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CME ARTICLE

# Review of Clinical Nerve Function Studies and Imaging: Part II

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***Learning Objectives: After participating in this activity, the physician should be better able to:***

1. Evaluate the clinical utility and limitations of various nerve imaging modalities.
2. Use imaging tests appropriately.

Pain is an intrinsically subjective condition, so any tools that can measure or document the physical changes associated with pain conditions can be as helpful to physicians as they are to patients. Clinical nerve imaging studies include a variety of methods that can provide visual documentation of these physical responses. This article, the second of 2 parts, will cover the remaining types of clinical nerve imaging so that clinicians can use them when appropriate and understand the limitations of each type of study.

## In This Issue



## Laser-Evoked Potentials

Laser-evoked potentials (LEPs) can show abnormalities that are strongly indicative of neuropathic pain, whereas a normal LEP is often more ambiguous. LEPs have high sensitivity and constitute a very reliable tool in assessing central and peripheral nervous systems damage.

LEPs are measurements produced when lasers are used to stimulate thermonociceptors selectively in the skin. The resulting LEP is a measurement of cortical response. Lasers can emit a radiant–heat pulse stimulus to selectively activate Aδ and C free nerve endings.

By specifically targeting pain and temperature pathways and measuring cortical responses, clinicians can identify tiny lesions in the spinothalamic pathways.

Treede et al,[1] in an excellent review of LEPs, clearly demonstrate their clinical use. In contrast to the ease of testing the visual or auditory pathways, which can be assessed electrophysiologically using visual or auditory-evoked potentials, the

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somatosensory pathway cannot be investigated completely by conventional somatosensory-evoked potentials because these only reflect function of large fibers, dorsal columns, medial lemniscus, and their thalamocortical projections mediating sensations like touch and vibration.

The other half of the somatosensory system, which transmits temperature and pain perceptions, uses a different set of afferents and different central pathways, which can be tested by LEPs. LEPs can document lesions of the spinothalamic tract, the lateral aspects of the brainstem, and the thalamocortical projections carrying heat-nociceptive signals.

In studying the peripheral nerve, LEPs can distinguish between large- and small-fiber neuropathies. The rapid heating of the skin by infrared laser pulses can be applied easily to nonkeratinized skin in any dermatome. In recent years, many clinical studies have demonstrated that LEPs can supply evidence for establishing clinical diagnoses when deficits of the nociceptive system are present.

However, there are limitations with the use of LEPs, including inability to localize the lesion along these pathways and the fact that LEPs can reliably show reduced nociceptive function, but not enhanced transmission, as in the hyperalgesia of complex regional pain syndrome.

## Quantitative Sensory Testing

Quantitative sensory testing (QST) is based on using very defined stimuli, which have well-defined modality, intensity, spatial and temporal characteristics, and the analysis of the quality of

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the evoked sensation and quantification of its intensity. In addition to assessment of sensory thresholds (ie, detection threshold of nocuous stimuli and the pain threshold), QST includes the assessment of sensations evoked by suprathreshold stimuli.[2]

Thermal, as well as static and dynamic mechanical stimuli, are used to assess the various sensory modalities corresponding to various types of receptors, peripheral nerve fibers, and central nervous system (CNS) pathways. Computerized systems include stimulators using the Peltier principle of brief thermocouple heating applied to the skin.[3]

Devices delivering calibrated mechanical stimuli (pressure, vibration) are still comparatively primitive and less standardized than Von Frey hairs or Semmes-Weinstein filaments.

Several algorithms have been published for the assessment of sensory thresholds, but the 2 most commonly used are the method of limits and the method of levels.[4]

In the method of limits, the intensity of a stimulus applied to the skin is increased until the subject perceives a stimulus (perception or detection threshold for innocuous stimuli) or feels it as painful (pain detection threshold) and stops the stimulus by using a feedback control (eg, by pressing a stop button).

The thresholds are then calculated as means of the values obtained during a series of stimuli (usually 3–5). This method involves the reaction time and, therefore, its results are highly dependent on the subjects' motor abilities and ability to stay focused on the test.

In the method of levels, a series of predefined stimuli (in terms of intensity and modality) are applied to the skin and, for each stimulus, the subject has to report (yes or no) whether the stimulus is perceived or not or whether it is painful or not (ie, "forced choice"). The intensity of the next stimulus in the series is systematically increased or decreased on the basis of the subject's response. One advantage of this method is that it does not depend on the patient's reaction time. However, this method is seldom used because it is very time-consuming.

A clinically significant application of QST is in the assessment of neuropathic pain and the analysis of the responses to suprathreshold painful stimuli, although it needs to be restricted to an absolute minimum number of stimuli for obvious ethical reasons.

The determination of stimulus-response function aids in the identification and quantification of hyperalgesia.

Thermal or mechanical suprathreshold stimuli have been used by some investigators.[5] However, there is no widely accepted consensus statement or standard regarding a specific assessment of thermal or mechanical allodynia and hyperalgesia. It is important to understand that the results can be influenced by a number of factors related to both the stimulus (type of the device, room temperature, the site of the stimulus, the size of stimulated area, stimulus velocity, and interstimulus interval) and the patient (age, sex, cooperation/motivation, vigilance, attention).

