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ORIGINAL RESEARCH

# Individuals With Prior Chronic Pain and Long-Term Opioid Treatment May Experience Persistence of That Pain Even After Subsequent Complete Cervical Spinal Cord Injury: Suggestions From a Prospective Case-Controlled Study



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**KEYWORDS**
Central pain;
Chronic pain;
Low back pain;
Analgesics, Opioid;
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Rehabilitation;
Tetraplegia;

**Abstract** *Objective:* To determine whether chronic pain persists after complete spinal cord injury (SCI).
*Design:* Prospective observational study regarding the outcome of pre-existent chronic pain of inpatients admitted with new clinically diagnosed complete cervical SCI. For patients who acknowledged chronic pain of ≥3 years duration before the SCI, further questions explored whether they still experienced that pain, whether they were experiencing current posttraumatic pain, and whether they had any past exposure to opioids. The included patients were identified during the initial consultation in the trauma center for treatment of the SCI.
*Setting:* Level I trauma center.

*List of abbreviations:* CHEP, contact heat-evoked potential; fMRI, functional magnetic resonance imaging; IRB, institutional review board; IASP, International Association for the Study of Pain; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; ISCoS, International Spinal Cord Society; MRI, magnetic resonance imaging; SCI, spinal cord injury; SSR, sympathetic skin response; SST, spinothalamic tract; WHO, World Health Organization.

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Spinal cord injuries

*Participants:* From a total of 49 participants with acute cervical SCI with clinically diagnosed complete motor and sensory tetraplegia admitted between 2018 and 2020, 7 were selected on the basis of a history of chronic pain.
*Intervention:* Collected complete history and performed physical examination with serial follow-ups during the acute hospital stay until death or discharge.
*Main Outcome Measures:* The primary outcome was a finding of chronic pain experienced before new clinical diagnosis of complete SCI, compared with whether or not that pain continued after the SCI injury. The secondary outcome was the relation of persistent pain with opioid use; it was formulated after data collection.
*Results:* Among 49 patients with clinically diagnosed complete cervical SCIs, 7 had experienced prior chronic pain. Four participants experienced a continuation of the prior pain after their complete tetraplegia (4/7), whereas 3 participants did not (3/7). All the participants with continued pain had been previously treated with opioids, whereas those whose pain ceased had not received chronic opioid therapy.
*Conclusions:* There may be a unique form of chronic pain that is based in the brain, irrespective of peripheral pain or spinal mechanisms. Otherwise healthy people with longstanding antecedent chronic pain whose pain persists after acute clinically complete SCI with tetraplegia may provide a new model for evaluation of brain-based pain. Opioids may be requisite for this type of pain.


The minds of humankind have long been captured by the nature of pain, and the nervous systems of even primitive organisms exhibit exquisite sensitivity to pain. Human chronic back pain provides a therapeutic challenge because of its relative resistance to treatment and the emotional toll on its sufferers.[1] Although chronic pain comprises multiple components, it has been proven to be difficult to definitively separate those in the peripheral nervous system (primary stimulation that incites and perpetuates pain) from those in the brain (reinforces and perpetuates pain with components of affect). The brain processes peripheral nociception (pain) at multiple levels, adding emotion and understanding to the pain experience. The perpetuation of chronic pain combines peripheral nociception with central sensitization, which describes changes in the sensitivity of pain perception in the spinal cord and brain.[2,3] Central sensitization is observed in subacute low back pain, with reorganization of hippocampal connectivity visible on functional magnetic resonance imaging (fMRI) within the first year.[4] Persistent pain results in altered functional connectivity of descending pain inhibitory pathways in the periaqueductal gray region of the brain.[5]

This combination of source pain and central sensitization in the brain, spinal cord, and dorsal root ganglia complicates the treatment of chronic low back pain whose perception (presumably because of peripheral nociception) cannot always be eliminated even with successful spinal injections.[6] Although neurostimulation of spinal cord pain pathways has had some success, treatment failure remains high.[7] In some cases, pain persists despite complete blockage of nociception transmission channels,[8,9] leading to speculation that central genesis of peripheral pain may extend beyond central sensitization. Extensive research to identify and analyze these central pain pathways used fMRI to determine how they are affected by various stimuli in acute and chronic pain and which properties predict the transition from acute to chronic pain.[10-12] Pain treatments that focus on these central pathways include centrally acting medications, transcranial magnetic stimulation, and deep brain stimulation. Clear identification of central versus peripheral elements in pain genesis would help clarify the utility of various modes of treatment for chronic low back pain.[13]

