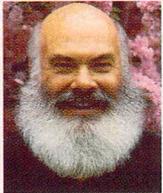


MOTHER NATURE'S LITTLE

A guru of alternative medicine makes his case for herbs and fatty acids

By **ANDREW WEIL, M.D.**



FRED KRONEBERG

In a clinical trial that got a lot of publicity last year, the herb St.-John's-wort failed to work better than a placebo in treating severe depression. The study also showed that Zoloft, one of the most popular prescription antidepressants, did no better than a placebo either, but that result attracted little attention. In the real world, people do not take St.-John's-wort for severe depression—they use it for mild to moderate conditions. Zoloft, on the other hand, is considered a powerful weapon in the ongoing war on mental illness.

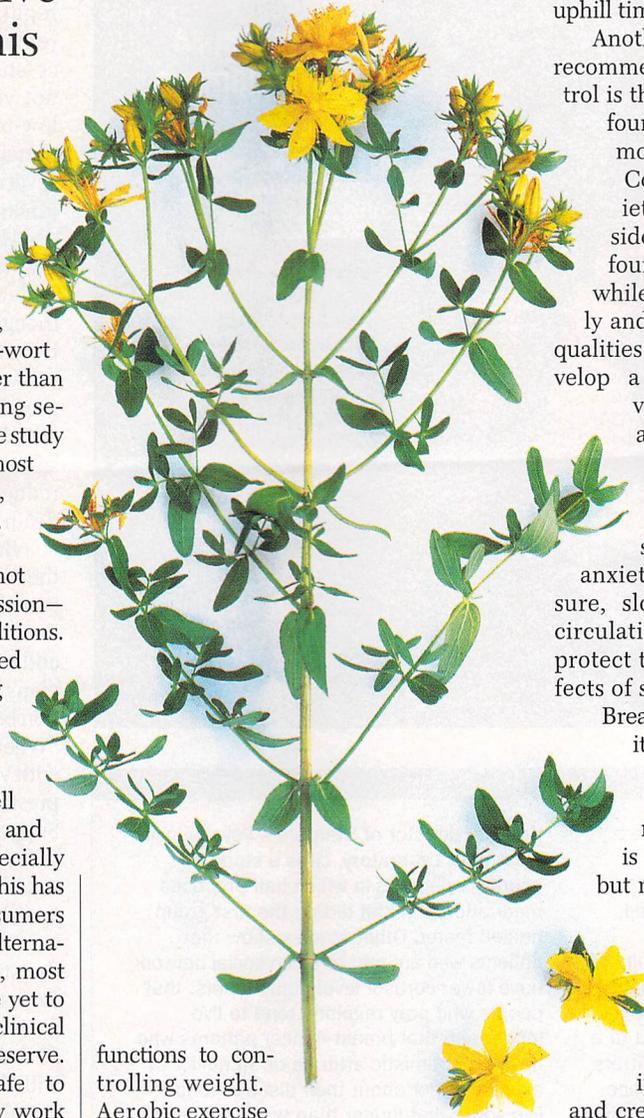
With good reason, a lot of people have questions about the efficacy of psychiatric medications, as well as concerns about their side effects and

**St.-John's
for the blues,
omega-3s
for autism,
breath work
for anxiety**

overuse, especially in children. This has led many consumers to explore alternative therapies, most of which have yet to get the fair clinical trials they deserve. But it is safe to say that many work for obvious reasons, some of them so simple they are often overlooked by psychiatrists, psychologists and researchers.

Take aerobic exercise. Not only is it a safe and effective treatment for depression, but it has many other health benefits as well, from improving cardiovascular and immune

functions to controlling weight. Aerobic exercise works, in part, by stimulating the release of endorphins, a class of endogenous antidepressants made in the brain. It both treats and prevents depression in susceptible individuals, and I prescribe it frequently. For best results, try to get 45 minutes of sustained aerobic activity an average of five days a week. Any activity that raises your heart rate and gets you breathing fast will do. Walking is fine if



you do it quickly enough or include some uphill time.

