

Understanding the new antidepressant medications

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Psychiatric medications can seem awfully bewildering at first. We have a long list of them and it's always expanding. Each of the drugs has both a trade name and a generic name and we often interchange them. Dosages vary wildly. Dozens of diagnoses now lead to a prescription for medications. Each drug is used for a host of different, seemingly unrelated conditions. And there has always been a tendency to attribute mysterious properties to psychiatrists and our treatments anyway.



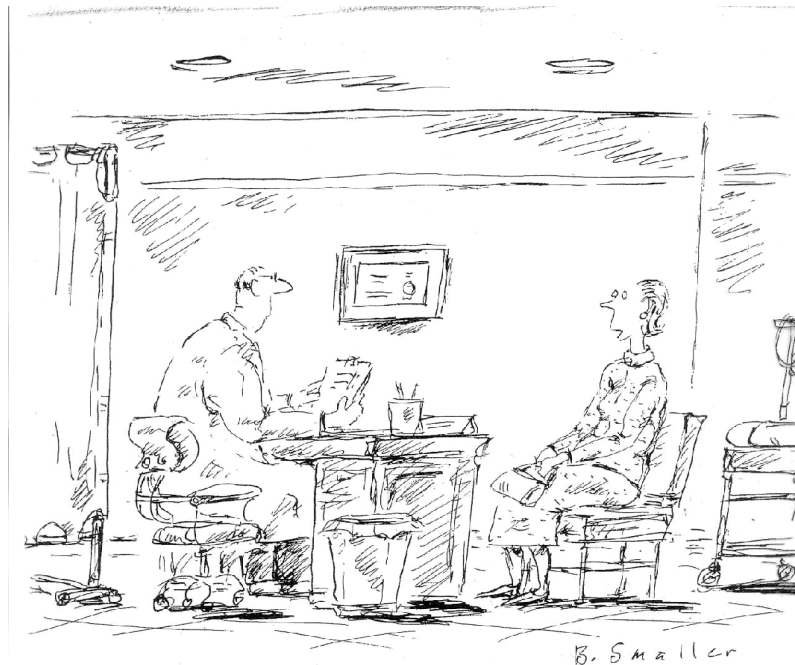
Prescribing medications to relieve psychiatric symptoms isn't really that difficult though. Just look at some of us that do it all the time. How hard can it be? If some basic principles are followed and the right information - which is now widely available - is obtained it's pretty easy to come up with a decent strategy to address the symptoms of any of the main disorders. The complications come when variables outside of the pill bottles are considered.

When they come to us for treatment most people want to know if there are any good alternatives to medications. It's a great question and our answers don't always do it justice. Whenever we have the luxury of time it's just common sense to try the gentlest,

least-intrusive treatments first. Sometimes they work very well. If treatment jumps immediately to using powerful artificial chemicals you never know if the simple changes would have been enough. As each group of medications is reviewed alternative approaches to treatment with them will be included.

If a decision is made to use medications it's important to follow the basic principles of prescribing them that were outlined in the last chapter. Mistakes will be minimized and it will be easier to tell if the medications are helpful if those simple strategies are used whenever possible. Getting the best information possible to the Doctor is vitally important too. Taking psychiatric medications is a serious thing and it only makes sense to go into it with the most accurate data available.

The Antidepressant Medications



"I think the dosage needs adjusting. I'm not nearly as happy as the people in the ads."

This class of medicines has evoked a wide variety of powerful reactions among the general public. Many people have concerns about the extent to which our society is becoming a medicated one. We bemoan the fact that many of the "natural antidepressants" like exercise, good nutrition, engrossment in stimulating activities, satisfying relationships with other humans, and a healthy, resilient sense of self appear to be increasing hard to come by in America. But, at the same time, nearly everyone knows

people who take these antidepressant drugs and it's clear that many of them have benefited from them in some way. It's difficult to find sweeping generalizations that will hold up. And when we can't reduce complicated issues to a level where sweeping generalizations suffice that gets pretty confusing for some of us.

