Central sensitization is a process that links a variety of chronic pain disorders that are characterized by hypersensitivity to noxious stimuli and pain in response to non-noxious stimuli. Among these disorders, treatments that act centrally may have greater efficacy than treatments acting peripherally. Because many individuals with post-treatment Lyme syndrome (PTLS) have a similar symptom cluster, central sensitization may be a process mediating or exacerbating their sensory processing. This article reviews central sensitization, reports new data on sensory hyperarousal in PTLS, explores the potential role of central sensitization in symptom chronicity, and suggests new directions for neurophysiologic and treatment research.


Post-Treatment Lyme Syndrome and Central Sensitization

Shweta Batheja, M.B, B.S.
Jenifer A. Nields, M.D.
Alla Landa, Ph.D.,
Brian A. Fallon, M.D., M.P.H.

The cause of persistent symptoms after treatment for Lyme disease remains a source of controversy. These symptoms can be quite distressing and debilitating, leading to a functional impairment comparable to that seen in patients with congestive heart failure. These symptoms most commonly include pain, fatigue, depression, and cognitive deficits. The key etiologic question has been whether the cause is persistent infection or a post-infectious process. The answer to this question has considerable public health significance, as persistent infection would lead a physician to prescribe antibiotic therapy, whereas a post-infectious process would lead to treatment modalities targeted at modulating the immune response or other post-infectious processes. Unfortunately, current laboratory assays are not sufficiently sensitive in determining whether or not infection persists as the cause of persistent symptoms. Treatment trials, however, confirm that a sizeable subgroup of patients continue to experience post-treatment Lyme disease symptoms despite repeated antibiotic therapy. Lack of response to antibiotic therapy suggests that the underlying mechanism for persistent symptoms among a subgroup of patients is no longer persistent infection. A comprehensive understanding of the pathophysiology that underlies symptom persistence is clearly needed to address both infectious and non-infectious causes of post-treatment symptoms.

Recent work in the area of fibromyalgia has demonstrated that patients can have activated central neural
pain networks that respond more intensely to sensory stimuli than patients without fibromyalgia. This demonstration of abnormally sensitized brain pathways among patients with fibromyalgia provides objective evidence of a physiologic abnormality that contributes to the widespread pain experienced by these patients. Further evidence for prominent central contributions to the experience of chronic widespread pain comes from the success of therapeutic trials with agents that work on central neurotransmitters, as well as from experimental pain and genetic studies.

A model that postulates central mechanisms underlying or contributing to chronic pain in fibromyalgia may enhance our understanding of central neurologic mechanisms that contribute to chronic pain in other disorders. Indeed, this hypothesis led Yunus to state that a large group of disorders that often are comorbid with fibromyalgia (e.g., chronic fatigue syndrome [CFS], irritable bowel syndrome [IBS], somatization) might better be redefined as disorders of central sensitization. Coining the term “central sensitivity syndrome” for this cluster of disorders, he notes that they share common clinical features (e.g., pain, fatigue) and a common “pathophysiologic glue” of central sensitization. Under this conceptual frame, could it be that post-treatment Lyme symptoms among those patients no longer responding to antibiotics may reflect central sensitization? If this is the case, then one would hypothesize that treatments effective for other disorders characterized by central sensitization might also be beneficial for a subgroup of individuals with persistent symptoms after treatment for Lyme disease. This conceptual model provides valuable new avenues of clinical investigation.

In this article, we will briefly review the disorder “post-treatment Lyme syndrome (PTLS)” and the umbrella category, central sensitivity syndrome (CSS), to enable the reader to better understand what these syndromal concepts have in common and how they differ. We will review the treatment approaches to CSS as these may have applicability to patients with PTLS. We will conclude by suggesting areas for future investigation that may help to clarify the relationship between these two syndromes.

LYME DISEASE: THE EXTENT OF THE PROBLEM

Lyme disease, the most common vector-borne illness in the United States, is caused by the spirochete Borrelia burgdorferi (hereafter referred to as Bb). According to the Center for Disease Control (CDC)’s nationwide surveillance reports for the year 2010 in the U.S., there were 30,158 new cases of confirmed and probable Lyme disease. These figures are thought to be gross underestimates of the actual number of cases, because most cases of the disease are not reported to the CDC.

