

Depression and anxiety

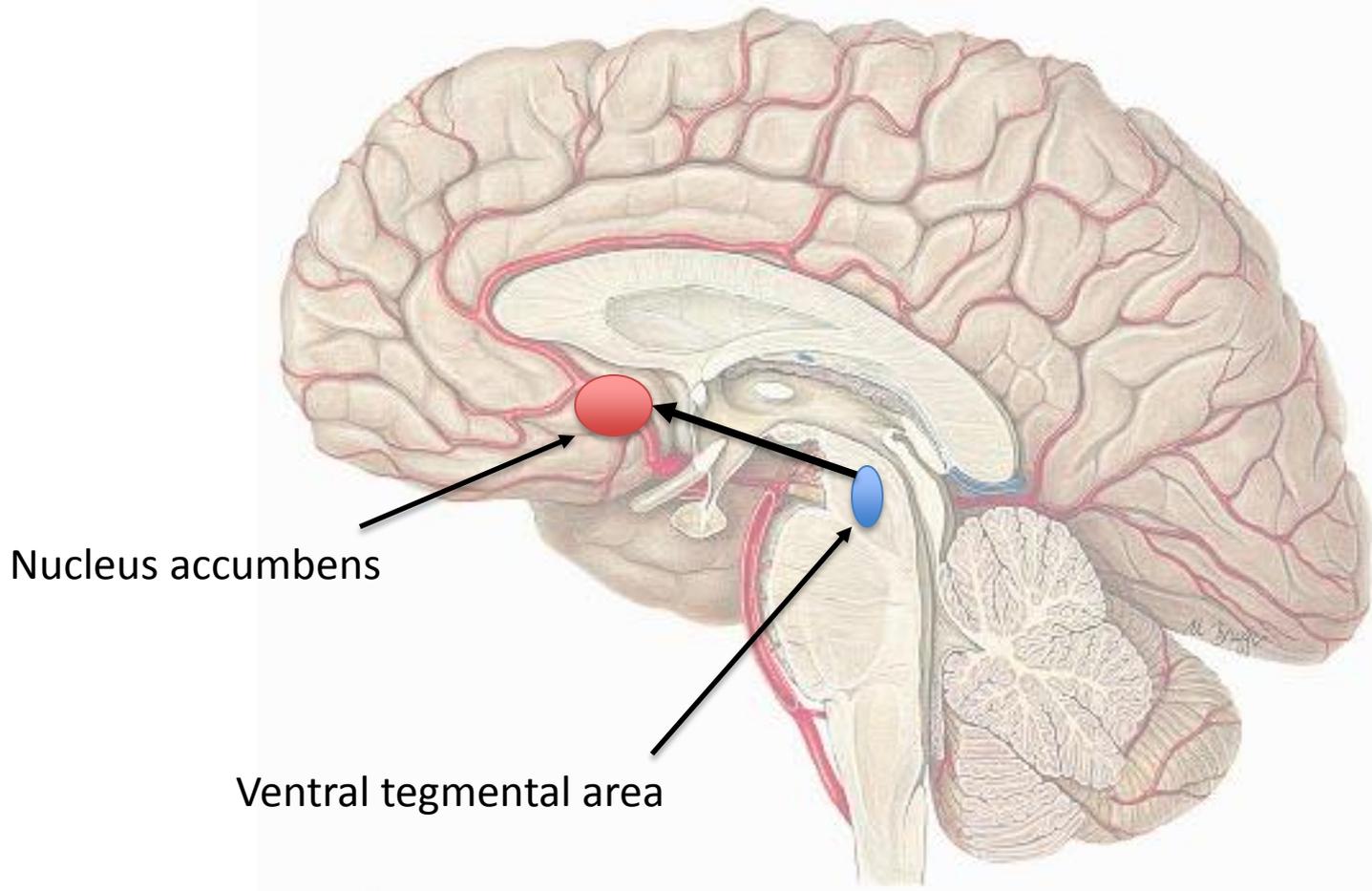
- They are very, very common.
- What are the symptoms of depression?
- What are the symptoms of anxiety?
- How do you treat it?
- Are antidepressants stimulants or depressants?