Antidepressant medications are usually broken down into two large groups: The newer "SSRI" meds and their relatives. And the older drugs that we used before the Prozac generation began. Since it's much more likely that the newer drugs will be encountered we'll review those first.

Members of the Prozac class of Antidepressants

Trade name	generic name	Daily dose range
Prozac	fluoxetine	10-80 mg
Zoloft	sertraline	50-200 mg
Paxil	paroxetine	10-60 mg
Celebra	citalopram	20-60 mg
Lexapro	escitalopram	10-20 mg
Luvax	fluvoxamine	50-300 mg
Remeron	mitazapine	15-45 mg
Wellbutrin	bupropion	150-450 mg
Effexor	venlafaxine	75-375 mg
Cymbalta	duloxetine	40-60 mg
Desyrel	trazadone	50-400 mg
Serzone	nefazadone	300-600 mg

What are they useful for?

We use these antidepressant drugs for just about any human problem these days. They are our first line agents for treating Major Depression, of course, but the same holds true for nearly all of the anxiety disorders. People with Obsessive Compulsive Disorder, Post Traumatic Stress Disorder, the phobias, Generalized Anxiety Disorder, or Panic Attacks are all likely to receive these drugs. Chronic pain, bedwetting, problems with sexual impulse control and just about any of the personality disorders are also treated with antidepressants. These drugs are now routinely used in the treatment of Schizophrenia, Schizoaffective disorder, and Bipolar Disorder. Young children receive these drugs for depression, behavioral problems, and Attention Deficit Disorder.

Relatively minor depressions, any complaints about excessive anxiety, or even vague

assertions from a patient they "don't feel quite right" can now lead to prescription of these expensive new drugs. And many people do feel less depressed, irritable or anxious when they take them. Any time that emotional responses to thoughts or external situations become too intense or painful these medications have the potential to help the person feel better. And any time that there are problems with the impulses that arise from the emotions we're likely to prescribe these medications too.

How do you choose a drug?

Predictably, the pharmaceutical companies have tried to play up the small differences between their drugs and the existing ones to create the perception that their new product represented some sort of major advance in treatment. In actuality there is little to guide a Doctor as he tries to guess which antidepressant will actually work best for an individual patient. Someone might respond to one of them while another patient with an identical presentation experiences no benefit from it.

The general rule of thumb is that the SSRI antidepressants (Those affecting primarily serotonin: Prozac, Zoloft, Celexa, Lexapro, Paxil, Luvox) tend to be better at easing the connections between thoughts and emotions. So we often choose these first when treating any of the anxiety disorders or when depressions have a strong component of anxiety. Similarly, they seem to do better when we want to reduce the connections between emotions and actions - whether the actions involve impulsive behaviors in the physical world or the of movement of symbols in the mind as in the obsessions and compulsions.

Some of the newer antidepressants are considered "dual action drugs". They are believed to have effects on both serotonin and norepinephrine (Wellbutrin, Remeron, Effexor, and Cymbalta are the commonly used examples). They tend to be better in the true Major Depressions, especially those with "melancholic symptoms" such as decreased sleep and appetite, inability to experience pleasure, and slowing of physical and mental movement. For some reason these drugs appear to be better at reducing pain too.

Each of us shrinks has our drugs in each class that we feel most comfortable with. Our experiences with them might even convince us that one is more effective than another. But when we study the all of the clinical evidence available we find that there isn't much at all that would lead us to choose one drug over another.

When specific treatment recommendations are offered, as in the Texas Medication Algorithms (<http://www.dshs.state.tx.us/mhprograms/TMAPover.shtml>), we see that the idea is generally to choose one of the newer drugs, try it for an adequate length of time, then if it isn't working try a different drug by itself. If that doesn't work, try a different one. After several trials of individual drugs are unsuccessful it's suggested that the antidepressant be tried with "augmenting drugs, like lithium, on board to see if that helps to increase the response. If there's still no response they suggest combining antidepressants.

