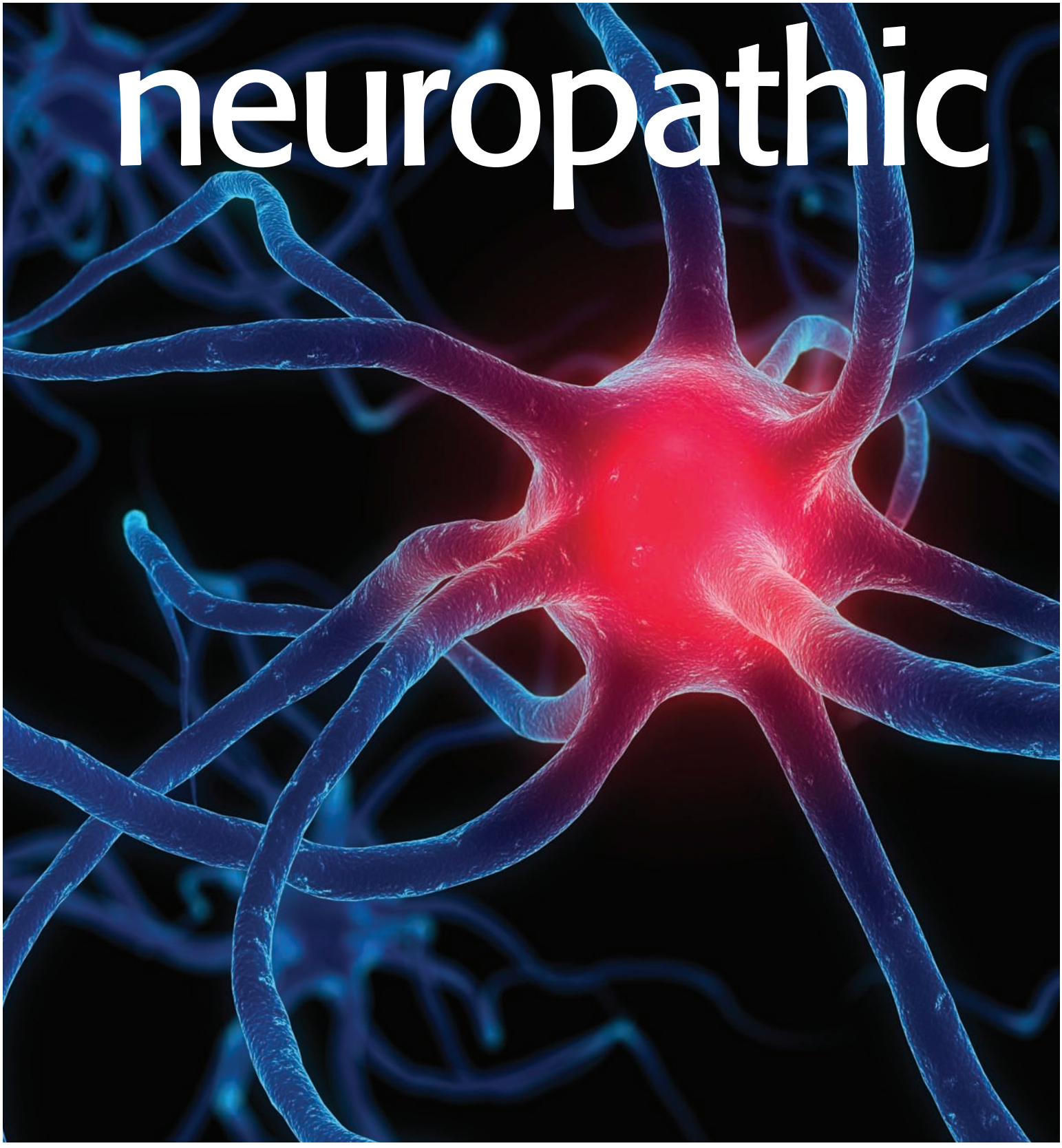
Living with the nightmare of neuropathic



Series: Rooting out neuropathic pain

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PATIENTS LIVING WITH a neuropathic pain syndrome will tell you that this vicious pain can ruin quality of life and spoil dreams. Some neuropathic pain, such as that from diabetic neuropathy, has a gradual onset, but other types, such as complex regional pain syndrome (CRPS), can develop suddenly. Some patients with neuropathic pain who have difficulty getting a diagnosis can experience increased pain and anxiety from the uncertainty of their pain condition.

