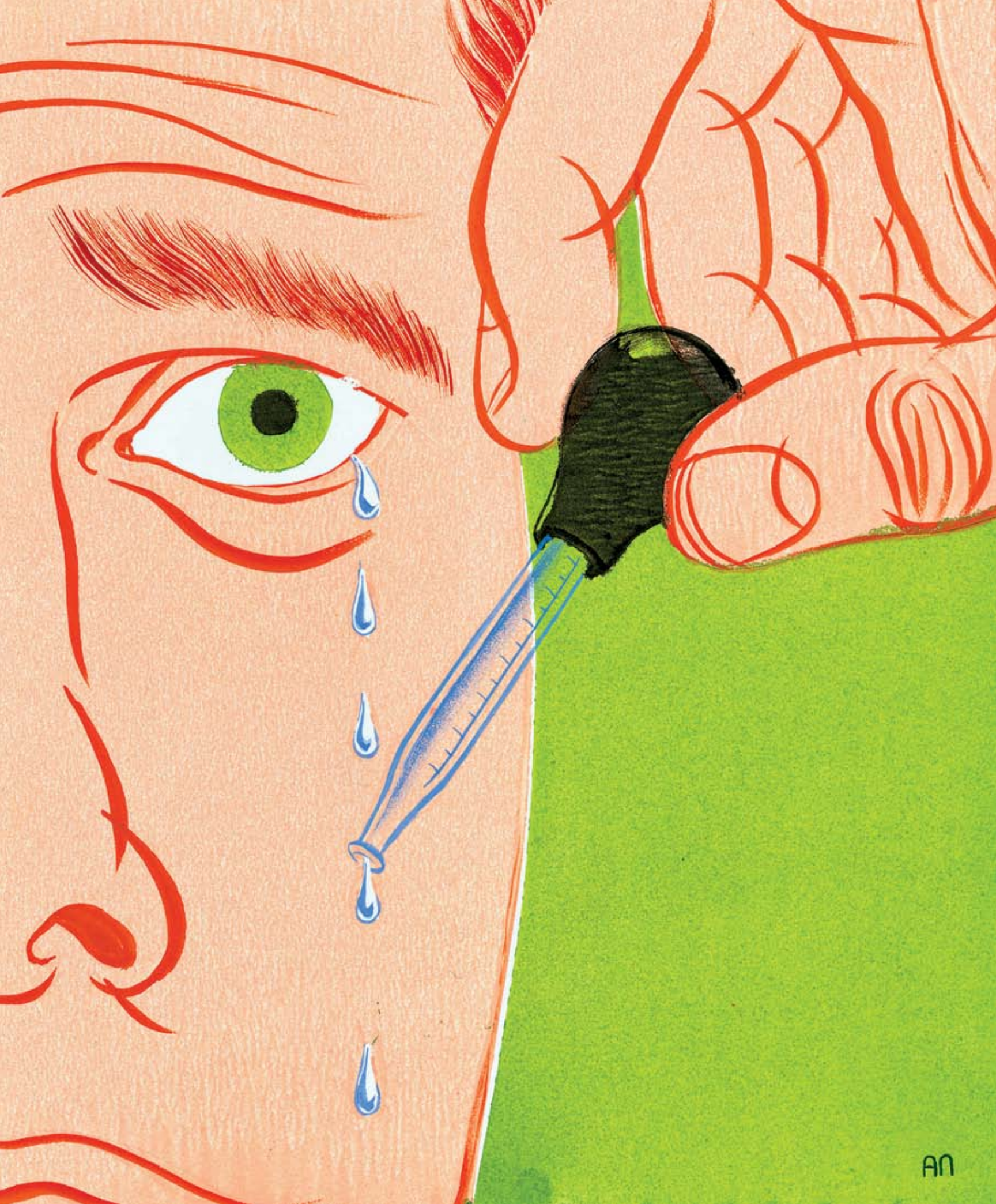


STRESS RELIEF:
Actors take it. // Cardiac patients take it. // People with post-traumatic stress disorder might one day take it. // Could a beta-blocker free victims from memories that just won't go away?