Another simple intervention I often recommend is breath work. Breath control is the most powerful method I have found to reduce anxiety, even in its most severe form of panic disorder.

Conventional drugs suppress anxiety but often cause significant side effects and dependence. I have found it is impossible to be anxious while breathing deeply, slowly, quietly and regularly. By working on those qualities in your breathing, you can develop a practical technique for preventing or cutting short an anxiety attack. Breathing exercises derived from yoga are even more effective. With practice, breath work quiets down the nervous system. This not only blunts anxiety but also lowers blood pressure, slows the heart rate, improves circulation and digestion, and helps protect the body from the damaging effects of stress.

Breath work is a natural segue to meditation, because the simplest meditation technique is concentration on the breath. The association of meditation with Eastern religion is an obstacle for some Americans, but many nonreligious forms exist. In essence, meditation is nothing other than focused awareness.

Although it can be used as a relaxation technique, I find it most valuable as a method of restructuring the mind, breaking habitual patterns of thought and creating seeds of balance to oppose erratic mood swings. Over time it can provide great mental-health benefits: relief from ordinary anxiety and depression, better rest and sleep, and increased resistance to disturbing influences on emotional equilibrium. Meditation has also proved quite valuable in preparing patients for surgery (*see following story*).

Of the nutritional approaches to mental disorders that I have studied, the most

2 ... and the body unleashes a flood of hormones ...

Adrenal glands react to the alert by releasing epinephrine (adrenaline), which makes the heart pump faster and the lungs work harder to flood the body with oxygen

The adrenal glands also release extra cortisol and other glucocorticoids, which help the body convert sugars into energy

Nerve cells release norepinephrine, which tenses the muscles and sharpens the senses to prepare for action. Digestion shuts down

3 ... that can cause significant damage

When the threat passes, epinephrine and norepinephrine levels drop, but if danger comes too often they can damage the arteries. Chronic low-level stress keeps the glucocorticoids in circulation, leading to a weakened immune system, loss of bone mass, suppression of the reproductive system and memory problems

Graphic by Lon Tweeten and Joe Lertola
Text by Michael Lemonick



made the senses sharper, the muscles tighter, the heart pound faster, the bloodstream fill with sugars for ready energy. Then, when the danger passed, the response would turn off.

In the modern world, stress usually takes other forms. But the fight-or-flight response hasn't changed. Sometimes it's still useful: a demanding job can lead to a sense of pride; a bout of precursive jitters can motivate a spectacular performance. But many modern stresses are continuing, not acute, and arise in situations we can neither fight nor flee: an unreasonable boss, a harrowing commute, a stormy relationship, a plummeting stock market, a general sense that life is out of control.

While some stress hormones can't stay elevated indefinitely, glucocorticoids can and do. Cortisol in particular can weaken the immune system, potentially making cancer and infectious diseases worse. Measuring the influence of stress, though, is tough. Some studies have shown no effect at all. Others offer intriguing clues. Dr. David

Spiegel, director of Stanford's Psychosocial Treatment Laboratory, cites a study of psoriasis patients in which half practiced meditation and half didn't; the first group healed faster. Other studies show that patients who are part of a rich social network have lower cortisol levels than loners, that people who pray regularly tend to live longer and that breast-cancer patients who have an optimistic attitude or an ability to express anger about their disease tend to live somewhat longer than those who don't.

Such positive results are encouraging, but they carry risks. Patients might blame themselves for not meditating hard enough, say, if they don't improve. And in the face of serious illness, stress reduction is likely to produce only minor effects compared with conventional medical treatment. But if meditation, prayer, exercise or relaxation techniques take even a little pressure off the immune system, that could add up over decades to a significantly healthier life.

—By Michael D. Lemonick.

Reported by David Bjerklie/New York

Zoloft, known as selective serotonin reuptake inhibitors, or SSRIs, were developed to keep serotonin from being reabsorbed quickly into nerve cells when it is produced.