Introducing Dopamine and Serotonin

DA and 5-HT

- One thousand times less common than the major neurotransmitters
- Mainly modulatory, slow
- Originate in brainstem, but released throughout the entire brain and spine

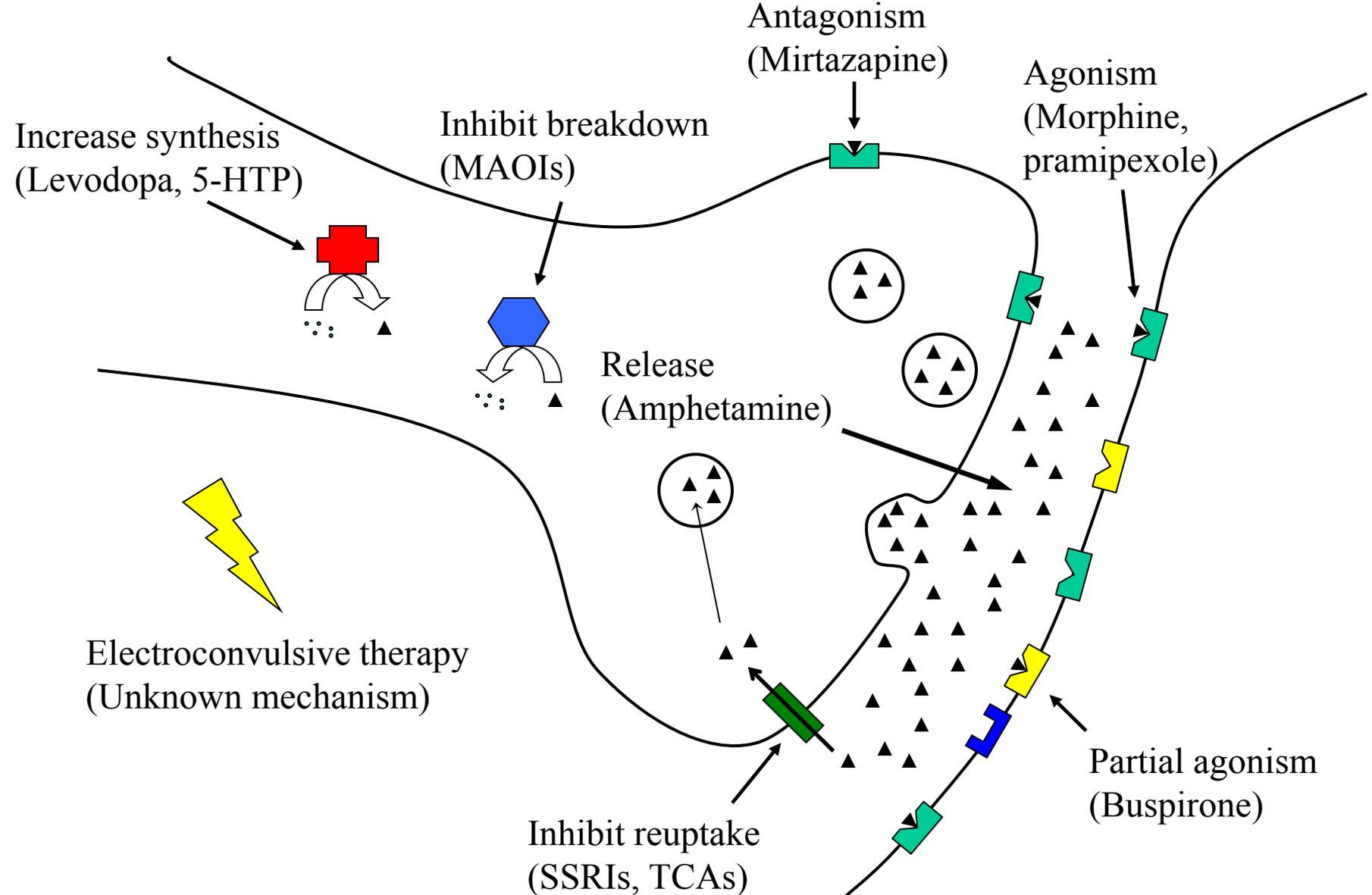
Midbrain Dopamine Neurons



5-HT, DA, and NE

- Effects of each
- Side effects of each
- When is each preferred?