Reversal of Misfortune

BY ANITA SLOMSKI // ILLUSTRATIONS BY ALEX NABAUM

A first kiss, a summons to the principal's office, JFK's assassination, the birth of a child—these are the memories that remain startlingly vivid even decades after the events occurred. It's not necessarily their content that makes them compelling but rather the intensity of feeling they provoked. Any emotional experience, positive or negative, triggers the release of stress hormones, particularly epinephrine (adrenaline), that make us instantly alert and prepared to fight, flee or enjoy. And lest we forget what stirred us up, epinephrine also helps sear the details of intense experiences into our long-term memory.

Extremely embarrassing or painful memories usually weaken with the passage of time. But in a cruel irony, the most horrific memories—of child abuse, combat, being trapped in the World Trade Center—can remain as intense and terrifying as if they had occurred just moments before. In his clinical practice devoted to treating post-traumatic stress disorder, or PTSD, Alain Brunet, assistant professor in the department of psychiatry at McGill University in Montreal, listens to accounts of debilitating nightmares and flashbacks, of lives spent sidestepping places and situations that might trigger a memory, of severe panic attacks and despair of ever connecting with people as relationship after relationship fails.

Acute stress not only deeply and indelibly burns a memory in place immediately after trauma but also, in a pernicious feedback loop, may prompt the release of additional adrenaline during each recall of the terrible event, intensifying the memory. So rather than fading, memories become even more painful, "often ruining people's lives," says Brunet.

Until recently, the most Brunet could offer patients was cognitive behavioral therapy, which helps people control their fears as they teach themselves that the things they associate with their traumas—a red car, say, or a loud noise—aren't inherently dangerous. Yet while two-thirds of individuals with PTSD initially get relief from psychotherapy, according to Brunet, about half will relapse within a year, typically when they are stressed or encounter the anxiety-provoking trigger in a new context. "Therapy doesn't break the fear association—you just have new learning laid over old learning," says Brunet. "It's been impossible to extinguish the fear in every context."

Now new research with an old drug is showing signs of being able to manipulate a learned fear so that an excruciating memory turns into a merely painful one. Propranolol, a beta-blocker developed 25 years ago, prevents the epinephrine spikes that can overstimulate the hearts of people with hypertension and cardiac disease, and may also guard against the intensifying effect of epinephrine on memory. "By giving a beta-blocker to people with PTSD, we think we can target the traumatic memory rather than simply teach people how to inhibit it," says Brunet.

This isn't well-established science. So far, only a handful of trials have supported the idea that it's possible to fend off a

cripplingly traumatic memory, and even those small successes have required almost immediate action, within hours of seeing or experiencing something you wish you could forget. Even more experimental is the next step, a controversial approach that seeks to attenuate the intensity of recalling a long-ago trauma. Yet even if some of today's thinking turns out to be wrong, it could entice researchers down unexplored pathways that lead to more effective therapies or simply expand scientific horizons, laying the groundwork for future discoveries.

Since the 1960s, scientists have regarded the site of emotional memories to be the amygdala, a structure deep within the brain's temporal region that assesses danger and triggers fear, among other emotions. Early on, James McGaugh and collaborators at the University of California at Irvine found that various drugs, injected into the amygdalas of rats conditioned to respond to a stimulus, could either dull or enhance the animal's fear of the stimulus, depending on the drug and how soon it was given after the rat learned its initial response. But it wasn't until 1994 that a series of ingenious experiments by McGaugh and Larry Cahill suggested a drug could assuage a traumatic memory without wiping out the content.

McGaugh and Cahill showed two groups of subjects 12 slides accompanied by a narrative. One group heard a neutral story about a mother and son visiting a hospital to watch a disaster drill. The second group heard the same story, but with a grisly embellishment: The boy had been struck by a car, and doctors had to reattach his severed feet. Two weeks later, those who had heard the emotionally arousing story had much better recall of the narrative's details, presumably because a jolt of epinephrine to their amygdalas had heightened their memory of it.