### *QST as a Complement to the Clinical Sensory Examination*

Standard sensory testing is the first step in the diagnostic workup of a patient with any neurologic lesion. Mapping any somatosensory deficit is an essential approach when surveying the somatosensory system. Simple devices such as a brush, a vibrating tuning fork,[6] or a needle are used to test various sensory modalities. Combinations of somatosensory aberrations may be found, all usually confined to the innervation territory of the affected peripheral or central nervous structure. The combinations can include quantitative (hyperesthesia and hypoesthesia), qualitative (eg, allodynia, dyesthesia or paresthesia), spatial (eg, faulty localization), and temporal (eg, aftersensation) somatosensory aberrations.

Each patient is his or her own control when comparing dysfunction profiles in the painful area and on the contralateral site. In peripheral neuropathy, it is fairly simple to compare the distribution of sensory abnormalities with the expected innervation dermatomes; this is a much more difficult task in patients with CNS lesions. The main limitations of traditional bedside examination are a result of its qualitative nature and the lack of control and standardization of the stimulus intensity.

QST was developed to overcome these limitations. The determination of detection and pain thresholds allows for a more precise assessment of the magnitude of sensory deficits and quantification of thermal and mechanical allodynia and hyperalgesia.

The main clinical diagnostic aim of QST in the patient with neuropathic pain is to support the hypothesis whether or not a lesion exists along somatosensory pathways, although it cannot provide insights as to where along the neuroaxis the lesion is localized.

However, very few studies have directly compared the results of QST with those of standard clinical examination and, therefore, the sensitivity and specificity of these techniques for the diagnosis of neuropathic pain have not been determined. The lack of standardization of the assessment algorithms and the relative paucity of normative data[4] have probably contributed to the very limited clinical application of QST.

*Editor's Note:*

The American Board of Anesthesiology Pain Medicine curriculum covers several areas of diagnostic testing. With respect to clinical nerve function studies and imaging, the key topics are delineated by the curriculum as follows:

**Clinical Nerve Function Studies and Imaging**

02.09.01 Electrical nerve stimulation EMG/(NCV)/evoked potentials: uses and limitations
02.09.02 LEPs: uses
02.09.03 QST: uses and limitations
02.09.04 Skin-punch biopsy: assessment of innervation density
02.09.05 MRI, fMRI, and MRS: uses
02.09.06 PET: uses
02.09.07 EEG, MEG: uses

We covered electromyography (EMG)/nerve conduction velocity (NCV) last month (*TPM* June 2011, volume 26, no. 11). In this issue, we review the remaining topics for clinical nerve function studies and imaging.

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Although QST cannot replace bedside examination, these approaches are complementary because the site of threshold measurements is determined on the basis of a previous standard bedside examination.

### *Clinical Applications of QST in the Evaluation of Neuropathic Pain*

The use of QST in the early diagnosis of some sensory neuropathies, especially diabetic polyneuropathy, has been well documented.[4-6] Measurement of vibration threshold and thermal detection thresholds is considered to be sufficiently reliable and reproducible and has been included in diagnostic criteria. In the context of neuropathic pain, the primary interest of QST is to reinforce and objectively document the physician's certainty about the existence of a lesion of the somatosensory systems.

One particular condition, painful small-fiber neuropathy, is almost uniformly associated with abnormal thermal thresholds, yet it is characterized by normal NCVs because such measures analyze only large-fiber function.[6,7] The comparison between the painful and contralateral corresponding site can be problematic because of the lack of information regarding what constitutes a meaningful difference. Moreover, somatosensory abnormalities may also be found in the focal or referred pain area in patients with nonneuropathic pain conditions.

## Skin-Punch Biopsy and the Challenge of Small-Fiber Neuropathy

Small-fiber neuropathy may not be detected by traditional physical, neurophysiologic, and neuropathologic tests. In the past decade, skin biopsy has become a popular method for investigating small nerve fibers. It allows practitioners to diagnose neuropathy (thereby avoiding delayed or incorrect diagnosis) and investigate its etiology, while focusing treatment on neuropathic pain.

Small-fiber neuropathy is associated with the following:

- Common metabolic disorders such as diabetes and hyperlipidemia;
- Immune-mediated conditions such as Sjögren syndrome, sarcoidosis, and celiac disease;
- Drug toxicity such as that caused by chemotherapy drugs and antiretroviral drugs; and
- Viral infections such as HIV.

Small-fiber neuropathy can also be a significant clinical sign of hereditary diseases (eg, familial amyloidosis and Fabry disease).

In the absence of known systemic disease, the diagnosis of small-fiber neuropathy can be difficult to make. Pain or burning (or both) in the feet are prominent symptoms in small-fiber disease and may be worse at night. Some patients report that contact with warm or cold water produces discomfort or pain (thermal allodynia). Reports of nocturnal pain, restless leg syndrome, cramps, and fatigue are also common.

These symptoms reflect the degeneration of somatic small nerves, namely unmyelinated C and thinly myelinated Aδ fibers, which carry thermal and pain sensation from the skin to the spinal cord and eventually the brain. Pain induced by nonpainful touch stimuli (mechanical allodynia) is due to large-fiber dysfunction and thus is mild or absent in small-fiber neuropathy.

Pinprick and thermal sensation may be reduced in the feet, whereas light touch and vibratory sensation and deep tendon reflexes are preserved, reflecting the sparing of large myelinated nerve fibers.

In most patients, the neurologic examination is essentially normal. Symptoms of autonomic impairment, such as altered sweating, flushing, and skin mottling have also been reported in small-fiber neuropathy.