Meanwhile, electroconvulsive therapy (ECT), better known as shock treatment, resets the electrical state of the brain by inducing a seizure. (Despite ECT's lurid reputation, it involves mild doses of current and can be almost miraculously successful in patients whose depression will not yield to drugs.) Even old-fashioned, low-tech talk therapy can help adjust a patient's brain chemistry and lessen the severity of depression, especially in conjunction with other treatments.

Unfortunately, the research that may unravel the interplay between depression and other diseases has barely begun. Even though there is a strong statistical link between depression and epilepsy, for example, we know very little about how to treat depression in epileptics. And as Charney has noted, it hasn't been proved, in a rigorous, scientific sense, that treating depression will reduce the excess risks of complication or death from a coexisting illness.

But if depression treatments rebalance the biochemistry that worsens disease, there is every reason to expect that they will reduce its deadly impact. So Charney, Evans and other experts want to make physicians more aware of the intimate connection between depression and other illnesses. "When you only have roughly eight minutes with your primary doctor," says Lydia Lewis, president of the Depression and Bipolar Support Alliance, "it's kind of hard to get into the realm of depression. And when you go to see a specialist, the cardiologist is thinking just about your heart."

So while researchers hold conferences, do studies and write scholarly papers, Lewis has some more immediate advice for patients. "We need to get people to go in and ask these questions of their physicians. Bill Valvo could not agree more. "I think people are totally unaware of what's going on," he says, "and I'm convinced that education is a key part of what we need to be doing." The essence of that education: cure the mind, and you might just help save the body. —Reported by David Bjerklie/New York

 Tune in to **ABC World News Tonight**, on Monday, Jan. 13, at 6:30 p.m. E.T., for a related story on the link between depression and osteoporosis

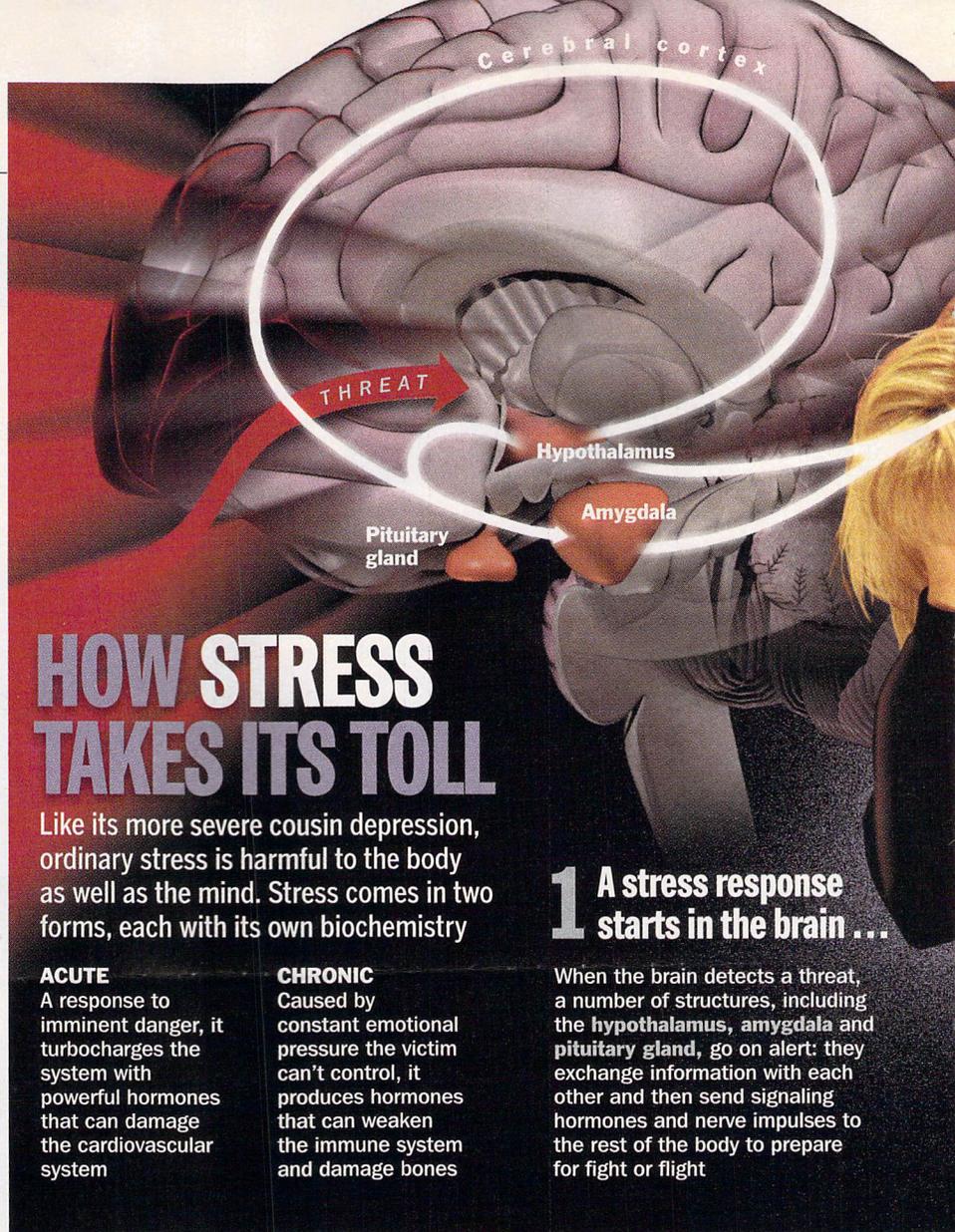
menopausal women who are depressed have a much higher rate of bone loss than their nondepressed counterparts—and this disparity increases as women pass through menopause. Indeed, Cizza estimates that some 350,000 women get osteoporosis each year because of depression. Cortisol appears to interfere with the ability of the bones to absorb calcium and offset the natural calcium loss that comes with menopause and aging. Another class of chemicals, the pro-inflammatory cytokines, have also been implicated in osteoporosis and diabetes, but their role is less clear.