To our knowledge, no prior study has prospectively examined patients with prior chronic pain who subsequently suffer from a clinically diagnosed acute complete spinal cord injury (SCI) to determine how often the pre-existent pain persists, how it changes, and whether opioids have any effect on this continued pain.

## Methods

### Study design

Ours is a prospective observational study regarding the outcome of pre-existent chronic pain in inpatients with new clinically diagnosed complete cervical SCI who were admitted to a level 1 trauma center in the mid-South during a 3-year period (2018-2020). Patients (or their family members) who acknowledged prior chronic pain (leg or low back) below the level of their injury of a duration that was >3 years were asked further questions in the study instrument that explored whether they still experienced the prior pain, whether they were currently experiencing posttraumatic pain, and whether they had any past use of opioid treatment. The requirement for obtaining informed consent was waived by the institutional review board (IRB) because the research involved only information that was collected as part of clinical care and was later deidentified. Neither patients nor the public were involved in the design, conduct, reporting, or dissemination plans of our research.

### Participants

Potential participants for this prospective study were identified during initial consultation with a physician (physiatrist) on referral from surgeons in the trauma service. The

inclusion and exclusion criteria used to recruit potential cases are summarized in the Strengthening the Reporting of Observational Studies in Epidemiology flowchart in figure 1. The inclusion criteria were acute cervical SCI, as defined by the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI),[14] that resulted in complete motor and sensory tetraplegia in patients who had a history of chronic pain before the SCI. Patients were excluded if their SCI was clinically incomplete or if they had no history of chronic pain. The patient's history of prior pain was initially reported to the consulting physiatrist on the first visit by either the family or the patient. Although some of the patients were unable to speak during the initial visit because of their reliance on mechanical ventilation, all of them later confirmed their history of antecedent chronic pain that preceded their current injury. During the initial hospital stay,

