Treating Tourette Syndrome: A Neuroscientific Perspective

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Camp Twitch and Shout Parent Workshop

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Download the slides: www.ronnieli.com/tourette

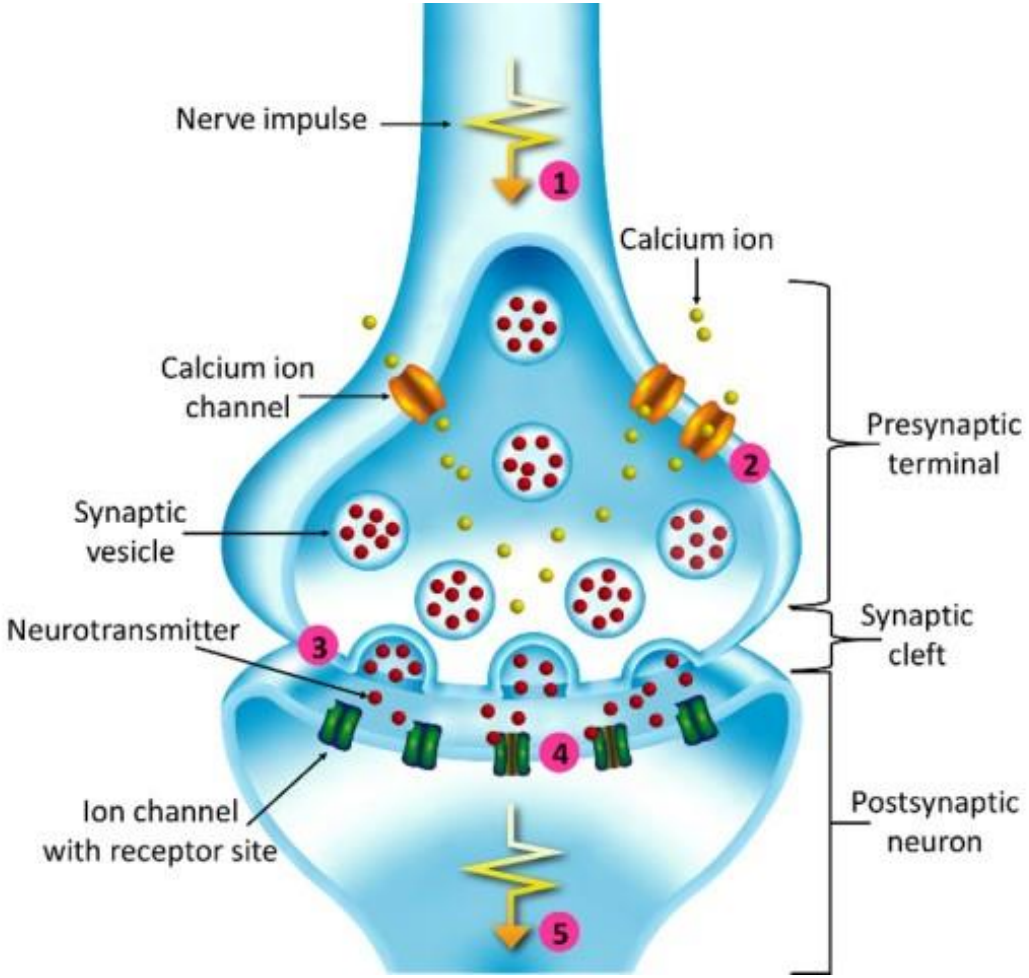
Hey, I’m Ronnie!

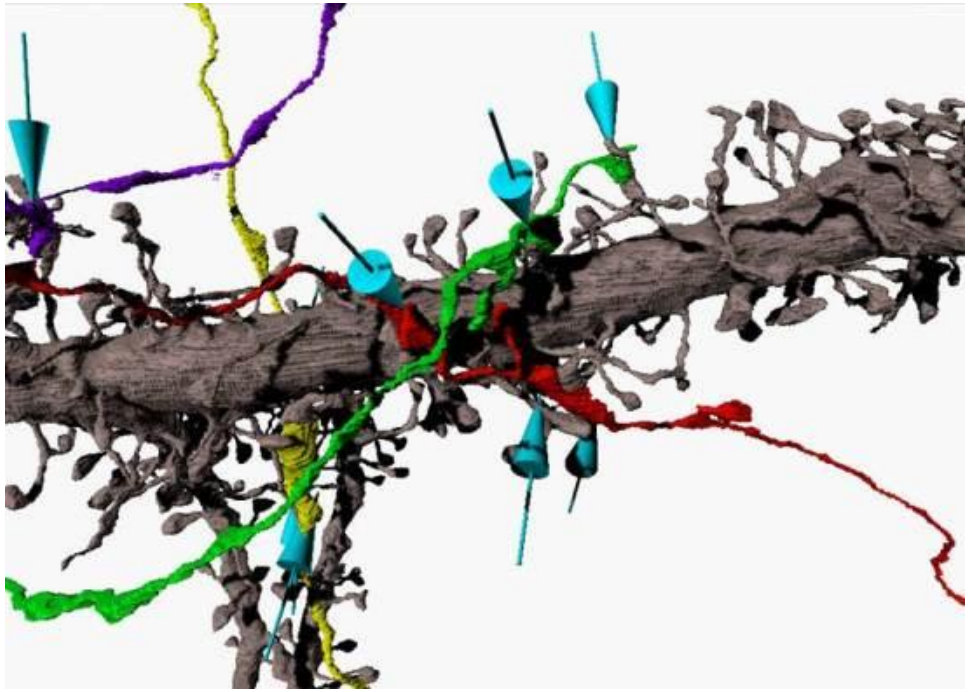
- Ph.D. Candidate in Neuroscience, Emory
  - Genomics and bioinformatics
  - Graduating end of this year
- B.S. in Neuroscience, Brown
- Qingdao, China → Long Island, NY → Providence, RI → Atlanta, GA
- Drawing/painting, rapping, reading, gaming, tennis and badminton, working on a memoir
- www.ronnieli.com

Outline and Objectives

Section	Learning Objectives
Neuronal communication: The synapse	1. Identify the key structures in neurotransmitter release and reuptake 2. List the basic steps required for synaptic transmission 3. Discuss where we can interfere with events in synaptic transmission
Medications and their mechanisms of action	1. Identify how medications mechanistically target tics 2. Understand why medications might have adverse side effects
My symptoms and challenges	1. Understand and validate the many struggles faced by people with Tourette 2. Appreciate the complexity of ethical and moral issues when dealing with coprolalia

