3 ANTIDEPRESSANTS

Now that you have been introduced to each of the major neurotransmitters, we're ready to talk about the drugs themselves. The first class we will cover are **antidepressants** which are among the most widely prescribed drugs in all of medicine, with over 10% of all adults in the United States reporting having taken an antidepressant in the past month.

Almost all antidepressants impact **serotonin** to some degree, which makes sense given this neurotransmitter's key role in emotional processing and feelings of satisfaction. The most common class of antidepressants are the **selective serotonin reuptake inhibitors** (SSRIs) which increase the amount of serotonin that is available in the synaptic cleft. In addition to SSRIs, there are also a few of other antidepressant types including **serotonin-norepinephrine reuptake inhibitors** (SNRIs), **tricyclic antidepressants** (TCAs), and **monoamine oxidase inhibitor** (MAOIs) as well as a grab bag of "atypical" antidepressants that don't fit neatly into any of these categories.

In this chapter, we'll first introduce the most commonly used medications in each class. When we talk about specific drugs, we will try to focus on what sets it apart from its peers (like why you would want to use one drug over another). From there, we will talk about the overall principles that you should consider when starting a patient on antidepressants.

One final note: from time to time, you may see additional terms like serotonin reuptake inhibitor (SRI) or norepinephrine reuptake inhibitor (NRI) used as well. These are broader terms that encompass *all* medications that inhibit the reuptake of that particular neurotransmitter, as opposed to terms like SSRI which are more specific to drugs that *only* involve serotonin. Keep in mind that these terms are related, but ultimately distinct, concepts.

And with that, let's get to know the antidepressants!

ANTIDEPRESSANT EFFECTS

So what do antidepressants *do* exactly? This is a much trickier question than it initially appears, but let's start with what we know. Most antidepressants work by increasing synaptic levels of serotonin in the brain. While there is no evidence that depression results from any sort of "**chemical imbalance**," the fact remains that medications that boost serotonin are effective at reducing depression symptoms in the majority of people who take them.

How does serotonin do this? One theory suggests that it has to do with the way that depressed people process information. To put it simply, people with depression see the world differently. Depression causes a tendency to focus on negative, rather than positive, stimuli. When presented with a list of words, for example, people with depression are more likely to focus on words like "hate" or "pain" rather than "love" or "comfort." When shown a variety of faces, a depressed person will fixate on people with negative facial expressions while blocking out those with positive expressions. This phenomenon is referred to as a **negative affective bias***: negative* for sad, *affective* for emotional, and *bias* for being drawn to certain stimuli over others.

*Example of a **negative affective bias** in a patient with **depression**.*

What is perplexing about serotonergic medications is that they increase serotonin within *minutes* of taking the drug, but the effect on depression isn't seen until weeks or months later. Why do antidepressants take so long to work? While antidepressants don't instantly cure depression, they *do* cause an immediate decrease in negative affective biases. Tellingly, this change in perception perfectly coincides with the drug's serotonin-boosting effect in the brain. Within minutes of taking an antidepressant, people with depression are more able to remember positive words and are less fixated on sad parts of images. These effects are seen even when people *without* depression are given these medications, suggesting a primary drug effect.

By targeting the negative affective biases found in depression, antidepressants set the stage for a *gradual* unlearning of depressive thought patterns. Like any form of learning, this process will not happen overnight. Rather, it will take days, weeks, months, or (in cases of severe depression) even years to learn to see the world as a more hopeful, less threatening place. In fact, studies have found that the extent to which an antidepressant will ultimately help someone can be predicted by how much it changes their emotional processing within even the first few days of treatment.

Ultimately, there is no getting around the fact that antidepressants are not simple, one-shot drugs that target depression like a silver bullet. They don't work in the way that many people think, leading to dashed hopes and unmet expectations. While this can be frustrating, there is a silver lining in knowing that, by catalyzing the process of learning new ways of thinking and interpreting the world, antidepressants can create lasting changes in a way that one-shot drugs rarely can.

So what are the downsides of using serotonin? Let's review its other functions using our **SPAROW**-tonin mnemonic so we know what side effects to expect here. These include changes in **S**leep and energy, **P**latelet dysfunction (mostly in patients already at high risk), **A**bdominal upset including nausea and diarrhea, **R**eproductive effects like low libido and anorgasmia, the risk of **O**verdose and serotonin syndrome, and finally the possibility of **W**eight gain when used long-term. Some side effects, like nausea and diarrhea, are most noticeable in the first few weeks of starting the drug and can be reduced by starting at a low dose and gradually increasing. In contrast, other side effects, like sexual dysfunction, will generally persist as long as the patient keeps taking the drug.

ANTIDEPRESSANT DISCONTINUATION SYNDROME

Serotonergic medications are also associated with a **discontinuation syndrome** when the drug is stopped abruptly. You can use the word **FINISH** to remember the unpleasant symptoms that this syndrome involves, including **F**lu-like symptoms and a general sense of malaise, **I**nsomnia and disturbed sleep, **N**ausea and upset stomach, **I**mbalance including light-headedness and vertigo, **S**ensory disturbances such as tingling and electrical sensations in the head (sometimes called "brain zaps"), and **H**yperarousal including increased energy and anxiety. These symptoms generally appear quickly after the drug is stopped and then resolve slowly over the next few weeks. While not everyone experiences a discontinuation syndrome, it is common enough that it is worth counseling your patients to avoid abruptly stopping their medications and instead aim for a slow taper over several weeks or even months!

Serotonergic medications can be associated with a **discontinuation syndrome**.

FINISH:
F*lu-like symptoms*
I*nsomnia*
N*ausea*
I*mbalance*
S*ensory disturbances*
H*yperarousal*

SEROTONIN-SPECIFIC REUPTAKE INHIBITORS

Now that we have a better understanding of serotonin's role in treating depression, let's take a look at the individual SSRIs to understand what makes each one unique!

FLUOXETINE

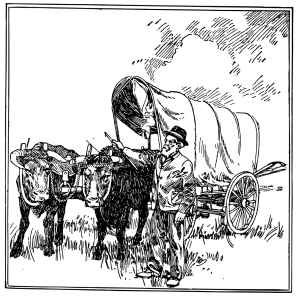
Fluoxetine (Prozac) is one of the more **activating** SSRIs, with patients often feeling increased energy and at times even some jitteriness. In addition, fluoxetine has one of the **longest half-lives** of any SSRI. Why is this important? Because fluoxetine (as well as its metabolite norfluoxetine) stay in the bloodstream longer than other SSRIs, it can be a good option for people who aren't great at remembering to take medications regularly. There also tend to be fewer rebound side effects because the drug effectively tapers itself. On the other hand, because it lingers in the system so long, you have to be careful not to add another serotonergic drug too fast to avoid causing serotonin syndrome. By focusing on the "flu" part of the name, you can remember that fluoxetine, like the flu, generally lasts about 1 to 2 weeks. So when you see **flu**oxetine, think of the **flu** and the **week** you spent in bed when you got it.