Studies have established links between the incidence of depression and several other diseases, including cancer, Parkinson's disease, epilepsy, stroke and Alzheimer's. In some cases at least, researchers have clues, if not definitive evidence, as to which molecules might be involved. In Parkinson's, the problem is the death of cells in the brain that produce the neurotransmitter dopamine. While dopamine is crucial to the control of movement, it's probably a major factor in mood as well. "Depression almost certainly has multiple causes that produce similar symptoms," observes Dr. Bruce Cohen, president of McLean Hospital in Belmont, Mass.

That could explain why drugs that improve serotonin chemistry don't always work on depression—and why Parkinson's and depression can feed on each another. Epilepsy, stroke and Alzheimer's, which, like Parkinson's, involve physical alteration of the brain, probably also affect that organ's ability to make or process neurotransmitters—not only serotonin and dopamine but also glutamate and norepinephrine, all of which may be involved in different forms of depression.

Most treatments for depression aim to restore the electrochemical imbalance that leads a depressed brain into warped thinking. The so-called tricyclic antidepressant drugs popular in the 1960s, for example, boosted the activity of the neurotransmitters serotonin and norepinephrine, and two other neurotransmitters, active throughout the body. That often relieved depression but caused side effects, including overwhelming sleepiness, blurred vision and dizziness. The drugs also proved potentially lethal when taken in overdose.

Then in the 1970s, neuropharmacologists realized that they could minimize side effects by focusing just on serotonin. Antidepressant drugs like Prozac, Paxil and



HOW STRESS TAKES ITS TOLL

Like its more severe cousin depression, ordinary stress is harmful to the body as well as the mind. Stress comes in two forms, each with its own biochemistry

ACUTE

A response to imminent danger, it turbocharges the system with powerful hormones that can damage the cardiovascular system

CHRONIC

Caused by constant emotional pressure the victim can't control, it produces hormones that can weaken the immune system and damage bones

1 A stress response starts in the brain ...

When the brain detects a threat, a number of structures, including the hypothalamus, amygdala and pituitary gland, go on alert: they exchange information with each other and then send signaling hormones and nerve impulses to the rest of the body to prepare for fight or flight

EVOLUTION'S ROLE

A Frazzled Mind, a Weakened Body

A major mental illness like clinical depression will send biochemical shock waves through the body. But the intimate relationship of body to mind isn't limited to serious disease. Researchers have come to understand that what lies below the neck can also be harmed by less acute kinds of brain disturbances. The chronic stress that millions of people feel from simply trying to deal with the pressures of modern life can unleash a flood of hormones that are useful in the short term but subtly toxic if they persist. Thus it shouldn't come as a surprise that stress-reduction strategies that take pressure off the mind—meditation,



yoga, relaxation exercises and such—can take the heat off the body as well.