Routine neurophysiologic examinations do not provide diagnostic clues in small-fiber neuropathy. Sensory nerve conduction studies evaluate only the large myelinated fibers, which are typically normal in small-fiber neuropathy.

QST to detect thermal and pain thresholds has been used extensively to assess small-fiber impairment (vide infra). Studies have shown that an increased warm threshold correlates with skin denervation in small-fiber neuropathy.[6]

Sural nerve biopsy has long been used for the histopathologic diagnosis of most peripheral neuropathies, but it has limitations. It is an invasive procedure performed in the operating room and carries the risks of pain and permanent sensory loss distal to the biopsy site.

Quantitative analysis of unmyelinated fibers is possible in the biopsy specimen but it is difficult and time-consuming. Furthermore, the unmyelinated C and myelinated Aδ axons, which have either somatic or autonomic function, are enclosed in bundles of the nerve, and cannot be differentiated from one another, which limits the usefulness of this technique for diagnosing small-fiber neuropathy. Finally, the biopsy cannot be repeated to monitor progress of the neuropathy except by using the opposite sural nerve.

Skin biopsy is a safe and inexpensive technique for evaluating small nerve fibers. The density of these fibers can be measured easily using bright-field microscopy in sections cut from the specimen and appropriately immunostained with antibodies against markers expressed by peripheral nerve fibers.

A skin biopsy can also be repeated within the same nerve territory to evaluate the natural progression of the neuropathy and the effect of treatments, such as corticosteroids or immunoglobulin. The positive predictive value of skin biopsy in diagnosing small-fiber neuropathy is estimated to be 93%; specificity is 97%, and sensitivity ranges from 69% to 82%.[8]

This technique has recently been shown to detect morphologic and quantitative changes in skin innervation earlier than neurophysiologic tests, and it can predict the progression of neuropathy.

Skin biopsy also allows small fibers with different functions to be investigated separately. This has important implications in


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clinical practice. Intraepidermal nerve fibers have an exclusively somatic function and express the capsaicin receptor, indicating that they are peripheral nociceptors. Therefore, in patients with painful neuropathy, skin biopsy can detect abnormalities of the target nerves, namely unmyelinated axons carrying pain sensation. Conversely, fibers innervating sweat glands, arrector pili muscles, and blood vessels have autonomic function, and their degeneration is indicative of an autonomic neuropathy, which may be subclinical in patients with peripheral neuropathy.

Comparative studies have strengthened the role of skin biopsy in diagnosing small-fiber neuropathy. An analysis of patients with small-fiber neuropathy showed that the density of unmyelinated intraepidermal nerve fibers could be low despite normal morphology of small nerve fibers from sural nerve samples on electron microscopic examination. A further study demonstrated that skin biopsy and sural nerve biopsy provide concordant results in approximately 75% of patients, but that skin biopsy can detect small-fiber neuropathy in 25% of patients with normal sural nerve morphology.

The distribution of skin nerve density can be useful in localizing the site of pathology.

In patients with distal and symmetrical peripheral neuropathies, such as in diabetic polyneuropathy, skin nerves are lost mainly at the distal rather than the proximal regions of the lower limbs, as the longest sensory axons degenerate first. This is consistent with the length-dependent pattern of sensory disturbances, which start from the feet and progress proximally.

In patients with diabetic and HIV neuropathy, intraepidermal nerve fibers can show diffuse and large swellings that precede the degeneration of axons and predict the progression of symptoms to overt neuropathy. Skin biopsy has shown that diabetes causes subclinical defects of nerve fiber functions early in the progression of the disease. The rate of regeneration of epidermal nerves after topical application of capsaicin, which causes transient denervation of the skin, is slower in patients with diabetes and no evidence of neuropathy than it is in healthy people.

### *Demonstrating Autonomic Neuropathy*

Skin biopsy can show the presence of autonomic neuropathy by providing a semiquantitative assessment of the denervation of sweat glands. This approach is more sensitive than functional examination of autonomic nerves using quantitative sudomotor axon testing.

### *Monitoring Neuropathy*

Patients with neuropathy can be evaluated over time by measurement of intraepidermal nerve fiber density. Follow-up biopsies can be taken adjacent to the previous biopsy site within the same nerve distribution. In patients with diabetes, HIV infection, or idiopathic disease, serial skin biopsies have shown that loss of intraepidermal nerve fibers correlates with the progression of neuropathy.

Regeneration of skin nerve fibers, which occurs after nerve injury, can be followed by recovery of heat-pain and pinprick sensation. In experimental models of neuropathy, skin biopsy proved to be a reliable tool for monitoring the efficacy of neuroprotective agents, such as erythropoietin and insulin-like growth factor-1.

Skin biopsy can be performed at any site of the body using a disposable punch, which is 3 mm in diameter, under sterile technique, and after local anesthesia with lidocaine. No suture is needed, and no adverse effects have been reported. Healing is usually complete within 1 week, and the scar is barely visible after 3 months.

The specimen is immediately fixed, frozen, cut into vertical sections, and then processed immunohistochemically to examine the innervation of epidermis, dermis, and sweat glands.

## Functional MRI

Functional MRI (fMRI) is based on the increase in blood flow to the localized vasculature that accompanies neural activity in the brain.[9] This increased blood flow results in a corresponding local reduction in deoxyhemoglobin because the increase in flow occurs without an increase of similar magnitude in oxygen extraction. Because deoxyhemoglobin is paramagnetic, it alters the T2-weighted MRI signal. Because of this physical property, deoxyhemoglobin is sometimes referred to as an endogenous contrast-enhancing agent and serves as the source of the signal for fMRI. Using an appropriate imaging sequence, human cortical functions can be observed without exogenous contrast-enhancing agents with a regular clinical strength (1.5-T) scanner.