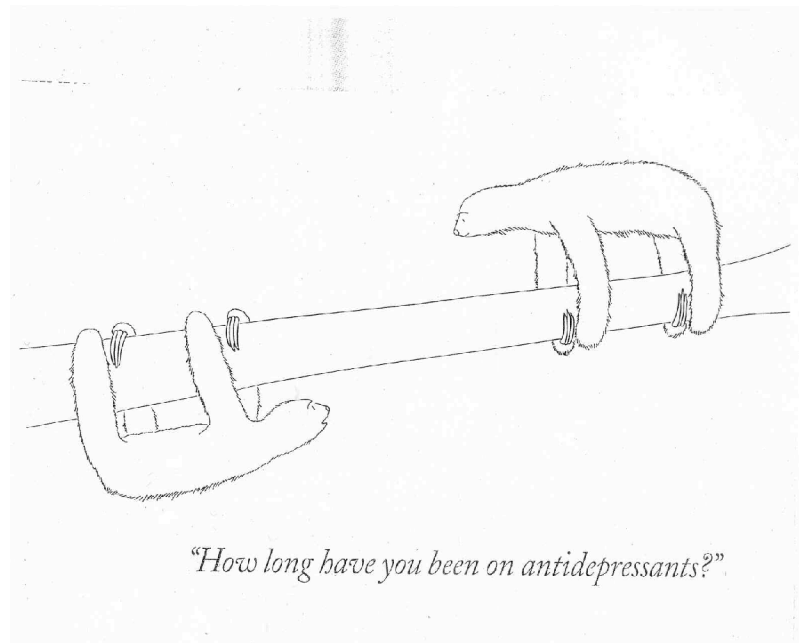
But in actual practice the decision to try multiple antidepressant drugs usually comes

much earlier. Doctors are often very quick to push up doses if patients don't respond quickly and if that doesn't work we often add second and third antidepressants. We want to do *something* to help when people are depressed and telling them to wait a while to see the full effects of the first drug doesn't feel very dramatic to anyone.

The "double blind" dosing studies usually show that increasing doses of a drug beyond the recommended ones doesn't have much chance of inducing response. But we commonly push doses up beyond the ones that have been studied and found to be most effective. In fact if a psychiatrist routinely uses outrageously high dosages of medications in his practice he may be viewed as more of an expert or as someone who is willing to try "heroic measures".

In reality it's not that any particular medication, dosage, or combination can be seen as better or worse than another. It's how the treatment is arrived at that's important. If simple medication regimens and modest dosages aren't tried first it's pretty hard to justify having patients on the high dose, multi-layered combinations.

They don't have side effects do they?



Because the new generation of antidepressants are so much safer and easier to use than the older ones we no longer feel the need to limit them to patients with severe, "major depressions". Family practitioners, internists, neurologists, and other physicians have become quite comfortable prescribing the new antidepressants - to a point where the majority of prescriptions for these drugs no longer come from psychiatrists.

Most people tolerate these drugs relatively well and they're generally safe in overdose. But any chemical that's powerful enough to be involved in something as fundamental as the connections between thoughts, emotions, and impulses is bound to have the potential for causing all sorts of problems.

Serotonin is a chemical that's found throughout the nervous system. Its role is usually to inhibit or turn down the transmission of nerve impulses. Over fifteen subtypes of serotonin have been identified so there can be a variety of effects - both good and bad - when drugs target this transmitter. Effects on the gut, such as nausea and diarrhea are common. Some people feel drowsy or lose their appetite. Dizziness, fatigue, and dry mouth can occur.

In extreme cases something called "serotonin syndrome" can develop. Typically this occurs when more than one serotonin boosting drug is on board, high dosages are used, or when patients are just unusually sensitive to the medicine.