Humanity's physical reaction to stress, known as the "fight or flight" response, probably evolved to help our primitive ancestors deal with a treacherous world. When confronted with imminent danger—a saber-toothed tiger, say, or a club-wielding enemy *Homo erectus*—the body had to be instantly ready either to defend itself or to run like hell.

So the terrified brain would signal the adrenal glands, located on top of the kidneys, to release hormones, including adrenaline (its more technical name: epinephrine) and glucocorticoids (see chart), and the nerve cells to release norepinephrine. These powerful chemicals

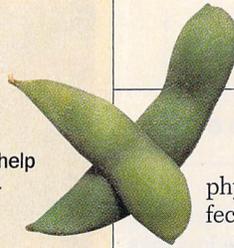


EDMUND ENGELMAN

ALTERNATIVE THERAPIES

TODAY'S TREATMENTS

■ More patients today help themselves to over-the-counter aids, from St.-John's-wort to ginkgo biloba and soybean extracts. But herbs, like prescription drugs, can have side effects, and researchers are investigating their efficacy. The popular supplement DHEA, for example, has been linked to an increased risk of cancer.



MARK FERRI—ENVISION

physiology of depression have effects throughout the body.”

Precisely how these powerful chemicals affect the course of heart disease, cancer and other illnesses isn't well understood yet, but preliminary research has yielded some tantalizing clues. When serotonin circulates in the bloodstream, for example, it appears to make platelets less sticky and thus less likely to clump together in artery-blocking blood clots. For years, heart-attack survivors have been advised to take a children's aspirin daily for clot prevention; such drugs as Prozac, which keep serotonin in circulation, seem to have a similar effect.

Another mechanism may also be at work. It turns out that the heartbeat of a person with depression is unusually steady. That's not necessarily a good thing, says Charney, who co-chaired the DBSA conference. “Ideally, your heart rate should be variable—it means your heart can respond appropriately to the different tasks it's called upon to respond to.” Yet another possible link between heart disease and depression is a chemical called C-reactive protein (CRP). The liver normally produces CRP in response to an immune-system alarm when the body is infected or injured, and CRP is associated with the inflammation that results. For reasons still unknown, though, a recent study of depressed individuals found elevated levels of CRP. And in patients whose arteries have been damaged by the buildup of cholesterol plaques, heightened inflammation may increase the chance that a bit of plaque will break off and shut down an artery.

Diabetes is another illness that doesn't go well with depression. It's well known that 10% of diabetic men and 20% of diabetic women also have depression—about twice the rate in the general population. It's natural to be depressed about having a chronic, potentially fatal illness, but that doesn't entirely explain the discrepancy. Moreover, depressed diabetics are much more likely than those without depression to suffer complications including heart disease, nerve damage and blindness. Somehow depression makes the body less responsive to insulin, the hormone that processes blood sugar—plausibly through the action of cortisol, a hormone that can interfere with insulin sensitivity and that is often elevated in depressed patients.

Cortisol may also make depressed patients more prone to osteoporosis. Studies by Dr. Philip Gold and Dr. Giovanni Cizza at the NIMH have shown that pre-

mild seizure—a rhythmic firing of neurons—that can push a depressed brain out of its rut.

ON THE HORIZON

■ Researchers are exploring a similar technique that sends an electrical current through the vagus nerve—a major conduit wiring the heart and intestines—which then delivers it to the brain. Another approach, called regional transcranial magnetic stimulation, uses an electric coil shaped like a figure eight to create a magnetic field inside the pre-frontal cortex, which plays a key role in mood regulation.