How neurons communicate – synaptic transmission





1. Identify the **key structures** in neurotransmitter release and reuptake
2. List the **basic steps** required for synaptic transmission
3. Discuss where we can **interfere with events** in synaptic transmission

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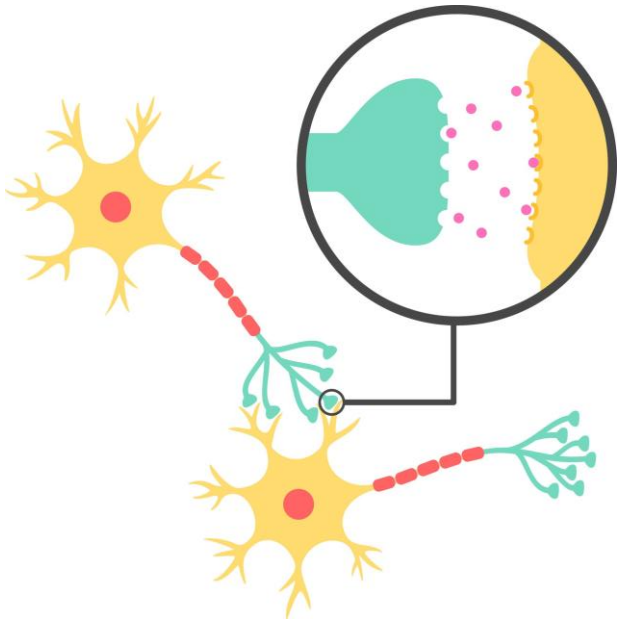
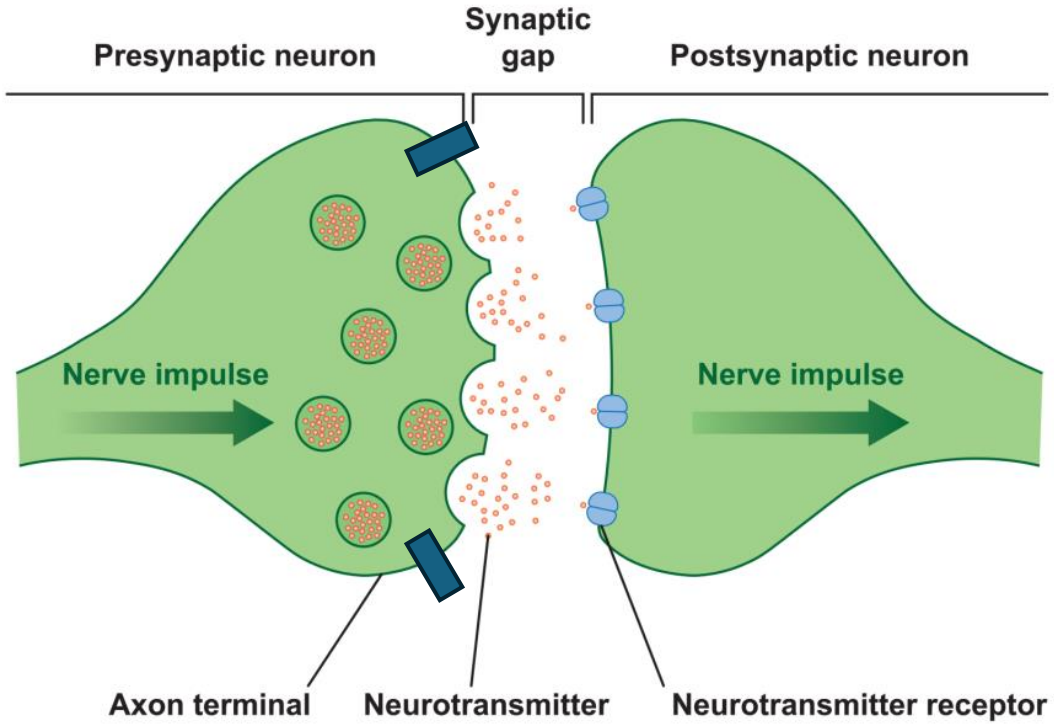
Basic steps of synaptic transmission





Neurotransmitters

- Dopamine
- Serotonin
- Glutamate
- GABA
- Acetylcholine
- Epinephrine (adrenaline)
- Norepinephrine (noradrenaline)

1. Nerve impulse (AKA **action potential**) reaches the end of a neuron
2. Synaptic **vesicles** containing **neurotransmitters** fuse with the membrane
3. Neurotransmitters are released into the **synaptic gap (cleft)**
4. Neurotransmitters bind to **receptors** on the other side, either activating or inhibiting the second neuron
5. Neurotransmitters drift away, get taken back up by **transporters**, or broken down by **enzymes**

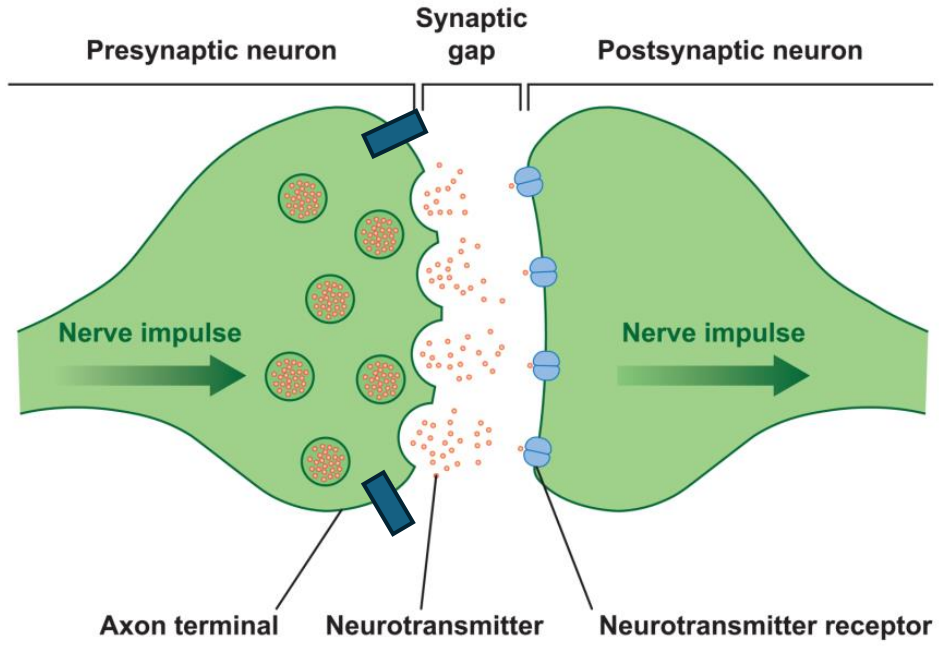
https://www.simplypsychology.org/synapse.html