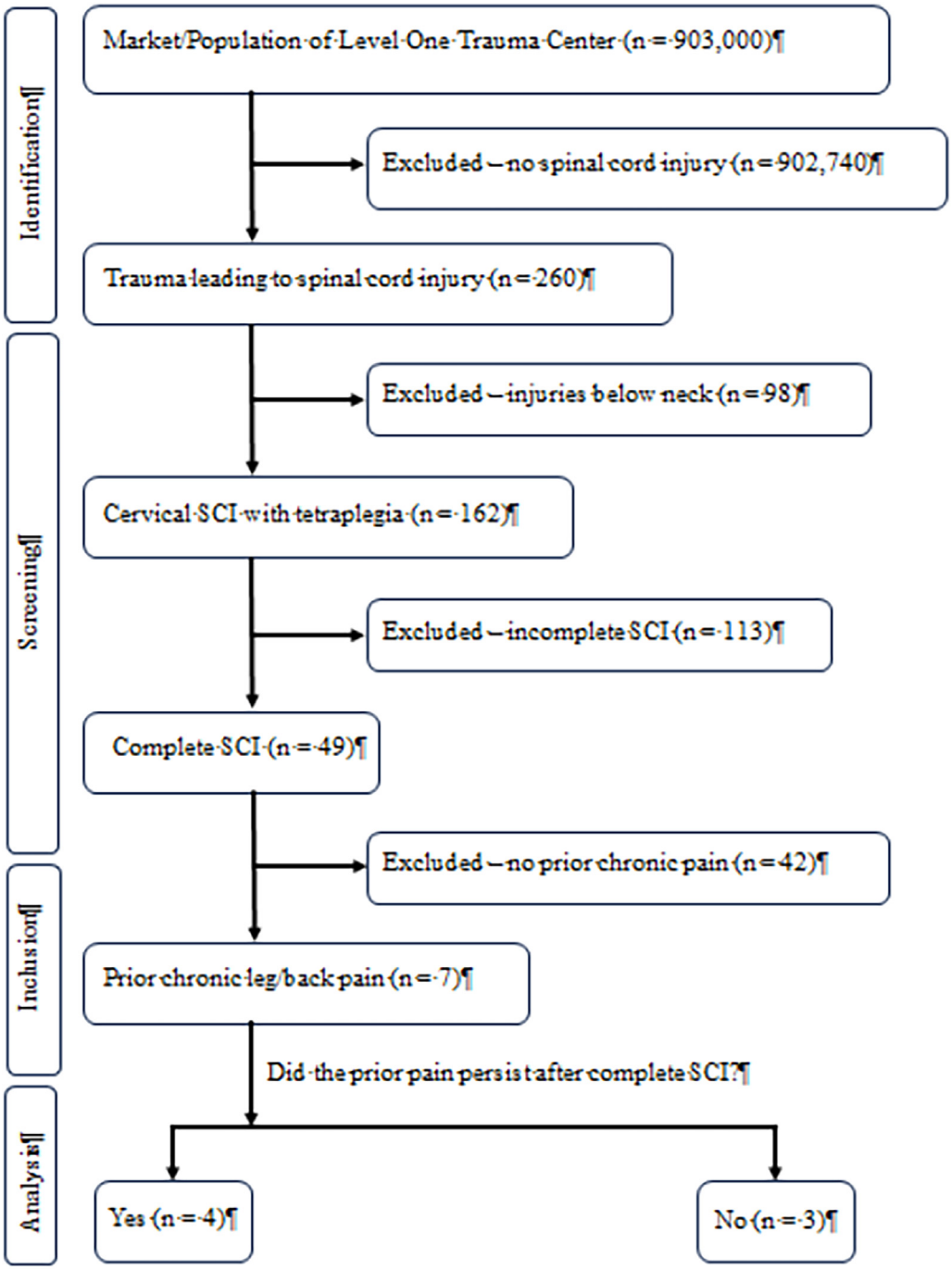


**Fig 1** Strengthening the Reporting of Observational Studies in Epidemiology flowchart for prior chronic pain persisting after complete spinal cord injury study. The Strengthening the Reporting of Observational Studies in Epidemiology diagram outlines the process of participant selection. The market/population of the trauma center includes 21 surrounding counties but excludes nearby states. The estimated prevalence of chronic pain in 2020 was 20%, n=180,000; of those, 55% had low back pain or leg pain, n=100,000.

no other professionals asked the patients about pre-existing pain. The patients were asked by the consulting physiatrist to rate their pre-existing chronic pain separately from their acute pain resulting from the new trauma using the standard 10-point rating scale.

During the study period, the hospital treated 260 patients with SCIs, 162 of whom had experienced cervical injuries, including 113 incomplete injuries and 49 complete injuries. The level and severity of the SCI were determined using the ISNCSCI criteria,[14] as administered by the consulting physiatrist at the time of their initial consultation. There were no zones of partial preservation present, ie, no patients had an area of spared touch sensation >1 level below their last normal level of protopathic (sharp-dull) sensory loss to safety pin during the physiatrist's examination. Patients' injuries were only considered complete if they had no sensation of any kind beyond the zone of partial preservation, with no sensation detected on deep pressure, light touch, or positioning. Of the 7 patients who met the inclusion criteria, 4 experienced continued pain after their complete tetraplegia, including 3 with low back pain and 1 with chronic foot pain. The enrolled patients were compared retrospectively with the entire cohort to identify the larger study population, and billing records and data from the National Trauma Data Bank were reviewed to ensure that no patients who met the inclusion criteria were inadvertently overlooked.

The patient demographics are shown in table 1. The histories of the included patients are detailed below and in tables 2-4, whereas the case descriptions are presented in the supplemental materials (available online only at http://www.archives-pmr.org/). All procedures followed an approved protocol in accordance with the ethical standards of our institution's IRB, which waived the requirement of obtaining informed consent because the research involved only information that was collected as part of clinical care and was later deidentified.