TALKING CURES

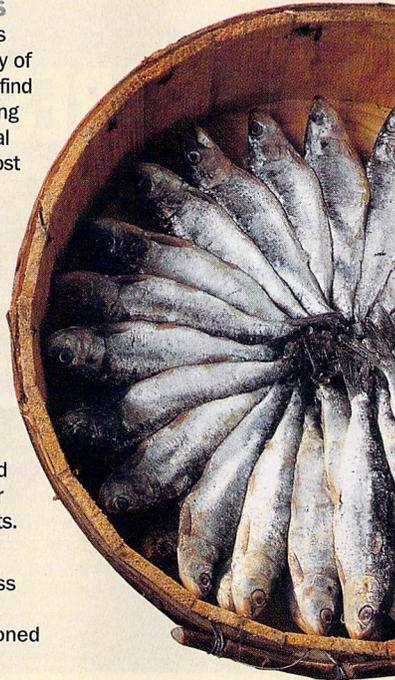
TODAY'S TREATMENTS

■ Most research today is focused on the physiology of depression, yet clinicians find that approaches combining medical and psychological treatments are still the most effective. Freud's techniques have been adapted and streamlined, but analysts still try to get patients to probe the unconscious roots of their problems.

■ Newer techniques like cognitive therapy, by contrast, teach patients to recognize destructive patterns in their lives and develop practical steps for changing bad mental habits.

ON THE HORIZON

■ Meditation, mindfulness training and biofeedback have long been championed as proven stress relievers. Now proponents believe these techniques may also provide relief to people with depression by lowering levels of cortisol.



AGENCE TOP—ENVISION

ON THE HORIZON

■ Omega-3 fatty acids (in fish oils) are good for the heart and also may be good for the brain by promoting the health of nerve-cell membranes. Studies are under way.

—By David Bjerklie

Dennis Charney, head of mood- and anxiety-disorders research at the National Institute of Mental Health (NIMH). But, he adds with proper scientific caution, “we don't have proof of that yet.”

The idea that treating depression might lessen the severity of other diseases, though, makes basic biochemical sense. Everyday experience makes it clear that brain chemistry governs more than just the emotions. When your mind feels terror, the resulting surge of adrenaline makes your

stomach churn. When your mind is sexually aroused, the body responds in unmistakable fashion. The effect is even more direct with the 60 or so chemicals known as neurotransmitters, which signal one cell that its neighbor has just sparked and that it should pass along the message. Brain chemicals such as serotonin circulate everywhere, not only in the brain. “Depression really is a systemic disorder,” says Evans, “and many of the neurotransmitters that we believe are involved in the patho-

is solidly in the medical mainstream.

More and more doctors—and patients—recognize that mental states and physical well-being are intimately connected. An unhealthy body can lead to an unhealthy mind, and an illness of the mind can trigger or worsen diseases in the body. Fixing a problem in one place, moreover, can often help the other.

The brain, after all, is only another organ, and it operates on the same biochemical principles as the thyroid or the spleen. What we experience as feelings, good or bad, are at the cellular level no more than a complex interaction of chemicals and electrical activity. Depression represents an imbalance in that interaction, one that can kill just as directly as more obviously physical ailments. Each year in the U.S., an estimated 30,000 people commit suicide, with the vast majority of cases attributable to depression. But depression's physical toll goes far beyond the number of people who take their own life and even beyond the impact on depressed people's relationships and productivity (which costs the U.S. economy some \$50 billion a year).

The pathology of depression shows with especial clarity that mind and body aren't separate at all; they are part of a single system. In the case of depression, this interconnectedness takes the insidious form of making other serious diseases dramatically worse. Once you have had a heart attack, for example, your risk of dying from cardiovascular disease is four to six times greater if you also suffer from depression.

It's not just that people tend to be depressed because they have a life-threatening illness or that depressed people smoke, are too lethargic to take their medicine or aren't motivated to eat right or exercise. "Even when we take those factors into consideration," says Dr. Dwight Evans, a professor of psychiatry, medicine and neuroscience at the University of Pennsylvania, "depression jumps out as an independent risk factor for heart disease. It may be as bad as cholesterol."

