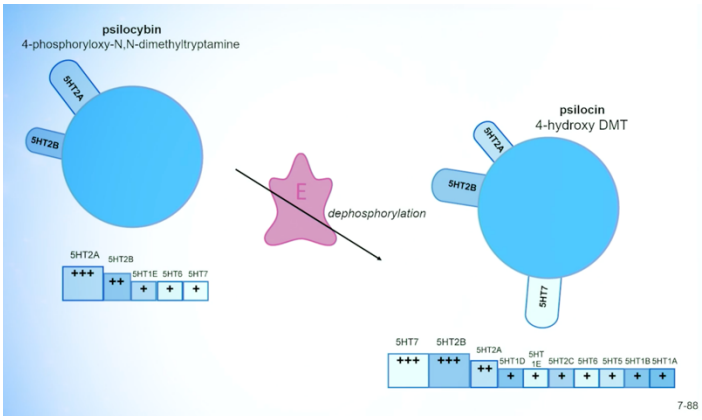
- "s-methadone"
- NMDA antagonist
- 40-100 fold less opioid activity than regular methadone.
- Orally available: in testing for treatment resistance depression

MDMA: Ecstasy



- Derived from methamphetamines
- Helps with PTSD and treatment resistant depression

Psilocybin



- “magic” mushrooms
- In research for treatment resistant depression

Treatments for Bipolar Spectrum Disorder

- Mood instability
  - Manic chaotic neurotransmission in brain circuits (bipolar) too much sodium ion flow through voltage sensitive sodium channels, too much calcium, too much release of excitatory glutamate. Depression part is not enough glutamate.
  - Mood stabilization is achieved by:
    - blocking neurotransmission in targeted circuits by blocking sodium and calcium.
    - Reducing glutamate release and actions at NMDA receptors.
    - Reducing dopamine hyperactivity with atypical and possibly lithium.
    - Reducing glutamate hyperactivity by blocking 5HT2A with atypicals
- Treatment for a manic episode (treating from above) is different from stabilizing (treating from above). Treatment for a depressive episode (treating from below)

Serotonin/Dopamine Blockers for Bipolar Spectrum

	Evidence of efficacy in mixed features	FDA-approved for bipolar depression	FDA-approved for bipolar mania	FDA-approved for bipolar maintenance	FDA-approved for MDD
Aripiprazole			Yes	Yes	Yes (adjunct)
Asenapine	Yes (MMX)		Yes	Yes	
Brexpiprazole					Yes (adjunct)
Cariprazine	Yes (MMX, DMX)	Yes	Yes		
Lurasidone	Yes (DMX*)	Yes			
Olanzapine	Yes (MMX)	Yes (with fluoxetine)	Yes	Yes	Yes (with fluoxetine)
Quetiapine	Yes (MMX)	Yes	Yes	Yes	Yes (adjunct)
Risperidone			Yes	Yes	
Ziprasidone	Yes (MMX)		Yes	Yes	

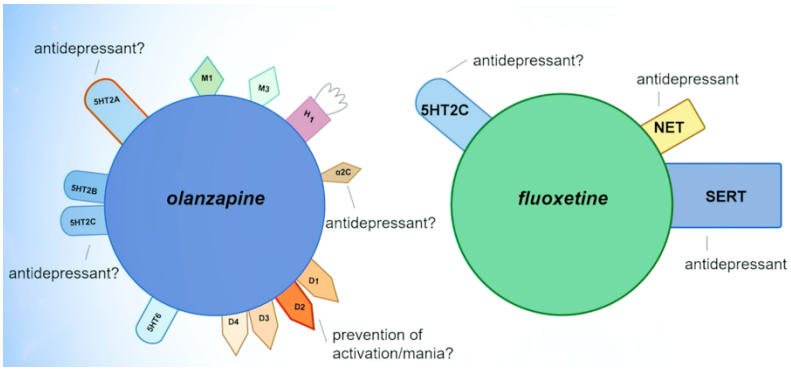
MMX: mania with mixed features. DMX: depression with mixed features.
*unipolar and bipolar depression