Antidepressant Mechanisms



Treatments

- SSRIs: Effective, safe, few side effects.
 - Discuss suicide problem, evidence
- TCAs: Other suicide problem. Dry mouth (sounds like what?)
- MAOIs: Not so dangerous after all.

Antidepressant mechanisms

- SSRI: Inhibit 5-HT reuptake
- TCA: Inhibit 5-HT and NE reuptake (also antagonize ACh receptors, causing what?)
- MAOIs: Inhibit MAO breakdown of 5-HT, NE, and DA
- SNRI: Inhibit 5-HT and NE reuptake (Effexor, Cymbalta, Meridia) Meridia is for weight loss only

Antidepressant mechanisms

- Amineptine, benztropine: Inhibit DA reuptake, good for cocaine addicts
- Trazodone, nefazodone: Inhibit 5-HT reuptake, bind to specific receptors
- Mirtazapine, mianserin: Antagonize presynaptic (negative-feedback) NE receptors, thus boosting NE and 5-HT release, and antagonize specific postsynaptic 5-HT receptors to relieve anxiety

Antidepressant mechanisms

- Atomoxetine (Strattera): Inhibits NE reuptake, very good for ADHD
- Bupropion (Wellbutrin): Inhibit NE and DA reuptake, very good for smoking cessation and stimulant addiction
- Tianeptine: Enhances 5-HT reuptake, the opposite of all other antidepressants. What the hell?
- NERI: Inhibits NE reuptake (Reboxetine, desipramine, nortryptiline)

Classification is really approximate at this time. For instance, Paxil is always called an SSRI, but it actually has significant effects on NE, so it is very similar to the SNRI Effexor.

Are antidepressants sedatives or
stimulants?

Do antidepressants cause suicide?

- Yes, sometimes.
- Children and adolescents at greater risk, adults at some risk too.
- Untreated depression causes more suicide, and heart attacks, cancer, lost productivity, and healthcare expenses
- The suicide risk always comes early in treatment, so careful observation right after starting a medication might completely eliminate the risk.

Do antidepressants cause suicide?

- One thing is for sure: A very, very small percentage of the suicides in this country are caused by antidepressants. The vast majority occur in untreated individuals or antidepressant-treated individuals who have been on the same dose for a long time and were clearly incited to suicide by something more recent.

Do MAOIs deserve such a bad
rap?

Discussion: Are antidepressants
overprescribed?

Balanced or all-5-HT approach?

- Some people say that 5-HT makes people the happiest, with the fewest side effects. Hence SSRIs.
- Some people say that a balance of 5-HT and NE makes people happiest, and recommend the use of either SSRIs with NERIs or just SNRIs. The two-drug approach can allow separate titration of each neurotransmitter.
- NERIs and SNRIs cause high blood pressure and insomnia, and are not clearly more effective.

Other treatments

- Lithium: Unknown mechanism, beefs up brain cells
- Benzodiazepines: For anxiety. Remember antipunishment effects?
- Opioids: Yup.

Animal models

- Depression: Forced swim test, learned hopelessness
- Anxiety: Elevated plus maze
- Reserpine
- Lots of stress hormones

Can you grow new brain cells?

Neurogenesis

- Depressed people have smaller hippocampi
- Human hippocampi shrink as depression progresses
- Depressed rats have fewer young cells in their hippocampi
- All antidepressants make the hippocampus grow larger
- Cells get bigger and more numerous (hypertrophy and hyperplasia)
- Irradiating the hippocampus blocks antidepressant benefit

Antidepressants cause neurogenesis

A great review of the evidence in layman's terms is here:

psycheducation.org/mechanism/MechanismIntro.htm

Depression and stress hormones

- Depressed humans and rodents have **too much cortisol** (stress hormone) in their blood
- Giving dexamethasone to depressed humans/rodents **does not suppress** cortisol release as much as it should
- Cortisol kills hippocampal brain cells
- Positive feedback loop
- HPA (hypothalamic-pituitary-adrenal) axis

Slow efficacy

- 5-HT, NE, and DA targeted antidepressants usually take 2-3 weeks before you see improvement. Some people see immediate improvement. Some studies show that 8 or 12 weeks are required for maximum effect.
- Short studies artificially deflate the efficacy of antidepressants, they work much better than placebo in long studies
- Side effects are immediate, and decline over a few weeks. Many patients give up before side effects subside and effectiveness takes hold.

