

ANTIDEPRESSANTS:

WHAT THEY ARE AND HOW THEY WORK

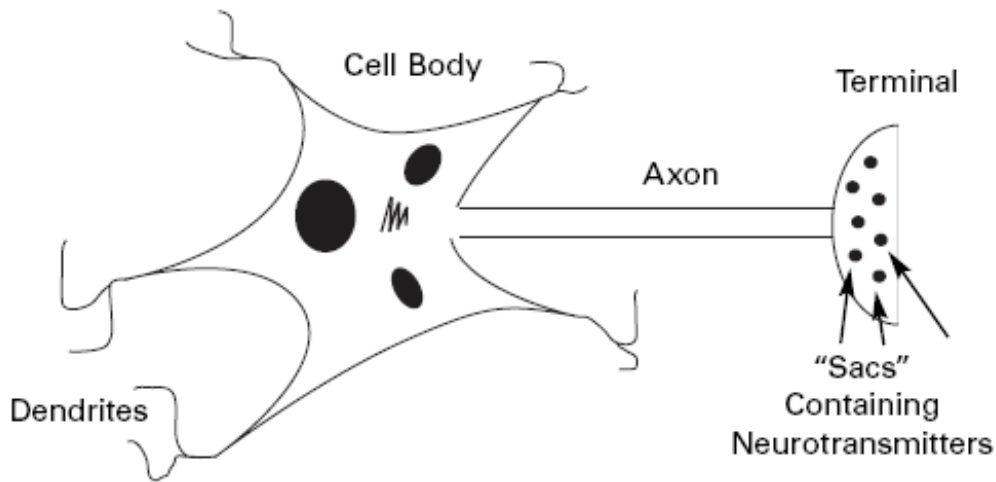
In 1990, Prozac became the first drug to be featured on the cover of a major U.S. news magazine, marking a turning point in pharmaceutical history. Prozac (fluoxetine), hailed as a “miracle” drug of sorts, was introduced in the United States in 1988. Two years later it was the most widely prescribed drug in this country, earning a place as *Newsweek*’s “cover drug” with the headline “Prozac: A Breakthrough Drug for Depression.”

Prozac may have emerged as a 20th century star, but many antidepressants have long been effective in managing not only unipolar depression, but also bipolar disorder, obsessive compulsive disorder, social anxiety disorder, substance abuse, panic disorder, eating disorders, premenstrual disorders and anxiety disorders. Fortunately for its more than 18 million sufferers, clinical depression is one of the most treatable of psychiatric illnesses. Medication, psychotherapy or a combination of the two is successful in more than 80 percent of cases.

HOW ANTIDEPRESSANTS WORK

A primary role of medication is to restore normal biological functioning. For antidepressants, the location of that functioning resides in the 100 billion nerve cells that are contained within the human brain. The nervous system depends on communication among these many nerve cells.

THE STRUCTURE



A nerve cell consists of a cell body, dendrites, an axon and a terminal.

Each *cell body* manufactures its own messenger molecules, more typically referred to as neurotransmitters. For the sake of this discussion, these are norepinephrine, serotonin, dopamine and GABA.

Dendrites are structures, shaped like tree branches, that fan out from the cell body. They accept and send information to the cell body, serving as a message-exchange system that facilitates intracellular communication.

Axons are fibrous tubes that serve to transmit impulses away from the cell body. After the neurotransmitters are manufactured, they travel along this tube-like passageway away from the body of the cell. Then they are stored within small "sacs" or vesicles within the presynaptic *terminal*.