Next, McGaugh and Cahill tested a new group of subjects. But this time, half of those who were to see the slides and hear the disturbing narrative first received an injection of propranolol, while half got a placebo shot. Two weeks later, the placebo group had excellent recall of the stimulating part of the story, but those who had taken propranolol had no better memory of the entire story than did those who had heard the dull version.

The drug keeps adrenaline from activating beta-adrenergic receptors in the amygdala, and in this case, that apparently prevented the enhancement of an emotional memory. "For the first time, we proved it was possible to stop the formation of strong memory in humans by blocking the action of a hormone released by emotional arousal," says McGaugh. The following year, when Cahill repeated the experiment on a German subject who was missing his amygdala because of disease, the man's recollection of the exciting story was just as bland as the memories of those who had received propranolol—further evidence that the amygdala modulates the strength of an emotional memory.

Timing, however, is crucial in loosening memory's grip. In order for new learning or the memory of an experience to be stored, nerve cells (neurons) must transmit information from one to the next, crossing junctions called synapses. And while communication within a neuron is conducted electrically, the information carried between neurons, across the synapses, normally travels via chemicals (neurotransmitters). When learning occurs, that chemical communication is enhanced, usually because an increased number of receptors have formed on neurons to process the neurotransmitters.

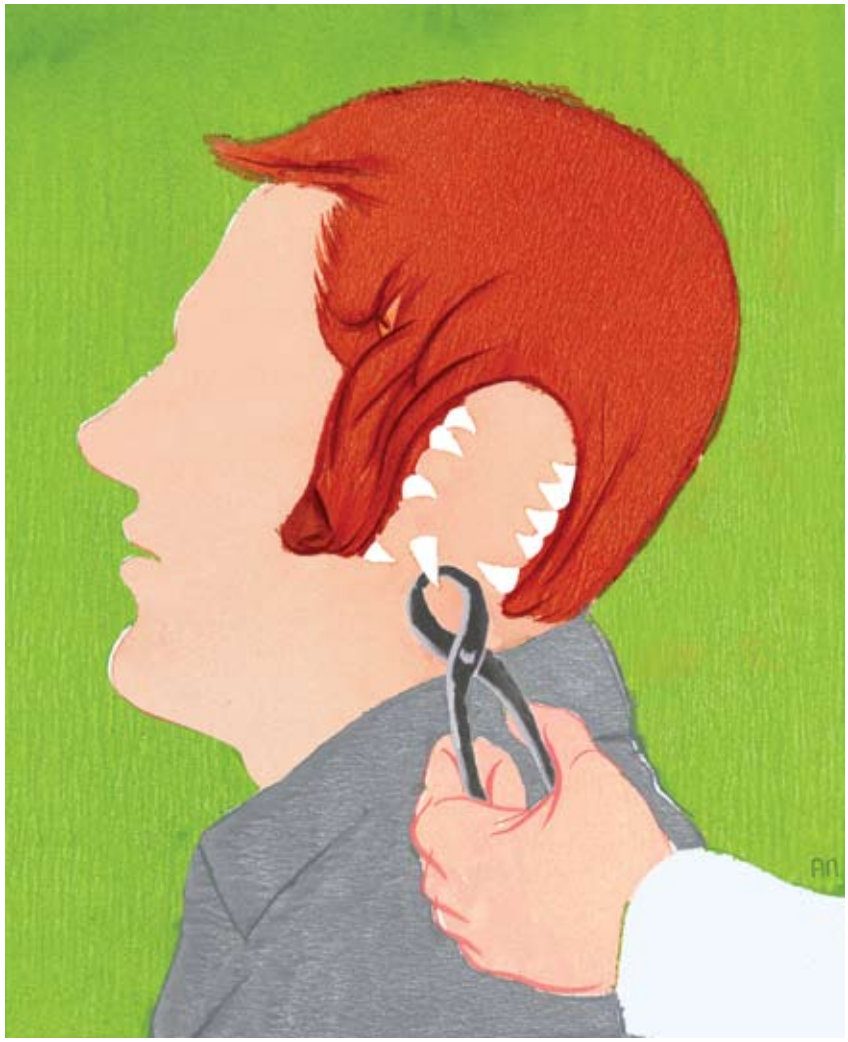
Learning then becomes fixed as a long-term memory. For that to happen, neurons synthesize proteins that generate new receptors and stimulate the growth of synapses—strengthening the communication network between neurons and enhancing the transmission of neurotransmitters. This process of creating permanent structural changes in the brain is called memory consolidation, and it's estimated to take from a few minutes to a few hours. That leaves only a brief window to interfere with a traumatic memory before it becomes permanent.