Recap of synaptic transmission

https://www.youtube.com/watch?v=WhowH0kb7n0

Audience exercise: manipulate the system

Let's brainstorm some generic ways we can manipulate some of the processes in this system!



e.g. Activate the receptors on the postsynaptic side
- Clonazepam, diazepam, alprazolam

1. Block the **receptors** on the postsynaptic (receiving) side
   - Aripiprazole, haloperidol, pimozide, olanzapine

2. Block the **transporters** on the presynaptic (giving) side
   - All SSRIs (fluoxetine, sertraline, fluvoxamine)

3. Increase the **amount** of neurotransmitter released
   - Dextroamphetamine, methylphenidate

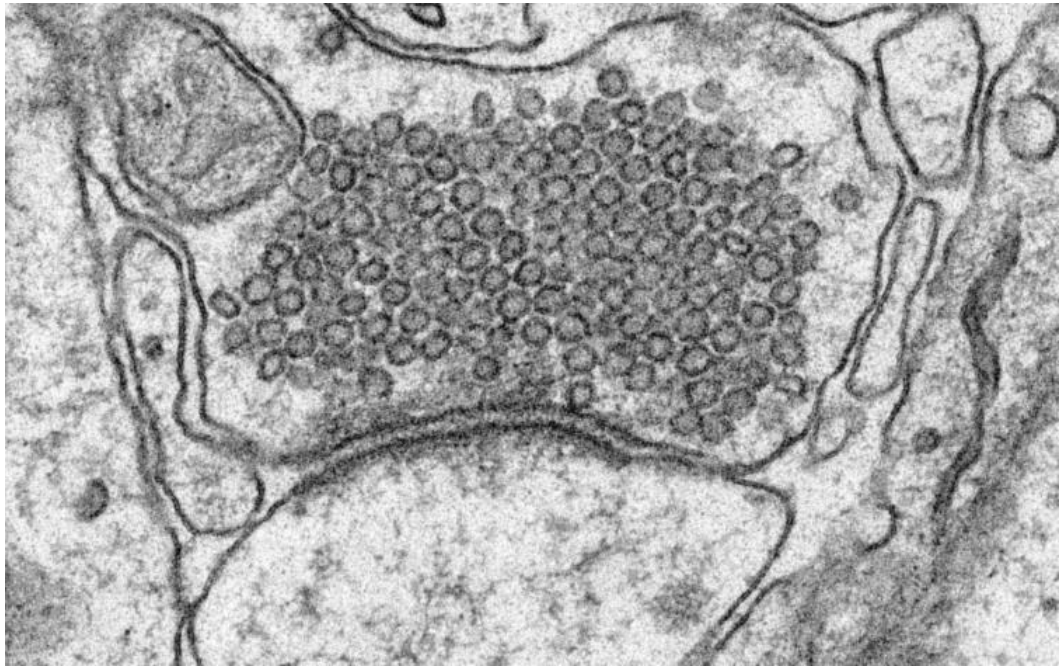
4. Prevent neurotransmitters from being **broken down**
   - Donepezil, rivastigmine

5. Prevent neurotransmitters from being **packaged into vesicles**
   - Tetrabenazine, valbenazine, deutetrabenazine

https://www.simplypsychology.org/synapse.html
https://web.mit.edu/zakf/www/drugchart/drugchart11.html

Summary: synaptic transmission

- The synapse is the basis for all communication between neurons in the brain
- Different neurotransmitters + different receptors = different outcomes
- Steps of synaptic transmission:
  1. Nerve impulse (action potential)
  2. Vesicles fuse with membrane
  3. Release of neurotransmitters
  4. Neurotransmitters bind to receptors on other side
  5. Neurotransmitters are reuptaken or degraded
- Most drugs work in the brain by targeting one of these processes