Although most patients with acute Lyme disease do recover completely if treated shortly after acquiring infection, others may have residual symptoms that last many months-to-years. In these cases, regardless of resolution of the objective symptoms of infection after antibiotic treatment, patients may have persistent subjective symptoms such as musculoskeletal pain, fatigue, and neurocognitive difficulties; this constellation of symptoms has been referred to as post treatment Lyme disease or chronic Lyme disease. The word “syndrome” is often preferred because it conveys that the pathophysiology of symptom persistence is unclear. For consistency within this article, the term PTLS will be used.

Estimates of the incidence of post-treatment Lyme syndrome vary. If, as has been suggested in the literature, there is at least a fivefold underreporting of cases to the CDC each year, and if 5% of newly-infected and treated patients develop symptoms that persist for more than 6 months and thus meet criteria for PTLS, then the actual incidence of new chronic cases (PTLS) is 7,500/year. If the underreporting to the CDC is as high as tenfold, and if 10% of cases go on to have PTLS, then the annual increase in new PTLS cases would be 30,000. Hence, Lyme disease and its sequelae represent serious public health issues, posing diagnostic, clinical, and treatment challenges for patients and health professionals alike.

The surveillance criteria for the confirmation of a case of Lyme disease require at least one externally visible clinical sign. These signs include a characteristic skin rash called erythema migrans (the most common presentation of early Lyme disease), seen in about 60%–70% of cases, arthritic features (e.g., polyarticular arthritis, most commonly affecting the knee), neurological manifestations (e.g., meningitis, cranial neuritis, radiculitis), and/or carditis or heart block. These objective signs of disease, however, are not always present; up to 20% of patients may have a constellation of flu-like symptoms, such as fatigue, arthralgias, and myalgias, but may not be recognized as having Lyme disease because the surveillance “objective” signs are not present.
Patients with the early skin manifestations of Lyme disease respond best to conventional oral antibiotic therapy, whereas patients with the later manifestations of a more disseminated infection have a more variable response to antibiotic therapy.

POST-TREATMENT LYME SYNDROME (PTLS)

According to a proposal from the Infectious Diseases Society of America (IDSA) in 2006, PTLS is defined by a documented episode of early or late Lyme disease that meets the CDC case definition and which, despite appropriate antibiotic treatment, leads within 6 months to a constellation of subjective symptoms resulting in functional impairment, consisting of at least one of the following: fatigue, widespread musculoskeletal pain, or cognitive problems. The course of PTLS may be continuous or relapsing, but it must span a period of at least 6 months. Different research groups use different operational criteria for PTLS. These vary depending upon the extent to which documentation of the initial manifestations of Lyme disease is required, whether one excludes or includes individuals with objective manifestations, the symptom cluster considered acceptable for subjective symptoms (e.g., Are individuals with localized, non-widespread pain accepted?), and the comprehensiveness of the work-up required to identify objective abnormalities (e.g., Are skin biopsies required to test for small-fiber neuropathy in those with subjective paresthesias, or must all patients have comprehensive neurocognitive testing, and what cutoff levels are used on which tests to determine objective abnormalities?) The pathophysiology of post-treatment Lyme syndrome remains unclear; however, several models have been proposed.

PERSISTENT INFECTION

PTLS may be due to an ongoing immune response triggered by fully viable persisting Bb, attenuated Bb, or remnants of Bb. There are reports of persistent Bb infection in humans after antibiotic therapy, but, in general, confirmation of persistent infection in humans has been difficult. The persistent-infection hypothesis has been studied best in animal models—mouse, pony, dog, and monkey. In these models, persistence of Bb has been demonstrated after antibiotic treatment by immunofluorescence, by real-time polymerase chain reaction (PCR), and/or by culture. A breakthrough in the ability to locate persistent organisms occurred through application of the xenodiagnostic method. In this method, uninfected ticks feed on previously infected and treated mice, and then the ticks are examined by PCR or culture. Remarkably, in repeated animal experiments, it has been shown that these previously uninfected ticks become infected, as demonstrated either by culture, by PCR, or by the ability to transmit the Bb organism or DNA to another uninfected host. A conclusion based on negative blood culture or negative host biopsy that the previously antibiotically-treated mouse no longer carried infection would have been understandable, but incorrect; this translational research then raises the reasonable hypothesis that some humans with PTLS may have persistent infection that cannot be detected by typical methods. When persistent Bb is found in the animal model, it is most often in a somewhat diminished functional status. A more recent study in the mouse model documented persistence of remnant proteins of the bacteria that are proinflammatory. What is clear from these studies is that the basic biology of Bb is one of persistence or antimicrobial tolerance; the implication, then, is that the immune system may remain activated because of persistent Bb spirochetes or Bb remnants.