## Outcomes

The primary outcome was chronic pain before complete SCI compared with its continuation after the SCI, whereas the secondary outcome was opioid use.

## Statistical methods

Descriptive statistics and frequency were used to describe the sample characteristics.

# Results

All 7 patients who met the inclusion criteria had experienced years of persistent (>3y), severe chronic pain before suffering a severe SCI that left them with complete tetraplegia, including total loss of motor function and sensation below the level of their injuries (tables 1-4). No patients were able to feel touch of any kind (light or deep) >1 level below their level of sharp (protopathic) sensory sparing. The nature of the traumatic injuries that led to the patients' tetraplegia, the level of each fracture, and any surgical interventions are detailed in table 2, whereas the neurologic classification of each SCI, pretrauma chronic pain, and opioid use are detailed in tables 3 and 4. Within a few days of their SCI, 4 patients endorsed that they continued to suffer from the same chronic pain that had existed before their SCI, whereas 3 did not (table 4). Remarkably, all 4 patients had been previously treated with long-term opioid therapy, whereas those who denied having continued chronic pain were not previously treated with long-term opioid therapy. The patients who described continuation of their chronic pain stated that the low back or foot pain they felt after their paralysis was exactly the same as the pain they felt before their injury, in quality, location, and severity as well as how much it bothered them, and that this pain responded to opioids as it did before the tetraplegia.

The patients without continued pre-existing pain also differed from the other 5 in that they had longer-lasting chronic pain (median: 12y; range: 10-50y vs median: 4y; range: 3-20y), as shown in table 4. They also had stable relations, had finished high school, and were employed before their SCI (table 1). Interestingly, the latter factors may be indicative of a more stable life that would not reduce chronic pain but might mitigate it by helping people to better cope with chronic pain and to refuse opioid use.

None of the patients had reasons to magnify their symptoms. When initially examined by the physiatrist, the

**Table 1** Relevant patient medical and social history

| Patient No. | Age Range (y) | Marital Status | Prior Trauma | Psychiatric History | Illicit Drugs | Alcohol |
|---|---|---|---|---|---|---|
| 1 | 50-59 | Divorced | Yes, multiple* | Severe depression* | IVDA | Yes |
| 2 | 40-49 | Divorced | Yes, fall from barn | Anxiety, depression | IVDA | Yes |
| 3 | 50-59 | Divorced | Yes, multiple | Anxiety disorder | IVDA | Yes |
| 4 | 60-69 | Single | No, but cancer | Anxiety disorder | THC | Yes |
| 5 | 50-59 | Married | Yes, hit in the head | Claustrophobia | No | Yes |
| 6 | 60-69 | Married | No† | Post-stroke depression | No | No |
| 7 | 20-29 | Married | No, but scoliosis | Bipolar, child of alcoholics | No | Yes |

Abbreviations: IVDA, Intravenous drug abuse; THC, tetrahydrocannabinol (marijuana).

* Before their admission for the current SCI, Patient 1 had been seen in the trauma center for 2 car wrecks and 2 falls from roofs with C2 injury. They had been noncompliant with their halo treatment, leading to a nonunion of dens (odontoid bone) fracture. They had other healed cervical spine fractures at C3 and C5-C7 and several thoracic fractures. They also reported prior suicide attempts.

† Patient 6 had experienced a stroke with right hemiparesis and no aphasia 18 months before the SCI. Ankylosing spondylitis was diagnosed at the trauma center on admission for the current SCI.

**Table 2** Nature of trauma leading to the current SCI

| Patient No. | Mechanism of Injury | LOC | GCS | RTS | Fracture | Spinal Surgery |
|---|---|---|---|---|---|---|
| 1 | Handgun assault | Unknown | 15/15 | 10/12* | C4 body | None |
| 2 | Van hit by a truck | Brief | 15/15 | 12/12 | C6 burst | ACDF C5-T1, halo |
| 3 | Bicycle wreck | Brief | 14/15 | 12/12 | C5 burst | Post Fusion C3-C6 |
| 4 | Fall from standing | No | 15/15 | 12/12 | C5-C6 dislocation | ACDF C5-C6 |
| 5 | Fall from ladder | No | 15/15 | 12/12 | C6, C7, T1 | ACDF C5-T2† |
| 6 | Fall from tractor | Brief | 15/15 | 12/12 | C5-C6 dislocation | ACDF C5-C6 |
| 7 | No, but scoliosis | Brief | 15/15 | 12/12 | C4 burst retropulsion | C4 corpectomy, posterior fusion |

Abbreviations: ACDF, anterior cervical discectomy and fusion; GCS, Glasgow coma scale; LOC, loss of consciousness; RTS, revised trauma score.

