BIOTECHNOLOGY

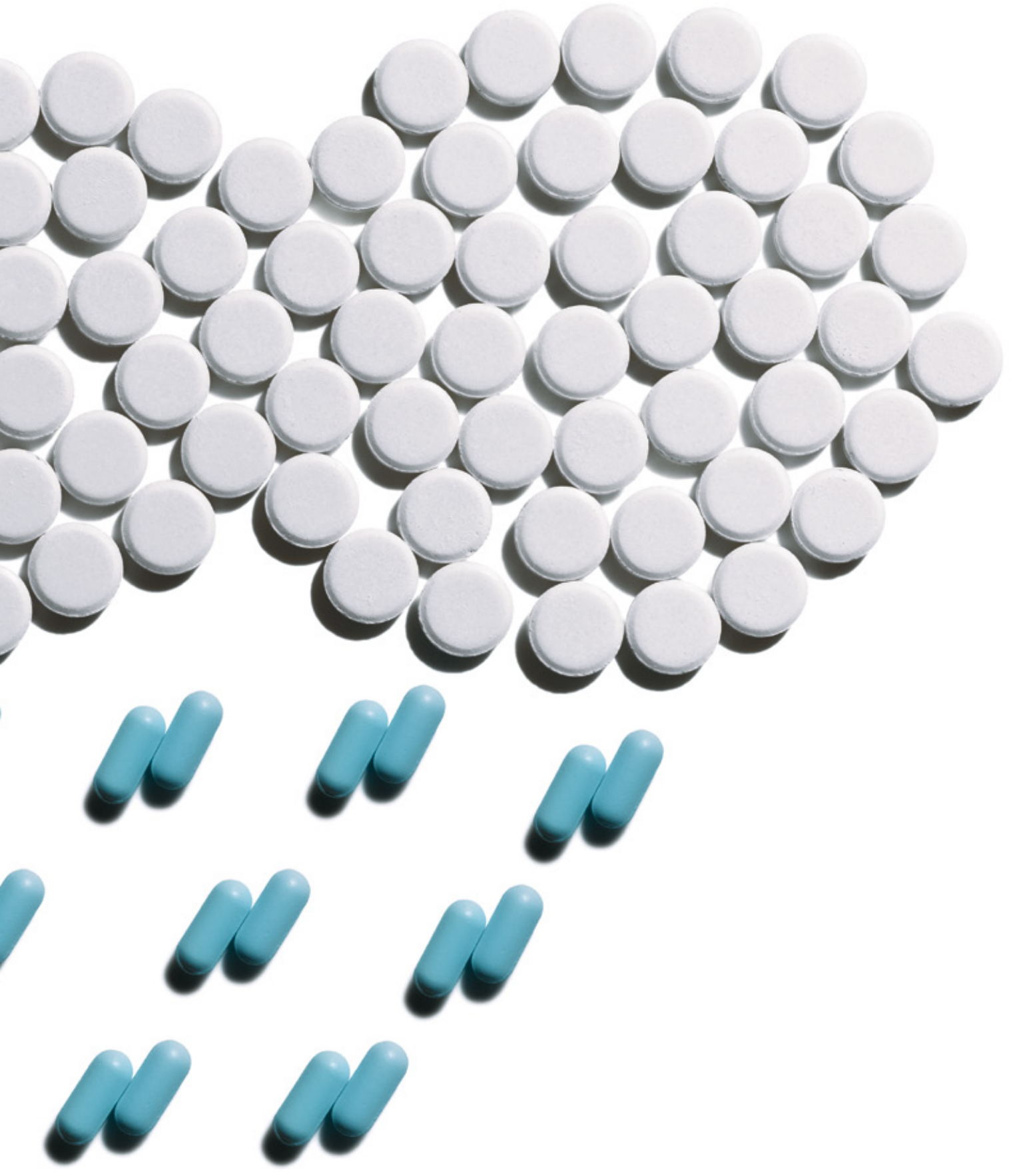
LIFTING THE BLACK CLOUD

Existing antidepressants leave a lot to be desired. They can take weeks to start working, and they fail many people. Researchers are scouting for better options