THE POST-INFECTION MODEL

Chronic symptoms may also be due to post-infectious processes. A chronic illness syndrome that develops after microbial infections is well documented for viruses and characterized by a very similar symptom cluster as seen in PTLS: persistent fatigue, pain, and cognitive problems. It would be reasonable to speculate that Borrelia infection can lead to a similar post-infectious, chronic-fatigue-like symptom profile. Cumulative evidence from many studies supports the conclusion that patients with chronic fatigue syndrome have a dysregulated immune response. That an aberrantly-activated immune response may also be involved in post-treatment Lyme symptoms has been well documented for chronic Lyme arthritis. Further evidence of persistent immune activation among patients with post-treatment Lyme symptoms has been demonstrated among patients with persistent encephalopathy after Lyme treatment; these patients have been shown to have elevated levels of complement cascade proteins in the...
cerebrospinal fluid. Among a more heterogeneous group of patients with PTLS, elevated levels of peripheral antineuronal antibodies have been documented. In-vitro data indicate that molecular mimicry may be one of the mechanisms perpetuating post-treatment syndromes in Lyme disease; this could be maintained by persistent Bb or remnants of infection or it may be a Bb-triggered autoimmune process.

Symptoms may also persist because of disorders triggered by Borrelia infection. For example, the initial infection and related immune response may result in persistently activated or abnormally enhanced neural circuits that mediate pain or lead to neurotransmitter imbalances that result in depression or central sensitization. It also needs to be emphasized that, in some cases, persistent symptoms will have nothing to do with Lyme disease, but rather relate to misdiagnosis; some of these patients may have an unrecognized tick-borne confection or an entirely unrelated disease, with symptoms that have been mistakenly attributed to Lyme disease.

The constellation of symptoms that comprise PTLS is likely determined by an array of factors, such as the pathogenicity of the invading Bb strain, the inherited genetic and developmentally modified epigenetic profile of the host, and the environmental exposures within the host currently or in the past that may modify that host’s response to infection (e.g., heavy metals, diet, previous or concurrent infections, or physical or psychological trauma or stress).

CENTRAL SENSITIVITY SYNDROME (CSS)

As noted above, many chronic pain states included under the category of central sensitivity syndrome (CSS) share the common features of augmented CNS pain and sensory-processing systems. A brief review of what is known about the umbrella category of CSS can be useful, as it provides both a set of pathophysiological mechanisms and an assortment of treatment approaches that may be useful for patients with PTLS.

According to Yunus et al., disorders that fall within the CSS category share common clinical features, most notably, pain, and display central sensitization on at least one sensory modality. CSS is thought to involve hyper-activation of central neurons, leading to various synaptic and neurotransmitter/neuromodulator changes. The primary manifestations of central sensitization include hyperalgesia (hypersensitivity to noxious stimuli) and allodynia (pain in response to normally non-noxious stimuli). Most central sensitization studies have been conducted using pressure or heat as stimuli, but more recent studies indicate that central sensitization can also be seen using the stimuli of light or sound. An expanding number of disorders have recently been included under the umbrella category of CSS, including fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity syndrome, posttraumatic stress disorder (PTSD), irritable bowel syndrome, temporomandibular disorder, tension-type headache, migraine, vulvodynia, and restless leg syndrome. The spectrum of psychiatric somatoform states have also been included in the CSS grouping, conditions such as somatization disorder, medically unexplained symptoms, and functional pain disorders; certainly many individuals meeting criteria for the new diagnostic category of “Somatic Symptom Disorder” proposed for DSM-5 would also likely fit within the CSS domain. The symptoms commonly shared by these disorders include pain, fatigue, poor sleep, sensory hyperarousal, and a high rate of comorbid mood disorders.

Patients with PTLS have many of the same symptoms experienced by other patients thought to have central sensitivity syndrome. As shown in Table 1, of 120 patients with a history of treatment for Lyme disease with persistent cognitive complaints and a recently-positive IgG Western blot for Lyme disease, many reported a history of pain, sensory hyperarousal, and mood symptoms that would overlap with CSS. These patients, all of whom were being screened for participation in a study of post-treatment Lyme encephalopathy, reported a history of myalgias (95%), headaches (87%), cognitive problems (98%), hyperarousal to light and sound (76%), and mood problems (91%). This
demonstrates the significant symptom overlap between PTLS and CSS. Insomnia and fatigue are also prominent persistent symptoms among patients with PTLS.34,35 The fact that so many PTLS patients report persistent pain, including pain to ordinarily non-noxious stimuli (such as light and sound), indicates that many would meet the Yunus criteria for CSS.