In serotonin syndrome patients can become very agitated and confused. They may experience manic-like symptoms including severe restlessness. Fever, flushing and sweating can occur. The muscles can become overly excitable, with increased reflexes, tremor, and spasms. Stopping the offending drugs immediately is essential to treatment but the symptoms may not be recognized as coming from antidepressants, especially if the doctor isn't too familiar with them.

Norepinephrine is an excitatory transmitter that's related to adrenaline. When it's affected the side effects can include different kinds of activation. Insomnia, agitation, tremor, restlessness, and increased anxiety can result whenever norepinephrine transmission is increased.

There can be a lot of overlap between the two neurotransmitters and their side effects. When you look up any of the newer antidepressants you'll see that just about all of the side effects listed above have been reported for it. For some patients they can be minor. Others have to stop the medications because of them. It's very hard to say in advance how any individual will tolerate these drugs.

The media now contains reports of lawsuits against drug companies involving both patient suicides and homicides. It turns out that, for some people, when their brain doesn't attach emotions like anxiety or dread to their terrible thoughts there isn't much standing in the way of carrying out their terrible impulses.

The allegations are that taking the new antidepressants has sometimes resulted in a disinhibition of destructive impulses that would have normally been held in check. It's hard to argue that this never occurs. When the basic action of a drug is to cause a weakening of the emotions that result in response to thoughts and ideas it seems that the occasional surfacing of negative behaviors is unavoidable. How much responsibility the drug companies should bear when the worst outcomes occur is a matter of debate. So is

the issue of how actively they've tried to suppress information about the possibility that their products might lead to those outcomes.

The sexual side effects of these drugs have turned out to be a bigger issue than we originally imagined too. In truth, while psychiatrists are quick to affirm the importance of sexuality for most healthy humans it's an area that a lot of us are uncomfortable talking about. So if patients aren't making a big deal about sexual problems we may be more than happy to ignore the whole issue.

Antidepressants that increase serotonin are now known to have potential negative effects on all phases of the human sexual response, from desire to pleasure to orgasm. There are now suggestions in the literature that reducing sexual desire and the ability to experience orgasms may be leading to powerful effects on our instincts around mating and reproduction. For example if a woman is taking an SSRI and her sexual desire declines so that she can no longer experience orgasms this may have profound effects on her interest in attracting a mate or her desire to sustain relationships with a current partner. Obviously, the same sorts of mechanisms can hold true for males.

These medications may even be decreasing the possibility of romantic love for some patients. One of the characteristics of people that have fallen in love is an obsessive-like focus on the object of their affections. The chosen person is experienced differently than all other humans. We feel different in their presence and when they're not around we tend to think about them a great deal. Those thoughts can be repetitive and they're often attached to pleasurable emotions. The antidepressants can interfere with all of these processes. How we feel around someone, whether we devote a lot of mental time to them, and the emotions that we attach to our thoughts about them all can be changed by drugs that increase serotonin.



*"You think I would have sunk forty thousand clams
into this lemon if I had known they were coming out
with a nine-dollar boner pill?"*

It's hard to do justice to just how important sexual impulse, desires, and mating practices are to humans. While we'd like to pretend that this is not the case a casual look around us tells us that we're immersed in sexuality.

People go to great lengths to convince themselves that they're attractive mates. We spend huge amounts of money on stylish clothing, impressive automobiles, cosmetics, and much larger homes than we need in an ultimate effort to increase our sexual rank within our social groupings. Television shows and advertisements, the print media, and the content of most gossip revolve in one way or another around sex. One could even argue that the American economy actually is driven by sexuality. If everyone bought only the things that they actually needed to comfortably survive, with no thought as to whether others were impressed by the purchases, the whole business of doing business would come to a screeching halt.

We really don't have any idea about how the sexual side effects of these widely used drugs will impact our patients or our society yet. The issue is very different now than it was even a decade ago. Before Prozac, antidepressants were used by a much smaller pool of people and they were typically prescribed for a limited period of time. Nowadays we have people taking these drugs for years on end. There's no way that we can say how being on antidepressants throughout the reproductive years might affect their lives. It seems at least possible that tampering with instincts and impulses that have shaped human society and behavior for thousands of years might have consequences that we haven't imagined. The fact that those effects are hard to study doesn't decrease them a bit.