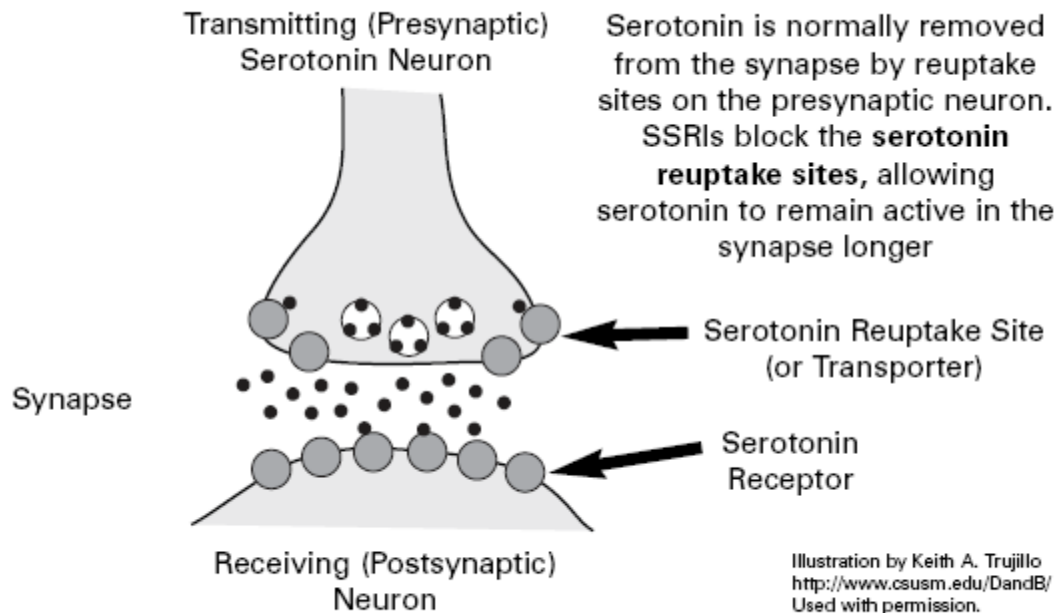
THE PROCESS

From the terminal, the intercellular communication process causes the release of neurotransmitters into a *synapse*, a tiny gap between nerve cells. The nerve cell that releases the neurochemicals into the synapse is called the *presynaptic* neuron. The nerve cell that receives the neurochemicals is called the *postsynaptic* neuron.

Once the neurotransmitter molecules are released by the presynaptic cell, they migrate across the synapse through a series of chemical and electrical impulses. They are then capable of binding to *receptors* that are located on the surface of the postsynaptic nerve cell. Receptors are tiny proteins that serve as catcher's mitts, intercepting neurotransmitter molecules as they whiz by. These are specific catcher's mitts—norepinephrine attaches only to a norepinephrine receptor; serotonin attaches only to a serotonin receptor, and so on. The binding of neurotransmitters to receptors, like a key fitting into a lock, essentially facilitates this intercellular communication, namely the way one nerve cell impacts the functioning of or “talks” to another nerve cell. For this reason, neurotransmitters are referred to as “primary messengers.”

Some of the neurotransmitters released into the synapse bind to postsynaptic receptors. Others are chemically degraded by enzymes, such as monoamine oxidase. Still others are rapidly reabsorbed back into presynaptic cells. This re-absorption occurs by way of a *reuptake transporter pump*. This pump facilitates a recycling process that allows neurotransmitters to be repackaged and reused.

Many antidepressants operate by way of reuptake inhibition, in which the drug molecule blocks the pores of the reuptake transporter pump. This lets neurotransmitters released into the synaptic cleft stay for a longer period of time, thus potentially enhancing postsynaptic nerve cell actions.



ANTIDEPRESSANTS

All of the antidepressants have similar efficacy, and most of them have different side effects. At least 50 percent of clients who will respond to antidepressants begin to demonstrate improvement in the first few days to a week. Remission of depression, however, is much more difficult to achieve and may take eight to twelve weeks.

The U.S. drug market now offers six major categories of antidepressants:

- Cyclics
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin and norepinephrine reuptake inhibitors (SNRIs)
- Norepinephrine reuptake inhibitors (NRIs)
- Monoamine oxidase inhibitors (MAOIs)
- Atypical antidepressants

CYCLICS

Also referred to as tricyclics, these are among the oldest group of antidepressants, dating from the 1950s. One of the very first cyclics, Tofranil (imipramine), was originally developed as an antipsychotic, but was subsequently found to possess antidepressant properties. Other cyclics include Elavil (amitriptyline), Anafranil (clomipramine) and Desyrel (trazodone). Many of these agents are dual-action in that they block the reuptake of both serotonin and norepinephrine.

Elavil (amitriptyline) has an established efficacy in the management of chronic pain. For years, Anafranil (clomipramine) was the drug of choice in the treatment of obsessive-compulsive disorder, but it was eventually supplanted by the selective serotonin reuptake inhibitors. Desyrel (trazodone) has proven to be quite effective in the management of depression associated with concomitant anxiety and insomnia.