By Robin Marantz Henig

TOM SCHIERLITZ *Trunk Archive*

A YOUNG WOMAN WHO CALLS HERSELF blueberryoctopus had been taking antidepressants for three years, mostly for anxiety and panic attacks, when she recounted her struggles with them on the Web site Experience Project. She said she had spent a year on Paxil, one of the popular SSRIs (selective serotonin reuptake inhibitors), but finally stopped because it destroyed her sex drive. She switched to Xanax, an antianxiety drug, which brought back her libido but at the cost of renewed symptoms. Then Paxil again, then Lexapro (another SSRI), then Pristiq, a member of a related class of antidepressants, the SNRIs (serotonin and norepinephrine reuptake inhibitors). At the time of the post, she was on yet another SSRI, Zoloft, plus Wellbutrin (a cousin of SNRIs that affects the activity of dopamine as well as norepinephrine), which was intended to counteract the sexual side effects of Zoloft. "I don't notice much of a difference with the Wellbutrin, but I'm



on the lowest dose now," she wrote. "I'm going back to my psychiatrist next week, so maybe he'll up it. Who knows."

This is the typical trial-and-error approach to prescribing antidepressants, not only for depression per se but also for related disorders such as blueberryoctopus's. The tactic, Andrew Solomon wrote in *The Noonday Demon,* his landmark book about depression, "makes you feel like a dartboard."

Troubling side effects are not the only reason for the dartboard approach. The SSRIs and SNRIs that have dominated the antidepressant market since their introduction in the 1980s and 1990s do not help everyone and eventually fail in more than a third of users. A pill that seems to be working today might well stop helping tomorrow. And the drugs can take several weeks to start having a marked effect, a waiting period that can be especially perilous. According to a 2006 report in the *American Journal of Psychiatry,* among depressed older adults (age 66 and older) taking SSRIs, the risk of suicide was fivefold higher during the first month of treatment than in subsequent months.

Clearly, patients critically need antidepressants that work faster and better, yet the pipeline for novel drugs is drying up. In fact, in the past couple of years such pharmaceutical giants as GlaxoSmithKline have announced their intention to abandon psychiatric drug development, finding it too expensive, too hard and too much of a long shot.

Some scientists in government and academic laboratories and at small pharmaceutical companies are trying to pick up the slack. Whether their efforts will succeed remains an open question. But new drugs cannot come too fast for the nation's approximately 15 million depressed patients. Many remain unhelped by talk therapy and medicines and are desperate to try anything to relieve the psychic pain, including such experimental treatments as putting electrodes in their head or burning holes in their brain.

IN SEARCH OF SPEED

INVESTIGATORS aiming to find faster-acting antidepressants have been studying compounds known to be lightning-quick mood lifters, hoping to figure out why they work so much more rapidly than the SSRIs, which enhance levels of serotonin, a signaling molecule, in the brain. One such compound is ketamine.

Ketamine is an anesthetic, an analgesic and a recreational drug known on the street as Special K. It can, among other things, affect consciousness and cause hallucinations, and experiments in rodents show it can be toxic to nerve cells—all of which make it a less than ideal candidate for an antidepressant. But it has proved to be a fascinating compound to study for ideas about how to make antidepressants reduce symptoms faster. As Ronald Duman and George Aghajanian of Yale University and their colleagues have demonstrated, within only two hours after an injection of ketamine lab rats start increasing production of proteins needed to build new synapses—the contact points through which signals flow between nerve cells—in the prefrontal cortex. This region of the brain, located right behind the eyes, is known to behave abnormally in depressed individuals. By 24 hours after the ketamine shot, the rats also start sprouting new synaptic spines, like cloves in a Christmas orange, along dendrites, which are the nerve cell projections that receive signals from other neurons. The more spines, the quicker the transmission. And in Duman and Aghajanian's experiments, the more synaptic spines, the less the animals display depressionlike behavior (such as abandoning activities they would normally engage in).

"A lot of work over the past 10 years or so has shown that in depression, there is atrophy, not growth, in the prefrontal cortex and also the hippocampus," says Duman, who directs Yale's Laboratory of Molecular Psychiatry. "Ketamine can rapidly reverse that atrophy" and restore normalcy. Just how rapidly is the subject of current research, as the Yale scientists examine rat brains only a few hours after the ketamine injection to see if the increase in synaptic spines occurs even sooner than 24 hours.