THE PRIMARY SYMPTOMS OF CENTRAL SENSITIZATION

Pain
Research indicates that there are three kinds of pain. First, peripheral, or nociceptive, pain is that which results from inflammation or tissue damage in the periphery. The second type, neuropathic pain, results from dysfunction or injury of peripheral nerves (e.g., diabetic neuropathic pain). The third type, “central,” or “non-nociceptive” pain, is characterized by atypical central nervous system (CNS) sensory processing of pain. This leads to diffuse hyperalgesia and allodynia. Behavioral and psychological factors play an important role in the modulation of central pain. Fibromyalgia is now considered a classic example of a central, or non-nociceptive, pain disorder.5

In the case of Lyme disease, it is likely that all three types of pain are involved to a different extent in any particular patient. For example, a patient may have inflammatory arthritis (peripheral pain), immune-mediated polyneuropathy (neuropathic pain), or diffuse widespread pain with or without prominent inflammation or neuropathy (central pain). In this latter case, in particular, central sensitization or the augmentation of CNS pain-processing may account for the persistent experience of widespread pain.

Sensory Hyperarousal
A defining feature of central sensitization is hyperarousal, as shown in Table 1, in at least one sensory modality. In patients with PTLS, sensory hyperarousal was reported by a majority of patients after acquiring Lyme disease, most often affecting hearing and/or vision. In an earlier study of 85 seropositive patients reporting symptoms consistent with PTLS,36 70% of respondents with Lyme disease reported a hypersensitivity to light. The individuals’ life may be quite altered by this hypersensitivity: wearing sunglasses indoors and avoidance of being outside during daylight, which, in turn, limits the ability to sustain a normal work and social life. The photophobia may be peripheral (e.g., uveitis) or centrally mediated, due to disrupted central sensory processing mechanisms that may arise from hyperexcitable second-order neurons in the trigeminocervical complex that could increase sensitivity to light.37

The auditory hyperacusis seen in Lyme disease patients can be intense and incapacitating. In that same survey of 85 patients with chronic symptoms after Lyme disease, 48% of patients experience heightened sensitivity to sound. Hypersensitivity to sound may be limited to louder sounds,36 but, in some individuals, even the volume fluctuations in a normal conversation can be noxious. These patients might be seen wearing earplugs or sound-protectors when in situations normally tolerable to others. A small case series suggested that the anticonvulsant carbamazepine may have positive effects in the treatment of auditory hyperacusis seen in Lyme patients.38 Some Lyme disease patients may also experience hypersensitivity in other sensory modalities, such as olfactory, tactile, gustatory, and temperature.36

Fatigue
Fatigue, like pain, can also have either central or peripheral origin and is another prominent symptom among patients with central sensitization syndromes. Central fatigue often has the significant correlate of cognitive impairment. In a population-based sampling of patients with chronic fatigue syndrome, Capuron et al. showed an association between mental fatigue and cognitive dysfunction; the primary cognitive impairments were in the domains of working memory and sustained attention/vigilance.39 It has been suggested that these cognitive difficulties can be attributed in part to central fatigue and hypersensitivity of the CNS.5,40 In studies of PTLS, problems with memory, working memory, processing speed, and verbal fluency are common.41 It should be remembered, however, that central fatigue and cognitive impairment often have distinct CNS mechanisms; this has been well demonstrated by studies showing that one treatment may help fatigue but not help to improve cognition.35 Finally, fatigue may be mediated through many mechanisms other than peripheral or central neurologic ones, such as, for example, impaired functioning of the hypothalmo–pituitary axis42,43 or through abnormal activation of the immune system, with the production of fatigue-inducing proinflammatory cytokines.
MECHANISMS OF CENTRAL SENSITIZATION

Genetic Susceptibility
One hypothesis that serves to link the disorders of central sensitization is that a group of individuals are genetically predisposed to have increased sensitivity for pain signals and that environmental factors (e.g., infection or trauma) in these genetically predisposed individuals trigger neuroplastic changes in the CNS that augment pain transmission. A rough estimation based on twin studies of fibromyalgia is that the chances of developing a CSS syndrome depend equally on genetic predisposition and environmental influences.32