All of these antidepressants are now recognized for their ability to cause manic symptoms. In some cases they seem to make people manic that would have never had those symptoms in the absence of the drugs. As you might guess, we Doctors are not always that adept at separating out the drug-induced mania from plain old bipolar illness. So some people with antidepressant side effects get tagged with a diagnosis of Bipolar Disorder and are treated for that, usually with a recommendation that they take a mood stabilizing medication regimen "for life".

Some people who try to stop taking these drugs- both the SSRI's and the dual-actions - have a difficult time of it. It's relatively common for patients to experience increased anxiety, depression, restlessness, insomnia, nightmares, or flu-like symptoms when they stop their antidepressants. A few have balance problems or even "electric shock" like sensations. Doctors often assume that these symptoms indicate that the initial depression has returned or gotten worse.

A big controversy in our field is whether antidepressants are, in truth, addictive drugs. We call the effects that occur when the drugs are stopped "antidepressant discontinuation effects" because it sounds a whole lot better than "drug withdrawal". But it's pretty clear that by older definitions we would have had to classify these drugs as addictive. Some people just cannot get off them, even after years of trying, because these discontinuation effects are too severe to tolerate. Others require increasing dosages to maintain the same therapeutic effects. In the DSM III "tolerance" and "withdrawal" were the cardinal features that determined whether a drug was considered addictive. Those criteria changed right around the time these new drugs came out.

The nervous system is incredibly plastic and responsive to changes in its environments - both the external one and the internal world of chemicals. When we increase the flow of any particular neurotransmitter the brain eventually responds by making fewer receptors for the transmitter. So when someone stops taking a drug their nervous system is in a different state than it was in originally. Removing drugs abruptly can magnify the discontinuation effects.

It would seem like a common courtesy to at least inform patients about the issue of discontinuation effects and the possibility that they might need to stay on the drugs indefinitely. But this is another area that we physicians often come up short in. Many patients will tell you that these topics were never once brought up when they agreed to start a drug or even while they were taking it. Once again it points to the fact that the quality of the relationship between Doctor and patient is of paramount importance when it comes to providing good medication treatment.

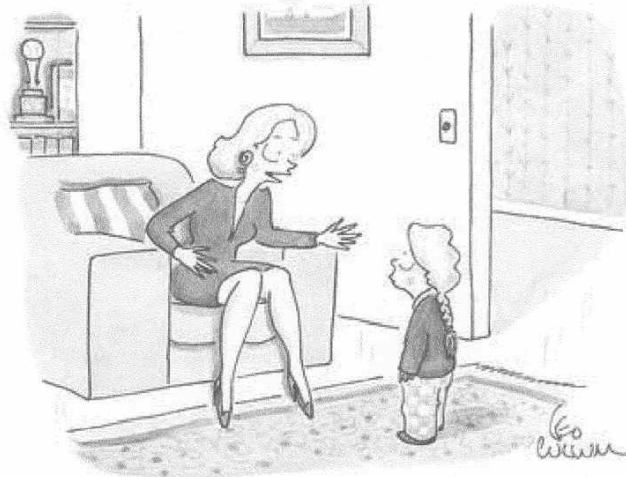
How do these drugs work?

As was emphasized in the earlier chapter it seems rather far-fetched to think that this class of drugs would have specific therapeutic actions in each of these diverse human problems. The more plausible explanation is that they work by somehow changing the balance between thought and emotion. One of the ways that they accomplish that task seems to be by affecting the birth of new brain cells in that brain area called the hippocampus. The possibility that this change in the hippocampus might result in an alteration in the balance between two basic emotional processors was suggested in the model of mental illness that was outlined earlier.