To get a better understanding of this pain, let's look at a patient who had an accident that resulted in a neuropathic pain syndrome that changed her life.

Meet the patient

Mrs. S, age 65, is a retired teacher who went to bed one night free from pain. During the night, she got up to use the bathroom without turning on the light and ran into a table leg quite hard, injuring her right foot. Because the pain was so severe, her husband drove her to the ED. There she rated her pain as an 8 on a pain intensity rating scale of 0 (no pain) to 10 (worst pain imaginable).

The healthcare provider (HCP) obtained an X-ray of her foot, which revealed no fractures. Believing that Mrs. S had only soft-tissue damage, the HCP prescribed an opioid-acetaminophen combination medication for moderate pain, and told her to elevate, ice, and rest her foot for several days.

Although Mrs. S very diligently rested her foot, used ice packs, and took her medications as needed, the pain didn't resolve. In fact, it increased and became constant. Over the

next 6 weeks, Mrs. S was evaluated by many HCPs, but none could give her a concrete diagnosis. Her pain was 7/10 at best and none of the pain medications she'd been given significantly relieved it; instead, they just made her sleepy. Because she had trouble putting weight on her foot, she started to use crutches. Her foot often felt cold, so she tried to put a sock on for warmth, but she couldn't stand the pressure it put on her foot.

Her husband was concerned about her unrelieved pain, loss of function, and lack of sleep due to pain. At 3 months, Mrs. S was referred to the local pain management specialist, who diagnosed her with CRPS, a neuropathic pain syndrome where the injury is located in the peripheral nerves but can also include changes in the central nervous system.[1] (See *Focusing on CRPS*.)

When Mrs. S asked about treatment, she was told the pain would most likely persist and that the best approach was to try medications designed to treat neuropathic pain to help reduce it. At this point, she broke into tears and told the specialist, "This can't be! I just retired after teaching for 30 years. I planned to travel the world and now I'm in constant pain. How could this have happened to me?"

What we know about neuropathic pain

Neuropathic pain is chronic pain caused by damage in the peripheral or central nervous system. It's been defined as pain that's the direct consequence of a lesion or disease affecting the somatosensory system.[2] (See *The language of pain.*)

This distinct type of pain encompasses a wide variety of neuropathic pain conditions. Unlike acute pain, it has absolutely no protective function and doesn't require any nociceptive input; that is, it exists *independent of a stimulus*. In contrast, *nociceptive pain* results from damage to tissue that's nonneural, such as surgical tissue damage or a tissue injury. Nociceptive pain is caused by activation of thermoreceptors, chemoreceptors, and mechanoreceptors, depending on whether the pain is caused by burns or muscle or tendon damage.[3]

Clinically, a patient such as Mrs. S doesn't have to move or walk on her affected foot to have pain. This type of pain persists without any pressure or sensory input.

Sorting out neuropathic pain

Of the many different types of neuropathic pain, some are caused by chronic diseases such as diabetes or HIV infection. Others, such as postmastectomy pain syndrome, result from surgery or treatments such as chemotherapy. Overall, neuropathic pain is thought to affect 1,765,000 people in the United States, not including those with back pain neuropathy.[4] (See *Sorting out common neuropathic pain conditions*.)

Neuropathic pain has many sources and causes. For example, the continued inflammatory process of osteoarthritis may create neuropathic pain. Fibromyalgia is now considered a disease caused by dysregulation of pain inhibition pathways and amplification of central pain.[5]

Pathophysiology: Getting to the root

Generation of neuropathic pain involves both the peripheral nervous system and the central nervous system, and both the ascending and descending neural pathways. It's maladaptive: Neuropathic pain promotes abnormal functioning of nerves in one or both systems leading to a difficult-to-treat chronic pain condition.[6] As the nerves change function, a phenomenon called *neural plasticity* occurs. These changes are responsible for heightened pain sensitivity and unpredictable, sudden pain exacerbations.