The main advantages of fMRI as a technique to image brain activity related to a specific task or sensory process include:

1. The signal does not require injections of radioactive isotopes;
2. The total scan time required can be very short (approximately 1.5 to 2.0 minutes per run); and
3. The in-plane resolution of the functional image is generally approximately 1.5 × 1.5 mm.

To put these advantages in perspective, functional images obtained by positron emission tomography (PET) require injections of radioactive isotopes and multiple acquisitions, and, therefore, extended imaging times. Furthermore, the expected resolution of PET images is larger than the usual fMRI pixel size. In addition, PET usually requires that multiple individual brain images are combined to obtain a reliable signal.

## MR Spectroscopy

Magnetic resonance spectroscopy (MRS) provides a measure of brain chemistry. The most common nuclei that are used are $^{1}H$ (proton), $^{23}Na$ (sodium), and $^{31}P$ (phosphorus). Proton spectroscopy is easier to perform and provides much higher signal-to-noise ratio than either sodium or phosphorus. Proton MRS can be performed within 10 to 15 minutes and can be added on to conventional MRI protocols. It can be used to monitor serial biochemical changes in patients with tumors, stroke, epilepsy, metabolic disorders, infections, and neurodegenerative diseases.[10]

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Each metabolite appears at a specific concentration (in parts per million), and each one reflects specific cellular and biochemical processes. *N*-acetylcysteine (NAA) is a neuronal marker and decreases with any disease that adversely affects neuronal integrity. Creatine provides a measure of energy stores. Choline is a measure of increased cellular turnover and is elevated in patients with tumors and inflammatory processes. The observable metabolites provide powerful information, but, unfortunately, many other important metabolites are not represented in brain MRI spectra. DNA, RNA, most proteins, enzymes, and phospholipids are not represented. In addition, some key neurotransmitters, such as acetylcholine, dopamine, and serotonin, are also absent.

### *Brain Tumors*

MRS can be used to determine degree of malignancy. As a general rule, as malignancy increases, NAA and creatine decrease, and choline, lactate, and lipids increase. NAA decreases as tumor growth displaces or destroys neurons.

### *Cerebral Ischemia and Infarction*

When the brain becomes ischemic, it switches to anaerobic glycolysis, and lactate accumulates. Markedly elevated lactate is the key spectroscopic feature of cerebral hypoxia and ischemia. Choline is elevated, and NAA and creatine are reduced. If cerebral infarction ensues, lipids increase.

### *Trauma*

MRS is not routinely used in the acute setting of head injuries. CT and MRI demonstrate the fractures and intracranial hemorrhage that require emergent surgical intervention. When the patient's condition has stabilized, however, MRS is helpful to assess the degree of neuronal injury and to predict patient outcome. In the case of diffuse axonal injury, conventional imaging often underestimates the degree of brain damage. However, using MRS, it has been determined that clinical outcome correlates inversely with the NAA:Cr ratio. The presence of any lactate or lipid indicates a worse prognosis.

### *Infectious Disease*

Brain abscesses destroy or displace brain tissue, so NAA is not present. Lactate, cytosolic acid, alanine, and acetate are the characteristic metabolites in patients with bacterial abscesses. In contrast, toxoplasmosis and tuberculous granulomas show prominent peaks from lactate and lipids.

Clinical investigators of HIV infection and AIDS have been very interested in the potential of MRS for measuring the effects of HIV infection on the brain and neurocognitive function. When patients start developing neurocognitive deficits and AIDS dementia complex, the MR spectra become abnormal with elevated choline and reduced NAA. Choline is the best marker for the white matter abnormalities, and the extent of NAA depletion seems to correlate directly with the degree of dementia. MRS is also very helpful in observing patients and assessing the effects of antiviral therapies.

## Positron Emission Tomography

PET is a nuclear medicine imaging technique that produces a 3-dimensional image or a picture of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (the tracer), which is introduced into the body on a biologically active molecule, for example, tagged glucose. Three-dimensional images of tracer concentration within the body are then constructed by computer analysis. In modern scanners, 3-dimensional imaging is often accomplished with the aid of a CT x-ray scan performed on the patient during the same session, in the same machine. Areas of the brain consume more energy when the neurons are actively firing as would happen when experiencing pain.

Coghill et al[11] have documented that numerous functional imaging studies of human subjects have identified a diverse assortment of brain areas that are engaged in the processing of pain. Although many of these brain areas are highly interconnected and are engaged in multiple processing roles, typically each area has been considered in isolation. Accordingly, little attention has been given to the global functional organization of brain mechanisms mediating pain processing.

Use of PET and then multiple regression analysis revealed statistically reliable relationships between perceived pain intensity and activation of a functionally diverse group of brain regions, including those important in sensation, motor control, affect, and attention.[11]

Pain intensity-related activation occurred bilaterally in the cerebellum, putamen, thalamus, insula, anterior cingulate cortex, and secondary somatosensory cortex; contralaterally in the primary somatosensory cortex and supplementary motor area; and ipsilaterally in the ventral premotor area.[11]

These results confirm the existence of a highly distributed, bilateral supraspinal mechanism engaged in the processing of pain intensity. The conservation of pain intensity information across multiple, functionally distinct brain areas contrasts sharply with traditional views that sensory-discriminative processing of pain is confined within the somatosensory cortex and can account for the preservation of conscious awareness of pain intensity after extensive cerebral cortical lesions.