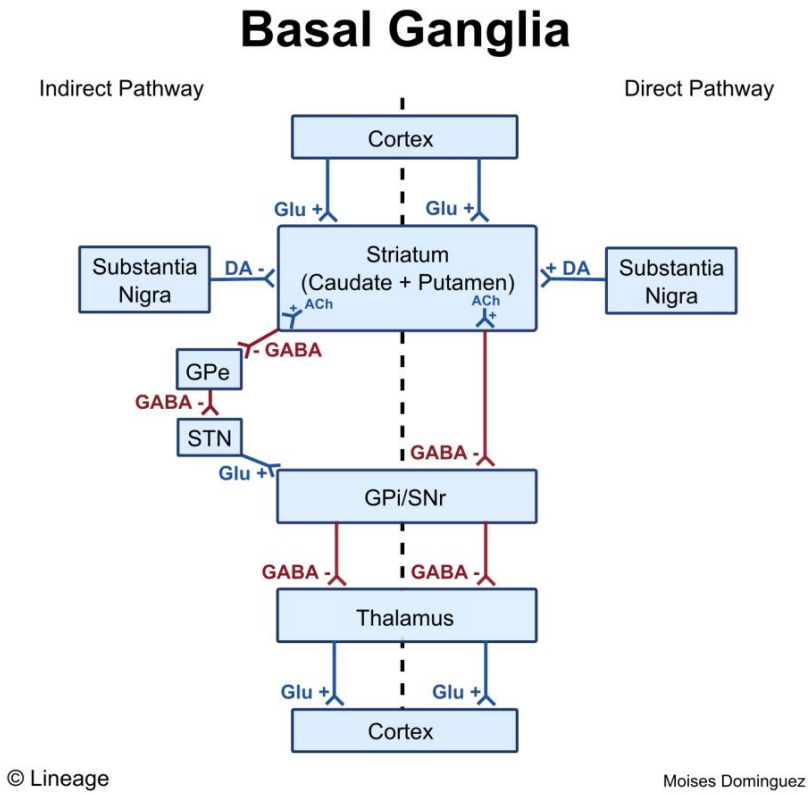


https://www.grc.org/synaptic-transmission-conference/2024/

Mechanisms of tic-targeting drugs

1. Identify how medications mechanistically target tics
2. Understand why medications might have adverse side effects

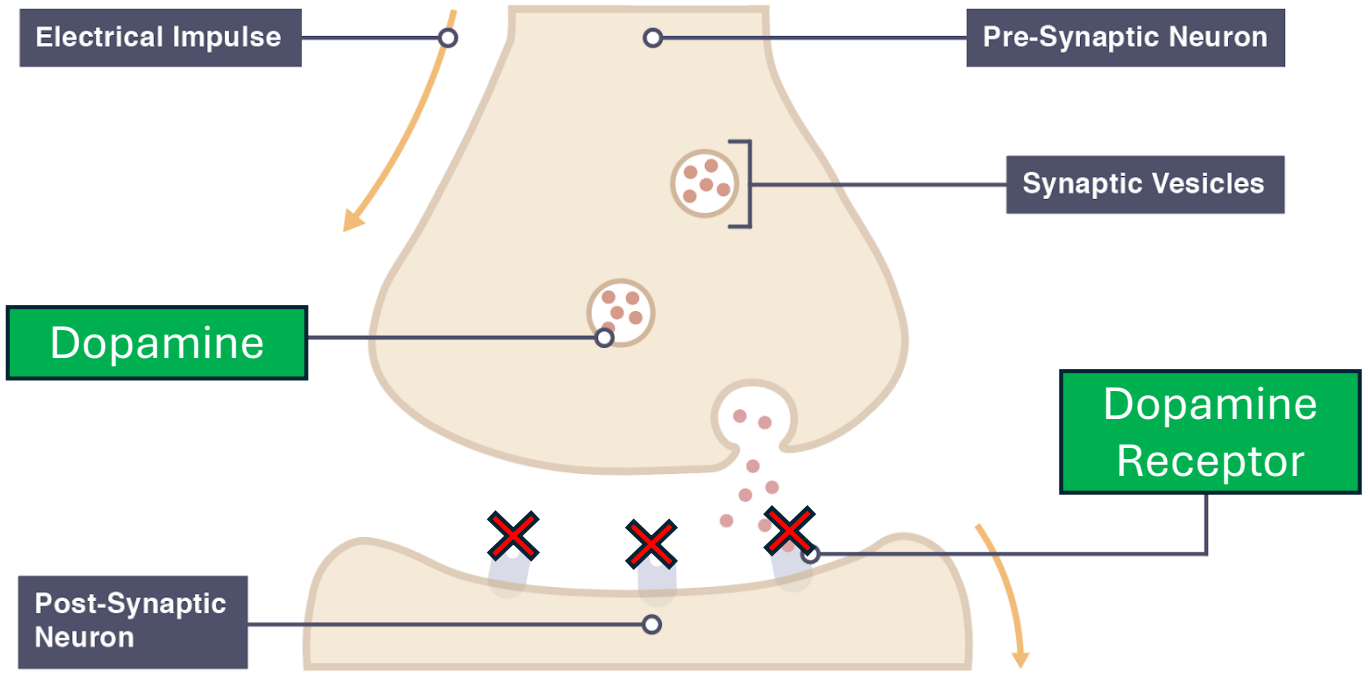
https://tenor.com/

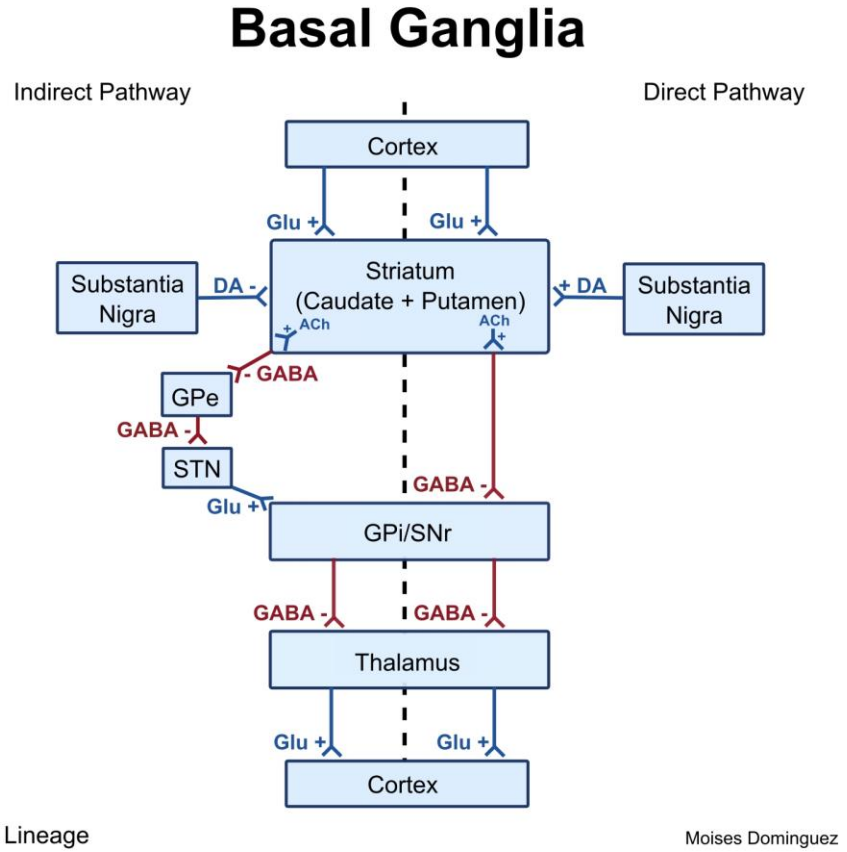


https://step1.medbullets.com/neurology/113008/basal-ganglia

Antipsychotics = dopamine blockers ("antagonists")

- Dopamine release in the basal ganglia generally promotes movement
- Loss of dopamine in the basal ganglia is the cause of **Parkinson's disease**
- Blocking dopamine receptors in the basal ganglia can lessen unwanted movements
  - **Antipsychotic** medications typically block **D2 receptors**
  - Examples: Haldol (haloperidol), Orap (pimozide), Abilify (aripiprazole)