Most of the drugs that work in mania or depression work in maintenance (not all)

Depression with mixed features can be heard to treat

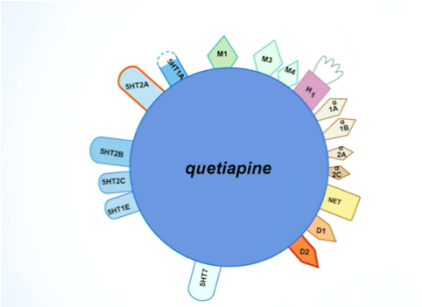
Serotonin Dopamine Blockers for Bipolar Disorder

Olanzapine + Fluoxetine



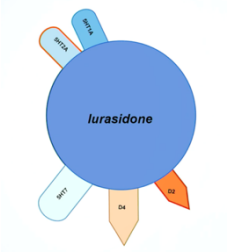
- weight gain

Quetiapine (Seroquel)



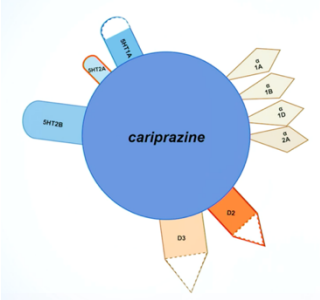
- problems with tolerability
- Metabolic problems
- Used for sleep, and mood stabilization
- Acute manic episode, mania, and depression episodes
- Dopamine, serotonin, and norepinephrine antagonist. Antihistamine (sleepy), and clinically negligible anticholinergic properties. Binds strongly to serotonin receptors. Patrial agonist 5HT1A receptors. D1,D3, D4 antagonist. 5HT1A and 5HT2C (weight gain)
- Dose: Bipolar Mania
    - Acute bipolar mania, monotherapy or adjunctive start 50 mg PO BID day 1, increase to no higher than 100 mg BID day 2, 150 mg BID day 3, 200 mg two BID day 4.
    - May increase as needed to 300 mg BID day 5 and 400 mg BID thereafter.
    - Usual effective dose is 400 to 800 mg/day.
    - Acute bipolar mania, monotherapy or adjunctive, extended-release, start 300 mg PO day 1, 600 mg day 2, 400 to 800 mg/day thereafter.
- Dose bipolar depression
    - Bipolar depression, regular and extended release; 50 mg PO bedtime day 1, 100 mg bedtime day 2, 200 mg bedtime day 3, 300 mg bedtime day 4. May increase as needed to 400 mg day 5 600 mg bedtime day 8.
- Dose: Bipolar maintenance:
    - continue dose required to maintain remission. In low doses (50-100 milligrams)
- Pediatric: : Bipolar I manic ages 10-17 acute monotherapy or adjunctive with Lithium and Valproate. 600 mg children and 800 adolescents