Additional research in a different group of depressed rats has revealed how ketamine makes these synaptic spines grow: by activating an enzyme in neurons known as mTOR. Duman and his colleagues discovered this connection by giving rats a drug that blocks the enzyme's action. Then they gave ketamine to the mTOR-blocked rats. Nothing happened, which meant that when mTOR was inhibited, ketamine had no effect on synaptic spine proliferation or reversal of depressionlike behavior. In other words, mTOR needs to be functioning for the ketamine to do its spine-sprouting work.

Given that ketamine is too risky to use routinely as a medicine, the researchers began searching for other mTOR activators. They knew that ketamine stimulates the enzyme by preventing glutamate (the main excitatory neurotransmitter in the brain) from acting on a particular docking molecule—termed an NMDA receptor—on the surface of neurons. They therefore tested another NMDA blocker and found that it, too, led to mTOR activity and quickly promoted spine formation and produced antidepressant effects in rats. Now, Duman says, he and his co-workers are examining other compounds that block NMDA receptors to see if any have promise as safe, fast-acting antidepressants.

Another compound that elevates mood swiftly is, like ketamine, already on the market for another purpose: scopolamine, sold as a skin patch for treating motion sickness. Scopolamine influences a different brain circuitry than ketamine does: it impedes binding of the neurotransmitter acetylcholine—involved in attention and memory—to molecules known as muscarinic receptors.

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IN BRIEF

Current antidepressants can take weeks to ease depression. In certain people, they do not work at all, and if they do work now, they may stop tomorrow.
Faster-acting agents and those with new mechanisms of action are needed, yet Big Pharma's pipeline of such drugs is limited.
Government and university laboratories and some small pharmaceutical companies are trying to fill in the gap and have some promising leads.

As far back as the 1970s, investigators knew that manipulating acetylcholine activity in the brain could lead to depression. When bipolar patients, who swing between mania and depression, were in their manic phase and were given a drug that enhances acetylcholine signaling, they developed symptoms of depression, such as sad mood and lethargy, within one hour. And when depressed patients were given a drug that increased the level of acetylcholine in the brain, the depression got worse.

You might assume, then, that scientists looking for new antidepressants would investigate ways to inactivate acetylcholine. Early interest got derailed, however, by that era's A-list neurotransmitter, serotonin. In fact, many psychiatrists thought that what made SSRIs so useful was specifically that they did not target brain circuits employing acetylcholine. They ignored acetylcholine after that, thinking that the older antidepressants had so many side effects because, unlike SSRIs, they acted on the cholinergic system, in particular on muscarinic receptors, which compose a subset of the acetylcholine receptors distributed throughout the brain.

Therefore, it goes against conventional wisdom to find a drug acting specifically on the muscarinic receptors that not only has relatively few side effects but is a fast-acting and effective antidepressant. Yet that is what some scientists are seeing in scopolamine.

In a trial involving 22 patients diagnosed with depression, Maura Furey, a staff scientist in the Experimental Therapeutics and Pathophysiology Branch at the National Institute of Mental Health, and her colleagues found that intravenous scopolamine relieved symptoms within three days. In fact, she says, patients typically reported waking up feeling better the very next day. At the end of the four-week trial, nearly two thirds of the subjects showed significant improvement in their symptoms, and one half achieved remission. These benefits lasted for two weeks after the final dose. The effects were later replicated in another 22 depressed patients.

The NIMH is hoping to find a pharmaceutical company to do the testing and clinical trials needed to bring scopolamine to market as a fast-acting antidepressant. Furey is "extremely disappointed" that there have been no takers so far because, she says, "I see how well this works for people."

Drug delivery is one stumbling block. Giving scopolamine intravenously, as is done by some anesthesiologists as part of an anesthetic mixture, is impractical. With a skin patch, blood levels of the drug do not get high enough; with an oral formulation, most of the scopolamine gets eliminated through the digestive system. Furey is now working on finding a method of administration that is both practical and effective.