The new generation of antidepressants are thought to work by keeping the neurotransmitters serotonin or norepinephrine out in the synapse transmitting nerve impulses for a longer time than it would otherwise be able to do. It typically takes from two to as many as eight weeks for the therapeutic effects of these drugs to emerge. So almost certainly there is some restructuring of the nervous system involved rather than a simple and direct impact on neurotransmission, i.e. the correction of a “chemical imbalance”. It's likely that the changes in the flow of these transmitters ultimately lead to some genes being turned on and others turned off, with an eventual change in the way the brain's important areas are structured and able to relate to each other.

The end result may be a reduction in the way that thoughts, ideas, and self-concepts can affect our emotions - and vice versa. People who take these medications will tell you that thoughts that previously produced worry and anxiety just don't seem to touch them in the same way. The emotions aren't as intense and their negative effects on the self-image aren't as powerful either.

Quirks of the class members



"Of course your daddy loves you. He's on Prozac—he loves everybody."

Prozac is a drug with a very long half life. As a result it can take as long as a month or more of regular use before its concentration in the blood stream become stable or "reach steady state". It also stays in the body for a long time after a person has stopped using it - sometimes as long as two months. So it can interact with other drugs that are prescribed long after the Prozac has been stopped.

Paxil seems to cause discontinuation effects that are of greater frequency and severity, especially if high dosages are used or they're stopped abruptly. Some of this may be due to its blocking effects on another brain transmitter called the muscarinic acetylcholine receptor. When the Paxil is stopped that transmitter can rebound significantly. And some might recognize acetylcholine as the transmitter that is targeted by "nerve gasses".

Lexapro is one of a new generation of medications. Chemicals like these antidepressants exist in two forms that are mirror images of each other, or "stereoisotopes". Lexapro is really just Celexa with one of the two forms removed. Taking out the type of the molecule that's not helpful in depression is said to result in a reduction of the amount of drug that's needed and fewer side effects.

Serzone is one of the few drugs that you can't get cheaper from Canada. It was pulled from the market there because of some cases of severe liver failure. Some patients on Serzone have had liver transplants and a few have died. The FDA hasn't yet

seen fit to take this drug off of the shelves of our American pharmacies though.

Bupropion is the generic name for the both antidepressant **Wellbutrin** and the "smoking cessation" drug **Zyban**. But if you buy the same exact drug as Zyban it can cost twice as much. Is there any other country where this sort of practice would be accepted without question? Regardless of how one buys it this drug can increase the risk of seizures so we try to avoid using it in people who have epilepsy.

Remeron is a strange drug in that it makes people sleepier on low doses than high ones. This is probably related to its effects on another neurotransmitter called histamine. Some Doctors believe that Remeron may be more effective for severe depressions than some of the others but that its therapeutic effects may also fade away more quickly. Some people have reported dramatic increases in their appetite with this drug, especially their craving for sweets.

Cymbalta is our newest antidepressant. It's unusual in that it was already studied in and marketed as a drug to reduce pain before it was released. In Europe it's been approved for urinary incontinence.