Lurasidone

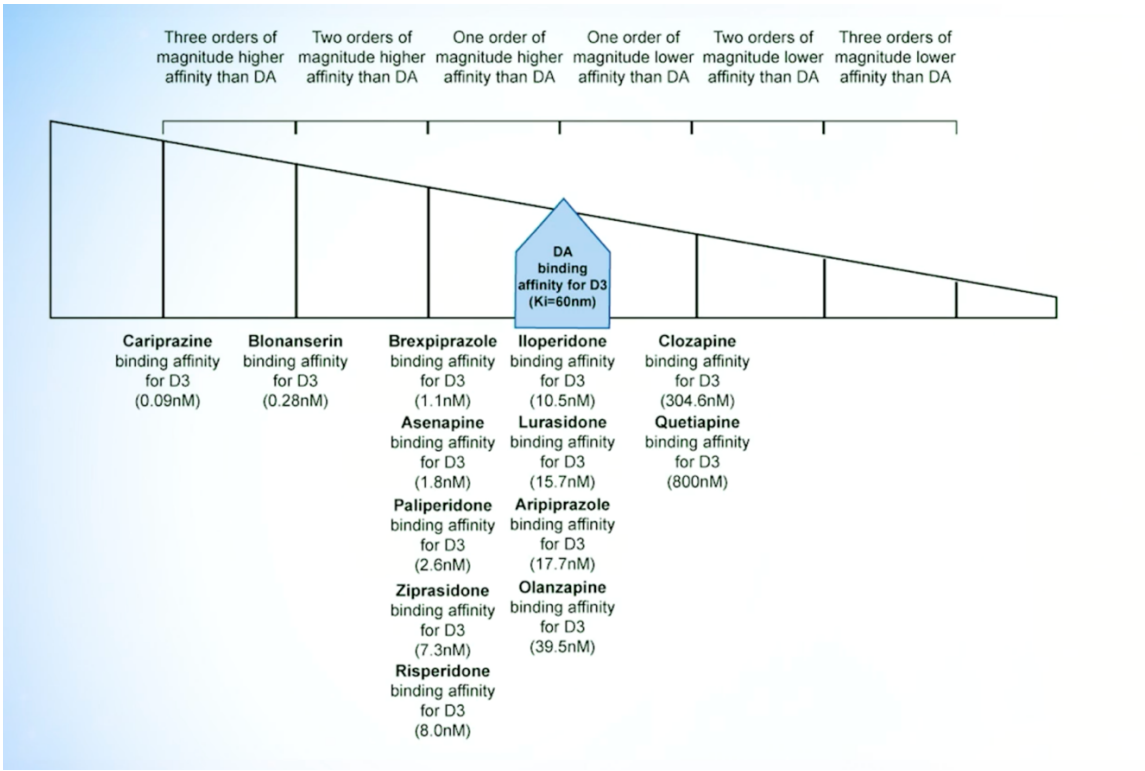


- go to drug for bipolar depression

Cariprazine



- Blocks D3



- Dopamine loves D3 receptor
- All the drugs near the dopamine binding wont work, dopamine will win at the receptor and knock all the drugs off. They will bind to a D2 receptor
- Two drugs that have a high affinity for D3 they will stay on the receptor Blonanserin and Cariprazine.
- Mesocortical dopamine pathway. If we can block D3 receptors with a D3 antagonist/partial agonist with something that has stonger affinity for dopamine will deliver dopamine in. the prefrontal cortex and reduce negative and affective symptoms

Lithium

- Classic mood stabilizer 0.6-1.2 therapeutic window
- Proven effective for acute mania and in maintenance (especially for the prevention of manic episodes). Blood levels should be around 1.0. Higher the dose the greater the side effects.
- Mechanism of action is thought to be inhibition of second messenger enzymes and interaction with downstream signal transduction cascades.
- Now it is usually given once a day at night due to side effects.
- Usually used in mania with euthymia. (Valproic acid and atypical antipsychotic is usually used in dysphoric manic, rapid cycling or more chaotic mania
- Lithium prevents suicide (if you stop it suicidal thoughts may come back)
- Used off-label to treat bipolar depression and as an adjunct in treatment resistant unipolar depression
- Dose:
    - 900 -2400mg/day in 3-4 divided doses or 900 -1800mg /day in two divided doses of extended release. Monitor serum concentrations and clinical response (efficacy and toxicity) to determine proper dose.

    - Usual dosages for maintenance treatment are 900-1200 mg per day in divided doses pediatric: Lithium: 12 and older: manic episodes, and prevention of recurrence: <25KG: 600 MG, 25-39KG: 900 MG, 40-50KG 1200 MG, >50MG 1500 MG
    - Lithium is typically started at 300mg BID and titrated based on plasma levels. Therapeutic plasma levels should fall within the 1.0- 1.5 mEq/L range for short term and 0.6 - 1.2mEq/L for long term use.
- Side effects
    - GI symptoms, weight gain, hair loss, tremors, sedation, decreased cognition, incoordination
    - Low doses as augmentation around 0.4 can help reduce sided effects
    - Monitor long term effects on thyroid and kidneys (narrow therapeutic index)