Make no mistake, the cyclics are indeed effective antidepressants. In fact, they were preferred treatments from the 1950s to the 1990s. Unfortunately, the cyclics are fraught with side effects that render them intolerable for many patients:

- As a class, they tend to be dangerous in overdose and can enhance the sedative effects of alcohol.
- They are sedating, in that they inhibit the effects of histamine, similar to the actions of Benadryl (diphenhydramine).
- They can cause annoying side effects—such as dry mouth, blurred vision, constipation, urinary retention and confusion—because they block the actions of the neurotransmitter acetylcholine.
- They can cause orthostatic hypotension, a drop in standing blood pressure.
- There is a risk of tachycardia, or rapid heart rate.
- Weight gain is associated with a metabolic slowdown in carbohydrate and fat metabolism. In some individuals, weight gain is contributed to by an increased craving for sweets and fats.

- A decrease in libido and an inability to perform sexually is linked to the serotonin effects of these antidepressants.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

The SSRIs are indeed popular—one of the most famous ending up on the cover of *Newsweek* magazine, as noted above. Prozac (fluoxetine) was the first of a new class of drugs called selective serotonin reuptake inhibitors (SSRIs) that went on to become the most prescribed class of antidepressants. By today's treatment standards, more than half of all new antidepressant prescriptions are for an SSRI.

These medications work by selectively blocking or inhibiting the reuptake of the neurotransmitter serotonin. In addition to Prozac, other SSRIs include Zoloft (sertraline), Paxil (paroxetine), Celexa (citalopram), Lexapro (escitalopram) and Luvox (fluvoxamine).

As a class, the SSRIs are better tolerated than the cyclics. They have the advantage of once-a-day dosing and are much safer in overdose than the cyclic agents. There is, however, insufficient data to support the efficacy of SSRIs over the cyclic antidepressants.

Side effects of the SSRIs tend to be related to an increase in serotonin activity, and they tend to be fewer than those of the older cyclic antidepressants. SSRI side effects also tend to be transient, with the exception of weight gain and sexual dysfunction, which are associated with long-term use. The main side effects include:

- Increased anxiety
- Sedation
- Significant insomnia (reported in up to 20 percent of cases)
- Sexual dysfunction
- Weight gain, but less than that associated with older antidepressants. One study noted an average weight gain of four pounds over a six-month period.

Discontinuing SSRIs is best done gradually to spare patients unnecessary upset. Abruptly stopping an SSRI is linked to a withdrawal syndrome in which some patients report

“electric shock sensations” in the hands and feet accompanied by painful “brain zaps” in the head. Although unpleasant, these effects are not considered dangerous to either the brain or the extremities.

SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

SNRIs are considered dual-action antidepressants. That is, they inhibit or block the reuptake of both serotonin and norepinephrine.

The model drug in this category is Effexor (venlafaxine). In 1994, this was marketed as “Prozac with a punch.” The “punch” refers to Effexor’s effect on norepinephrine. At doses of less than 150 mg, Effexor (venlafaxine) is essentially no different from a typical SSRI. But at doses of 150 mg or higher, Effexor is said to block the reuptake of serotonin and norepinephrine.

Cymbalta (duloxetine) became available in 2004. Both Cymbalta (duloxetine) and Effexor (venlafaxine) are believed to be more effective than the SSRIs in managing severe depression. But unlike Effexor, Cymbalta is also approved for the treatment of diabetic neuropathic pain. It is also demonstrating promising results in the management of chronic pain and stress urinary incontinence.

Effexor (venlafaxine) may cause high blood pressure, especially at doses of 225 mg per day or higher. Patients taking Effexor at these doses are encouraged to monitor their blood pressure a minimum of once per day. The effects of Cymbalta (duloxetine) on blood pressure are not well established. Otherwise, the side effects of the SNRIs are similar to those of the SSRIs.

The newest entry into the antidepressant market is Pristiq (desvenlafaxine). Pristiq (desvenlafaxine), is in the SNRI category of antidepressants and is manufactured by the Wyeth Corporation. This drug received FDA approval in March, 2008. Faced with the fact that Wyeth is losing patent protection for its top-selling antidepressant Effexor XR (venlafaxine XR), the

company needed a brand product that would potentially replace some of the revenue loss when Effexor XR goes generic in 2010. Sales of Effexor XR in 2007 hovered around 3.8 billion dollars (*New York Times*, March, 2008).