Fluoxetine has a very **long half-life**.

*Like the **flu**, **flu**oxetine generally lasts about **1-2 weeks**.*

PAROXETINE

Paroxetine (Paxil) is more **sedating** than most SSRIs, so try to dose it at bedtime. In addition, paroxetine has been linked to birth defects, so it should be avoided in pregnant patients. Finally, in contrast to fluoxetine, paroxetine has a very **short half-life** of less than 24 hours! This means that any rebound effects will likely happen much faster and will be more uncomfortable than, say, fluoxetine. How to remember this important fact? When traveling by wagon, you will move much **faster** with a **pair** of **ox**en than with a single ox. Use this to remember that **parox**etine is a **fast** SSRI.



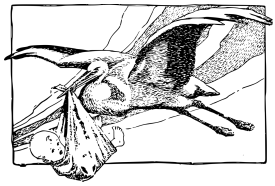
Paroxetine has a **short half-life** (less than 1 day) and is very **rapidly absorbed**.

*A **pair** of **ox**en moves **faster** than a single ox.*

SERTRALINE

The serotonergic effect of sertraline (Zoloft) should be is easy to remember, as the "**ser**" of **ser**otonin is built right into the name! Interestingly, sertraline also appears to inhibit the dopamine transporter, so some have argued that it should be classified as an SDRI. In general, however, it is classified as an SSRI.

In terms of what makes this drug unique, two things stand out. First, sertraline can have harsher **gastrointestinal** side effects such as nausea and diarrhea compared to other SSRIs, which has earned it the endearing nickname of "**squirt**-raline" among patients. Tell patients to take it with a meal to help aid absorption and decrease GI effects. Second, sertraline is one of the safest SSRIs for **pregnant** or **breastfeeding** patients, as less of the drug gets into the fetal circulation or breast milk. If you use your imagination, the mnemonic **squirt**raline can help you this connection as well!



Sertraline has **more GI side effects** but is safer when **pregnant** or **breastfeeding**.

*Think **squirt**-raline to remember **diarrhea** and **breast milk**.*

CITALOPRAM AND ESCITALOPRAM

These next two SSRIs are basically twins. Citalopram (Celexa) is the base drug, with escitalopram (Lexapro) being a purified version of its S-enantiomer which is the active form. This means that a 10 mg dose of escitalopram is equivalent to a 20 mg dose of citalopram. Dosing aside, citalopram and escitalopram is basically the same. Both are very "**clean**" SSRIs that don't have many drug interactions. However, the downside is that they can **prolong the QTc interval** which is a marker of the electric properties of the heart. Theoretically, QT prolongation can increase the risk of arrhythmias and even sudden death, although there is a lack of data linking either of these drugs to *actual* cases of harm. Nevertheless, it is still recommended to track EKGs for patients taking these drugs and to avoid prescribing it to anyone with pre-existing arrhythmias. You can remember this association by thinking of a **car seat** to remind you that **seat**-alopram and es-**seat**-alopram require an electro-**car**-diogram.

Citalopram and **escitalopram** can cause **QTc prolongation**.

*Think of a **car seat** to remind you that **seat**-alopram and es-**seat**-alopram require an electro-**car**-diogram.*

FLUVOXAMINE

The last SSRI we will talk about is fluvoxamine (Luvox). In contrast to other SSRIs (and especially citalopram and escitalopram), it is very "**messy**" and has many drug-drug interactions. Because of the complications this introduces (such as having to re-dose other medications that the patient is taking), it is not frequently used these days.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

While serotonin is commonly used during treatment of depression, it is not the only neurotransmitter at our disposal. As you will recall from Chapter 2, norepinephrine is associated with increased **F**ocus and energy from getting **F**ired up, both of which could be helpful in treating depression. Indeed, drugs that boost both norepinephrine and serotonin (known as **serotonin-norepinephrine reuptake inhibitors** or SNRIs) do appear to be effective antidepressants while also having positive effects on other conditions like anxiety.

However, you might be asking yourself why increasing norepinephrine is helpful for treating anxiety. After all, isn't **F**ear one of the effects that norepinephrine has in the brain? Couldn't this make anxiety and depression *worse*? While this is a completely logical conclusion, for whatever reason norepinephrine reuptake inhibitors actually *help* anxiety and depression. There are no good explanations for this "noradrenergic paradox" yet, although it is possible that norepinephrine may have different effects depending on whether it is arrives in a "flash flood" (as in sympathetic nervous system activation) or as a "steady trickle" (as in long-term medication administration).

The downside of norepinephrine involvement is that the **F**ull body response can add some additional side effects over what is seen from serotonin alone. Increases in **heart rate** and **blood pressure** can be seen with norepinephrine reuptake inhibitors which requires careful monitoring, especially at higher doses.

VENLAFAXINE AND DESVENLAFAXINE

The next two drugs we will talk about boost not only norepinephrine but serotonin as well, making them serotonin-norepinephrine reuptake inhibitors or SNRIs.

We'll first go over venlafaxine (Effexor) You can remember the involvement of **N**orepinephrine by focusing on the **en** sound of v**en**lafaxine. So how does the presence of norepinephrine impact treatment? When venlafaxine first came out, there was excitement that the dual mechanism would result in a more effective antidepressant, or at least one with a unique profile of positive effects. Despite the hype, it has become increasingly clear that venlafaxine is more similar to most SSRIs than it is different. In fact, at low to moderate doses, this drug is **basically an SSRI**, as the norepinephrine transporter is only affected at higher doses.

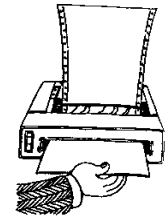
If anything, the main way that venlafaxine has differentiated itself is in terms of new side effects, with **hypertension** being seen at higher doses. In most cases, the vascular effects are short-lived, but in some cases venlafaxine can induce sustained hypertension. Because of this, close monitoring of blood pressure is a requirement.

Venlafaxine is an **serotonin-norepinephrine reuptake inhibitor** that can cause **hypertension** at higher doses.

*V**en**lafaxine impacts **n**orepinephrine at higher doses and can cause hypert**en**sion.*

Like paroxetine, venlafaxine has a **short half-life** of less than 24 hours, even in extended release formulations! Because of this, it tends to produce more severe discontinuation side effects than, say, fluoxetine. In some patients, the rebound

syndrome can be so severe that it takes months to fully taper them off of the drug. Keep this in mind if you will be taking someone off venlafaxine, and be prepared to go very slowly! To remember this side effect, focus on the **fax** part of venla-**fax**-ine. This should remind you that it is **faster** to send a **fax** compared to regular mail. However, even with the availability of newer and better technology like emails, fax machines are still around, showing that they **take a long time to go away**!