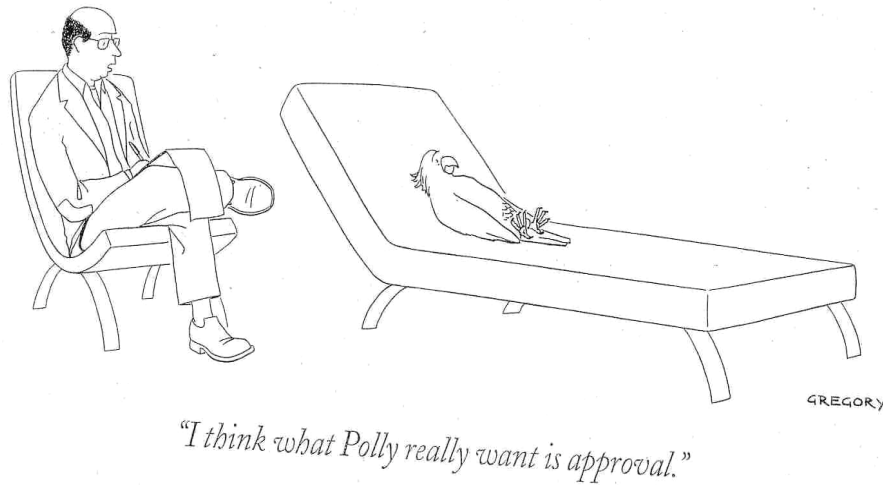
Trazadone is an antidepressant that is more typically used for sleep than depression. It can be very helpful for insomnia and is often given when other antidepressants cause that problem. It does leave many patients feeling groggy when they wake up. Trazadone is known for one particularly nasty (but rare) side effect. It can cause priapism in males - erections that go on for too long. In some cases surgery is required to get the erections to go down and that surgery can leave a man without the capacity to ever experience erections again. Some of us would insist upon being given intravenous valium (a powerful sedative and muscle relaxant) to try to relieve the erection before we'd turn our privates over to the surgeons.

Effexor is one of the dual action drugs and is known as one of the more effective ones for severe depressions. It's also known for having more chance of causing severe discontinuation effects than some of the others. Some Doctors think that it may increase the likelihood of alcohol abuse, perhaps by changing the liver enzymes involved with breaking down alcohol itself.

Are there alternatives to antidepressants?

Depression is one psychiatric disorder that a lot of different treatments have worked in. Some of this is due to the fact that most depressions will eventually get better on their own. The brain just isn't wired to maintain any particular mood or emotion indefinitely. Sooner or later the transmitters wear out or the brain adjusts in some other way. For the same reason, any attempts to keep a person in a state of perpetual happiness are unlikely to be effective. We all have our ups and downs and that doesn't mean everyone is bipolar,

as some shrinks now seem to believe.



Psychotherapy has been helpful in many depressions. In some studies outcomes for treating depression with psychotherapy have been better than with our medications, especially when the longer-term effects were looked at. Seeing ourselves in new ways has all sorts of effects and many of them must be rooted in very real changes in brain function and structure.

Traditional ideas have held that depression is a reaction to loss. The emotions around grief and bereavement are certainly similar to depressive illness. But it's looking like depression can be a reaction to a wide variety of other environmental stressors.

Depression may be a signal that we somehow feel trapped in a situation that we might be better off changing. It can serve as a punctuation mark in our lives, a necessary part of one phase ending and another's beginning. Depressive symptoms can signal surrender when overt conflicts around authority would be against our best interests. Depression can result from challenges to our established way of thinking about ourselves. When the gap between how good we think we are and the idealized version of ourselves widens depression is a common result.

Seeing a good psychotherapist to try to sort it all out is never a bad idea, especially if you're the kind of person who's curious about themselves and there aren't suicidal risks involved. It's rare to meet someone who gave psychotherapy a serious try and doesn't feel

like they gained anything.

The same cannot be said for Electroconvulsive Therapy (ECT). In severe depressions shock treatments still rank as the most effective of all the antidepressants. ECT can be useful when suicide risks are high or when other treatments aren't effective or well tolerated. But it's very unusual to talk to people who look back with contentment on their previous shock therapy. Many complain of memory problems that go far beyond what the party line suggests ECT can cause. Other people feel bitter about the whole experience for reasons they can't explain. Maybe handing over so much control to another human just doesn't feel good.

While shock treatments are very effective for depression (and severe mania too) there haven't yet been studies showing that any benefit of ECT lasts beyond thirty days. And the economics of the treatment have to be considered. There is nothing that private psychiatrists can do that is more lucrative than giving shock treatments. The costs of a single treatment can run to \$800 or more. A study on the use of ECT in Texas found that its use in 65 year olds was increased by 360% over people that were 64 or less. By some strange coincidence Medicare started paying for shock treatment when people turn 65.

