



SELF-DEFINITION
"I don't let the pain
define who I am
anymore," Max
Sokolnicki says.

More Than a Feeling

New approaches to treating complex regional pain syndrome are helping redefine “mystery pain.”

BY DEBRA GORDON, M.S.

Max Sokolnicki knows all too well how the pain of complex regional pain syndrome (CRPS) can take over your life. Sokolnicki, 52, of Chesterfield Township, MI, used to be a project manager in a technical training firm in the automotive industry before a botched hip replacement surgery in 2002 damaged his sciatic nerve and triggered CRPS. Today the former soccer player and coach is unemployed, lives on disability, and uses a cane or wheelchair to get around.

The pain is centered in his right foot, he says, which feels as if it is surrounded by a block of ice and is often so cold that it burns. That's only part of the sensation, however; the other part feels like “some kind of small animal chewing at my foot as someone tries to peel my skin back.” While he has found some relief with neurostimulation, he says he is never pain free.

Molly Skipper, who also suffers from CRPS, spent her 16th birthday bedridden, rocking back and forth in pain, terrified that doctors were going to amputate her leg. All because a few months before she'd slipped and fallen, banging her left knee on the handle of a kitchen cabinet.

It's an injury that in most people would have resulted in nothing more than a bruise and some minor discomfort. But for Molly and thousands like her, a bump, fracture, or surgical procedure can turn into intense, unrelenting pain that sends them careening from doctor to doctor in search of relief.

These people have a condition called complex regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy (RSD) or causalgia (from the Greek words for “heat” and “pain”). Relatively rare—it affects an estimated 26 out of every 100,000 people—CRPS is up to four times more common in women and affects people of all ages, including children as young as three.

Traditionally, anesthesiologists and other pain specialists have treated CRPS. But it is first and foremost a neurological condition, according to Anne Louise Oaklander, M.D., associate professor of neurology at Harvard Medical School in Boston and an expert on the disease.

Her research has begun to unravel the specific neurological mechanisms that may be at work in CRPS. Thus, she says, more neurologists need to be trained to diagnose and treat this devastating injury as a neurological condition, not a pain condition.

“Having the pain reformulated as a neurologic problem opens the door to the kind of approaches neurologists are expert at,” she says. “Not just giving pain medication but curing the underlying problem.”

WHAT IS CRPS?

The primary symptom of CRPS is pain out of proportion to the initial injury that continues long after the trauma heals. The pain

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Symptoms of CRPS

In addition to hypersensitivity to touch and ongoing pain, patients with CRPS may have one or more of the following. (No two patients are the same, however, making diagnosis difficult.)

Swelling. The leg or arm may swell so much that the skin appears tight and shiny and may even begin to break down.

Excessive sweating.

Change in skin color. The area may turn red, blue, or purple.

Change in skin temperature. The area may become very hot or very cold, depending on blood flow.

Muscle changes, such as tremors, weakness, joint stiffness, or inability to control movement. This is likely related to dysfunction of nerves in the spinal cord that control movement.

Fast hair and nail growth that eventually fades, leaving hair sparse and nails brittle.

FIRE AND ICE
Molly Skipper spent her 16th birthday consumed by the burning/freezing pain of CRPS.



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typically occurs in the hands, arms, legs, or feet, but can occur anywhere in the body. Left untreated, it can spread to other parts of the body, most commonly the “mirror limb” opposite the one where the damage first occurred. The pain is sometimes described as “burning,” and may be so bad that patients thrust the affected limb into buckets of ice or drape it in wet, cool cloths to stem the sensation. Others, however, can’t tolerate any cold and find their pain worsens in the winter.

Over the years, doctors have used numerous tests to definitively diagnose CRPS, including X-rays, bone scans, MRI, thermography (which measures heat), and electromyogram (which measures nerve conduction). Sometimes these tests can help; but just as often, they can all be negative even in someone with CRPS. Plus, the testing itself can be extremely painful to someone with the condition.

Basically, then, CRPS is diagnosed based on the patient’s description of the symptoms, a comprehensive medical and physical history, and the exclusion of other conditions. That’s one reason the condition remains significantly under-diagnosed even by neurologists and pain specialists, says Joshua Prager, M.D., who directs the Center for the Rehabilitation of Pain Syndrome at the University of California, Los Angeles.

In fact, a survey by the support group American RSDHope (rsdhope.org) found that people with CRPS often see five or more doctors before receiving a diagnosis. Patients are often told they are depressed, anxious, or have some other psychiatric condition; suspected of trying to get drugs; or accused of “malingering,” says Dr. Oaklander.

The reality, however, is that the pain itself typically causes mental health issues. The RSDHope survey found that 67 percent of people with CRPS had considered suicide.

The best option to ensure you get the correct diagnosis, says Dr. Oaklander, is to see a peripheral nerve specialist, a common neurology subspecialty.