* Patient 1 had an RTS of 10/12 at the scene of the injury due to hypotension of 66/52, yielding a partial RTS of 2/4 for blood pressure. At the scene, the patient was treated with pressor agents and because of reduced respiratory effort, was intubated and paralyzed. Consequently, on arrival at the trauma center, the patient's GCS was 3/15 and RTS was 4/12.

† Patient 5 also had discectomies at 2 levels, C5-C6 and C7-T1

patients discussed the new acute pain of their SCI and only endorsed their ongoing premorbid pain when this information was gathered as part of their medical history and review of systems. Patients who did experience continued chronic pain after SCI reported that the specific nature and severity of the prior pain remained unchanged. The antecedent pain continued despite the physical disconnection between their brain and the thoraco-lumbar-sacral part of their central and peripheral nervous systems occasioned by their SCI that prevented neuronal transmission of their chronic pain.

### Statistical results

The patients' median age was approximately 50 years, as shown in table 1. Four of the 7 participants reported a prior incidence of traumatic injury (table 1) and all participants reported a previous history of psychiatric issues, including anxiety, bipolar disorder, claustrophobia, and depression (table 1). Four of the 7 participants reported illicit drug use and 6 reported consuming alcohol (table 2). Unfortunately, the small sample size prevented meaningful statistical analysis beyond descriptive statistics (data not shown). The 4 participants who reported pain after paralysis had prior chronic opioid use, whereas the 3 participants without chronic pain after SCI had no prior opioid use (table 4).

## Discussion

Although the study site is a busy trauma center with over 4000 cases annually, including a large number of acute SCIs, it only infrequently encounters patients with *the combination of* complete tetraplegia and chronic back pain persisting for over 3 years. During the study period, we found only 7 patients who met the inclusion criteria, 4 of whom experienced persistence of their antecedent chronic pain after SCI. Unexpectedly, all 4 of the patients with prior chronic pain also reported prior chronic opioid use. In contrast, all 3 participants whose chronic pain did not persist after complete SCI reported no prior chronic opioid use (table 4). This dramatic association of the variables for persistence of chronic pain with past use of chronic opioids was unexpected. Some readers might wonder whether the patients who received long-term opioids had more severe and refractory chronic pain than those who did not. Perhaps so. However, the authors feel that the patients who were not taking opioids did so by choice for personal reasons rather than the pain itself, as indicated by the case studies supplied as supplemental materials and the data presented in table 4.

The concept of a central locus for pain is not new. Melzack and Loeser[15] proposed the existence of a central pattern-generating mechanism as the reason for phantom

**Table 3** Neurological classification of spinal cord injury level using international standards (ISNCSCI Criteria[14])

| Patient No. | Sensory (Pin) | Motor (R, L) | | | | |
|---|---|---|---|---|---|---|
| | | Elbow Flex (C5) | Wrist Ext (C6) | Elbow Ext (C7) | Finger Flex (C8) | Finger Abd (T1) |
| 1 | Mid-neck (C3) | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 |
| 2 | Thumb (C6) | 5/5, 5/5 | 3/5, 4/5 | 0/5, 3/5 | 0/5, 0/5 | 0/5, 0/5 |
| 3 | Acromion (C4) | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 |
| 4 | Acromion (C4) | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 |
| 5 | Long finger (C7) | 5/5, 5/5 | 5/5, 5/5 | 4/5, 4/5 | 0/5, 0/5 | 0/5, 0/5 |
| 6 | Acromion (C4) | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 |
| 7 | Lateral antecubital (C5) | 3/5, 3/5 | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 | 0/5, 0/5 |

NOTE. No patient was able to feel any touch (light touch, deep pressure, changes in position) in more than one dermatome below this sharp-dull (protopathic) level of sharp sensory perception of a pin. This total loss of sensation below the level of injury includes the chest, abdomen, legs, and perineum.