If the source of the neuropathic pain is in the periphery, continued pain stimuli from the peripheral nerve injury create sensitization that over time creates abnormal

Focusing on CRPS

CRPS, or complex regional pain syndrome, was formerly called causalgia or reflex sympathetic dystrophy.[3] It's usually the result of a crush injury or repeated tissue trauma. Continuing pain or abnormal sensation is out of proportion to the event that initiated it. At some time, the patient experiences edema, skin blood flow changes, or abnormal sudomotor activity in the region of pain. No other condition is identified that could explain the pain or dysfunction.[15]

The International Association for the Study of Pain defines two types of CRPS:

- **CRPS I, which doesn't require the presence of a nerve lesion.**
- **CRPS II, which includes the presence of a nerve lesion.**

Although the true cause of CRPS hasn't been determined, the most accepted rationales include the following:

- **enhanced peripheral neurogenic inflammation**
- **sympathetic nervous system dysfunction**
- **structural reorganization in the central nervous system.**

Source: Fechir M, Geber C, Birklein F. Evolving understandings about complex regional pain syndrome and its treatment. *Curr Pain Headache Rep*. 2008;12(3):186-191.

neural activity along the afferent nerve pathways leading to the central nervous system.[7] This sensitization causes the release of what's commonly called an "inflammatory soup" of pain-promoting substances such as cytokines, tumor necrosis factors, bradykinin, and substance P. This in turn leads to hypersensitivity of the nerves, allowing them to crosstalk with each other, release pain-facilitating substances, activate higher level pain-generating functions such as N-methyl-D-aspartate receptors, and fire faster.

Sodium channels on nerve fibers play a part in the creation of neuropathic pain. In normal neural functioning, nerve depolarization occurs when the stimulus reaches the activation point and the nerve is forced to fire. When neuropathic pain is created, more primary and secondary sodium channels are activated, allowing for an ectopic neural discharge.[4]

Pain that originates from the central nervous system is even more difficult to manage. Pain that's centrally controlled can be created by a continued barrage of pain stimuli to the peripheral neurons, causing central neurons to become hyperexcitable. This hyperexcitability has been transferred to the central nervous system through the synaptic junction between the two nervous systems. As a result of this central sensitivity, synaptic connectivity reorganizes, causing lower activation thresholds and increased responses to stimuli.[8]

Additionally, collateral neurons may sprout and create larger fields of effect with the ability to crosstalk with each other and recruit additional neurons for pain creation. This phenomenon, called *wind-up*, causes an increased response to painful stimuli.[6] Meanwhile, the descending pathway inhibition potential used to block pain is adversely affected, letting more pain reach the patient.

This explains the pain that Mrs. S is continuing to have. Continual pain stimuli from the periphery have created central sensitization and the wind-up effect has been created related to neuronal plasticity. Because the pain had continued at high levels for so long, the central nervous system pain-facilitating process was activated, which will make her pain much harder to manage.

Signs and symptoms

When assessing neuropathic pain, the nurse must ask the patient to describe the pain. Aside from the numeric pain intensity scale, the descriptors the patient uses are the best means of identifying the pain. If the patient uses words such as burning, shooting, electric, painful numbness, or tingling, the pain has a neuropathic source. After a mastectomy, some patients complain of strange painful sensations or painful pruritus in the ipsilateral axilla or upper arm. This is also classified as neuropathic pain.

Using fiber wisps for sensation testing or alcohol to create a cool sensation and touching the painful areas can determine just how large an area is affected. Ask patients if they experience *hyperalgesia,* increased pain from a stimulus that's normally painful, such as a pinprick, or *allodynia,* a painful response to a stimulus that isn't normally painful, such as touch from clothes or bedsheets.[6] Assess for other signs of neuropathic pain. Other common types of neuropathic pain include *paresthesia*, an abnormal sensation that isn't unpleasant, such as numbness or tingling, and *dysesthesia,* an unpleasant sensation such as painful pruritus or feeling as though bugs are crawling under the skin.[6]