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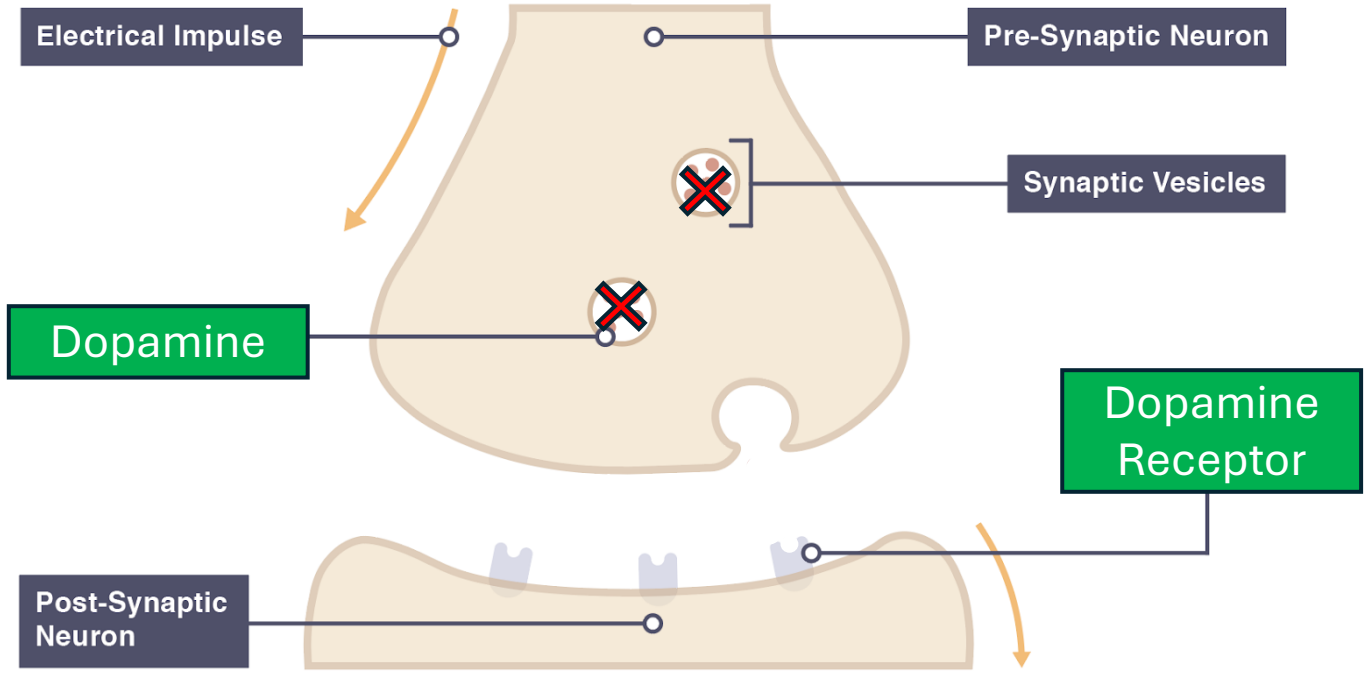
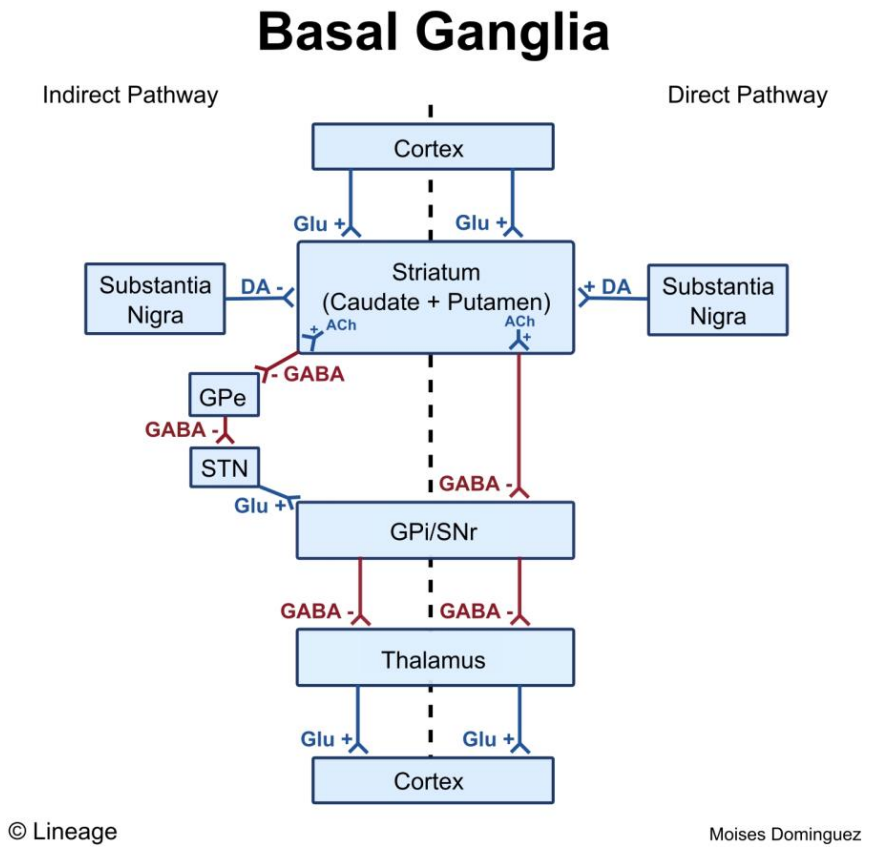
https://igcse-biology-2017.blogspot.com/2017/06/289-understand-role-of.html

A word on VMAT inhibitors (dopamine “depleters”)

- These drugs work upstream of the actual receptor binding events
- They prevent dopamine from being packaged into vesicles in the first place
  - Examples: Xenazine (tetrabenazine), Ingrezza (valbenazine), Austedo (deutetrabenazine)