Wyeth claims that Pristiq has distinct advantages over Effexor XR. Among them are that patients can begin taking Pristiq at the therapeutic dose of 50 milligrams thereby circumventing the “start low, go slow” gradual increases associated with determining the appropriate dose for an individual. Another advantage of Pristiq, according to Dr. Philip Ninan, a Wyeth vice president for neuroscience, is that Pristiq is unlikely to interact with other medications metabolized by the liver.

But several analysts are skeptical of Pristiq, claiming that it has not set itself apart from other antidepressants on the market, and that its release appeared primarily to have the drug serve as a “patent extender” for Effexor XR. This is because Pristiq is a primary active metabolite of Effexor, meaning Pristiq is the chemical compound that results after Effexor is taken, metabolized and processed by the body. Interestingly, Wyeth is also seeking FDA approval for the use of Pristiq in decreasing menopausal related hot flashes. The most commonly reported side effect of Pristiq is nausea. Also, blood pressure needs to be monitored.

NOREPINEPHRINE REUPTAKE INHIBITORS (NRIs)

The antidepressants Strattera (atomoxetine) and Vestra (reboxetine) selectively block the reuptake of norepinephrine. Strattera (atomoxetine) is FDA-approved for the treatment of ADHD. Although pharmacologically considered an antidepressant, it is not FDA-approved for the treatment of depression. Vestra (reboxetine) remains unavailable for use in the United States, but is available in Europe. NRIs are noted for providing an energy boost, as well as for decreasing distractibility and improving attention span.

Remeron (mirtazapine), works indirectly on norepinephrine and serotonin as did Serzone (nefazodone) before it was removed from the U.S. drug market by its manufacturer Bristol-

Meyers Squibb in June, 2004. Serzone (nefazodone) was linked to dozens of liver failures in Europe, Australia, New Zealand and Canada, and was taken off those markets prior to its removal in the United States.

Remeron (mirtazapine) seems to help with the anxiety and sleep problems common to depression. With Remeron, however, weight gain due to an increase in appetite is very common. In rare instances, Remeron (mirtazapine) also decreases white blood-cell count.

MONOAMINE OXIDASE INHIBITORS (MAOIs)

Monoamine oxidase inhibitors (MAOIs) were first developed in the 1950s and today are rarely used, due to their numerous and potentially serious drug-drug interactions and drug-food interactions.

Monoamine oxidase is an enzyme that circulates in the central nervous system to metabolize neurotransmitters at presynaptic nerve endings. The antidepressant properties of the MAOIs are linked to the fact that these agents inhibit the actions of this enzyme. Two common MAOIs are Parnate (tranylcypromine) and Nardil (phenelzine).

A monoamine oxidase inhibitor transdermal delivery system (patch) called Emsam (selegiline) is now available. Pharmacokinetically, the patch delivers its active ingredient by way of absorption through the skin. Purportedly, this delivery system is associated with fewer side effects when compared with the oral administration of the MAOIs.

MAOIs are linked to a host of drug-drug interactions. For example, an extremely dangerous and possibly fatal interaction may occur when Demerol (meperidine) is combined with an MAOI. Patients taking an MAOI also need to be cautioned about the use of over-the-counter drugs, such as the common cough remedy dextromethorpan.

Potentially serious drug-food interactions also make the MAOIs problematic. Tyramine is an amino acid that plays a role in maintaining blood pressure and is metabolized by monoamine oxidase. Foods containing tyramine, if combined with MAOIs, can result in a hypertensive crisis as arterial blood pressure rises, at times suddenly. Patients should be provided with a list of tyramine-containing foods to avoid while taking MAOIs. Also, MAOIs should *never* be combined with SSRIs for fear of the development of “serotonin syndrome.” Characterized by fever, profuse sweating, rigidity, twitching, rapid pulse, high blood pressure, confusion and altered consciousness, this syndrome can result in a coma or even death.

Figure 5-1. Food Products that Contain Tyramine

Because of potentially serious drug-food interactions—for example, a sudden, dangerous spike in blood pressure—the following foods should be avoided while taking monoamine oxidase inhibitor drugs (MAOIs). This is not a complete list, and patients should consult their physicians.