Venlafaxine is **rapidly metabolized** with unpleasant **discontinuation effects**.

*Like a **fax** machine, venla-**fax**-ine is **fast** but **takes a long time to go away**!*

Most of the venlafaxine that a patient takes is converted to its active metabolite desvenlafaxine which is itself available as a drug (marketed as Pristiq). Like citalopram and escitalopram, the efficacy and side effects of these drugs are basically the same.

DULOXETINE

Another common SNRI is duloxetine (Cymbalta). Unlike venlafaxine (which is basically an SSRI until you hit higher doses), duloxetine impacts serotonin and norepinephrine more evenly at all doses! This means that the same warnings about blood pressure apply here as with venlafaxine. Focus on the **dual** part of **dual**-oxetine to remind you of the **dual** mechanisms at play. Duloxetine has another unique feature which helps to differentiate it from other antidepressants. In addition to treating depression, duloxetine can also help with **chronic pain** conditions such as neuropathic pain or fibromyalgia, as it seems to lessen pain sensation to some degree. You can remember this **dull**ing effect by thinking of it whenever you see **dull**-oxetine.

Duloxetine is a **serotonin-norepinephrine reuptake inhibitor** that not only treats depression but can be used for **chronic pain** as well.

***Dual**-oxetine has a **dual** mechanism.*
***Dull**-oxetine helps to **dull** the pain.*

MILNACIPRAN AND LEVOMILNACIPRAN

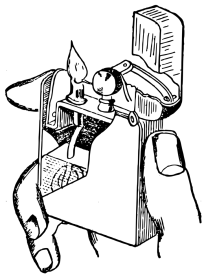
The final two SNRIs we will talk about are milnacipran (Savella) and levomilnacipran (Fetzima). (Like escitalopram, levomilnacipran a purified enantiomer of milnacipran, but the two can generally be treated similarly.) Compared to other SNRIs, milnacipran has **strong effects on norepinephrine** (versus the weak effects of venlafaxine and the moderate effects of duloxetine). However, this doesn't translate into much clinically, with the same benefits (pain relief) and same side effects (high blood pressure), so there is not much reason to use (levo)milnacipran over its less expensive alternatives.

"ATYPICAL" ANTIDEPRESSANTS

In addition to SSRIs and SNRIs, there are several other medications that have been useful as antidepressants. They don't fit as neatly into discrete mechanistic classes as SSRIs or SNRIs, so they are often referred to as "other" or "atypical" antidepressants.

BUPROPION

If adding norepinephrine into the mix works for depression, why not try dopamine as well? As you'll recall from Chapter 2, **motivation** and **attention** are core functions of dopamine which are both lost in depression. Could boosting dopamine help to reverse these symptoms? Out of this thought came a drug called bupropion (Wellbutrin).



Unlike the other antidepressants we've studied thus far, bupropion doesn't have significant effects on serotonin receptors. Instead, it works as an **norepinephrine-dopamine reuptake inhibitor** (NDRI). Despite the lack of serotonin involvement, studies show that it is equally effective at treating depression as its SSRI and SNRI counterparts. You can remember this mechanism by focusing on the "**bu**" part of **bu**propion and associate it with the word "**bu**tane". The word "**bu**tane" (if you misspell it slightly) will help you to link "**bu**" to "**DA-NE**," which represents **D**op**A**mine and **N**or**E**pinephrine.

Bupropion boosts **dopamine** and **norepinephrine** but lacks serotonin involvement.

Bu*propion =* ***D****op****A****mine +* ***N****or****E****pinephrine =* ***Bu-DA-NE*** *(butane).*

"**Budane**" can also help us remember two unique features of bupropion. First, the fire from a butane lighter should make you think of something **hot** and **steamy**: sex! Use this to remind yourself that bupropion does not have significant sexual side effects (owing to its lack of serotonin involvement) and may even improve sexual function for some patients! Given that sexual side effects are the number one reason why people stop treatment with an antidepressant, this is an incredibly valuable option for some patients.

Second, bupropion has been shown to help people **quit smoking** (it is marketed for this indication under the trade name Zyban). Bupropion and its metabolites have effects at the nicotinic receptors as well, which may account for this action. Visualize using a butane lighter to **light a cigarette** to remember this important association (more on this in Chapter 10).

Bupropion has **no sexual side effects** and can be used for **smoking cessation.**

A ***butane lighter*** *is* ***hot,*** *like bupropion's lack of* ***sexual side effects****.*
It can also be used to ***light cigarettes****.*

So what's the downside to all of this depression-busting, sex-crazed, cigarette-quitting excitement? By virtue of its excitatory properties, bupropion has a tendency to lower the **seizure** threshold. This is particularly troublesome for patients with bulimia nervosa who are engaging in frequent vomiting, as this can cause electrolyte imbalances that further raise the risk of seizure. For that reason, giving bupropion to a bulimic patient is **absolutely contraindicated**.

Bupropion has **no sexual side effects** and can be used for **smoking cessation**. However, it can also increase risk of the **seizures in patients with bulimia**.

Bu*propion should be avoided in patients with* ***bu****limia.*

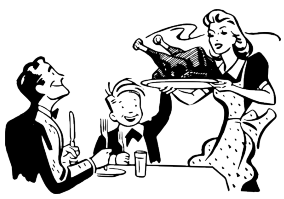
MIRTAZAPINE

Mirtazapine (Remeron) has a unique mechanism of action for an antidepressant, as it works as an **α-2 receptor antagonist**. This means that it *inhibits* an *inhibitor* of the sympathetic nervous system, resulting in *increased* sympathetic output overall. You can remember this unique mechanism by thinking of it as mirt-**α-2**-apine to remind yourself that it is an **α-2** receptor antagonist.

Mirtazapine is an **α-2 receptor antagonist** that works as an **antidepressant**.

*Mirt-****α-2****-apine is an* ***α-2*** *receptor antagonist.*

Mirtazapine has two major side effects to know. **Sedation** is common due to mirtazapine's interactions with histamine receptors. While this is an inconvenient side effect for some, for other patients (such as those struggling with insomnia) it can be a major selling point! Paradoxically, sedation is more prevalent at *lower* doses, as the antihistamine effect is seen at *lower* doses while the **F**ired up effect of norepinephrine is mostly seen at *higher* doses.



The second major side effect of mirtazapine is **increased appetite**. Like sedation, this side effect is a double-edged sword: some people won't appreciate the weight gain, while others (such as patients with cancer or AIDS who struggle to keep weight on) will welcome the effects on appetite. (Mirtazapine also tends to decrease nausea, in contrast to most SSRIs!)

You can remember both of these associations if you change the name to **meal**-ta**zzz**apine! This will remind you that this drug makes you want to eat a **meal** and that it will help patients to catch some **zzz**'s.

Mirtazapine can cause increased **appetite**, **weight gain**, and **sedation**.