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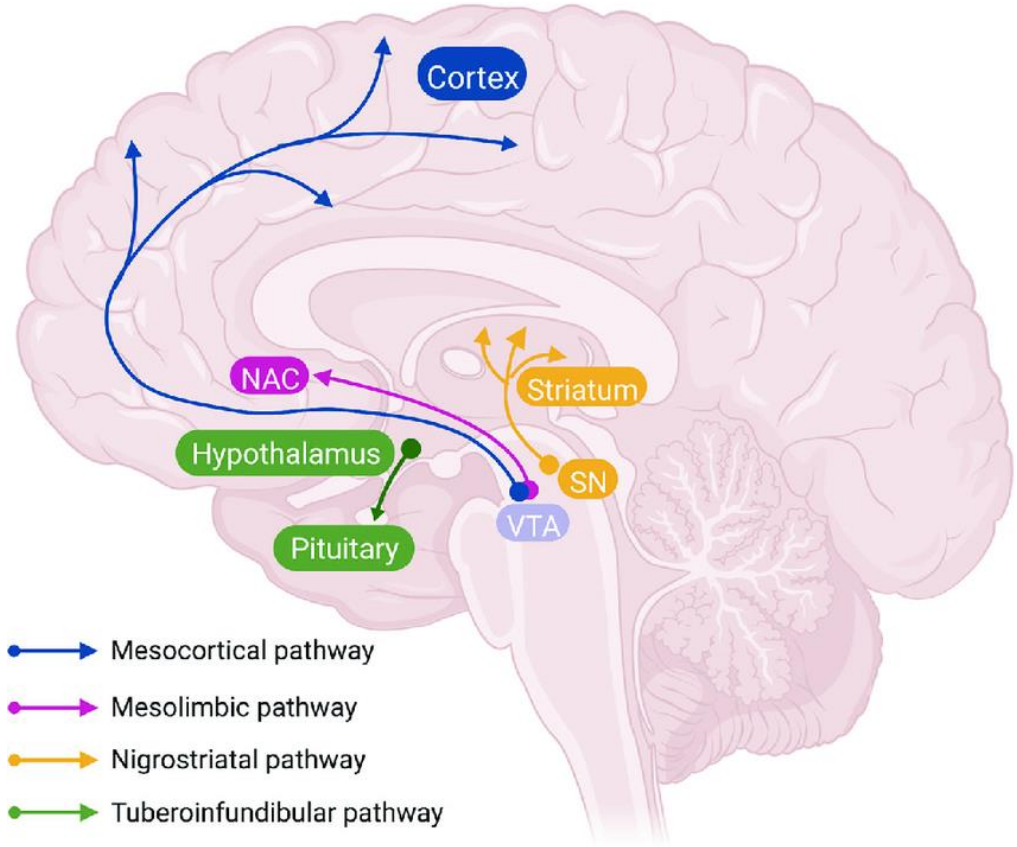
Why the side effects?

- Dopamine is present everywhere in the brain!
- It's impossible for a swallowed pill to target just one brain area

- "D2 are highly expressed in the caudate, putamen (basal ganglia), nucleus accumbens (NAC), ventral tegmental area (VTA) and the substantia nigra and in lower concentrations in the septal region, amygdala, hippocampus, thalamus, cerebellum and cerebral cortex."
  - VTA → NAC pathway is responsible for our feeling of reward
  - All drugs of abuse activate this pathway
  - Might explain depressive effects of antipsychotics

- Places in the body that have dopamine:
  - Gastrointestinal tract → constipation
  - Renal (kidney) microcirculation → urination problems



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https://psychopharmacologyinstitute.com/publication/d2-receptors-in-psychopharmacology-2116
https://www.researchgate.net/figure/Dopaminergic-pathways-in-the-brain-Dopaminergic-pathways-in-the-brain-include-the_fig2_365194389
https://www.webmd.com/drugs/2/drug-8661/haloperidol-oral/details

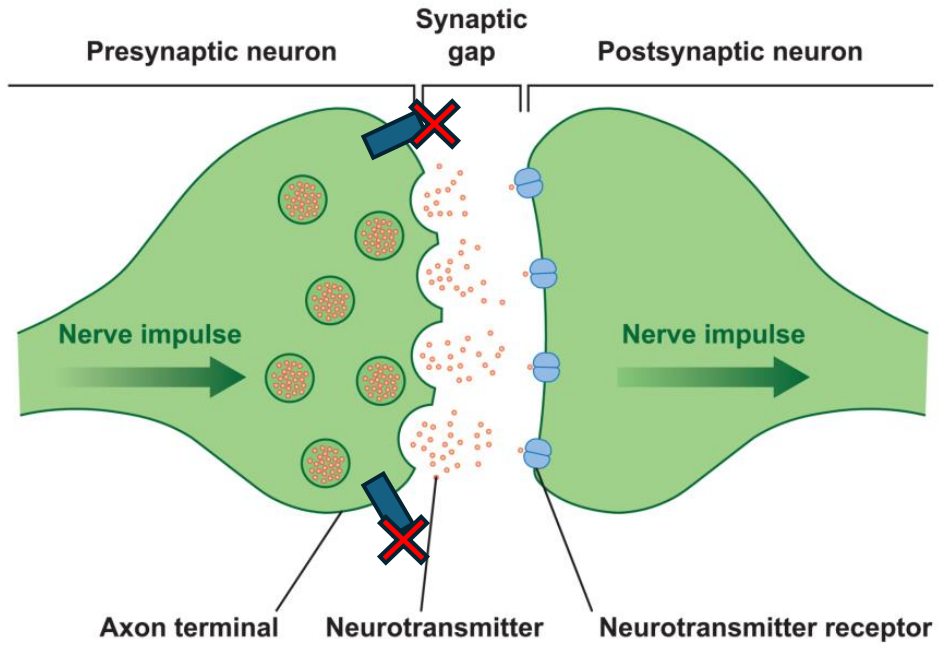
Selective serotonin reuptake inhibitors (SSRIs)

- Examples: Prozac (fluoxetine), Zoloft (sertraline), Lexapro (escitalopram)

- These are antidepressants that **block** serotonin **from being taken back up** by the cell
  - Overall result: more of it hangs around for longer
  - More serotonin is linked to better mood and decreased anxiety, can also help with OCD symptoms

- However, just like dopamine, serotonin is <u>everywhere</u> in the brain, so you will get side effects!