The language of pain

- ***Allodynia:*** painful response to a stimulus that isn't normally painful**,** such as touch from clothes or bed sheets.
- ***Crosstalk:*** new communication, or neural sprouts, between nerves that don't normally synapse with one another.
- ***Dysesthesia:*** an unpleasant sensation, such as painful pruritus or feeling as though bugs are crawling under the skin.
- ***Hyperalgesia:*** increased pain from a stimulus that's normally painful.
- ***Neural plasticity:*** continued noxious stimuli and inflammation causing an elevation of nociceptive input from the periphery to the central nervous system, which then creates an increased response at the cortical level to change its somatotopic organization for the painful site, inducing central sensitization.
- ***Neuropathic pain*****:** chronic pain caused by damage in the peripheral or central nervous system that's the direct consequence of a lesion or disease affecting the somatosensory system.
- ***Nociceptive pain:*** pain that results from nonneural damage to tissue.
- ***Paresthesia:*** an abnormal sensation that isn't unpleasant, such as numbness or tingling.
- ***Wind-up:*** an increased response to painful stimuli. Add, on a new line as source format:

Source: Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10(2):113-130.

In the acute phase, patients who are developing CRPS after an injury continue to report high-intensity pain despite escalating doses of opioids. As the condition develops, besides allodynia, patients report edema, skin discoloration due to changes in blood flow, temperature differences between the affected and nonaffected extremity, changes in hair and nail growth, weakness, and tremor.[9]

Mrs. S is having difficulty with severe pain and she can't put any pressure on her foot. She has allodynia, and she's started to use descriptors indicative of CRPS, such as painful coldness.

Treatment options

One of the best ways to manage neuropathic pain is to use a stepwise approach. To adequately assess and diagnose a patient with neuropathic pain, the HCP will need to perform a focused physical exam. If possible, the HCP will identify the source, make a diagnosis, and examine any contributing comorbidities such as diabetes. Remember that the patient may not understand that pain descriptors may be the key to adequate management.

Besides explaining the diagnosis to the patient and discussing treatment options, the HCP will set realistic achievable goals. Many patients with neuropathic pain have seen multiple HCPs with no success; receiving a diagnosis may end the uncertainty that these patients have experienced and give them some hope for reducing the pain. Although complementary techniques such as relaxation or yoga may be beneficial for adjunct pain relief, the mainstay is pharmacologic management.

Stepping up to medications

Using the stepwise approach to treatment includes using first-line medications with the highest level of evidence for success in controlling neuropathic pain. (See *Lining up medications for neuropathic pain.*)

After patients begin drug therapy, nurses need to reassess the efficacy of the therapeutic regimen. If the first medication chosen doesn't provide pain relief or increase functionality, the HCP may try titrating the dose upward. If that doesn't provide adequate pain relief, the HCP may consider combining two first-line medications.

If careful drug choices in the first-line category don't provide adequate pain relief, trialing second-line options may be a way of optimizing pain relief. As always, adding nonpharmacologic therapies, such as yoga, pool therapy, or meditation, can help with pain relief and relaxation.

For Mrs. S, our patient with CRPS, using one or more first-line therapies should provide some level of pain relief. Her current medication is an opioid, which is a second-line option. Using first-line medications either alone or in conjunction with the opioid may optimize her pain relief, and a consultation with physical medicine and rehabilitation professionals to work on increasing functionality is highly recommended. Mrs. S may never be pain free—that isn't a reasonable goal for her—but she should be able to move to a higher level of physical activity and perhaps begin to take short trips to see some of the places she's been dreaming about.

New options on the horizon

Research evidence supports the use of some antiepileptic drugs for certain types of neuropathic pain such as painful diabetic neuropathy. However, lacosamide, an antiepileptic drug, was trialed for managing neuropathic pain and fibromyalgia but failed to show significant benefit. The FDA has declined to approve its use for neuropathic pain.[10] Another therapy that produced better outcomes is topical application of high-dose capsaicin, 8% patch, which is thought to produce desensitization. It's indicated for a particularly difficult-to-treat neuropathic pain syndrome called postherpetic neuralgia. In six studies involving 2,073 patients, a small number of participants with postherpetic neuralgia and HIV neuropathy with high pain levels benefited.[11] Pain relief lasted for up to 12 weeks. In studies, 11 or 12 patients had to be treated to get 1 positive outcome of reduced pain (this is known as *numbers needed to treat* and is considered high).[11] However, some patients did benefit, and their pain was significantly reduced.