Meal*-ta****zzz****apine makes you want to eat a* ***meal*** *and is* ***sedating****.*

TRAZODONE

While trazodone (brand name Desyrel, but everyone just calls it trazodone) was initially marketed as an antidepressant, it is now used primarily as a **sleeping aid**. This is because its sedative effects are seen at lower doses (starting at around 25 mg), while its antidepressant potential is not realized until at least 150 mg. Therefore, to get any effect on depression, patients are on such high doses that they are often too sedated to get much done. Even dosing at night does not fully prevent this, as many people report a "hangover" effect the next day. Its effects on sleep seem to work best in patients with depression, but it can also be used as all-purpose sleeping pill.

Aside from sedation, trazodone has a particularly dreaded side effect: **priapism**, which is defined as an erection lasting at least four hours. Priapism is a **medical emergency**, as blood flow to the engorged organ gets compromised after a while, leading to ischemia, tissue loss, and even gangrene in some cases. Because of the emergent nature of priapism, it's worth counseling your patients (even your female patients – priapism can happen in either sex) to go to the nearest emergency room should they experience this side effect. You can remember the association of trazodone with both sedation and priapism by thinking of it as tra**zzz**o-**bone**.

The Greek god Priapus. Eek.

Trazodone is useful as a **sleep aid** but can cause **priapism**, a medical emergency.

*Think of trazodone as tra**zzz**o-**bone** to remember **sedation** and **priapism**.*

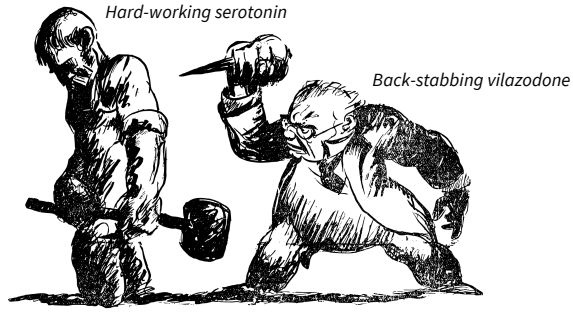
Mechanistically, trazodone is a very "messy" drug, as it appears to not only inhibit serotonin reuptake but also act as either an agonist or an antagonist at various 5-HT receptors directly. You will likely never be asked about the mechanism.

NEFAZODONE

Nefazodone (Serzone) is another "messy" drug that, like trazodone, not only inhibits serotonin reuptake but also interacts with various 5-HT receptors in various ways. Nefazodone is not used much anymore, as it is associated with a rare but potentially deadly side effect of **liver failure**. Even for patients who survive, a liver transplant may be needed. Because there are so many other antidepressants with equal efficacy that *don't* involve the risk of death, nefazodone is rarely prescribed. You can think of **nefa**-zodone as having **nefa**-rious intentions towards the liver to remember this side effect.

VILAZODONE

Vilazodone (Viibryd) is a newer antidepressant that works not only as an SSRI but also as a **partial agonist** at the serotonin receptor. (Recall from Chapter 2 that partial agonists activate receptors but to a lesser degree than a full agonist.) This means that it increases the amount of serotonin in the synapse while also ensuring that the receptors don't get oversaturated. You can remember this unique effect by thinking of this drug as **villain**-zodone: while it appears to be helping serotonin (by inhibiting its reuptake), it's secretly stabbing it in the back and preventing it from reaching its full potential by acting as a partial agonist!



So what does this mean clinically? Vilazodone's partial agonist activity appears to block some of the side effects seen with full saturation of serotonin receptors, with **sexual side effects** in particular being less noticeable with vilazodone compared to "pure" SSRIs. On a mechanistic level, you can basically think of vilazodone as "**SSRI + buspirone**." (We haven't talked about buspirone yet, but it is another drug that works as a partial agonist at the serotonin receptor. We will cover it more in Chapter 6 as it is primarily used for treatment of generalized anxiety disorder.)

Vilazodone inhibits serotonin reuptake while also acting as a **partial agonist** at the serotonin receptor, leading to **fewer serotonergic side effects**.

***Villain**-zodone seems to be **helping serotonin** but is actually **holding it back**!*

VORTIOXETINE

The final atypical antidepressant we will talk about is vortioxetine (Trintellix). This is a newer antidepressant that not only acts as an SSRI but also modulates serotonin receptors. Vortioxetine is even more complex than vilazodone as it can be an agonist, partial agonist, or even antagonist depending on the particular 5-HT receptor subtype! You can associate this drug with a "swirl" of different effects on serotonin by calling it **vortex**-etine. However, this doesn't appear to translate into any clinically meaningful differences. Vortioxetine is often advertised as being better at improving cognition in patients with cognitive deficits secondary to depression, but with each passing year it seems clearer that this is more marketing hype than actual effect. Overall, vortioxetine is not prescribed regularly due to its high cost and the lack of clinically meaningful differences from standard antidepressants.

TRICYCLIC ANTIDEPRESSANTS

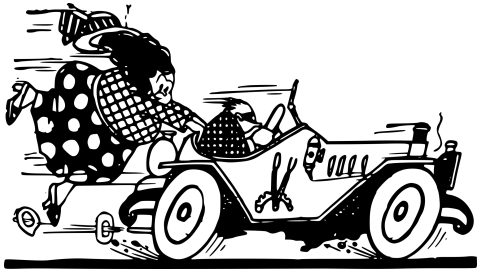
We just got done talking about some of the newest antidepressants on the market, so let's travel back in time and talk about the oldest: the **tricyclic antidepressants** (often shortened to just "tricyclics" or "TCAs"). You can generally recognize TCAs by their name, as they usually have either the suffix –**triptyline** (as in amitriptyline and nortriptyline) or –**ipramine** (as in clomipramine and imipramine).

Tricyclics have incredibly complex mechanisms of action which result both in their efficacy as well as their increased side effect burden. The complexity of TCAs should remind you of the Second Rule of Neurotransmission: "With great power comes great responsibility." The more things you mess with in the brain, the higher chances of having an effect, but also the higher chance of causing serious side effects. Consistent with this, there is some evidence to suggest that TCAs are more effective than more modern antidepressants, but given their side effect profile they generally should not be first-line options.

To better understand TCAs, let's take a moment to review their pharmacologic effects. TCAs act as *ag*onists at two neurotransmitters, *antag*onists at another two, and inhibitors of two ion channels. We can consolidate this into the mnemonic **Trans, Chans, and Ans** which, conveniently, spells out **TCAs**! The "s" at the end of each word reminds us that there are two of each.

T is for Transmitters. TCAs inhibit reuptake of both **serotonin** and **norepinephrine** (similar to SNRIs). This is what is primarily responsible for their antidepressant effects.