## Magnetoencephalography

Magnetoencephalography (MEG)[12] is a noninvasive technique used to measure magnetic fields generated by small intracellular electrical currents in neurons of the brain. MEG provides direct information about the processing of evoked and spontaneous neural activity and the location of their sources in the brain.

MEG and electroencephalography (EEG) are closely related, the latter detecting the electric potentials generated by neural currents instead of the corresponding magnetic fields. However, it turns out that the ability to localize the sites of brain activation is often more straightforward from MEG than from EEG. This


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is due to the electric and magnetic properties of the tissues in the cranium and also to the fact that MEG is very sensitive to currents flowing in the tangential plane to the scalp, corresponding to sulcal activations. On the other hand, the interpretation of EEG is often complicated by the simultaneous presence of both sulcal and gyral sources, the latter corresponding to radial currents, which cancel each other out.

MEG measurements are conducted externally, using an extremely sensitive device called a superconducting quantum interference device (SQUID). The SQUID is a very low noise detector of magnetic fields, which converts the magnetic flux threading a pickup coil into voltage allowing detection of weak neuromagnetic signals. Because the SQUID relies on physical phenomena found in superconductors, it requires cryogenic temperatures for operation. In a modern MEG device, an array of more than 300 SQUIDS is contained in a helmet-shaped, liquid-helium-containing Dewar vessel, allowing simultaneous measurements at many points over the head. The MEG system is operated in a shielded room that minimizes interference from external magnetic disturbances, including the earth's magnetic field, noise generated by electrical equipment, radiofrequency signals, and low-frequency magnetic fields produced by moving magnetic objects, such as elevators and cars.

The temporal resolution of the MEG is milliseconds, which allows real-time recording of the brain activity. The spatial resolution ranges from several millimeters to a couple of centimeters. The MEG is completely noninvasive and nonhazardous.

Signals can be recorded over the whole cortex. MEG does not provide structural/anatomic information. Therefore, MEG data often must be combined with MR data into a composite image of function overlaid on anatomy to produce activation maps.

Clinically, MEG is used to detect and localize epileptiform-spiking activity in patients with epilepsy. It is also used to localize brain areas important for speech, which should be avoided by the surgeon in planning for removal of brain tumors. In chronic pain states, there are a variety of locales beyond the usual somatosensory cortex that are activated (vide supra).

## Conclusion

With the advent of new technology, the American Board of Anesthesiology Pain Management curriculum has expanded to include new testing modalities. Some of these have direct clinical application, whereas others are important for research and development of our understanding of pain states. In ordering any test, the practitioner must always bear in mind the costs, risks, and benefits. In this article, we have identified those tests with direct clinical application and their associated risks so that the practitioner can maximize the capabilities of imaging technology using the most appropriate tests for each patient. ■

## References


1. Treede RD, Lorenz J, Baumgärtner U. Clinical usefulness of laser-evoked potentials. *Neurophysiol Clin.* 2003;33(6):303-314.

2. Samuelsson M, Leffler AS, Hansson P. Dynamic mechanical allodynia: on the relationship between temporo-spatial stimulus parameters and evoked pain in patients with peripheral neuropathy. *Pain.* 2005;115:264-272.

3. Jamal GA, Hansen S, Weir AI, et al. An improved automated method for the measurement of thermal thresholds. 1. Normal subjects. *J Neurol Neurosurg Psychiatry.* 1985;48:354-360.

4. Chong PST, Cros DP. Technology literature review: quantitative sensory testing. *Muscle & Nerve.* 2004;29:734-747.

5. Cruccua G, Anandc P, Attal N, et al. EFNS guidelines on assessment of neuropathic pain and treatment. *Euro J Neurolo*. 2004;11:1-10.

6. Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: clinical and research application in neuropathic pain states. *Pain.* 2007;129:256-259.

7. Devigili D, Tugnoli V, Penza P. The diagnostic criteria for small-fibre neuropathy: from symptoms to neuropathology. *Brain*. 2008;131:1912-1925.

8. Gibbons CH, Griffin JW, Polydefkis M, et al. The utility of skin biopsy for prediction of progression in suspected small-fiber neuropathy. *Neurology.* 2006;66:256-258.

9. Cole LJ, Farrell MJ, Duff EP. Pain sensitivity and fMRI pain-related brain activity in Alzheimer's disease. *Brain*. 2006;129:2957-2965.

10. Apkarian AV, Bushnell C, Treede RD, et al. Human brain mechanisms of pain perception and regulation in health and disease. *Euro J Pain.* 2005;9:463-484.

11. Coghill RC, Christine N, Sang CN, et al. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J Neurophysiol*. 1999;82:1934-1943.

12. Chen AC. New perspectives in EEG/MEG brain mapping and PET/fMRI neuroimaging of human pain. *Int J Psychophysiol.* 2001;42(2):147-159.


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# Researchers at University of Maryland School of Nursing Develop Tool for Noncommunicative patients

Significant developments in palliative pain care are coming from nurse-led research, which should come as no surprise. Nurses usually are the practitioners who administer palliative care in homes or at the patient's bedside in the hospital. Their discipline is rooted in advocacy for their sometimes-noncommunicative patients.