The amygdala stores the emotional, unconscious component of a memory, while conscious memory resides in the nearby hippocampus, although scientists suspect the hippocampus may be only a way station, holding the memory temporarily before transferring it to other brain regions for permanent storage. Recall a strong memory, and your amygdala will cause your body to react—setting your heart racing, for example—at the same time your hippocampus releases explicit details. And even though two brain regions are reading out data independently, we perceive our memories as seamless.

In 2002, operating under the time constraint that memory consolidation imposes, emergency room nurses at the Massachusetts General Hospital (MGH) recruited trauma victims to participate in a research trial to determine whether propranolol could prevent PTSD. Eventually 41 people agreed, and each received either a placebo or propranolol four times a day for 10 days and then a reduced dose for another nine

days. The subjects also wrote accounts of their traumas, which ranged from rape to auto accidents, and researchers summarized and read the reports into a tape recorder. Three months later, as subjects listened to their taped stories, 43% of the placebo group experienced racing hearts, sweaty palms and twitching muscles. But none of the subjects who had taken propranolol showed a strong physical reaction when revisiting the trauma. Yet when asked whether traumatic memories were affecting their lives, both groups offered the same range of responses. In both groups, some people remained very troubled, while others seemed little affected.

Still, Roger Pitman, a psychiatrist at the MGH and professor of psychiatry at the Harvard Medical School, was encouraged that the physical signs of PTSD appeared to be blocked by propranolol, and he has launched a larger study of individuals who come to the emergency room after trauma. Only a few studies have been attempted, says Pitman, largely because it's difficult to recruit subjects within minutes or hours of a horrible event. A French trial showed that propranolol reduced PTSD symptoms, but it lacked a control group, and Pitman surmises that those who agreed to take the drug may have done well after trauma regardless of treatment. Another study, at the Veterans Administration Hospital in San Diego, found no positive effects of propranolol on PTSD, but Pitman thinks that may have been because the drug was given too late, as long as 24 hours after an event. "Memory consolidation may happen within as few as 30 minutes," he says.



If propranolol were given when an old memory is reactivated, it might be possible to defang the memory.

And there's the rub, of course. Getting immediate treatment for someone who has been wounded on a battlefield or almost killed in a five-car pileup may be almost impossible. Even if a quick dose of a beta-blocker were available, who should get it? There are no definitive risk factors to identify those most likely to suffer PTSD, which afflicts just 20% of those who experience trauma. Moreover, although propranolol is considered relatively safe, with millions of people taking it for hypertension—and actors and musicians often using it to ward off stage fright—simply giving it to everyone might expose them to side effects (such as aggravated asthma). The best way to give propranolol in the emergency room, according to Pitman, is for doctors to know who is at high risk for developing PTSD and which of those individuals will respond favorably to propranolol—neither of which is currently possible. For effective treatment, a different approach was needed.

In the late 1990s, Karim Nader, professor of psychology at McGill University, was casting about for a research project. Listening to a talk on memory consolidation, he had what seemed like a bizarre idea—that perhaps when a memory is retrieved, it has to undergo the same process of consolidation in the brain that it underwent when the event first occurred.