TINY NERVE FIBERS

Every time you touch something hot, bang your shin, or get a paper cut, the communication network of your body switches into high gear. The pain signal travels along axons, fiber-like extensions from neurons that function like individual wires in a large fiber optic cable. The axons use special chemicals

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called neuropeptides to transmit the pain signal to nearby neurons. Eventually, the signal reaches the spinal cord and shoots up to the brain where it is “read.” All in a split second, of course.

Axons come in all lengths, some longer than your leg. Until recently, researchers focused on large axons, the kind covered in fatty sheathing called myelin (hence the name, “myelinated fibers.”) As the tools used to observe nerve fibers have improved, researchers have been able to identify very tiny axonal fibers in peripheral nerves like those in the arms and legs.

More recently, Dr. Oaklander and others examined skin biopsies from patients with CRPS and found significant damage to these small-fiber axons. In some cases, they found, even the slightest injury to these fibers can cause misfiring and the release of excess neuropeptides. Essentially, the nerve fibers become stuck in the “on” position and burn out, leading to the numbness and loss of sensation people with CRPS often describe in the originally injured area. What appears to happen next is that other nearby fibers step in and also begin overfiring, says Dr. Oaklander. The result is hypersensitivity and chronic pain.

Dr. Oaklander’s finding of small-fiber axonal damage is important because it helps convince clinicians that CRPS is a real neurological condition. It also helps patients get approval for disability benefits or even certain medications, something that is difficult if no clear cause for the pain can be seen. “So being able to show damage with an objective test is critical,” says Dr. Oaklander.

Functional MRI studies, which image blood flow to different parts of the brain in response to various stimuli, also show underlying changes in people with CRPS. A study published in November 2008 in the journal *Neuron* found significant alterations in the white matter of the brain, the part that transmits chemical messages between neurons, and shrinkage in the neuronal area, or gray matter. The changes are likely due



MOLLY'S JOURNEY
Now 18, Molly Skipper
just returned from back-
packing across Europe.

to the pain itself, says Dr. Oaklander, since other MRI studies find such changes reverse when the pain improves.

INSANE WITH PAIN

One of the earliest written descriptions of CRPS comes from S. Weir Mitchell, a Civil War doctor who was struck by the severe, persistent pain experienced by some soldiers even after their wounds healed—pain that occurred with just the lightest touch. “He is. . .nervous and hysterical to such a degree that his relatives suppose him to be partially insane,” Dr. Mitchell wrote of a young man who had been shot at Gettysburg. “It is difficult even to examine him properly on account of his timidity, and his whole appearance exhibits the effects of pain. . .and want of rest.”

When Molly Skipper was in the midst of her CRPS episode, she was lucky if she averaged four hours of sleep a week. Her pain began about a week after she fell, just as she started her dream job at a newspaper in Meridian, MS. Within a few days she was on crutches. Then she couldn't walk at all. “I couldn't touch my leg, it was so painful,” she recalls.

She saw numerous doctors, including a psychiatrist. Initially, the doctors thought she was imagining the pain. They came to believe it was real, however, when she was still in agony even after five nerve blocks, a procedure in which a local anesthetic is injected near the nerve. At one point she was taking 13 different medications and still found no relief. Doctors told her she would never walk again.

Finally, in the spring of 2006, her father's coworker learned about Dr. Oaklander and her practice at Massachusetts General Hospital. Molly's mother, Leslie Doolittle, called the doctor's office and left a message. Dr. Oaklander returned the call on a Saturday morning and, after listening to a description

of Molly's condition, said, “I think I can help your daughter.” Molly's mother burst into tears.

This initiated a months-long stay in Boston. Because Molly's foot had shifted into an odd, painful position, Dr. Oaklander had a cast put on it, shifting the cast over time to gradually move the foot back into its normal position.

She also weaned Molly off all medication and began a regimen of occupational and physical therapy designed to reduce

the swelling, desensitize the leg, and gradually strengthen it and increase its use. By the time the cast was removed three months later, Molly's foot was in a normal position and the pain was gone.

This multidisciplinary approach offers the best track record for treating CRPS, says Dr. Prager. “If you don't treat pain as a multidisciplinary problem then you can't rehabilitate the patient,” he explains. The essence of CRPS treatment is therapy—physical, occupational, and psychological. And not just an hour or two a day, but six or more hours a day of intensive physical and occupational therapy. It might begin with very simple steps, such as learning to tolerate the sensation of open air on the painful area. This desensitization escalates in a step-wise approach until eventually patients are able to actually scrub the region with a brush. The therapy may also involve hypnosis, biofeedback, and intensive physical therapy with range-of-motion exercises to strengthen the affected muscle and limb.

The psychological therapy used is called cognitive behavioral therapy. This form of therapy educates patients about their condition, helps them avoid “catastrophizing” (in which their perception of the pain makes it worse than it is), and teaches them techniques to better manage the pain and their response to it.