Deborah McGuire, PhD, RN, and her colleagues[1] at the University of Maryland School of Nursing have developed a valid and reliable tool to assess acute pain in noncommunicative patients, according to data they published in the March issue of the *Journal of Palliative Medicine*.

Called the Multidimensional Objective Pain Assessment Tool (MOPAT), it is the product of 4 small-scale research projects in several locations over many years. It consists of 2 standardized forms for nurses and other care providers to score values of behavioral and physical indicators—or signs—from the patient.

**At the end of their lives, an estimated 75% of patients have unrelieved pain.**

MOPAT consists of scoring patients' pain levels on 2 sets of signs from patients: behavioral and physical signs of pain. Behavioral signs include facial expressions, moaning, and muscle tension. Physical signs include heart rate, blood pressure, and sweating.

The authors cite data showing that at the end of their lives, an estimated 75% of patients have unrelieved pain.

In the public debate over whether the law should allow physicians to help terminally ill patients who choose to end their lives, prominent pain physicians such as Kathleen Foley, MD, have countered that undertreatment of pain—or the fear of undertreatment—is still the major challenge that must be addressed.

McGuire and her colleagues[1] said that their tool addresses a tremendous need in medical care because patients who cannot self-report are at risk for undertreatment of pain, partly because assessing their pain has not always been consistent between practitioners.

Tests of the MOPAT tool on noncommunicative hospice patients before and after nurses administered medication show that the patients' pain is lessened, says lead researcher McGuire, professor and director of the school's Developing Center of Excellence in Palliative Care Research and director of the Oncology Graduate Program. She says, "We have found that this tool is very sensitive. We are very happy that it is valid."

## MOPAT Can Be Useful for More Than Hospice Patients

"We are hoping that it will be used as a standardized tool to help providers to assess pain for noncommunicative patients in a variety of settings," says Karen Kaiser, PhD, RN-BC, AOCN, CHPN, adjunct professor at the University of Maryland School of Nursing and clinical practice coordinator at the University of Maryland Medical Center (UMMC).

The researchers have now expanded their study with the help of UMMC nurses who assisted in using the MOPAT to rate pain in patients with a wide variety of medical conditions and from 22 different patient units in the hospital. The hospital testing results, yet to be published, says McGuire, confirm that the tool is highly valid, adequately reliable, and clinically useful. Nurses are also testing MOPAT at the Hospice of Lancaster County, Lancaster, Pennsylvania.

McGuire has been interested in the idea of such a tool for the past 15 years, including during her work at Emory University and the University of Pennsylvania before joining the University of Maryland in 2004.

"With further study, we hope to see if the MOPAT is helpful in monitoring any shifts in pain levels and aiding nurses and other care providers in management of noncommunicative patients' pain," says Kaiser. The tool theoretically could be used as "a common language," says Kaiser, which does not currently exist. "The way we have tested this is unique, because we used completely noncommunicative patients, who are very hard to study."

A hospice pharmacist, Mary Lynn McPherson, PharmD, BCPS, CDE, says, "This is a huge advance for practitioners working with patients with advanced illness. Pain relief is a basic human right, and the validation of a tool that allows us to provide appropriate analgesics for this fragile population is a tremendous asset." McPherson is a professor at the University of Maryland School of Pharmacy.

The research team developed MOPAT on the basis of earlier work by nurses in postanesthesia units, where sedated patients could not self-report pain. They wrote that the tool "offers a unique approach to assessing palliative-care patients across populations and settings."

The World Health Organization defines *palliative care* as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual." ■

### Reference

1. McGuire DB, Reifsnyder J, Soeken K. Assessing pain in nonresponsive hospice patients: development and preliminary testing of the Multidimensional Objective Pain Assessment Tool (MOPAT). *J Palliat Med.* 2011;14(3):287-292. doi:10.1089/jpm.2010.0302.


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# Early Palliative Care Improves Quality of Life for Lung Cancer Patients

**Sonia Elabd, MA**

A study of patients with metastatic non-small-cell lung cancer who started receiving palliative care soon after diagnosis experienced better quality of life, less depressive symptoms, and longer median survival than patients who did not receive early palliative care, according to an August 2010 study published by Temel et al[1] in *The New England Journal of Medicine*. The study examined 151 patients who had been newly diagnosed (within 8 weeks) with metastatic non-small-cell lung cancer, which is the leading cause of death from cancer worldwide.

"The estimated prognosis after the diagnosis has been established is less than 1 year," wrote Jennifer Temel, MD, assistant professor of medicine at Harvard Medical School, principal author of the study, and assistant professor of hematology/oncology at Massachusetts General Hospital.

**The most significant aspect of the study is that palliative and oncology care are not mutually exclusive. Not only is it feasible to provide both at the same time, but it is beneficial to patients.**

Patients were randomly assigned to 1 of the 2 groups. Both groups received standard oncologic care. In addition to standard oncologic care, 1 group received palliative care within 3 weeks of enrollment in the study. These patients met with members of the palliative-care team, including physicians and advanced-practice nurses, at least monthly after the initial visit, and as requested, with an average of 4 visits per patient. The palliative-care team members assessed the patients' physical and psychosocial symptoms, helped with decisions about treatment, and assisted in determining goals of care. The other group of patients received standard oncologic care and met with the palliative-care team only if requested by the patient, a family member, or the oncologist.