- Common side effects are sleep disturbances and insomnia
  - Serotonin promotes wakefulness



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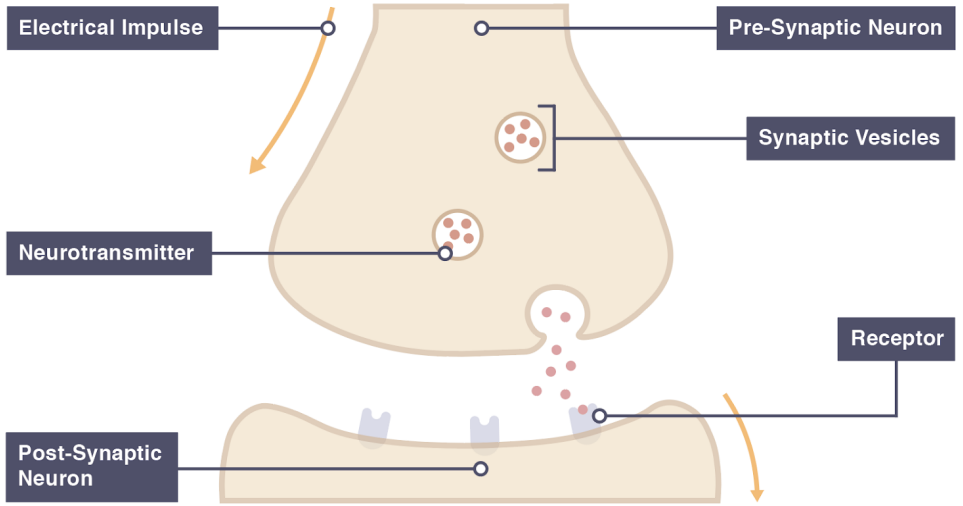
Pharmacological treatments for Tourette in brief

Drug class	Common examples	Work by…	Used to treat…	Watch out for…
Typical antipsychotics	• Haldol • Orap • Prolixin • Trilafon	Blocking dopamine (D2 receptors)	Vocal and motor tics, bipolar disorder	Sedation, anhedonia, akathisia, tardive dyskinesia, weight gain, constipation, dry mouth, QTc prolongation (heart)
Atypical antipsychotics	• Abilify • Zyprexa • Risperdal • Invega • Seroquel • Geodon • Vraylar	Mostly blocking dopamine (D2), but have effects on serotonin, norepinephrine, histamine, etc.	Vocal and motor tics, OCD, bipolar disorder	Similar to above
Dopamine depleters (VMAT inhibitors)	• Xenazine • Ingrezza • Austedo	Preventing dopamine from being packaged	Vocal and motor tics, tardive dyskinesia	Suicidality, drowsiness, dizziness
SSRIs	• Prozac • Zoloft • Lexapro	Increasing serotonin	Depression, OCD, anxiety	Sleep issues, dizziness, nausea, headache
Benzodiazepines (“benzos”)	• Xanax • Klonopin • Valium	Increasing GABA (inhibition)	Anxiety, muscle spasms, seizures	Sedation, light-headedness, dizziness
Antihypertensives	• Catapres • Tenex / Intuniv	Decreasing blood pressure and “fight or flight” response	Vocal and motor tics (milder), ADHD	Dizziness, blurred vision, constipation, dry mouth

Summary

- At a basic level, drugs treat tics by manipulating synaptic transmission, changing how neurons communicate
- **Antipsychotics** mostly work by blocking dopamine receptors
  - Newer-generation antipsychotics work on other systems, too
- **VMAT inhibitors** "deplete" the cell of dopamine and prevent it from being packaged
- **SSRIs** help with mood and OCD by increasing the amount of available serotonin at the synapse
- Side effects arise because these neurotransmitters are everywhere in the brain and body



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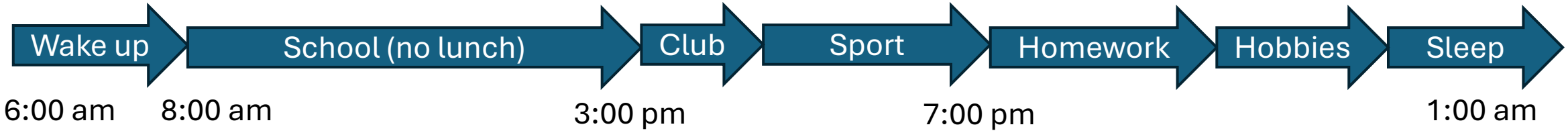
Personal stories and challenges

“How did you get into Brown?”

Tourette's, schmorette's

- Growing up, I was pushed "to the limit" academically because I was bright and motivated
  - "A bit of pain now for an easy life later"
  - "Talent without hard work is wasted talent"

Typical day of high school



- Having Tourette's was never a reason I couldn't do something
  - Pros: Expectations weren't lowered solely because of my disability
  - Cons: There are times that a disability prevents you from doing something

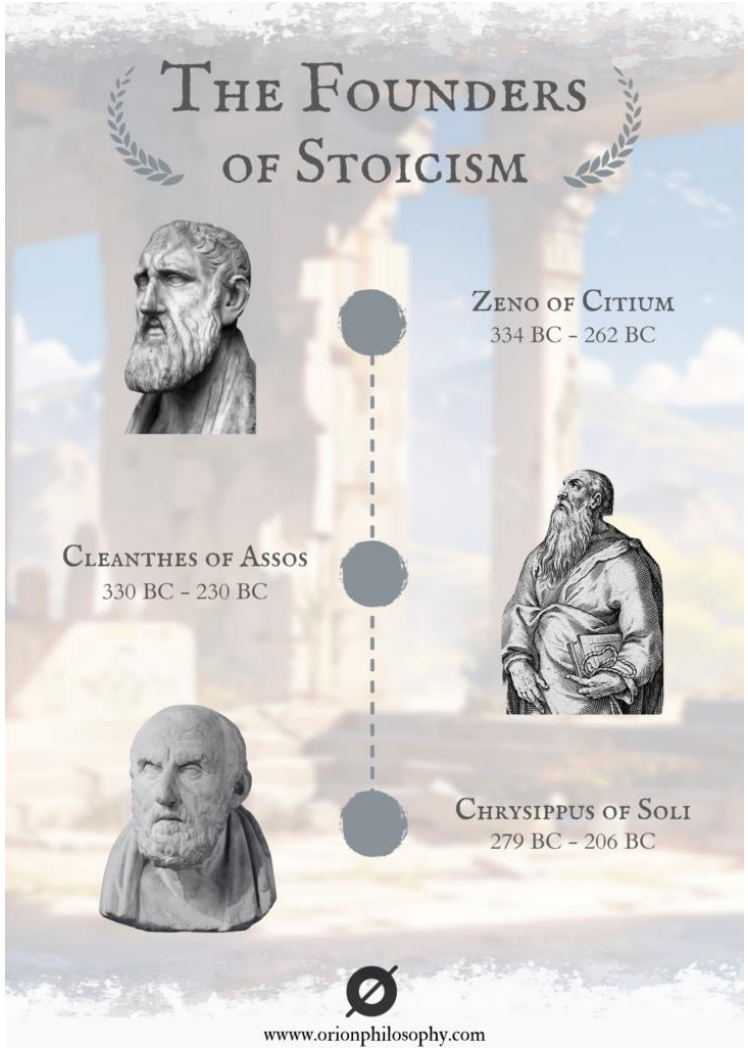
"I sacrificed a lot of my childhood to get into Brown. I'm not saying that's a good or bad thing because, frankly, I still don't know that myself. Every moment of pride is sprinkled with a dose of regret."