Abbreviations: Abd, abduction; Ext, extension; Flex, flexion; L, left; R, right.

**Table 4** Acute posttraumatic pain, pre-existent chronic pain, and opioid use

| Patient No. | Acute Pain Posttrauma | Pretrauma Chronic Pain | | Pretrauma Opioid Use | |
|---|---|---|---|---|---|
| | | Location | Duration (y) | Use Before SCI | Pain Clinic |
| 1 | Head, neck, low back* | Low back* | 4 | Yes (abuse) | Not accepted† |
| 2 | Neck, low back* | Low back* | 3 | Yes (abuse) | Yes |
| 3 | Neck, low back* | Low back* | 20 | Yes | Yes |
| 4 | Neck, bilateral feet* | Feet, bilateral* | 5 | Yes | No (by PCP)‡ |
| 5 | Neck, radiating to arms | Low back | 10 | No | No |
| 6 | Neck | Low back and hip | 50 | No | No |
| 7 | Neck, radiating to arms | Low back | 12 | No | No |

Abbreviations: PCP, primary care provider.

* All 4 patients with prior pain who noted the same pain after their complete SCI stated that the quality and severity of the pain was the same before and after the SCI.

† Patient 1 tried several times to return to the pain clinic but was denied because of a history of abuse.

‡ Patient 4 was prescribed opioids that were managed by their PCP rather than the pain clinic.

body pain in patients with paraplegia that persisted after removal of an entire section of the spinal cord (segmental cordectomy). The present study expands their concept and sheds new light on chronic pain, ie, that some forms of chronic pain are based in the brain irrespective of ongoing peripheral pain. We believe that this pain is distinct from the centralized pain that results from changes in the dorsal horns of the spinal cord and from widespread pain syndrome, which might help explain why some interventional pain procedures are ineffective in stopping the pain despite having been performed correctly.

We speculate that our observations may provide the basis for a new model for evaluation of brain-based pain isolated from the original source of their pain that could be useful to neuroscientists studying chronic pain who need to isolate brain processes from connection to the thoracic and more caudal spinal cord. A new understanding that the use of opioids may establish and maintain this type of pain rather than alleviating it may lead to development of new treatments for those who suffer from acute pain or chronic intractable pain. The expanded perspective that some seemingly peripheral pain may be localized to the brain itself may benefit primary care physicians and others who treat chronic pain.

We found no other reports in the literature of patients continuing to experience antecedent peripheral pain after complete disruption of the neurologic pathways between their brains and thoracolumbar spinal cord, and/or peripheral nerves, in these cases by cervical SCI. Multiple studies of pain in patients with SCI use survey materials that query perception of pain in general and do not explore pre-existing chronic pain or its persistence after SCI.[16-19] Perhaps some of the patients with complete injuries also experience chronic pain that predated their SCI.

One fascinating possibility that the SCIs we describe could actually be discomplete injuries.[14] Because we have no direct evidence that any of the patients with persistent chronic pain after SCI experienced a complete cord transection (ie, physical severing of the spinal cord), we are unable to rule out the possibility that these patients may have experienced discomplete SCI with residual axonal sparing, as described in the literature. For example, one study examined 8 of 12 patients who experienced residual pain after clinically complete SCI and found that on application of a topical heat stimulus plus capsaicin or a cold stimulus, the sensation of pain was momentarily restored in 7 of 8 patients (heat) or 1 of 8 patients (cold), believed to result from residual axonal activity in the spinothalamic tract (SST).[20] A recent study of 23 individuals with clinically complete SCI of ≥4 years duration, who were examined using neurophysiological methods, found strong evidence that 4 of 23 patients had SCIs that were discomplete, "possible evidence" of discomplete injuries in 5 of 23 others, and 10 of 23 patients who experienced subjective sensations during testing.[21] In another recent study, 32 subjects with thoracic SCI were administered test stimuli (pinprick or contact heat) below their spinal cord lesion, whereas contact heat-evoked potentials (CHEPs) and sympathetic skin responses (SSRs) were recorded above the lesion. In subjects with absent pinprick sensation, heat sensation was detected in 10% of patients, CHEPs in 33%, and SSRs in 48%, suggestive of discomplete spinal cord lesions.[22] We recommend that further research in this area should include measures to control for subclinical discomplete lesions, including neurophysiological examination, evoked potentials (sensory, laser, and motor), electroneurography, SSR, and electromyography[21] or pain-autonomic measurements.[22]