Family studies of fibromyalgia demonstrate a strong familial component, with some studies even suggesting an autosomal dominant mode of inheritance.44,45 Compared with a sample from the general population, one study showed that first-degree relatives of patients with fibromyalgia have an eightfold greater risk of developing fibromyalgia.46 Family members of fibromyalgia patients also have a lower pain threshold on experimental pain testing than family members of general population controls.46 Further evidence of a genetic component connecting the disorders within the CSS cluster is that relatives of individuals with fibromyalgia have a greater risk of having other chronic pain conditions, such as IBS, regional pain syndromes, temporomandibular joint disorder (TMJD), and headache.47,48 Many candidate genes have been investigated for chronic pain conditions. In a review, genetic markers such as catechol-O-methyltransferase (COMT), val158Met polymorphism and human leukocyte antigens (HLA) class 2 were reported to be associated in some studies with chronic pain conditions like TMJD and CFS.47,49–51 COMT, which is partially regulated by estrogen, is of particular interest, as it has a differential effect in male and female patients52 and may help to explain long-standing differences in pain sensitivity between women and men.

CNS Neurotransmitter Imbalance
Central sensitization may also arise as a result of an increase in neurotransmitters that facilitate pain (Substance P and nerve growth factor [NGF]) or a decrease in neurotransmitters that inhibit the pain pathways (serotonin, norepinephrine [NE] and dopamine).53 The appropriate balance of these neurotransmitters is essential because they serve as a “volume control” for pain and sensory processing. For example, serotonin is known to have an important role in pain-modulation and Stage 4 sleep,54,55 as well as in the modulation of fatigue, depression, and anxiety.56 Medications that block the neurotransmitters that facilitate pain or augment the functioning of the neurotransmitters that inhibit pain would be expected to be therapeutic for patients with central sensitivity syndromes. Pharmacologic modulation of some of these neurotransmitters has been shown to be effective in fibromyalgia and in IBS, as is indicated below.

Neural Networks
Once developed, central sensitization to pain and sensory stimuli is hypothesized as becoming self-sustained because of neuroplastic changes in the CNS; that is, repetitive nociceptive input from the periphery results in structural and functional changes in the brain, mainly through cortical reorganization and by inducing changes in neuronal pathways within somatosensory and motor systems.2,28,57 Experimental pain studies of fibromyalgia and IBS, using fMRI, support the existence of central pain augmentation in these disorders.1,58 Common across many of these fMRI studies is the finding of heightened activation of the insula; this is of considerable interest because the insula has a key role in sensory integration, including the processing of input from within the body (viscera), as well as from peripheral nerve stimulation. Within the insula, there appears to be a “posterior-to-anterior” pattern of increasing levels of integration of sensory input.59 For example, activation of the posterior insula occurs in response to a pain stimulus,60,61 whereas the anterior insula becomes activated when the subject is attending to the stimulus60 as well as in anticipation of a painful stimulus, either in oneself or in a loved one.61 The anterior insula, in particular, along with the dorsal anterior cingulate cortex, have been proposed as crucial “hubs” of a multimodal network involved in the detection of salient events for the body, integrating the most relevant or challenging internal and external sensory stimuli.

ENVIRONMENTAL FACTORS THAT TRIGGER CENTRAL SENSITIZATION
A variety of factors can trigger or perpetuate central sensitization (Table 2). Notably, in relation to Lyme disease, infections in general are known to activate
central sensitization in some patients, possibly through release of inflammatory cytokines. Chronic fatigue syndrome, for example, can be triggered by infections such as Q fever, rickettsia, protozoal infection, and Epstein-Barr virus (EBV). In a large, prospective, cohort study of patients infected with one of the three different viruses, namely, EBV, Ross river virus, and C. burnetti (leads to Q fever), roughly 9% of infected patients continued to present with a post-infective fatigue syndrome (chronic fatigue-like syndrome) 12 months after infection. Not surprisingly, CFS has also been seen in a case report as a sequela of infection with the H1N1 influenza virus. Urinary tract infections in a minority of patients can lead to interstitial cystitis and painful-bladder syndrome. Similarly, in 5%-32% of patients, enteric infections may predispose to later IBS.