Embracing stoicism, understanding control

- I couldn't control my body, but I could control my mind

- My modus operandi:

1. Focus on what you can control
2. Life is a tennis match – one point at a time
3. Negative energy is wasted energy
4. Within every obstacle is opportunity
5. Trust the process – things work out



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Medications I've tried

Clonidine	Haloperidol	Aripiprazole
Guanfacine	Levetiracetam	Guanfacine ER
Pimozide	Methylphenidate	Fluphenazine
Risperidone	Tetrabenazine	Deutetrabenazine
Perphenazine	Dextroamphetamine	Valbenazine
Topiramate	Fluvoxamine	Sertraline
Olanzapine	Propranolol	Ziprasidone
Fluoxetine	Quetiapine	Clonazepam
Botulinum toxin	Cariprazine	

Current medications

Medication	Dose and frequency	Used to treat…
Vraylar (cariprazine)	3 mg daily	Excess "energy" associated with tics
Prozac (fluoxetine)	20 mg daily	Anxiety and OCD symptoms
Botox (botulinum toxin)	1.25 units bilaterally	Loud vocal tics

A neuroscientist's advice to parents

- Children are not blank slates
- Hindsight is always biased
- Prioritize reinforcement over punishment
- Your child might not "outgrow" their tics

Thank you!

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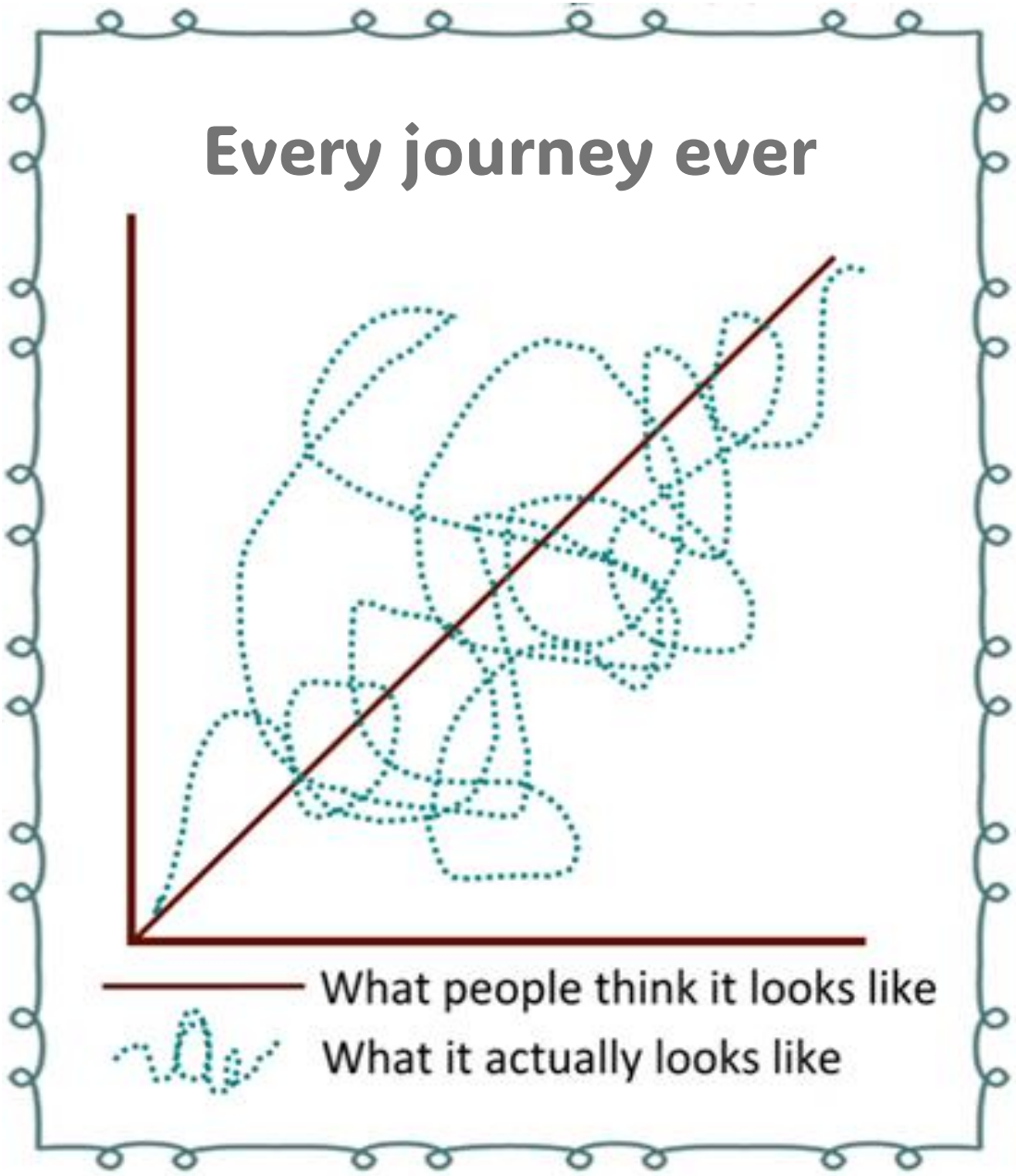

https://recoveryresources.com.au/wp-content/uploads/2014/07/Road-to-Recovery.png