Anticonvulsant Mood Stabilizers

Agent	Putative clinical actions				
	Epilepsy	Mania-minded		Depression-minded	
		Treat from above	Stabilize from above	Treat from below	Stabilize from below
Valproate	++++	++++	++	+	+/-
Carbamazepine	++++	++++	++	+	+/-
Lamotrigine	++++	+/-	++++	+++	++++
Oxcarbazepine/ licarbazepine	++++	++	+	+/-	+/-
Riluzole	+			+	+/-
Topiramate	++++	+/-	+/-		
Gabapentin	++++	+/-	+/-		
Pregabalin	++++	+/-	+/-		

Valproic Acid/ Valproate/Divalproex/Depakote

- Inhibits the enzyme that breaks down GABA, therefor increases GABA neurotransmission.
- Decreases glutamate concentration
- Acts on sodium and calcium channels (blocks). Enhances GABA and reduce glutamate
- Site it may possibly work is the voltage sensitive sodium channels
- Works for manic episodes of bipolar
- Broad spectrum anticonvulsant
- Commonly used in maintenance. Antidepressant actions are not well established
- Efficacy for migraine
- Dose
    - Mania associated with bipolar disorder; 250 mg PO three times per day (Depakote) or 25 mg/kg once daily (Depakote ER); max 60 mg/kg/day.
    - The usual dose is 750 to 3000 mg/day.
    - The loading dose in some systems used is 20-30 mg/kg/day for 5 days. Another way to initiate treatment is to start with 750 mg and increase by 250-500 mg every 2-3 days.
    - Pediatric: Bipolar I manic or mixed ages 10-17 Monotherapy or adjunctive with lithium or valproate: 30 mg children and adolescents
- Side effects can be a deterrent, may be related to chronic exposure
    - Hair loss, sedation, 5HT2C weight gain, metabolic complications, possible risk of amenorrhea, and polycystic ovaries, cognitive function (5HT2C)
    - Warnings for bone marrow, liver, pancreatic, and fetal toxicities
    - Hepatotoxicity: reduced in the elderly

- Valproate does not induce its own metabolism. It increases blood levels of phenytoin and carbamazepine.

Carbamazepine

- Proven effective for acute mania
- Efficacy for neuropathic pain
- Risk of bone marrow suppression requires initial monitoring of blood counts
- Notable induction of CYP450 3A4
- Can cause fetal toxicities

Lamotrigine (Lamictal)

- Proven actions on glutamate release, reduces the release of glutamate (reduce excitatory glutamate)
- slight effect on calcium channels
- May also work by blocking the alpha subunit of voltage sensitive sodium
- Approved to prevent recurrence of both mania and depression
- First line treatment for bipolar depression
- Not approved for acute episodes
- Most experts consider it effective for bipolar depression
- Generally well tolerated
- Requires slow initial titration due to possible risk of serious rash (Stephen Johnson syndrome) If using with valproic acid slow titration 50% target dose.
- Drug interactions: valproic acid, raises Lamictal levels
- Not useful for treating mania
- Lower doses with hepatic, renal impairment or elderly
- Dose:
    - Monotherapy for bipolar is 100-200mg/day.
        - Bipolar monotherapy is dosed by administering 25mg/day for first two weeks; increase to 50mg at week 3; increase to 100mg at week 5; and increase to 200mg at week 6.
    - Adjunct therapy is 100mg/day in combination with Valproate or 400mg/day in combination with enzyme inducing antiepileptic drug like carbamazepine, phenobarbital, phenytoin, or primidone.
        - Bipolar disorder adjunct to valproate:dose by administering 25mg QOD for first two weeks; increase to 25mg QD at week 3; increase to 50mg QD at week 5; and increase to 100mg QD at week 6.
        - Bipolar disorder adjunct to enzyme-inducing antiepileptic drug is dosed by administering 50mg QD for first two weeks; increase to 100mg/day in divided doses at week 3; and at week 5 increase by 100mg/day each week; maximum dose is 400mg/day in divided doses

Combos for bipolar disorder

- 5HT/DA blocker + Lamictal
- 5HT/DA blocker + Lithium
- 5HT/DA blocker + Valproic acid
- 5HT/DA blocker + Lamictal + monoamine reuptake blocker (monoamine reuptake blocker can cause mania, so be careful)