C is for Channels. TCAs work as **sodium** and **calcium** channel inhibitors. Clinically, this property may account for some of their analgesic properties. However, it may also account for their **toxicity in overdose**. TCAs are some of the most potentially deadly drugs that are still prescribed in psychiatric, with a therapeutic index of 7 (meaning that taking just 7 times the normal amount of the drug could cause death). Slowing these ion channels affects electrical conduction in both the brain and the heart. In the brain, this leads to altered mental status or even coma. In the heart, this leads to arrhythmias, with a **widened QRS complex** on an EKG being highly specific for a TCA overdose. This is very high yield, enough that it bears repeating: a wide QRS in the context of a suspected overdose is highly specific for TCA toxicity! An equally high-yield fact is that **sodium bicarbonate** is the treatment for TCA overdose. To remember this association, picture a car running into a tricycle. It's no contest: the **car** is going to absolutely *destroy* that **tricycle**. If you extend this to the idea that sodium bi-**car**-bonate beats a **tricycle**, you'll remember the antidote for TCA poisoning.



A **wide QRS** on an EKG in the context of **suspected overdose** is likely **TCA overdose**. Treatment involves **sodium bicarbonate**.

*Sodium bi-**car**-bonate runs over a **tricycle**.*

A is for Antagonists. Finally, TCAs antagonize **acetylcholine** and **histamine** which accounts for much of their side effect profile. The anticholinergic effects that were captured in the "Blind as a bat…" rhyme all apply here, with blurry vision, dry mouth, constipation, urinary retention, tachycardia, and cognitive impairment all being seen to some degree. Antagonism of histamine results in a soporific effect, with drowsiness and sedation being common complaints while on a tricyclic.

TCAs increase **serotonin** and **norepinephrine**, inhibit **sodium** and **calcium** ion channels, and antagonize **acetylcholine** and **histamine**.

***TCA**s affect **T**rans, **C**hans, and **A**ns.*

While the overall pattern captured in "Trans, Chans, and Ans" holds true for most TCAs, it would be a mistake to assume that every medication in this class has the *exact* same neurotransmitter profile. In fact, some TCAs boost serotonin more than norepinephrine, others do the opposite, and still others hit them both equally. The same holds true for anticholinergic and antihistaminergic effects as well! The nuances here really are what set one TCA apart from its peers, as we'll discover now as we talk about each of the individual TCAs. Keep in mind that we won't be covering every single TCA, as many are no longer commonly prescribed. Instead, we will focus on those that are used most often or have unique effects!

IMIPRAMINE

Imipramine (Tofranil) is a prototypical TCA which also has the distinction of being the first antidepressant ever discovered! One thing that sets imipramine apart is that it is sometimes used for treating **nocturnal enuresis** (bed wetting). The anticholinergic effect of imipramine prevents the bladder from contracting, thus holding the urine. Because of its significant side effects, it is not used as a first-line option for bed wetting but can be useful in refractory cases. You can remember **imipramine** as "**I'm-peeing-ramine**" to associate it with bedwetting.

Imipramine is a TCA that is useful for treating **nocturnal enuresis**.

***I'm**-i-**P**-ramine can be thought of as **I'm**-**pee**ing-ramine.*

CLOMIPRAMINE

Like any TCA, clomipramine (Anafranil) can be used to treat depression. However, in the modern day it is most often used to treat **OCD**. In fact, clomipramine is considered to be the **gold-standard** for medication treatment of OCD, as it was found in several randomized controlled trials to be more effective than any other antidepressants. Clomipramine is one of the strongest serotonin reuptake inhibitors known, which most likely accounts for its incredible efficacy in treating OCD. Due to its higher side effect burden, however, it should be reserved for more severe or treatment-refractory cases of OCD, with SSRIs as the first-line option.

Clomipramine is the gold-standard treatment for **obsessive-compulsive disorder**.

*Use **clom-**ipramine for obsessive-**clom**pulsive disorder.*

AMITRIPTYLINE AND NORTRIPTYLINE

Two other commonly prescribed TCAs are amitriptyline (Elavil) and nortriptyline (Pamelor). Amitriptyline is actually converted to nortriptyline is the liver, which is why the two are grouped together. In addition to treating depression, you will also see them prescribed for chronic pain issues, such as diabetic peripheral neuropathy, chronic low back pain, or pelvic pain. Amitriptyline is fairly balanced in its effects on serotonin and norepinephrine, while nortriptyline is much more selective for norepinephrine. In addition, nortriptyline tends to have fewer anticholinergic effects and is less associated with sedation and orthostatic hypotension. For these reasons, it is preferred for elderly patients for whom sedation and falls can be very big deals!

Nortriptyline is associated with **less sedation** or **orthostatic hypotension** compared to other tricyclics.

*Elderly patients will fall less on **no-trip**-tyline than other TCAs.*

DOXEPIN

The final TCA we will talk about is doxepin (Sinequan). Compared with most TCAs, doxepin has extremely strong **antihistaminergic** effects, and at lower doses it is basically a pure antihistamine. This property makes it a useful option for insomnia as well as for severe cases of allergies. However, generally speaking there are better options for both of these indications that don't come with the same side effect burden (like trazodone for insomnia and second-generation antihistamines for allergies), so doxepin is generally reserved for cases where other things haven't worked yet.

MONOAMINE OXIDASE INHIBITORS

We now move onto another old class of antidepressants: the **monoamine oxidase inhibitors** or **MAOIs**. Rather than inhibiting the *reuptake* of neurotransmitters out of the synaptic cleft, MAOIs instead act upon an enzyme known as monoamine oxidase (MAO) that *breaks down* the neurotransmitter. Overall, though, the effect is the same: the drug makes the amount of monoamine in the synapse increase!

There are two distinct types of the MAO enzyme that each have different levels of ability when it comes to breaking down monoamines. MAO-**A** is an **A**dvanced operator and is capable of inactivating all three of the monoamines implicated in depression (serotonin, norepinephrine, and dopamine). In contrast, MAO-**B** is much more **B**asic and can only handle one (dopamine).

There are **2 subtypes of monoamine oxidase** that each **break down** the three monoamines implicated in depression to different degrees.

*MAO-**A** is **A**dvanced (all 3), MAO-**B** is **B**asic (dopamine only).*

There are four MAOIs that are used to treat depression. Phenelzine (Nardil), tranylcypromine (Parnate), and isocarboxazid (Marplan) all inhibit both MAO-A and MAO-B, making them some of the only antidepressants capable of increasing synaptic levels of **all three monoamines**. In contrast, **sele**giline (Emsam) is unique in that it is **sele**ctive for MAO-B, meaning that only dopamine is increased. For this reason, you may see selegiline being used not only to treat depression but also other disorders (such as Parkinson's disease) where only dopamine needs boosting.

Phenelzine, **tranylcypromine**, and **isocarboxazid** inhibit **both** MAO-A and MAO-B, while **selegiline** is **selective** for MAO-B.