A SOLUTION FOR THE REST

THE OTHER MAJOR DRAWBACK to current-generation antidepressants, in addition to how long they take to start helping, is that they do not work for everyone. To address that problem, researchers are focusing on several novel mechanisms of actions. Some are investigating a second class of acetylcholine receptors, known as nicotinic receptors (so named because they also respond to nicotine). In particular, scientists at Targacept, a small biopharmaceutical company in Winston-Salem, N.C., are looking at an experimental drug called TC-5214 that blocks a specific nicotinic receptor; they hope to market the compound as an add-on therapy when a single antidepressant does not reduce symptoms enough.

In early trials involving 265 subjects, patients who did not respond to the SSRI citalopram (Celexa) alone had either TC-5214 or a placebo added to the regimen. In 2009 Targacept reported that subjects taking citalopram plus placebo improved by 7.75 points on a standard assessment tool (the Hamilton Rating Scale for Depression), while those taking citalopram plus the experimental drug improved by 13.75 points.

AstraZeneca then signed on with Targacept to conduct more extensive efficacy studies (phase III trials) in which subjects receive either a placebo or TC-5214 in addition to the original antidepressant. The first two trials, involving a total of 614 subjects, yielded disappointing results (no improvement, when compared with placebo, in depression scores after eight weeks). But Targa-

SOURCE: "ACUTE AND LONGER-TERM OUTCOMES IN DEPRESSED OUTPATIENTS REQUIRING ONE OR SEVERAL TREATMENT STEPS: A STAR*D REPORT," BY A. JOHN RUSH ET AL., IN *AMERICAN JOURNAL OF PSYCHIATRY*, VOL. 163, NO. 11; NOVEMBER 2006

NUMERICAL PICTURE

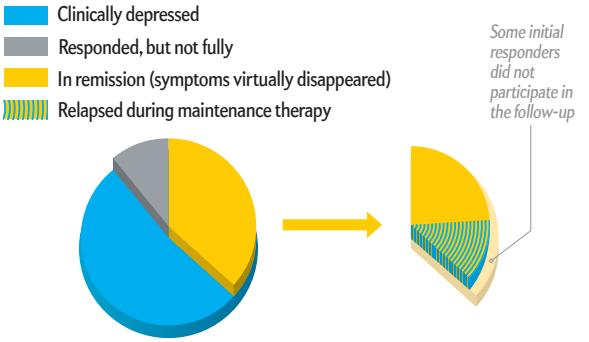
A Huge Gap

The need for better antidepressants is underscored by data from the Star*D trial, which monitored the effects of drug therapy in about 3,000 patients. The results, published in 2006, show that although medications do help many people, a large fraction of patients do not respond fully or relapse even when the agents work for a time. The drugs can also take weeks to become maximally effective.

The trial was complex, but in essence, patients initially received citalopram (Celexa), a selective serotonin reuptake inhibitor—the class of agents most widely prescribed today. Those who did not find relief were given any of several alternative treatments, generally switching up to three times in total. Subjects who did well were followed for a year while on maintenance therapy.

The data below come from the trial's first stage of treatment, with citalopram. Overall, 67 percent of patients who went through all stages of the trial achieved remission (at least for a time), but with each successive stage the percentage of patients who were helped declined and the likelihood of relapse increased.

The Best Case: Results from the First Treatment Stage of Star*D



Response to antidepressant
37 percent of treated subjects went into remission, doing so on average at 6.3 weeks. (The remitters were among the 49 percent who "responded"—had symptoms decline by at least half.)

Relapse rate
34 percent of patients who were in remission when they began maintenance therapy became symptomatic within 12 months.