Why the latent period?

Maybe receptor populations need to change. For instance, maybe feedback mechanisms initially prevent the 5-HT level from rising, but over time those feedback mechanisms give up.

Maybe it takes time for new brain cells to grow.

Maybe it takes time for the drug level to build up in the bloodstream.

Maybe it is psychological: Depression is learned helplessness and despair that was reinforced over years of bad experiences and anhedonia. It takes time for the brain to change gears, and learn to be optimistic.

About the latent period

It is not universal, and it is not predictable.

Sometimes it is one week, sometimes it is twelve weeks. Sometimes there is no latent period, but rather a “honeymoon” which quickly fades.

Anxiety might improve before depression, or vice versa.

OCD usually takes the longest to respond, quite probably because it takes a long time to forget old habits even after the chemicals driving them have been fixed.

Antidepressants cure everything!

- Melancholic depression (not sleeping, not eating, hopelessness, guilt, shame, nothing makes you happy)
- Atypical depression (good things make you happy, you might eat too much, you might sleep too much)
- Psychomotor depression (you are so unhappy that you talk and move slowly)
- Agitated depression (you are so unhappy that you are frantic and edgy all the time)
- Bipolar depression (this is a symptom of bipolar disorder/manic depression, antidepressants are second-line medications for this disease)

Antidepressants cure everything!

- Psychotic depression (plus antipsychotics)
- Schizophrenia, schizoaffective disorder (psychotic people are often depressed, with very blunt emotions)
- PMS/PMDD
- Seasonal affective disorder (SAD)
- Posttraumatic stress disorder (PTSD)
- Social anxiety
- General anxiety
- Panic disorder
- OCD (Especially SSRIs)
- ADHD (certain antidepressants, atomoxetine)

Antidepressants cure everything!

- Sleep disorders (narcolepsy, especially MAOIs)
- Insomnia (trazodone most popular hypnotic)
- Fibromyalgia (diffuse pain in many body parts, perhaps caused by sleep disorder, perhaps psychogenic, probably neurological in some way)
- Pain (Dr. House would be on additional drugs, not just Vicodin. He would probably be on antidepressants.)
- Headaches
- Premature ejaculation (Paxil treats it)
- Anorgasmia (Wellbutrin treats it)

Antidepressants cure everything!

- Eating disorders (too much and too little)
- Irritable bowel syndrome
- Autism spectrum disorders
- Alcoholism

Antidepressants cure everything!

- Drug addiction
 - Antidepressants help drug addicts in many ways.
 - Many addicts are depressed or anxious. Sometimes that is why they started using drugs, or sometimes it is a consequence of the damage the drugs did to their life, friends, brain, and body. Either way, antidepressants treat depression and anxiety.
 - Bupropion (Wellbutrin, Zyban) is good for smokers.
 - Amineptine and nomifensine are good for cocaine addicts, they increase DA levels.
 - Desipramine is good for PCP, ketamine, and cough syrup addicts, it can cure withdrawal from that class of drugs.

Antipsychotic/Antidepressant: The psychiatrist's speedball. Talk about how antidepressants alone cause suicide. Relate to Chris Farley, River Phoenix, why speedballs are so appealing. Relate to cocaine having faster elimination, and heroin overdoses being slow. Relate to benzodiazepine abuse to "come down" from stimulants. Relate to stimulants causing crashes, which is really just being half high, and sedatives causing hangovers, which (aside from alcohol) is just being half high as well.

MIT OpenCourseWare
<http://ocw.mit.edu>

ES.S10 Drugs and the Brain
Spring 2013

For information about citing these materials or our Terms of Use, visit: <http://ocw.mit.edu/terms>.