- Alcohol: Beer and ale (including non-alcoholic varieties), red wine, port, whiskey, liqueurs, vermouth, sherry, Riesling, sauternes.
- Aged cheeses: American, blue, Boursault, brie, camembert, cheddar, Roquefort, Stilton, Swiss, parmesan, processed, mozzarella, gruyere, Romano
- Fish: Smoked, pickled, dried or fermented. This list includes herring and fish roe, such as caviar.
- Aged or cured meats: Including sausages, bologna, salami, pepperoni, game
- meats and canned meats
- Meat tenderizer, meat extracts
- Fermented bean curd products: tofu, miso soup
- Fava beans
- Fruits and vegetables: Overripe avocados and figs; raisins, bananas, red plums, tomatoes, spinach and eggplant
- Sour cream, yogurt
- Sauerkraut
- Shrimp paste

- Brewer's yeast or yeast extracts
- Powdered and liquid protein dietary supplements
- Vitamins and supplements containing yeast

ATYPICAL ANTIDEPRESSANTS

Atypicals don't fit specifically into an antidepressant "family" as the others do. In this category, the antidepressant of note is Wellbutrin (bupropion). Since its release in the late 1980s, the mechanism of action has at times been described as sketchy. Wellbutrin (bupropion) exerts no effect on serotonin and has only a modest effect on the norepinephrine system. This medication's considerable effectiveness as an antidepressant is likely linked to its action on dopamine nerve cells. It can be considered a dopamine and norepinephrine reuptake inhibitor (DNRI). Some studies suggest that Wellbutrin (bupropion) does not destabilize the moods of bipolar patients, resulting in fewer of them tipping into mania or rapid cycling.

According to the National Institute of Mental Health, as many as 60 percent of depressed individuals who are unresponsive to other antidepressants improve on Wellbutrin (bupropion). This is why it is commonly used in Treatment Resistant Depression (discussed in Chapter 6).

The primary side effects of Wellbutrin (bupropion) are anxiety and insomnia. The insomnia can be significant to the point of requiring management with a prescription hypnotic (sleep-aid). Wellbutrin (bupropion) is associated with few, if any, sexual side effects. But there is a seizure risk at doses greater than 400 mg a day, which is why for the most part it is contraindicated in seizure disorder. This medication is also contraindicated in alcohol withdrawal, since that condition can lead to seizures, as is also the case in patients with eating disorders.

Zyban (bupropion HCL) is a slow-release form of Wellbutrin that has been approved by the FDA as a treatment for smoking cessation. A dosage of 150 mg twice daily is recommended to help people abstain from smoking and avoid subsequent weight gain.

WHAT YOU AND YOUR CLIENTS NEED TO KNOW

Depression is a real illness, not a character flaw or a weakness. Clinicians should do their best to “destigmatize” depression, emphasizing that it is an illness no different from diabetes or hypertension. Additionally, depression is highly responsive to appropriate treatment. Clients should be educated about the possible adverse effects of antidepressants, how long it typically takes to see improvement (discussed earlier), and the importance of taking medication properly, including avoiding abrupt discontinuation. They should also be told that if one medication is unsuccessful, others may be tried until an appropriate one is found to produce the desired therapeutic effect.

CASE STUDY: DEPRESSION—“I JUST DON’T HAVE ANY ENERGY LATELY.”

Rhetta is a 25-year-old woman who presents to her family practitioner for her annual physical examination and Pap smear. She is a single heterosexual female, a vegetarian who does not drink alcohol or smoke, and tests negative for substance abuse. She is currently taking Lo-Ovral-28, an oral contraceptive, one tablet daily. She relates a 14-pound weight loss in the last two months. She also complains of a lack of energy, but she has trouble falling asleep. She works part-time as a youth director at a local church while pursuing a master’s degree in art at a local university. She complains of the stress generated by her demanding job and attending school at the same time. She has had considerable difficulty concentrating over the past four weeks and has not turned in a class project that was due last week. Being a talented artist, some of her work has been on display at statewide festivals and exhibits. Presently, however, she expresses little interest in painting and is thinking about leaving graduate school. Rhetta is the youngest of four siblings, with alcoholic parents. When she was eight years old, her mother died of liver cirrhosis. She was placed in foster care in the fourth grade. An older sister is taking Zoloft for depression.