Nader didn't know it then, but, in fact, researchers in the 1960s had done experiments with rats suggesting that reconsolidation is a real phenomenon. Four decades ago, prominent memory scientists argued against the idea, and when Nader mentioned his idea to his mentor, Joseph LeDoux, professor of neuroscience and psychology at New York University and director of the university's Center for the Neuroscience of Fear and Anxiety, LeDoux told him not to waste his time. "There was 40 years of research that said once a memory is consolidated it doesn't become unstable again," LeDoux says.

Still, Nader persisted, and reconsolidation, though still controversial, has become one of the hottest topics in memory research. It could have particular applications in treating PTSD, possibly enabling a kind of therapeutic forgetting to take place long after a memory has presumably become permanent and symptoms of PTSD have already appeared.

Nader hypothesized that because a memory can be edited—so that you remember things your way, and not necessarily how they happened—it must first enter a vulnerable state before it's restored to long-term memory. Imagine that each time you recall an event, you're taking down a box from a shelf and opening it. Then, when you're finished, you stow it away again. Nader thought that while the box was open, it might be possible to alter the memory.

To test this idea, Nader conditioned rats to fear a musical tone, and when he activated the fear memory by playing the tone and the animals froze in fear, he injected anisomycin, a protein synthesis inhibitor, into their amygdalas. (The technique had previously been proven to erase new memories in rats.) In the following two hours, the rats continued to freeze when the tone was played, but 24 hours later, the tone had ceased to affect their behavior.

Nader theorized that the anisomycin had blocked the reconsolidation process, causing the memory to be lost. "What happened to it?" asks Nader. "There's no way to know. Even if the animal never again showed fear of the tone, the memory might still be there, inaccessible but present. Clinically, though, it doesn't matter, as long as the animal is no longer impaired."

Although useful in investigating the possibility of reconsolidation, anisomycin isn't a viable therapy. The drug is approved only for use in animal tests, and it blocks protein synthesis in all cells, so it would be toxic if taken systemically by animals or people. Moreover, it doesn't just get rid of a troubling association—the issue for people with PTSD—but also wipes out the memory itself in animals. "Having a memory vanish obviously isn't a sound therapeutic approach in humans, because it's our memories that define us," says Nader. "For many patients with PTSD, their trauma is part of their identity. If they wake up one day and can't remember what happened to them, then why were they sitting at home for the past 20 years?"

But if propranolol were given when a memory is reactivated, it might be possible to tone down the memory's intensity while it undergoes reconsolidation. "If this is really how things work, we could have a second crack at PTSD, having

The Ethics of Altering Memory

James McGaugh, a neurobiologist at the University of California at Irvine, has published more than 500 scientific papers on the neurobiology of memory and learning, and when he was invited to give a presentation to the President's Council on Bioethics, he expected council members to applaud his evidence that the beta-blocker propranolol might prevent post-traumatic stress disorder (PTSD). "Instead, I became the poster child of evil," McGaugh says.

The council's 2003 report *Beyond Therapy* comes down hard against "rewriting" memories pharmacologically. "Would dulling our memory of terrible things make us too comfortable with the world, unmoved by suffering, wrongdoing or cruelty?" the report asks. And doesn't robbing individuals of their traumatic memories deny them the opportunity to develop their "ultimate character" and "true identity"?

But some people don't want that opportunity, says Adam Kolber, a law professor at the University of San Diego who challenged the ethics council's views in a recent law review article. Kolber points out the example of baggage handlers who developed PTSD symptoms after they had to collect body parts following a plane crash in San Diego in 1978. "Some traumatic memories don't offer anything redeeming," he says.

Rebecca Dresser, a council member, and professor of law and ethics and medicine at Washington University in St. Louis, says she has no problem with providing a drug to people who are really suffering. "But in giving a drug to everyone who has trauma, we are cutting off those who can get through an awful experience on their own," Dresser says. Those people might be able to use it productively, she suggests: "Think of all the meaningful literature that came out of the Holocaust."

patients remember the traumatic event in a controlled setting and giving them the medication and then weakening the memory," says Pitman. "That would be a major advance."