Graphic by Jen Christiansen

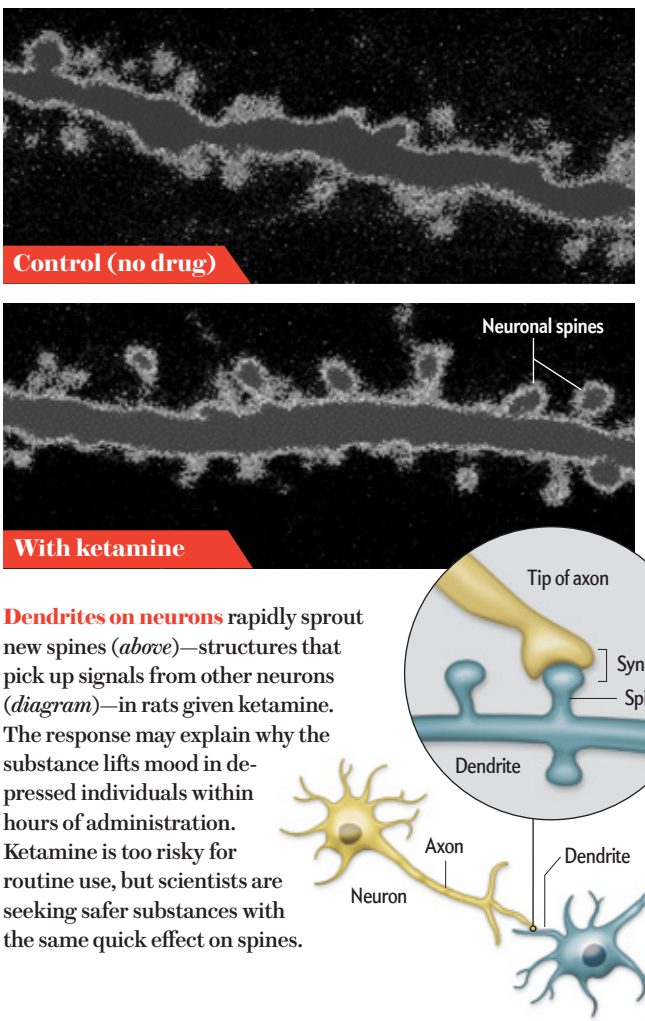
cept and AstraZeneca officials are continuing with two more planned efficacy trials, involving more than 1,300 subjects at centers around the world, as well as with a long-term safety study. They say they hope to file a new-drug application for TC-5214 with the Food and Drug Administration in the second half of 2012.

With a mechanism of action unrelated to its effect on serotonin or norepinephrine, Targacept's nicotinic receptor antagonist aims to assist depressed patients who are not being helped by drugs now on the market. Another way to target nonresponders is to shift gears even more radically—not by targeting signaling through this or that receptor but by acting on a different biological process. That process is neurogenesis (the growth of new neurons), in particular in the hippocampus, a small structure at the base of the brain thought to be one of two regions in the adult human brain where neurogenesis occurs.

Structural changes in the hippocampus have long been implicated in depression. Brain autopsies of clinically depressed people often show atrophy in that region and a significant reduction in volume. The SSRIs and SNRIs already in use ease depression not only by manipulating serotonin levels but also by increasing new hippocampal cell growth. That growth happens slowly, though, which is probably part of why the pills' benefits take so long to kick in. Scientists at the small pharmaceutical company Neuralstem in Rockville, Md., are hoping they have found a different way to spark neurogenesis—and to maintain it even after the drug has been stopped.

To find their spark, Neuralstem researchers relied on cultures of neural stem cells derived from human hippocampal cells—the only such cultures in the world, according to the company. First, they screened some 10,000 compounds for their effect on the hippocampal cells in culture. The goal, chief scientific officer Karl Johe says, was to see which compounds increased the rate of cell proliferation after seven days. Fewer than 200 made the cut, he says, and from those the Neuralstem team devised a dozen candidate compounds that seemed most likely to stimulate hippocampal neurogenesis. In 2004 the workers began animal testing, injecting the preparations into healthy normal mice. The compounds best at provoking growth of new hippocampal cells were given to mice with depressive behavior, and from this protocol the single most promising one emerged.

Now Neuralstem is conducting early safety tests (phase I trials) of a pill form of the substance, called NSI-189, in humans. If all goes as planned, Neuralstem officials expect to begin tests of efficacy later this year. These studies will use magnetic resonance imaging to determine whether the drug increases neurogenesis and will use other measures to determine whether it relieves symptoms of depression. Even if NSI-189 works, though, it will not have rapid effects. "It's not like somebody having epilepsy, where you give a drug to stop the epilepsy instantaneously," Johe says. "This treatment requires changes in the cell at the genetic level." Hippocampal atrophy takes years to occur, he adds, and "to reverse the process will also require a long period of time." He hopes, however, that the effect will be long-lasting, so that NSI-189 may be needed only intermittently. That notion still has to be demonstrated, but it is "an exciting possibility," Johe says.