Rhetta is appropriately dressed with clean clothes. She sobs at times during the interview. Her affect is sad, her mood is depressed, and she admits to having suicidal ideation but no specific plan. She is oriented to person, place, and time, but she displays some recent memory

deficits accompanied by poor concentration. She is of above average intelligence with satisfactory insight and judgment, and she denies hearing voices or having other hallucinations.

Diagnostic Considerations

Rhetta's treating physician concludes that she is experiencing a major depressive episode. Though this depression seems to have developed due to her difficulty in adjusting to work and school demands, symptomatically she is experiencing physiological symptoms as well. As a result, her doctor recommends she try an antidepressant. She agrees to do so and is started on Zoloft (sertraline), 25 mg daily for one week, then increasing to 50 mg daily for one week, and then 100 mg daily thereafter. The physician explains the common side effects associated with Zoloft (sertraline), that it may take three to four weeks for symptoms to improve, and that she should do her best to not miss any doses. He also mentions that since she has a sister taking Zoloft (sertraline), it may prove to be a good choice for her also.

Treatment Course

Rhetta responds quite favorably to this Zoloft regimen. Although she does experience some of the side effects her doctor mentioned, they are manageable. After six weeks, practically all of the clinical depression symptoms have abated. She is instructed to remain on the Zoloft (sertraline) for another six months and to then schedule a follow-up appointment for re-evaluation.

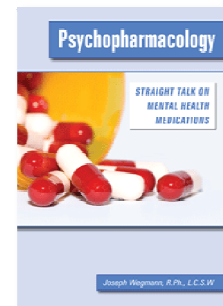
DOSAGE RANGE CHART — ANTIDEPRESSANTS

BRAND NAME	GENERIC NAME	CLASS	DAILY DOSAGE RANGE *
Anafranil	clomipramine	cyclic	150 mg - 250mg
Celexa	citalopram	SSRI	20 mg - 80 mg
Cymbalta	duloxetine	SNRI	20 mg - 80 mg
Desyrel	trazodone	cyclic	150 mg - 400 mg
Effexor	venlafaxine	SNRI	75 mg - 350 mg
Effexor XR	venlafaxine XR	SNRI	75 mg - 350 mg
Elavil	amitriptyline	cyclic	100 mg - 300 mg
Emsam (patch)	selegiline	MAOI	6 mg - 12 mg
Lexapro	escitalopram	SSRI	10 mg - 40 mg
Luvox	fluvoxamine	SSRI	100 mg - 400 mg
Nardil	phenelzine	MAOI	45 mg - 60 mg
Norpramin	desipramine	cyclic	150 mg - 300 mg
Pamelor	nortriptyline	cyclic	75 mg - 150 mg
Parnate	tranylcypromine	MAOI	20 mg - 60 mg
Paxil	paroxetine	SSRI	20 mg - 50 mg
Prozac	fluoxetine	SSRI	20 mg - 80 mg
Remeron	mirtazapine	atypical	15 mg - 45 mg
Sarafem	fluoxetine	SSRI	20 mg - 80 mg
Sinequan	doxepin	cyclic	150 mg - 300 mg
Strattera	atomoxetine	NRI	60 mg - 120 mg
Tofranil	imipramine	cyclic	150 mg - 300 mg
Wellbutrin SR	bupropion SR	atypical	150 mg - 300 mg
Wellbutrin LA	bupropion LA	atypical	150 mg - 300 mg
Zoloft	sertraline	SSRI	50 mg - 200 mg

* Suggested adult dose

Note: Dosage ranges may vary depending on source, and may also vary according to age.

Joe Wegmann is a licensed pharmacist and clinical social worker with more than 30 years of experience in the area of psychotropic medication. His diverse professional background in psychopharmacology and counseling affords him a unique perspective on medication management issues. Joe's new book, "*Psychopharmacology: Straight Talk on Mental Health Medications*" is available at: www.Pesi.com.



Joe has presented psychopharmacology seminars to over 10,000 healthcare professionals in 46 states and maintains an active psychotherapy practice specializing in the treatment of depression and anxiety. To learn more about Joe's programs or to contribute a question for Joe to answer in a future article, email him at: joe@thepharmatherapist.com.