**PATHOPHYSIOLOGY**

Substantial research into the pathophysiology of central sensitization has been conducted over the last decade, expanding our understanding of peripheral and central pain mechanisms. Subsequent to infection, inflammation, or peripheral injury, there is a release of peptides or lipid mediators (e.g., bradykinin, serotonin, prostaglandins, and substance P), which leads to increased nociceptive signaling. A-delta fibers activated by these substances carry sharp and localized pain, whereas activated C fibers involved in chronic pain carry dull and diffuse pain. Nociceptive input then travels to a range of neurons in the spinal cord. Nociceptive as well as non-nociceptive fibers are carried by second-order neurons; hence, activation of nociceptive fibers may also activate non-nociceptive fibers. Nerve growth factor, substance P, vasointestinal peptide (VIP), glutamate, aspartate, and brain-derived neurotrophic factor (BDNF) are expressed at the nerve terminals of activated C fibers, thereby leading to excitement of postsynaptic receptors. This leads to calcium influx, membrane changes, protein kinase activation, and c-fos expression. Hypersensitivity to a varied range of peripheral stimuli is thought to be mediated by the physiological changes that lead to escalating hyperexcitability of the second-order neurons.

**Temporal Summation**

One mechanism involved in abnormal sensory processing among patients with CSS is temporal summation, which can be seen in second-order neurons. After repetitive stimulation of peripheral C fibers of adequate intensity and frequency, there is escalation in electrical discharges, leading to progressive increase in pain and prolongation of its decay. This enhanced temporal summation of pain implicates central sensitization and has been shown to occur to a greater extent among patients with fibromyalgia than among healthy study participants. Dull and burning pain has been attributed to temporal summation. N-Methyl D Aspartate (NMDA) receptors, widely distributed in peripheral and CNS tissues, are thought to play a crucial role in chronic pain; in support of this hypothesis, NMDA receptor-antagonists (e.g., ketamine) have been shown to reduce clinical pain and temporal summation of pain in fibromyalgia patients.

**MANAGEMENT OF CENTRAL SENSITIZATION SYNDROMES**

Because patients with PTLS may benefit from the management approaches used for central sensitivity syndrome, we will review briefly what is known about the treatment of CSS.

**Pharmacologic Therapies**

**Antidepressants** Various antidepressant medications are used in chronic pain management, many of which address neurotransmitters that inhibit the central pain pathways as well as improve mood. Tricyclic antidepressants, particularly amitriptyline, are widely prescribed for patients with central and peripheral pain syndromes. The selective serotonin reuptake inhibitors (SSRIs) have a better side-effect profile but only modest efficacy. Some of the newer antidepressants (e.g., duloxetine, milnacipran), which have a dual action as

**TABLE 2. Factors That Trigger or Predispose to Central Sensitization**

<table>
<thead>
<tr>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic nervous system overactivity or decreased tone of myelinated vagal pathways</td>
</tr>
<tr>
<td>Endocrine dysfunction (HPA axis)</td>
</tr>
<tr>
<td>Activated peripheral nociceptors (e.g., rheumatological diseases)</td>
</tr>
<tr>
<td>Environmental stimuli (e.g., weather, noise)</td>
</tr>
<tr>
<td>Genetic predisposition and epigenetic changes</td>
</tr>
<tr>
<td>Traumatic injury</td>
</tr>
<tr>
<td>Psychological stress</td>
</tr>
</tbody>
</table>

**J Neuropsychiatry Clin Neurosci 25:3, Summer 2013**

http://neuro.psychiatryonline.org
reuptake inhibitors of both serotonin and norepinephrine (SNRIs), have proven efficacy in reducing pain in fibromyalgia, chronic pain syndromes, and/or neuropathic pain.\textsuperscript{80} Certain antidepressant drugs therefore can achieve significant pain relief and reduce disability in patients with CSS; such drugs may be effective as a treatment option in the post-infectious subgroup of patients with PTLS.