***Sele**giline is **sele**ctive for MAO-B.*

MAOIs are among the most effective of all antidepressants, especially in a particular form of depression known as **atypical depression**. Atypical depression is characterized by mood reactivity, interpersonal rejection sensitivity, increased appetite, hypersomnia, and leaden paralysis (the sensation that one's arms are too heavy to lift). For reasons that are still not clear, atypical depression responds better to MAOIs than other types of treatments like SSRIs, SNRIs, or TCAs. Remember to use **MAWIs** when your patients tell you, "**M**y **A**rms' **W**eight **I**ncreased!"

MAOIs are particularly effective for **atypical depression** which features **mood reactivity** and specific symptoms such as **leaden paralysis**.

*Use **MAWIs** when patients tell you, "**M**y **A**rms' **W**eight **I**ncreased!"*

In line with the Second Rule of Neurotransmission, MAOIs are very effective but can also have some very severe side effects, including a few that can be life-threatening. Because of this, MAOIs are not prescribed often in modern psychiatry and are typically used as a "**last resort**" after a patient has failed multiple other medications from several different classes first.

There are two main life-threatening side effects to be aware of here. The first is known as a **hypertensive crisis** which can occur when someone who is taking an MAOI ingests anything with **tyramine** in it. Tyramine is found naturally in many **aged foods** such as cheeses or wine. Once ingested, it causes the release of norepinephrine and dopamine from pre-synaptic vesicles. Ordinarily, this wouldn't cause too much trouble, but in the presence of an MAOI, the released norepinephrine and dopamine can build up to dangerous levels, leading to widespread vasoconstriction and incredibly high blood pressures. This is a **medical emergency** and needs to be recognized promptly. Because of this, all patient's taking MAOIs need to be counseled on how to recognize and avoid foods which contain tyramine. To remember this severe interaction, imagine a young man on a romantic vacation with his girlfriend **Tyra Mine** at a beachside resort on **Maui** (MAOI). He takes her out on a picnic over fine **aged wines and cheeses**. As he nervously prepares to pop the question, you can bet that his **blood pressure** would be **sky high**! This mental image will help you associate these disparate words and concepts (MAOIs, tyramine, aged food and drink, blood pressure, and "last resort" antidepressants) together.

MAOIs can cause a **hypertensive crisis** when combined with **tyramine**,
Which occurs naturally in **aged food and drink**.

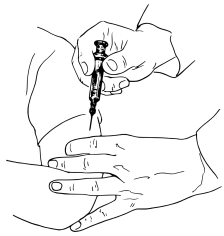
*Picture a young man about to propose to his girlfriend **Tyra Mine** at a **(last) resort** on **Maui** over **wines and cheeses**. He would probably have **sky high blood pressure**!*

In addition to hypertensive crisis, the other potentially lethal side effect of MAOIs to be aware of is **serotonin syndrome**. While hypertensive crisis results from MAOIs causing an excess of dopamine and norepinephrine, serotonin syndrome results from MAOIs causing an excess of serotonin. Recall from Chapter 2 that, while any two serotonergic medications can theoretically cause serotonin syndrome, the biggest risk by far comes when one of those drugs is an MAOI. To prevent this, it is recommended to have a "washout" period of at least 2 weeks when switching from a serotonergic drug to an MAOI. (The exception to this is fluoxetine which, due to its long half-life, requires a 5 week washout!)

KETAMINE

Is ketamine (Ketalar) an antidepressant? It's certainly the strangest drug we will learn about in this chapter. It's not a pill that you take by mouth (it must either be injected or taken intranasally), it doesn't inhibit the reuptake of anything, and it doesn't even involve serotonin, norepinephrine, or dopamine! Instead, ketamine is classified as an **NMDA receptor antagonist**, although it appears to have other actions as well.

From the time that clinical use of ketamine first began in 1970, it has primarily been used as an **anesthetic**, as it induces a state of **dissociation** characterized by pain relief, sedation, memory loss, perceptual disturbances, and hallucinations (remember that **D**issociative hallucinogens are the **D** in NM**D**A mnemonic!). Its analgesic and amnestic properties make it ideal for emergency pain relief (such as treating wounded soldiers on the battlefield), while its hallucinatory properties make it a popular recreational drug as well.



While ketamine has been in use for over 50 years, it is only in the last decade or two that its antidepressant effects have been noted. Depressed patients who received ketamine for other reasons often noted a total resolution of depressive symptoms within days or even hours of taking it. The **speed and extent of improvement** in depression was remarkable, especially considering that most traditional antidepressants can take weeks or months to work! The downside, however, is that these improvements disappear just as quickly as they come, with improvements **rarely lasting beyond a few days** and almost never past a week. In this way, ketamine is the poster child for the phrase "**easy come, easy go**." Different strategies for extending the initial antidepressant effect of ketamine, such as repeat infusions or combination with more traditional antidepressants, are still being explored. For now, there is insufficient evidence to recommend ketamine as a routine treatment for depression, but with additional time ketamine's place in our treatment algorithms may become more clear. We'll talk more about ketamine in Chapter 12!

ADDITIONAL OPTIONS

While the drugs we have covered so far make up the bulk of treatment options for depression, there are some additional options as well. Some of these (like psychotherapy) can be used instead of medications as a first-line treatment, while others are typically reserved for patients who have not responded to several trials of antidepressants.

PSYCHOTHERAPY

Medications are not the only treatment option for depression! There are several highly effective psychotherapies for depression such as cognitive behavioral therapy (CBT). Medications and therapy are both equally effective on their own, and they can both be considered good first-line options. However, research has shown that the best outcomes are seen when the two are combined!

ANTIPSYCHOTICS
Several antipsychotics have been shown to treat unipolar depression when added to existing antidepressants, including aripiprazole (Abilify), quetiapine (Seroquel), and ziprasidone (Geodon), among others. Not all antipsychotics are helpful for treating depression! These antipsychotics all have greater action at serotonin receptors than most others, which likely accounts for their increased utility in depression. However, they are all associated with significant side effects (to be explored in more detail in Chapter 4) that make them unsuitable as a first-line treatment. The only exception to this is cases of depression with psychotic features, as adding an antipsychotic results in a better and faster response than an antidepressant alone. For this reason, combined therapy with an antidepressant and an antipsychotic is the standard of care for patients who have psychotic depression.

LITHIUM
Lithium (Eskalith) is primarily known for its use in patients with bipolar disorder. However, there is good evidence that lithium can be an effective treatment for unipolar depression as well, both on its own and when combined with traditional antidepressants. Because of its side effects (to be covered more in Chapter 5), it tends not to be used very frequently for this purpose despite its efficacy.

THYROID HORMONE
Pharmaceutical-grade forms of thyroid hormone such as liothyronine (Cytomel) can be used to treat residual symptoms of depression even in patients with normal thyroid function. In essence, your goal is to induce a state of subclinical hyperthyroidism, which can be helpful for addressing the low energy and anhedonia that are commonly seen in depression.