Pitman, Brunet, Harvard Medical School researcher Scott Orr and Nader are putting Nader's hypothesis to the test, giving propranolol to people who have had PTSD for more than 10 years. In a pilot study of 19 people, half were given a dose of propranolol after they wrote about their trauma and half received a placebo. A week later, they returned to the lab to listen to a recording of their stories while researchers measured signs of stress and arousal. The people on the beta-blocker showed a 19% reduction in PTSD symptoms compared with an 11% decrease among those in the control group.

Although that difference appears insignificant, Brunet was heartened that there was a difference at all. "It's pretty amazing we got such a strong result with a dose of propranolol lower than that prescribed for hypertension," he says. "People on antidepressants have to take their meds for four to six weeks before there's an effect." In the current trial, following up on that pilot, subjects are asked to recall their traumatic memories and then to take propranolol once a week for six weeks. Then they're revisited at intervals of several months so that researchers can gauge any symptoms of PTSD. The six-week regimen of treatment could tone down parts of the memory that a single dose didn't touch, says Brunet.

"People in the pilot felt modestly better but they weren't jumping up and saying, 'Yahoo, let's get out of here,'" says Nader. "But if you've had PTSD for 10 years, it may take a while to notice any improvement. And maybe the drug will have a bigger effect if we give it just before we trigger the memory." Perhaps having the beta-blocker already in the body would reduce the intensity of the recalled trauma.

Once dismissive of reconsolidation, LeDoux now researches the phenomenon in rats and is attempting a clinical study that will have people with long-standing PTSD take propranolol immediately after they have an unprompted flashback. But recruiting subjects has been difficult because he needs people who aren't taking antidepressants or anti-anxiety medications. That rules out a lot of those with PTSD.

LeDoux was discouraged by the results of an earlier experiment in which he gave propranolol to people conditioned to have an adverse reaction to a blue square after receiving a mild shock. Although 24 hours later, those who'd received the beta-blocker reacted less strongly to the sight of the square, their fear ultimately returned. "It's much easier to study reconsolidation in animals," says LeDoux. "People can willfully regulate their amygdalas to counteract fear by thinking of other things, so maybe this isn't a good way to gauge reconsolidation."

Of course, the problem with reconsolidation experiments could be more fundamental. "Maybe reconsolidation is more complicated than it first seemed," says LeDoux, and for now, at least, that's what memory pioneer McGaugh has concluded. Although other laboratories have confirmed the basic findings of reconsolidation, his laboratory and others have been unable to replicate the results of Nader's experiments, and some who've had partial success have found that the fear memory is only temporarily extinguished. "Reconsolidation is a controversial theory right now," says McGaugh. "It will take at least a few years before we know whether it really happens."

Pitman, who has spent his career studying PTSD, acknowledges that it's possible that reconsolidation of traumatic memories doesn't occur. "That turns out to be the case for many things we try in medicine," he says. "But based on how patients in the Montreal study have responded to propranolol, we are off to a good start. Sooner or later we may well find a drug that can prevent PTSD or at least reduce the intensity of the memories to a level that a person can more easily live with them." ■

DOSSIER

1. **"Memory Traces Unbound," by Karim Nader, *Trends in Neurosciences*, February 2003.** Nader lays out the hypothesis that consolidated memories can be modified, strengthened or erased, and eloquently argues that this reconsolidation theory will finally reconcile a 70-year-old dichotomy that memory is both fixed and dynamic.
2. ***Memory and Emotion: The Making of Lasting Memories*, by James L. McGaugh, Columbia University Press, 2003.** After having studied memory for half a century, the renowned behavioral neuroscientist explains its mysteries: how memories are made, why some disappear while others are indelible, and the role of stress hormones on our ability to remember and learn.
3. **"Pilot Study of Secondary Prevention of Posttraumatic Stress Disorder with Propranolol," by Roger K. Pitman et al., *Biological Psychiatry*, Jan. 15, 2002.** Preliminary findings that support the hypothesis that propranolol holds promise as a treatment of PTSD.