"The most significant aspect of the study is that palliative and oncology care are not mutually exclusive. Not only is it feasible to provide both at the same time, but it is beneficial to patients," said Temel. "Early palliative care improved quality of life and mood, an important finding because patients with metastatic lung cancer experience significant physical and emotional suffering. Having an intervention which improves that distress is incredibly important and meaningful."

Researchers measured health-related quality of life using the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale and the lung cancer subscale (LCS) of the FACT-L, and assessed mood using the Hospital Anxiety and Depression Scale and the Patient Health Questionnaire–9.

**Contrary to widely held assumptions, palliative care helps patients with serious or chronic illness to fight their disease with the maximum possible strength.**

At 12 weeks, patients in the early palliative-care group had higher scores than the standard-care group for all measures: FACT-L, LCS, and Total Outcome Index, the sum of the scores on the lung cancer, physical well-being, and functional well-being subscales of FACT-L.

## Most Emotional-Health Symptoms Are Better for Palliative-Care Group, but Anxiety Higher in Palliative-Care Group

The percentage of patients in the early palliative-care group with depression was also lower than the standard-care group. However, the percentage of patients with anxiety was higher in the early palliative-care group than the standard-care group, and the proportion of patients obtaining new prescriptions for antidepressants was the same between the 2 groups.

"Contrary to widely held assumptions, palliative care helps patients with serious or chronic illness to fight their disease with the maximum possible strength, and as a result, they tend to do better: They live longer, they feel better, and the quality of their lives is better," said Diane Meier, MD, FACP, professor of geriatrics and internal medicine at Mount Sinai School of Medicine and director of the Hertzberg Palliative Care Institute at Mount Sinai School of Medicine.

"One of the unexamined beliefs among medical professionals is that palliative care is what they do when there's nothing more that they can do, when it's really about making the dying process as good as it can be," added Meier,[2] who is also director of the Center to Advance Palliative Care, and wrote an editorial that accompanied the Temel et al study.

"Palliative care is focused on quality of life, and most people with advanced illness are not dying," she said.

Temel and coauthors[1] also assessed the use of end-of-life care among both groups. Among the patients who survived more than 6 months, more patients in the standard-care group received aggressive end-of-life care measures, defined as receiving chemotherapy within 14 days before death, receiving no hospice care, or admission to hospice 3 days or less before death, compared with patients in the early palliative-care group (56% vs 33%).

An added benefit of introducing early palliative care into standard oncologic care is that by better documentation of

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end-of-life care preferences, including resuscitation directives, costly interventions may be avoided.

## Cost Savings Data

A 2008 study analyzing cost savings achieved by hospital palliative-care consultation teams by Morrison et al[3] showed that "the palliative-care patients who were discharged alive had an adjusted net savings of $1696 in direct costs per admission and $279 in direct costs per day. The palliative-care patients who died had an adjusted net savings of $4908 in direct costs per admission and $374 in direct costs per day, including significant reductions in pharmacy, laboratory, and intensive care unit costs compared with usual care patients."

## Conservative Care Not Just About Saving Money

Although cost savings may be an attractive indirect benefit, less-aggressive intervention provides the patient with the best possible care that addresses all his or her needs and concerns. Despite the less aggressive measures, patients in the early palliative-care group had a longer median survival period (11.6 vs 8.9 months). The reasons for the longer survival are not clear, and although the study did not directly investigate possible factors that contributed to this phenomenon, Temel et al offered a hypothesis.

**Despite the less aggressive measures, patients in the early palliative-care group had a longer median survival period.**

"Previous data have shown that a lower quality of life and depressed mood are associated with shorter survival among patients with metastatic non–small-cell lung cancer," wrote Temel and colleagues in the article. "We hypothesize that improvements in both of these outcomes among patients assigned to early palliative care may account for the observed survival benefit. In addition, the integration of palliative care with standard oncologic care may facilitate the optimal and appropriate administration of anticancer therapy, especially during the final months of life. With earlier referral to a hospice program, patients may receive care that results in better management of symptoms, leading to stabilization of their condition and prolonged survival. These hypotheses require further study."

Despite the growing amount of evidence showing the benefits of introducing early palliative care to patients and families, Meier noted in her editorial that despite the availability of palliative-care services in most hospitals across the country, the use of palliative-care services remains low. There are many possible reasons why this disparity exists. Meier stated that most patients have never heard of palliative care.

She also conjectured that the need for education and training among physicians who have been practicing for many years may help bridge the gap.

"Most physicians were trained at a time when palliative care did not exist and therefore have always practiced without it," Meier said. "Younger physicians who have trained and done their residencies at hospitals that had a well-integrated palliative-care program are comfortable with palliative care and make much more use of the services."

**Her message to clinicians is simple: "Consider palliative care earlier in the course of disease for patients with life-threatening, metastatic cancers."**

Despite the promising results of the study, the authors clarified its limitations as follows:

"Our study was a single-institution study with one metastatic population and with palliative-care and oncology teams who have a great deal of experience working together," Temel et al said.

Further investigations in a variety of settings with other types of cancer and chronic and advanced illnesses need to be conducted to determine the benefits that implementation of early palliative care may have on patients' quality of life, physical and psychological health, and survival.

"While this study is tantalizing and promising, we cannot generalize to say that it is a model that will work for everybody without further study," said Meier. She added that the study examined patients in an office-based setting who were well enough to travel to the office, whereas most palliative-care services are delivered in the hospital setting.