STIMULANTS
Stimulants such as methylphenidate (Ritalin) and amphetamine (Adderall) (which will be discussed further in Chapter 7) can be used to address certain symptoms of depression (such as fatigue and difficulty concentrating). However, repeated studies have failed to show that they actually improve the course of depressive illness.

ELECTROCONVULSIVE THERAPY
This will be covered in much more detail in Chapter 15, but in brief, electroconvulsive therapy is the **single most effective treatment** for treatment-resistant depression, with a response rate of approximately 50%. It should be considered for patients with severe depression who have failed to respond to multiple trials of medication.

TRANSCRANIAL MAGNETIC STIMULATION
Transcranial magnetic stimulation (TMS) is a type of brain stimulation where magnetic coils are placed on the head in order to generate an electric current in the brain. While not nearly as effective as ECT, TMS does have the benefit of being non-invasive and generally safe, with the main downside being its time-consuming nature.

HOW TO USE ANTIDEPRESSANTS

As their name implies, antidepressants are most often used to treat **major depressive disorder**, a disorder characterized by depressed mood as well as a variety of signs and symptoms including poor **S**leep, decreased **I**nterest in activities, feelings of **G**uilt or hopelessness, low **E**nergy, impaired **C**oncentration, decreased **A**ppetite, **P**sychomotor retardation, and **S**uicidal thoughts (which can be easily recalled using the mnemonic **SIGECAPS**). Having **at least 5** of these symptoms for **2 or more weeks** qualifies the patient for major depressive disorder per current standards. (You can remember the timeframe for depression using the phrase "**two blue weeks**.")

When considering an antidepressant for one of your patients, there are some key principles to keep in mind:

1. Antidepressants don't work overnight.
Decades of research and clinical practice have established that antidepressants do not fully "bloom" until 4 or even 8 weeks after being started. Patients can sometimes feel like stopping the drug early, as the side effects (like diarrhea) are immediate while the positive effects are still catching up. It's important to counsel patients on the need to do a full trial period of a month or two before saying that the drug is or isn't working.

2. Remember the Rule of Thirds!
If patients do stay on the antidepressant for the full 8 weeks, a "**Rule of Thirds**" is generally observed, with one-third of patients getting completely better with no symptoms remaining (**remission**), an additional third getting somewhat better but still with some residual symptoms (**response**), and a final third not getting any better at all (**treatment resistance**). While it can be frustrating that such a large percentage of patients do not respond to treatment (after all, we want to get 100% of our patients feeling better!), it is reassuring that *most* patients do benefit from treatment to some degree.

3. All antidepressants are about equally effective.
It's worth noting that the Rule of Thirds is seemingly independent of the particular drug that is chosen. Because of this, most of the medications discussed under SSRIs, SNRIs, or "atypical" antidepressants would be a reasonable first-line treatment. (TCAs or MAOIs would, in general, not be used until other options have been exhausted due to their higher side effect burden and higher lethality in overdose.) Because all antidepressants are equally effective, you should…

4. Choose based on side effect profile.
If efficacy does not differ significantly, then choose based on side effects, as these *do* differ significantly between the drug classes and even within the specific drugs in each class. For example, if a patient is worried about weight gain, then mirtazapine might not be the best option. If they are concerned about sexual side effects, we should avoid SSRIs. If they often forget to take medications, fluoxetine may be a good choice. If they are pregnant, sertraline might be a good option. By keeping our patients' lives and preferences in mind, we can be savvy with our treatments and increase their chances of getting better.

5. Know your options for treatment resistance.
So you've started your patient on an antidepressant and waited the full month or two to see if it is working. However, your patient is not feeling any better. What then? You have a few options: staying the course, increasing the dose, switching to another drug, or adding a new medication. While it is standard practice to increase the dose, the fact is that most studies have found that (provided the drug was within the therapeutic dosing range) increased doses *don't* result in better outcomes and, if anything, only seem to increase the side effect burden! Switching antidepressants also doesn't seem to work much better than staying the course. In fact, the only option that's been shown to be any good is adding a new medication, with the combination of an SRI and mirtazapine appearing to be particularly effective. However, this has to be balanced with the high risk of new side effects as well. Ultimately, the decision on what to do should be based on the patient's desires and preferences, as there is no "one size fits all" approach that works for treatment-resistance.

6. Don't "set it and forget it."
In most cases, antidepressants are not life-long drugs. Research suggests that patients should continue taking antidepressants for **at least 6 months** from the time they first feel better, as stopping earlier than this involves a higher risk of relapsing back into depression. However, as long as your patient has cleared this threshold, you can and *should* try to taper off the medication. For most patients, their depression will not return (at least not for a long while). In a minority of patients (typically those with severe depression), you may need to continue medication treatment for longer, with some needing to be on the drugs for life. This is the exception rather than the rule, however, and you should try to taper after 6 months for most of your patients.

7. Antidepressants don't inherently prevent suicide.
While it is tempting to think that you are helping to prevent suicide just by prescribing an antidepressant, the fact of the matter is that antidepressants do not lower the risk of suicide in and of themselves. In fact, in certain populations (such as people under the age of 25), thoughts of suicide can even *increase* in the period after starting an antidepressant. The reasons for this are complex. For some patients, the increase in energy from the drug can happen before any improvement in hopelessness or other negative thought patterns, making for a dangerous situation where someone who is still depressed now has the energy to act upon their thoughts. On the other hand, some have argued that the association between suicidality and antidepressants is a statistical artifact rather than a true increase in suicidality. Regardless of which side is true (it's likely that both are to some degree), the fact remains that you should not rely on antidepressants as your only form of suicide prevention. Instead, work with your patients and their families to come up with a safety plan for if they start to feel unsafe.

8. Pair antidepressants with psychotherapy for best results.
Don't forget about psychotherapy! We'll talk about specific types of psychotherapy in Chapter 15, but for now it is enough to know that therapy is just as effective as drugs and that the two of them together are better than either one alone. For this reason, you should always have a discussion about therapy with any patient you are treating for depression!

PUTTING IT ALL TOGETHER

In some ways, antidepressants are incredibly easy, especially if you avoid older classes like TCAs and MAOIs. Pick any one you want, they all have the same odds of working! If the first one doesn't work, try another! Don't worry about side effects, none of them will kill the patient!

And the worst part is, most of these things are true! This means that it is remarkably easy to do a bad job of choosing antidepressants, as the consequences are not always obvious and likely won't happen for a long time. However, we need to set our sights higher than simply "not killing the patient." While it's true that most antidepressants are equally effective at reversing the symptoms of depression, that doesn't account for the rest of someone's experience. For example, if a patient's depression has improved but they are horribly unhappy with their sex life, struggling to keep focus at work, concerned about their appearance after gaining 15 pounds, or unable to eat the foods that they want, then it's not as clear that their life has improved for the better. By taking our patient's preferences and combining that with a detailed knowledge of the unique aspects of these medications, we can help our patients at a higher level than if we just throw random drugs at them.