## Lessons learned

Our findings confirm what has long been suspected by many experts in the pain field, ie, that persistent peripheral pain can lead to such reorganization in the brain that the sensation of pain would persist even if the source of the pain were eliminated. Such reorganization can start with acute pain[23] and predict the progression to chronic pain.[4,24] However, the term "centralization of chronic pain" can also be used to describe the increased sensitivity of peripheral pain receptors rather than progression from acute to chronic pain.[25] Centralization or central sensitization can refer to changes in the dorsal horns of the spinal cord[26-28] or the dorsal root ganglia[29,30] Although these changes contribute to the chronicity of acute pain or cardiovascular or central neuropathic pain after SCI, we believe that the 4 patients we

describe who experienced persistent pain after complete SCI suffered from a unique phenomenon that occurred within their brains.

Interestingly, patients with chronic pain who were treated with chronic opioid medication experienced persistence of their pain, whereas the patients who did not take opioids did not experience such persistence. This leads to the question of whether exposure to opioids is necessary for pain to be localized to the brain, which is highly relevant to the work of others studying effects of opioids on the brain both anatomically and functionally in modulating the perception of pain and other effects. This is also relevant to those who treat patients with acute and chronic pain and to those who establish the guidelines for treatment of pain.[31]

Although opioids reduce acute pain, they have the paradoxical effect of increasing pain on chronic use. This was demonstrated in a study of patients who were weaned from chronic use of high-dose opioids prescribed to treat a chronic pain condition that had not resolved in the prior year.[32] To manage pain during detoxification, the patients were switched to ibuprofen. Over 91% of these patients reported a significant decrease in pain after detoxification. The authors speculated that the use of high-dose opioids may lead to opioid-induced hyperalgesia that decreases the patients' pain threshold, contributing to their continued sensation of pain and perhaps masking the resolution of the condition that caused the pre-existing pain.[32] This opioid-induced hyperalgesia is a form of central sensitization that is characterized by elevation of a patient's pain level in parallel with the opioid dose. The effects of opioids on the brain in modulating pain reception and other effects, both anatomically and functionally, continue to be an intriguing and fertile area of research.[33]

To our knowledge, before we described these cases, no model existed for reproduction of chronic peripheral pain by the brain. We speculate that awareness of our new model for central genesis of peripheral pain should spur the study of additional patients with complete tetraplegia to better define the pain locus in their brains. Further research with this population should involve the role of opioids in induction and perpetuation of chronic pain, specifically asking whether patients with chronic pain and no previous history of opioid treatment experience persistence of their pain after SCI. Imaging studies would be helpful to compare patients with tetraplegia and chronic pain to those with tetraplegia in the absence of chronic pain. Understanding the etiology of brain-centered pain will ultimately help many other patients with centralized chronic pain.

## Study limitations

This study has many limitations. During their first visit with the consulting physiatrist, most patients were initially unable to rate their prior chronic low back or leg pain using the criterion standard 10-point numerical rating scale because of distress from their SCI trauma, their acute neck pain, and, for some, their reliance on a mechanical ventilator to breathe. Ultimately, the 4 patients who had persistence of their chronic pain were able to rate it as being the same after their complete SCI as it had been before the injury in intensity, quality, and perceived location in their body.