"The biggest gap we face in providing palliative care is making it available to the community in office-based settings where most of the illness occurs and where most of the need is," said Meier.

Temel's focus on palliative care started early with her interests in improving care and quality of life for patients with advanced cancer. "I have always been struck by the amount of suffering cancer patients go through, so I chose to focus my research on studying ways to minimize this suffering," she said.

Her message to clinicians is simple: "Consider palliative care earlier in the course of disease for patients with life-threatening, metastatic cancers." ■

### References:


1. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non–small-cell lung cancer. *N Engl J Med.* 2010;363:733-742.
2. Kelley AS and Meier DE. Palliative care—A shifting paradigm. *N Engl J Med.* 2010;363:781-782.
3. Morrison RS, Penrod JD, Cassel JB, et al. Cost savings associated with US hospital palliative care consultation programs. *Arch Intern Med.* 2008;168(16):1783-1790.



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# *Topics in Pain Management* CME Quiz

To earn CME credit, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **June 30, 2012.** Only two entries will be considered for credit.

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1. **LEPs can document lesions of all of the following areas *except* the**
   A. spinothalamic tract
   B. lateral aspects of the brainstem
   C. thalamocortical projections
   D. paleothalamic tract
2. **In the method of limits for QST, the intensity of a stimulus applied to the skin is increased until the subject perceives a stimulus (perception or detection threshold for innocuous stimuli) or feels it as painful (pain detection threshold) and stops the stimulus by a feedback control (eg, by pressing a stop button).**
   A. True
   B. False
3. **In the method of levels for QST, a series of predefined stimuli (in intensity and modality) are applied to the skin and, for each stimulus, the subject has to report (yes or no) whether the stimulus is perceived or not or whether it is painful or not (ie, "forced choice''). The intensity of the next stimulus in the series is systematically increased or decreased on the basis of the subject's response.**
   A. True
   B. False
4. **In patients with diabetes, HIV infection, or idiopathic disease, serial skin biopsies have shown that loss of intraepidermal nerve fibers does not correlate with the progression of neuropathy.**
   A. True
   B. False
5. **Small-fiber neuropathy is associated with all of the following conditions *except***
   A. diabetes
   B. Sjögren syndrome
   C. HIV infection
   D. yaws
6. **Proton MRS can be used for serial monitoring of biochemical changes in patients with all of the following conditions *except***
   A. tumors
   B. epilepsy
   C. metabolic disorders
   D. osteoarthritis
7. **All of the following statements regarding fMRI are true *except***
   A. The signal does not require injections of radioactive isotopes.
   B. The total scan time required can be very short (approximately 1.5 to 2.0 minutes per run).
   C. fMRI can be performed in patients who have implantable spinal cord stimulators.
   D. The in-plane resolution of the functional image is generally approximately 1.5 × 1.5 mm.
8. **Which one of the following statements regarding PET is *false*?**
   A. PET clearly demonstrates the lesion of small-fiber neuropathy.
   B. PET requires injection of radioactive isotopes.
   C. PET requires extended imaging times because multiple scans must be obtained.
   D. The expected resolution of PET images is larger than the usual fMRI pixel size.
9. **All of the following statements regarding MEG are true *except***
   A. The temporal resolution of MEG is milliseconds, which allows real-time recording of the brain activity.
   B. There is 1-to-1 correspondence with EEG recording.
   C. The spatial resolution ranges from several millimeters to a couple of centimeters.
   D. MEG is completely noninvasive and nonhazardous.
10. **Which one of the following statements regarding MEG is *false*?**
    A. MEG is used to detect and localize epileptiform-spiking activity in patients with epilepsy.
    B. MEG may be used to localize brain areas important for speech, which should be avoided by the surgeon in planning for removal of brain tumors.
    C. MEG can be performed in any outpatient facility near a major highway.
    D. No pain states are particularly well suited to detection with MEG.

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# NEWS IN BRIEF

## Little-Studied Blood Syndrome Gains Researchers' Attention

Motivated by the lack of treatment options for patients with antiphospholipid syndrome (APS), 27 rheumatology researchers convened an international committee to address the problem directly.

Their creation, APS ACTION (Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking), is bringing together some of the foremost experts on APS—a little-known blood condition that can cause pain as well as severe health consequences. The new organization's goal is to design clinical trials and registries focused on improving patient outcomes. Many of those affected are young adults.

As a result of its first-ever meeting this past November, APS ACTION determined that distinct variations of APS—which causes frequent abnormal blood clots in arteries and veins—made it a challenge to conduct patient studies on the condition.

These painful blood clots form because the immune system mistakenly produces antibodies against phospholipid-binding plasma proteins, which puts those affected at risk for stroke and pregnancy complications. APS is considered a comorbidity of lupus.

"We concluded there are few controlled clinical trials that have included a heterogeneous group of APS patients who exhibit many different forms of the disease and antiphospholipid antibody test results. Comparison between patients is very difficult when APS looks different from one patient to another," reported rheumatologist Doruk Erkan, MD, who is an associate physician-scientist at the Barbara Volcker Center for Women and Rheumatic Disease and clinical co-director of the Mary Kirkland Center for Lupus Care at Hospital for Special Surgery in New York.

Erkan is also the newly-elected executive committee chair of APS ACTION.

Since APS ACTION formed, the physician members have been vocal in their determination to advance APS research and treatment and not to be derailed by differences of opinion related to clinical practice, according to a press release put out by the organization. ■

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