Dendrites on neurons rapidly sprout new spines (*above*)—structures that pick up signals from other neurons (*diagram*)—in rats given ketamine. The response may explain why the substance lifts mood in depressed individuals within hours of administration. Ketamine is too risky for routine use, but scientists are seeking safer substances with the same quick effect on spines.

COURTESY OF GEORGE AGHAJANIAN AND RONG-JIAN LIU *Yale University*

DIGGING DEEPER

RECENTLY INVESTIGATORS have realized that chronic inflammation—which has been linked to such diverse diseases as cancer, atherosclerosis and diabetes—contributes to depression, and the insight has opened yet another avenue of attack.

Several lines of research have made the connection between depression and inflammation, which more typically is the body's response to a perceived invader. Some studies have shown that depressed people have high circulating levels of small proteins called cytokines that orchestrate inflammatory processes; the cytokines go by such names as interleukin-6 and TNF-alpha. In addition, about a decade ago scientists observed that when skin cancer patients received inflammatory cytokines as a treatment, they became depressed.

"I interviewed one of these cancer patients early on," says Andrew Miller, director of psychiatric oncology at Emory University's Winship Cancer Institute, "and was struck by how similar the depression was to depression I might see in my office as a psychiatrist."

The particular nefariousness of cytokines is that they interfere with the neurogenesis prompted by SSRIs and SNRIs. "If you knock out neurogenesis, you're almost pulling the rug out from under these antidepressants," Miller says. This effect helps to explain why depressed people with the highest level of chronic inflammation are also the ones most likely to be hard to help. In 2006 a group of scientists reported in the *Lancet* that etanercept, a drug being tested to treat psoriasis in 618 subjects, often relieved depression, even in those for whom the psoriasis did

Illustration by George Retseck

not improve. That effect apparently stems from neutralization of the inflammatory cytokine TNF-alpha. "At this point, no one should run to their doctor and ask for this drug for depression," said one of the team members, Ranga Krishnan of Duke University, at the time, noting that the depression results were anecdotal. "But the science is very exciting to us."

Miller also found the science exciting and contacted Krishnan to discuss a depression trial of a cytokine antagonist: Remicade, an anti-inflammatory already on the market to treat rheumatoid arthritis and other autoimmune diseases. It took more than five years, but Miller and his Emory colleague Charles Raison finally got funding from the NIMH to conduct the study. They have completed a trial of Remicade on 60 treatment-resistant depressed patients and say they will be releasing some promising findings soon.

Some researchers are training their sights on serotonin again but are looking to pump up its activity in a fresh way: by enhancing the number of serotonin receptors available to respond to the neurotransmitter in synapses. Even more radical, the investigators intend to achieve that effect through gene therapy.

Mention gene therapy to biologists, and you are likely to get an eye roll and a dismissive shrug. Recently, though, scientists announced preliminary success with gene therapy for one brain disorder, Parkinson's disease. And an investigator involved in the Parkinson's research wants to try something similar for depression.

The candidate gene for depression therapy is *p11,* which codes for a protein needed to move certain serotonin receptors to the cell surface; without *p11,* the receptors remain trapped inside the cell, which renders cells less able to respond to serotonin's messages. In 2006 Paul Greengard and his colleagues at the Rockefeller University demonstrated that rodents with depressionlike behavior (such as giving up formerly pleasurable activities) had low levels of *p11;* depressed humans, too, were shown on autopsy to have lower than normal levels.