Heart disease is one of a long list of illnesses that worsen with depression. People with such afflictions as cancer, diabetes, epilepsy and osteoporosis all appear to run a higher risk of disability or premature death when they are clinically depressed. The effect is potentially so significant that the medical profession has begun to focus serious attention and resources on trying to understand

WHAT YOU CAN DO

We've come a long way from Freud's couch. The big breakthrough arrived in the late 1980s with the advent of safer and more widely effective drugs, like Prozac. According to Dr. Bruce Cohen of Harvard's McLean Hospital, we're on the cusp of a new era in treatment as the search for a single magic pill for depression gives way to a broad spectrum of therapies.

DRUGS

TODAY'S TREATMENTS

■ Most antidepressants work by tweaking levels of various neurotransmitters, the chemicals that carry signals from one neuron to another. Prozac, Paxil, Zoloft and the other SSRIs slow the absorption of serotonin. Effective antidepressants that

neurotransmitters, especially norepinephrine, but the drugs had significant side effects. Another class of first-generation drugs, the monoamine oxidase inhibitors (MAOIs) such as Nardil and Marplan, can be effective but can also produce dangerous side effects. A transdermal patch just approved by the Food and Drug Administration will give new life to MAOIs by reducing the side effects they sometimes caused when taken orally.

ON THE HORIZON

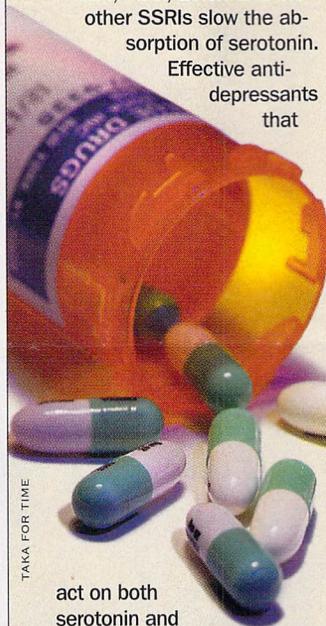
■ Researchers are exploring two related molecules, gaba and glutamate, that are responsible for 90% of chemical signaling in the brain. Because they control so much of the brain's activity, the trick is to fine-tune their levels in ways that relieve depression but don't affect other brain functions. Other targets of drug development: the sex hormone testosterone (a transdermal patch proved effective in a recent clinical trial for men); the stress hormone cortisol, which researchers are trying to regulate with the abortion

drug RU 486 and compounds called CRF antagonists; the dynorphins (the evil twins of feel-good endorphins); and a chemical called substance P, involved in pain pathways closely related to depression.

ELECTRICAL AND MAGNETIC

TODAY'S TREATMENTS

■ Electroshock therapy, despite its unsavory reputation, is actually quite effective, especially for patients who don't respond to drugs and seniors for whom drug interactions pose problems. The treatment today uses a small current to trigger a



TAKA FOR TIME

act on both serotonin and norepinephrine include Effexor and Remeron. Drugs like Wellbutrin work in a similar way but probably on the neurotransmitters norepinephrine and dopamine. The tricyclic antidepressants (such as Elavil and Tofranil) also blocked the absorption of

what's going on. At a national conference in Washington in November, Evans served as co-chairman of a meeting, sponsored by the nonprofit Depression and Bipolar Support Alliance (DBSA), to get a better handle on how widespread the problem is. For two days, experts in cancer, AIDS, heart disease, diabetes and other diseases, along with patient advocates, listened to the evidence linking depression with one illness after another.

Fortunately, scientists have made great strides in sorting out the underlying causes

of depression: it is almost certainly a defect in some combination of key genes, plus the right triggering environment. And researchers are well along in developing some promising therapies, pharmacological and otherwise, to supplement what is already available. But while the disease-depression connection is becoming more and more clear, how to uncouple them is an uncharted process. "You would think that treatment would alter the negative relationship between depression and other illness," says Dr.

MARK HARMEL FOR TIME