**Anti-Epileptic Agents**  Antiepileptic drugs like pregabalin or gabapentin are also being used for the treatment of the fibromyalgia symptoms of chronic widespread pain, fatigue, and sleep disturbance, making them worth consideration in patients with PTLS. Pregabalin is a GABA analog with rapid distribution into the CNS, and it is approved for the treatment of chronic pain.\textsuperscript{81} A recent trial reported that using centrally-acting alpha2 adrenergic agonists like tizanidine in patients with fibromyalgia could lead to significant improvements in parameters like sleep and pain, which could also be helpful in PTLS patients.\textsuperscript{82}

**NMDA Antagonists**  A recent study by Wood et al.\textsuperscript{83} showed that after giving a low dose of ketamine (a noncompetitive NMDA antagonist) to patients with fibromyalgia, a large subset of patients reported significant improvement in their symptoms of pain and fatigue. NMDA antagonists such as ketamine and dextromethorphan may be useful as a treatment option for treating the chronic pain and fatigue seen in PTLS and other disorders in the CSS spectrum.\textsuperscript{2}

**Non-Pharmacologic Therapies**  The treatment of chronic pain syndromes requires a multidisciplinary approach, as has been advocated for patients with fibromyalgia. In addition to pharmacologic strategies, this would include psychotherapy, physical therapy, exercise, and complementary and alternative medicine. These have been well reviewed elsewhere.\textsuperscript{85–88} More recently, brain or nerve stimulation approaches have been reported as helpful.

**Transcranial Magnetic Stimulation**  In a recent review of nine well-designed studies, Marlow et al.\textsuperscript{89} assessed the efficacy of applying repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) for patients with fibromyalgia syndrome (FMS). The stimulation areas in the studies involved either the primary motor cortex (MI) or the dorsolateral prefrontal cortex (DLPFC). The authors concluded that most (80\%) of the rTMS studies measuring pain reported significant decreases, whereas all of the tDCS studies (100\%) with pain measures reported significant decreases. The most sustained improvement in pain was associated with excitatory MI rTMS/tDCS. The treatments appeared effective and well-tolerated. This represents a treatment approach that should be studied among patients with persistent widespread pain after Lyme disease treatment, especially among those patients who may have difficulty tolerating pharmacologic regimens.

**Vagal Nerve Stimulation**  In a trial by Lange et al.\textsuperscript{90} involving 14 study participants, preliminary research results suggest that daily intermittent vagus nerve stimulation may be a helpful adjunct for treating fibromyalgia patients, specifically, those who are resistant to conventional drug treatment. The report also suggests that vagal nerve stimulation may diminish the abnormal sensory pathways and pathophysiological mechanisms leading to central sensitization. However, these are preliminary results and require a controlled research study for validation.

**CONCLUSIONS**  The relationship between CSS and the symptoms of PTLS is certainly of interest, but research has not yet been conducted to determine whether patients with PTLS have central sensitization. At this point, the relationship is a hypothetical one that requires further study. Given the shared clinical features between PTLS and other syndromes under the CSS umbrella and the evidence that a sizeable subgroup of patients with PTLS do not benefit from repeated antibiotic therapy, it would be extremely valuable to conduct studies exploring whether patients with PTLS have heightened sensitivity to noxious and non-noxious stimuli and neural activation patterns similar to that found among patients with other CSS disorders. If this can be confirmed, then it is likely that patients with PTLS would benefit from the array of treatment strategies that have been reported to be helpful for patients with CSS. It is reasonable to speculate that Borrelia infection activates local nociceptors that initiate or sustain central sensitization, particularly in genetically or environmentally predisposed individuals. Conceptualizing that one
of the pathways to PTLS may involve the central nervous system is a reasonable research hypothesis and one that could help chart the way toward more effective therapies.

This work was supported in part by the Lyme & Tick-borne Diseases Research Center at Columbia University Medical Center, established by the Lyme Research Alliance, Inc. and the Lyme Disease Association, Inc.

References

28. Wallace DJ, Clauw DJ: Fibromyalgia and Other Central Pain Syndromes. Baltimore, MD, Lippincott Williams & Wilkins, 2005
42. Brönnegård M, Werner S, Gustafsson JA: Primary cortical resistance associated with a thermolabile glucocorticoid receptor in a patient with fatigue as the only symptom. J Clin Invest 1986; 78:1270–1278
52. Russell IJ: Neurotransmitters, Cytokines, Hormones, and the Immune System in Chronic Non-Neuropathic Pain, Fibromyalgia, and Other Central Pain Syndromes. Baltimore, MD, Lippincott Williams & Wilkins, 2005
POST-TREATMENT LYME SYNDROME

89. Marlow NM, Bonilha HS, Short EB: Efficacy of transcranial direct-current stimulation and repetitive transcranial magnetic stimulation for treating fibromyalgia syndrome: a systematic review. Pain Pract 2012; (e-pub ahead of print)