"Knockout mice" developed in Greengard's lab—mice in which the *p11* gene had been destroyed—were then shown to develop depressionlike behavior. The next step was to see if delivering a functional *p11* gene to mice that lacked it would relieve the symptoms. That work was done by Michael Kaplitt, director of the Laboratory of Molecular Neurosurgery at Weill Cornell Medical College, and his colleagues; he was already conducting similar studies on gene therapy for Parkinson's. Using the same defanged adeno-associated virus he relied on to deliver a gene to Parkinson's patients, the team put the *p11* gene directly into the nucleus accumbens of *p11*-deficient mice, and their depressive behavior decreased.

Every neuroscientist has a favorite brain region, and Kaplitt's is the nucleus accumbens. "The reason I like it is that it's considered an important center in the brain for reward and satisfaction, where dopamine acts," he says. One common symptom of depression, anhedonia—an inability to get pleasure from life—is among the most devastating, Kaplitt says, and is probably related to dopamine signaling. Another reason he likes the nucleus accumbens is that functional MRI studies in animals and humans show that it is widely connected to many regions of the brain known to be involved in depression.

A third reason he likes the nucleus accumbens is that it has already been the surgical target for another experimental treatment for depression, a technique called deep-brain stimulation (DBS). An electrode is permanently implanted into the nucleus accumbens, and periodic electrical impulses are delivered through it [see "Depression's Wiring Diagram," by David Dobbs; Head Lines, SCIENTIFIC AMERICAN MIND, March/April 2009].

In Kaplitt's view, gene therapy performed directly on the brain will be simpler than deep-brain stimulation because "instead of an electrode for DBS, you'd be putting in this little catheter and leaving no hardware behind." (In deep-brain stimulation, not only is the electrode permanently in place, so is the neurostimulator, a pacemakerlike device implanted near the collarbone that generates the electrical impulses.) He and his colleagues have shown, in their work on Parkinson's, that the viral vector is safe and that the correct gene can be delivered through a catheter to the intended brain target, resulting in improved symptoms.

Now studies are in progress at the NIMH, under the direction of Elisabeth A. Murray of the Laboratory of Neuropsychology and Pam Noble of the primate care facility, to test *p11* gene therapy for safety and efficacy in monkeys. Success there would bolster a case for trials in humans.

As for blueberryoctopus, better treatments cannot come too soon. "Antidepressants definitely changed my life," she wrote on the Experience Project Web site, "but I'm dismayed that it was at the expense of my sex life." She was not yet 25 years old. "Eventually I'd like to come off [antidepressants] and resume having a normal sex life. I just don't think I'm ready yet." There should be better options. No one should have to choose between libido and despair; no one should be told, after trying and rejecting a series of depression therapies, that there is nothing left to try. If the promise of next-generation antidepressants comes to fruition, maybe the trade-offs will someday be less grim. SA

TOM SCHIERLITZ *Trunk Archive*

MORE TO EXPLORE

Breaking Ground, Breaking Through: The Strategic Plan for Mood Disorders Research of the National Institute of Mental Health. 2001 report. 136-page PDF available at the NIMH Web site, which also has some good depression basics: www.nimh.nih.gov/about/strategic-planning-reports/breaking-ground-breaking-through-the-strategic-plan-for-mood-disorders-research.shtml

The Noonday Demon: An Atlas of Depression. Andrew Solomon. Scribner, 2002.

Depression: Out of the Shadows. A PBS documentary that aired in 2008, which has a comprehensive Web site where you can watch the program and find further information: www.pbs.org/wgbh/takeonestep/depression/index.html

Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms. Christopher Pittinger and Ronald S. Duman in *Neuropsychopharmacology Reviews,* Vol. 33, pages 88–109; 2008.

Stuck in a Rut: Rethinking Depression and Its Treatment. Paul E. Holtzheimer and Helen S. Mayberg in *Trends in Neuroscience,* Vol. 34, No. 1, pages 1–9; November 2010.

The NIMH has an interesting interactive on its Web site about the prevalence of depression and a variety of other mental illnesses, as well as treatment options: www.nimh.nih.gov/statistics/index.shtml

Sherwin Nuland gives a TED talk about depression (largely his own) and electroshock therapy (his own): www.ted.com/talks/lang/eng/sherwin_nuland_on_electroshock_therapy.html

SCIENTIFICAMERICAN ONLINE

Learn how researchers model depression in animals at ScientificAmerican.com/mar2012/depression