People with CRPS may also require medication or other options to bring the pain to a manageable level so they can even begin thinking about physical therapy and rehabilitation.

Although narcotics can be used, the condition tends to respond better to drugs used to treat other neurologic conditions: anticonvulsants like gabapentin, phenytoin, and carbamazepine; low-doses of antidepressants like nortriptyline, doxepin, desipramine, and trazodone, which block nerve impulses; and corticosteroids, which stem inflammation. Topical

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pain relievers like EMLA anesthetic cream (which contains lidocaine and prilocaine) and lidocaine patches may also help.

Some doctors try bisphosphonates or calcitonin, drugs typically used to treat osteoporosis and cancer-related bone pain. There is some evidence they can relieve the pain of CRPS, most likely by reducing painful bone breakdown.

One approach that Dr. Oaklander says patients should avoid is the nerve blocks that Molly underwent. Not only is the relief temporary, wearing off when the anesthetic wears off, but repeated nerve blocks can result in even more nerve damage.

One approach that is being evaluated in clinical trials involves the infusion, over several days, of ketamine, an anesthetic that blocks receptors for glutamate. Glutamate is a neuropeptide used to convey messages from neuron to neuron; if the chemical doesn't clear out quickly after delivering its message, it can damage nerves. Studies find high amounts of glutamate and glutamate receptors in people with CRPS, suggesting some underlying contribution to the condition.

Some patients travel to Germany or other countries where they are put into a five-day "ketamine coma" to end the pain. But ketamine can have significant side effects, including hallucinations and delirium. Ketamine can also trigger changes in blood pressure and heart rate, as well as breathing problems. Dr. Prager also noted at least two significant complications with the ketamine coma, including one patient who needed a tracheostomy to breathe and another who died. "But the results are fairly miraculous," he says, particularly since the approach is only used in those for whom nothing else has worked. One study in which 20 patients with intractable CRPS pain were given doses of ketamine similar to what is used during anesthesia for five days found that all were pain free a month after treatment, 17 were still pain free at three months, and 16 remained pain free at six months. Although there are no published results from randomized controlled trials on the use of ketamine in people with CRPS, one trial is currently ongoing (see box, "Clinical Trials on CRPS").

None of these medications have been approved for CRPS and studies are few and far between on their effectiveness. However, insurance covers most treatments except the ketamine infusion, says Dr. Prager.

Some patients find relief from neurostimulation, in which a small electrical device implanted in the spine sends regular signals to nerves in the affected area, blocking the transmission of pain signals to the brain. "I believe in it," says Dr. Prager, who implants about 100 devices a year. Plus, it's fully reversible. "But I also believe that as a single solution it's not good," he adds.

Case in point: He had one patient whose pain was completely relieved with neurostimulation but who then tried to commit

suicide. Why? Because after living for years with the pain she had no job, no friends, and no support. Now the pain was gone, but she still had no job, no friends, and no support.

That's why people with CRPS—indeed, any type of chronic pain—require a multidisciplinary approach to treatment, one that also involves psychological therapy. "The idea of treatment of CRPS is functional rehabilitation beyond the pain," says Dr. Prager. "It's better to get rid of the suffering from the pain than to just get rid of the pain." Suffering from the pain differs from the pain itself, he explains, and it is the suffering—the way the pain takes over your life and affects all that you are—that accounts for much of the condition's debilitation.

TAKING CONTROL

In the past year, Max Sokolnicki made a conscious decision to view his pain differently. "Instead of the pain having me, I'm saying that I have the pain," he explains. It might seem like a small distinction, but it puts *him* in control of the pain, and control is an important thing when you are disabled and spend your days in pain. "I don't let the pain become a character in my life and define who I am anymore," he says.

Today Sokolnicki volunteers at a hospice, runs a chronic pain support group, and has begun writing about his experiences. "People feel they are alone with this, and that keeps them from healing," he says, explaining why he started the group. "But even if the pain doesn't go away, it can get better, and that's what the pain group helps with."

As for Molly, who is now 18, she just finished backpacking through Europe with her boyfriend. She worked as a paid intern for an international news organization and followed the Pope as he toured Ground Zero and Yankee Stadium in New York City. Later that day she flew to North Carolina to work on the Obama presidential campaign. As she recalls: "It was a pretty great birthday!" NN

Clinical Trials on CRPS

At least 20 clinical trials into CRPS treatments are currently ongoing, many of which are still recruiting patients. Doctors at Drexel University in Philadelphia, PA, are conducting a clinical trial on the benefits of 10 days of outpatient ketamine infusions for four hours a day. For information about the trial, contact Robert J. Schwartzman, M.D., at 215-762-7090 or rschwartz@drexelmed.edu. To view a full list of current trials, visit clinicaltrials.gov and search for "CRPS."