Providing electroconvulsive therapy is about as "medical" as we shrink get. The treatments are usually given in surgery areas or emergency parts of the hospital, needles are used, and there are very impressive-looking machines involved. The psychiatrist's part in the treatment usually comes down to simply pushing a button.

Phototherapy lights are a gentle but effective way to treat some seasonal depressions. The bodies of many people, especially of Northern European origin, essentially decide to hibernate when the short days of winter arrive. We lose energy, our taste for sweets increases, and our mood can get pretty gloomy. When the right spectrum of light is provided in the right intensity, sitting in front of a lightbox for twenty minutes in the morning artificially lengthens the day and tricks the brain into thinking that it's still summer. The antidepressant effect can occasionally be too dramatic. Sometimes people will even experience manic symptoms as a result of the light treatment.

Sleep deprivation is an old remedy for depression that is sometimes effective. The person is instructed to skip an entire night's sleep and to stay awake until going to bed at his normal time the next evening. This is another treatment with a powerful enough biological basis to sometimes trigger mania.

The literature on St. John's Wort is mixed. It certainly wouldn't qualify as a first line treatment for severe depression but there's no question that some people do become less depressed or anxious on it. Other herbs like valerian root and kava kava are effective anti-anxiety treatments for some people.

The role of estrogens in relieving depression in women is an evolving area. It's clear that the hippocampus is very sensitive to estrogens and that there is a powerful link between estrogens and mood. Whenever estrogen levels fall, as in the premenstrual phase of a

woman's monthly cycle, following childbirth, or at the time of menopause, the incidence of depressive symptoms rises. Sometimes the depressions can be quite severe. Treating women with estrogens can be very helpful. But there is a link between estrogens and uterine cancers so it's not the type of therapy that should be taken lightly. Some psychiatrists believe that adding estrogens should only be done by gynecologists or others with special knowledge of these hormonal systems.

The role of estrogens derived from plants, or "phytoestrogens" in the treatment of depression is currently receiving some research interest. Some women swear by them for menopausal symptoms. Trying a diet rich in soy products and flaxseed oil would seem like a reasonable option for the treatment of PMS and depressions of lesser severity, especially when the risk/benefit ratio is examined. It's another case where trying gentle treatments that don't carry much of a side effect burden doesn't have much of a downside.

Another natural antidepressant that's been getting attention is SAME or S-adenosylmethionine. It's an over the counter preparation that's been used for depression and arthritis in Europe for several decades. There has been agreement that SAME is an effective antidepressant when given by daily injection but the rap on it has been that the oral form doesn't work. But now some decent, albeit small scale, studies have found oral SAME to have antidepressant effects that are comparable to conventional antidepressants with a much reduced rate of side effects. The idea that someone can walk into his local drugstore to buy an effective antidepressant that's cheaper and has fewer side effects than our prescription drugs is not one that our big pharmaceutical companies have much interest in researching or promoting.

The role of omega III fatty acids in maintaining healthy brains and good moods has been reviewed earlier. There is now good evidence that depression is more likely to occur when diets are poor in omega III's. Some studies are finding that providing supplements can reduce symptoms of depression, decrease frequency of episodes, and even make conventional antidepressant drugs more effective.

As has been stressed, lifestyle factors such as exercise, stimulating activities, decent sleep, and challenges for the memory can all be helpful in reducing depressive symptoms and making our brains more resistant to depression. When taken together all, of this would suggest that there are a variety of ways that depression can be treated effectively.

A treatment program that consisted of a regular exercise program, living in a good environment, having someone to talk things out with, a diet rich in fish oil, and one of the more innocuous therapies like phototherapy, SAME, or phytoestrogens might be every bit as good-or better- than that quick visit to a psychiatrist for a pricey new artificial compound. But as effective as treatment approaches like those might be, it's unlikely that you'll find psychiatrists prescribing them anytime soon. It's hard to get all of those factors on a prescription pad and nobody will fill the script anyway.