As noted above, it does remain possible that the SCIs we describe are actually discomplete.[14] Following the standard of care in clinical practice, the study relied on the clinical diagnosis of complete SCI made by a trained physician experienced with the ISNCSCI/American Spinal Cord Injury Association standards[14] after a careful clinical examination rather than through the use of objective tests such as those for somatosensory evoked potentials,[21] motor evoked potentials,[21] or CHEPs,[22] most of which are used to examine patients with more chronic SCI than the acute injuries described here. These patients were not examined by fMRI analysis, which would have helped to define the areas of the brain most affected in these individuals, and in its absence, our study sheds no light on the genetic and environmental factors involved in the localization of chronic pain to the brain.

We were also unable to rule out the existence of pathways for communication between the brain and peripheral source of pain that do not involve the spinal cord. One such alternative communication pathway is nonsynaptic paracrine signaling via cerebrospinal fluid.[34] Relative to our study, cervical SCI sometimes but not always interferes with cerebrospinal fluid flow.

Patients who qualified for the study were rare, with only 7 such patients identified in 3 years at a busy trauma center. Larger multicenter studies involving more patients would be of value in confirming or modifying these findings, but it cannot be done retrospectively. The key would be a study protocol that identifies these issues at admission, facilitates a detailed ISNCSCI exam within the first few days of the SCI to identify complete injuries, and then adds questions about chronic pain that preceded the SCI and its possible continuance after the SCI. Currently, hospital staff rarely inquire about pre-existent chronic pain in new patients with SCI, let alone whether it continues after their injury.

This study was also limited by the lack of available long-term outcomes for all patients because of either death or lack of follow-up. Although our study provides interesting ideas about the persistence of prior chronic pain after complete SCI, the rarity of this clinical scenario meant that we were able to enroll too few patients to permit meaningful statistical analysis. Not only was the study too small to be representative of individuals in the region that surrounds our trauma center but it also lacked diversity in sociodemographic and other factors relative to the larger U.S. and global populations.

The influence of previous opioid use on the persistence of chronic pain in these patients was dramatic. Additional research with a larger population is needed to determine whether this trend will be upheld. Based on our findings so far, we hypothesize that patients with pre-existent chronic pain in their lower body will be more likely to experience persistence of the antecedent chronic pain after spinal cord level deafferentation if they have received long-term opioid treatment. Additional research in this population will be required to determine whether or not this is the case.

Our results indicate there were other differences between the 2 groups besides use of opioids and duration of their chronic pain. Some might consider that the sociologic factors would mitigate against continued pain. We feel that

they are possible confounders and thus worthy of consideration, but we feel that it is more likely that these factors helped some of our patients refuse long-term opioids.

There is no historical comparison group in the literature. Of the 17,700 new SCIs per year in the United States, only 11.5% (2035) result in complete tetraplegia,[35] although it remains unknown how many of these patients experience pre-existent chronic pain. It would be valuable if future studies of pain in patients with SCI would use an expansion of the usual survey tool, the SCI Pain Basic Data Set, to inquire about pre-existent chronic pain and identify how many patients with complete SCI retain the same pain after injury and how it compares to other types of post-SCI pain.[36]

## Conclusions

Chronic pain can persist even after the pathway between the brain and the pain source is eliminated. Opioids appear to be critical to this persistence. Opioids are commonly used to treat chronic pain, yet the opioids themselves can worsen pain or its perception, such as that observed with opioid-induced hyperalgesia. Chronic pain is complex and reflects changes at multiple levels of the nervous system. Sometimes treatments that eliminate the only peripheral source of pain are ineffective, for reasons that remain unclear.

Tetraplegia offers a new model for the study of pain centralized to the brain. Classification changes may be needed because "central sensitization" can also refer to changes at the subcortical and spinal cord levels. This study has the potential to stimulate further research on the persistence of other types of pre-existent chronic pain in the brain after complete SCI. Would phantom limb pain persist? What is the role of opioid pathways? If opioid use is a causal factor in either converting pain from acute to chronic or maintaining chronic pain in the brain, the implications of this research would extend beyond patients with SCI and lead to a better understanding of chronic pain. Other investigators might use this group of patients or a relevant animal model with neuroimaging to evaluate the role of the brain in the persistence of chronic pain. Additionally, we hope the implications of this article will come to the attention of primary care providers, specialists, and therapists confronted with acute pain, stimulate a deeper understanding of pain, and encourage even more judicious use of opioids.

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