Ultimately, these medications can be incredibly helpful, but they are not the only solution for depression. Other interventions like therapy can be just as effective and result in longer lasting changes in mood and self-esteem. Always keep an eye on the patient's overall goals in seeking treatment, and try to use (or not use) these drugs in a way that maximizes the patient's chances of success.

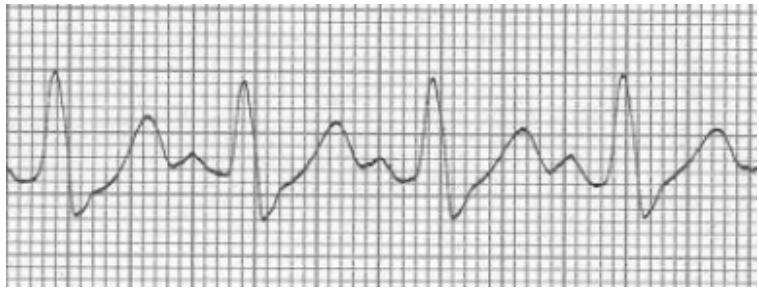
REVIEW QUESTIONS

1. A 47 y/o M with a history of depression comes into his doctor's office reporting that he stopped taking his fluoxetine after "a couple of embarrassing nights" where he was unable to get an erection with his wife, which he finds intolerable. What is the most reasonable replacement for fluoxetine in this patient?
    A. Citalopram
    B. Sertraline
    C. Venlafaxine
    D. Bupropion
    E. Imipramine
    F. Nortriptyline

2. A 24 y/o M presents with a five year history of severe anxiety over having forgotten to lock the door. It has gotten to the point where he must wake up 4 hours early so that he can repeatedly check the locks before leaving for work. He describes his behavior as "extremely upsetting" to him but says he is unable to stop. He has never before been in treatment for this condition. What is the most reasonable medication to suggest?
    A. Clomipramine
    B. Trazodone
    C. Bupropion
    D. Fluoxetine
    E. Phenelzine

3. A 26 y/o G2P1 single mother who recently gave birth brings her baby boy in for a 1-month check. The baby is back to his birth weight and seems to be doing well. She has been exclusively breastfeeding. During the interview, she lets on that she has been feeling sad and tearful since delivering. A complete history is consistent with post-partum depression. What medication is most often recommended to treat this condition?
    A. Sertraline
    B. Paroxetine
    C. Fluoxetine
    D. Escitalopram
    E. Trazodone

4. A 36 y/o F with a long history of treatment-refractory depression and OCD is found passed out on the floor with an empty bottle of medications nearby. She is non-responsive. Vital signs are HR 138 and BP 92/58. EKG is shown below:



Cardiac enzymes are normal x1. What is the most appropriate treatment after hydration and supportive measures?

A. N-acetylcysteine
B. Atropine
C. Propranolol
D. Sodium bicarbonate
E. Flumazenil

5. A mother brings her 7 y/o boy into his pediatrician's office with complaints of bed wetting. She states that this behavior has been present since he was 4, but she believed that he would soon outgrow it. Now that he is 7, she worries that it will be an issue at sleepover parties. She requests treatment. What is a reasonable therapy to try?

A. No therapy (continue to wait)
B. Bedwetting alarms
C. Citalopram
D. Imipramine
E. Amitriptyline

6. A 51 y/o M comes to his psychiatrist's office for a follow-up appointment. He was initially diagnosed with major depressive disorder 9 months ago and started on citalopram at a therapeutic dose. He noticed minor improvements but overall did not feel that this medication was working for him, so his psychiatrist switched him to mirtazapine 6 months ago. Within 2 months, he felt that his depression had "gone away completely" and that he was "back to my old self." During his appointment today, he asks his psychiatrist, "How long do I need to stay on this drug? It's worked wonders, but I'm not used to taking medication and don't really want to take it if I don't need it." What is the best response?

A. "There's no reason to keep taking it! We can stop today."
B. "Let's wait at least another couple of months before stopping."
C. "It's best if we give it another year."
D. "Ideally you should be taking this medication for at least a few years."
E. "You will likely need to take this medication for life."

1. **The best answer is D.** Serotonergic drugs are known to cause sexual side effects. Of all the listed options, bupropion is the only medication with no significant serotonergic effects. It is a useful antidepressant for patients who experience sexual side effects with traditional serotonergic drugs.

2. **The best answer is D.** Fluoxetine is the most reasonable option listed, as all SSRIs are helpful in treating OCD. Clomipramine may be tempting as it is the gold standard for pharmacologic treatment of OCD, but because of the high amount of side effects it should be reserved until the patient has failed therapy with an SSRI (answer A). Trazodone is serotonergic, but it is not a good first-line option due to its sedating nature (answer B). Bupropion does not have serotonergic effects and is unlikely to improve OCD symptoms (answer C). The side effect profile of MAOIs makes phenelzine an inappropriate initial pharmacotherapy (answer E).

3. **The best answer is A.** Sertraline is often recommended for post-partum depression, as little of it gets into the breast milk. Paroxetine (answer B) would be a particularly bad choice, as it is rapidly absorbed and could result in uncomfortable withdrawal symptoms if discontinued. Fluoxetine (answer C), escitalopram (answer D), and trazodone (answer E) are not entirely incorrect, as all can be used to treat post-partum depression, but given that the patient is actively breastfeeding sertraline is a better option.

4. **The best answer is D.** The question stem describes a patient who has likely overdosed on TCAs, as wide QRS complexes on an EKG in the context of a medication overdose is very likely to be TCA overdose. Sodium bicarbonate is the treatment for tricyclic overdose. N-acetylcysteine (answer A) can be used to treat acetaminophen overdose, while flumazenil (answer E) can at times be used to treat benzodiazepine overdose; however, neither are antidotes for TCA overdose. Atropine (answer B) will only contribute further to tachycardia, while propranolol (answer C) will further lower the blood pressure.

5. **The best answer is B.** The patient is certainly at the age where some form of therapy should be considered (answer A). While TCAs such as imipramine (answer D) and amitriptyline (answer E) are effective at inhibiting urination via their anticholinergic effects, behavioral therapies should always be pursued before medications to avoid their significant side effects. Should the patient fail behavioral therapy, then imipramine or desmopressin could be considered. Citalopram has no significant effect on nocturnal enuresis (answer C).

6. **The best answer is B.** Current guidelines recommend waiting at least 6 months from the time that the patient is in remission from their depression before tapering off of an antidepressant, as stopping before this time is associated with a higher rate of relapse. While the patient has been taking the medication for 6 months, he has only been in remission for 4 months so waiting another 2 months is best at this time.