Although single medications used alone can positively affect neuropathic pain, combination therapy demonstrates superior pain relief. Some agents caused problematic sedation.[12] Unfortunately, there weren't enough comparative or replication studies to identify particular combinations of drugs that had improved

Sorting out common neuropathic pain conditions

Peripheral syndromes and U.S. patients affected

- Painful diabetic neuropathy; 600,000
- Postherpetic neuralgia; 500,000
- Cancer associated; 200,000
- HIV associated; 100,000
- Phantom limb pain; 50,000

Central syndromes and U.S. patients affected

- Spinal cord injury; 120,000
- CRPS I and II; 100,000
- Poststroke; 30,000

Source: Irving GA. Contemporary assessment and management of neuropathic pain. *Neurology*. 2005;64(12 suppl 3):S21-S27.

pain relief. In a meta-analysis with 386 patients, gabapentin plus an opioid was superior to gabapentin alone, according to a modest but clinically significant finding.[12]

One of the most exciting ideas for managing neuropathic pain is attempting to use molecular approaches. Chromaffin cells release a combination of pain-reducing neuroactive compounds, including catecholamines and opioid peptides.[13] Encapsulating the cells and implanting them in the subarachnoid space has relieved pain in both animal and human studies.[13]

In these cell transplantation studies, encapsulated cells with permeable membranes turn into cellular pumps that create and dispense analgesic compounds.[13] Future research targets include astrocyte cells that are genetically modified to secrete enkephalin and genetically engineered cells designed to secrete gamma-aminobutyric acid, a pain inhibitory substance.[13] Patients thought to be good candidates for study include those with low back pain and knee pain; these can have neuropathic elements. Understanding the pathways and physiology of neuropathic pain transmission can help researchers look for ways to use these specialized cells to reduce pain right at the source of pain generation.

Other options for managing neuropathic pain include using autologous bone marrow-derived progenitor cells to repair damaged neurons in patients with diabetic peripheral neuropathy and gene transplants applied to peripheral nerves, injected into dorsal root ganglia, or introduced into the intrathecal space of the spine via lumbar puncture or injected directly into the brain.[13] Gene transplants have been tested only in animals using the herpes simplex virus.[13]

Stem cell transplantation also provides promise for pain research. Mesenchymal stem cells can be harvested from bone marrow, are fairly stable, and can, once transplanted, migrate to injured tissue and have immunosuppressive characteristics.[14] They can also differentiate into astrocytes and neurons and migrate to injured neuronal areas to mediate functional recovery.[14] Although many of the finer points of the process are yet to be discovered, studies of mice have shown that the transplanted stem cells relocated themselves into key areas

Lining up medications for neuropathic pain[10]

These medications are the recommendations of the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain. Many are used off label.

Medications	Examples
First-line medications[10]	
Antidepressants, including serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs). These block sodium and potassium ion channels and affect neurotransmitter reuptake.	• SNRIs such as duloxetine and venlafaxine • TCAs such as nortriptyline, desipramine, and amitriptyline (amitriptyline isn't recommended for older adults due to the risk of orthostatic hypotension)
Calcium channel alpha2-delta ligands inhibit neurotransmitter release, modulate sodium and calcium channels, and decrease neuronal hyperexcitability.	• gabapentin • pregabalin
Topical lidocaine provides localized pain relief.	• 5% lidocaine patch
Second-line medications[10]	
Opioid use is limited due to mixed data on efficacy. Higher doses produce better effects but increase the potential for opioid-induced hyperalgesia.[13]	• morphine • oxycodone • methadone • tramadol (inhibits reuptake of serotonin and norepinephrine but can lower seizure threshold).
Third-line medications[3,10,13]	
Antidepressants	• bupropion • citalopram • paroxetine
Antiepileptic drugs	• carbamazepine • lamotrigine • oxcarbazepine • topiramate • valproic acid
Other agents	• topical capsaicin • dextromethorphan • memantine • mexiletine.

for neuropathic pain generation in the brain.[14]

Although many new management options are still being studied in animals, they hold promise for human use in the future. Researchers are attacking the pain process from many different directions and using the known pain pathophysiology to direct the therapy to targets that may yield good results.

In the foreseeable future, patients like Mrs. S won't be limited to medications or interventions for intractable pain syndromes such as spinal cord stimulators. Instead, they'll have options that include stem cell transplants for nerve repair or genetically engineered cells that will enhance the production of pain-reducing substances. Using these new techniques will help many patients leave the nightmare of neuropathic pain behind and fulfill their dreams. ■

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