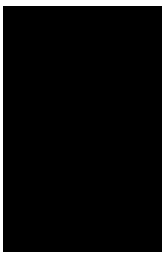

# Pain Handbook Introduction

To our readers,

Chronic pain is something that ALL medical professionals will encounter, no matter if they practice in primary care or a surgical/procedural specialty. Moreover, it is something that likely you will personally experience in your own life as well. To this point, we were not aware of a handbook that encapsulates the many pillars of Pain Medicine into a concise, easy-to-follow guide.

As double board-certified Anesthesiologists and Interventional Pain Medicine Physicians, we believe we have created just that: an easy-to-utilize handbook that covers all the major areas of pain medicine that will undoubtedly help you in your medical careers.

This handbook is appropriately set up in the following sections: Introduction to Pain and Pain Signaling Pathways, Common Categories of Pharmacologic Medications Utilized to Treat Chronic Pain, various Chronic Pain Conditions (in order from head and neck down to the lower extremities), Miscellaneous Pain Conditions, and finally Adjunctive/Complementary Modalities.

We believe that this handbook will provide you with all the pertinent information you will need to treat the vast majority of chronic pain issues, whether you are a physician, fellow, resident, medical student, nurse practitioner, nurse, nursing student, pharmacist, physician assistant, medical assistant, or any other medical professional in healthcare.

Thank you,

Omar Viswanath, MD
Ivan Urits, MD

Part I Introduction to Pain: Pain Signaling Pathways

Chapter 1

# Central Neuropathic Pain Signaling Pathways

Karina Charipova and Kyle Gress

## Central Neuropathic Pain (CNP)

- A chronic neuropathic pain condition
- Results directly from injury to the central nervous system (CNS) or disease of the somatosensory nervous system (1)
- Pathophysiology of CNP is unclear, but the condition can likely be attributed to an increase in inflammatory mediators, voltage-gated ion channel dysfunction, and afferent nerve sensitization (1)
- Central pain syndromes included under the umbrella of CNP include central poststroke pain (CPSP), spinal cord injury (SCI) pain, and multiple sclerosis-related pain (1)
- Symptoms can be chronic or paroxysmal and may be provoked by various stimuli (e.g., mechanical touch, temperature) (2)
- Characterized by allodynia and spontaneous shooting, tingling, or burning pain that is moderate to severe in intensity and functionally limiting (2)
- Long-term pain relief and functional improvement are poor; symptoms are likely to worsen over time (3)

## Epidemiology and Risk Factors

- Symptom progression
  - Early development of symptoms is predictive of symptom persistence (4)
  - Of patients with symptoms 1 month after injury, 72% experienced persistence at 6 months and 69% at 12 months (4)
  - Neuropathic pain increases over time as musculoskeletal pain decreases (5)
- Common risk factors
  - Increased age (4)

  - Initial preservation of motor and sensory function following minor injury (6)
  - Early post-injury onset of allodynia (5)
  - Psychologic symptoms secondary to CNS injury (e.g., PTSD, anxiety, stress, depression, pain catastrophizing) (7)
- Characteristic EEG findings such as reduced alpha and absent theta and beta bands in response to eye openings may be predictive of CNP secondary to SCI (8)
- Biomarkers such as Differentially Expressed Genes and miRNAs have been proposed as predictors of CNP and have potential as therapeutic targets (9)

## Pathophysiology

### Altered Neuronal Cell Signaling

- Exact pathophysiology of CNP is still under investigation
- The condition is likely rooted in inflammation resulting from local glial and macrophage activation, migration, and proliferation resulting from a CNS insult (10, 11)
- Following injury, microglia cells produce proinflammatory markers such as brain-derived neurotrophic factor (BDNF), leading to increased neuronal excitability (10, 11)
- Colony-stimulating factor (CSF1R) signals microglial proliferation, which promotes an influx of $Ca^{2+}$ and increases tactile allodynia (12)
  - CSF1R plays a similar role in macrophages by upregulating inflammatory cytokines (13)
- GABAergic neurotransmitters are also thought to be implemented in CNP (14)
  - In the healthy spinal cord, $GABA_A$ and glycine exert an inhibitory effect on the firing of dorsal horn neurons (14)
  - SCI has been shown to increase the concentration of alpha-2-delta-1 ($\alpha_2\delta$-1) subunits of voltage-gated calcium channels in dorsal horn neurons, decreasing pain thresholds (14)
  - Pregabalin has been shown to decrease tactile allodynia and $\alpha_2\delta$-1 concentration, suggesting a direct effect on the neuropathic pain response (14)

- SCI downregulates expression of the potassium chloride cotransporter (KCC2), rendering $GABA_A$ and glycine ineffective and inducing spasticity and pain (15)
  - Downregulation of KCC2 also associated with decreased pain thresholds (15)
  - Treatment with TCB-2 [(4-bromo-3,6 dimethoxybenzocyclobuten-1-yl)methylamine hydrobromide] shown to upregulate KCC2 and decrease post-SCI allodynia (15)
  - TCB-2 also shown to decrease neuropathic pain targeting microRNA to prevent overexpression of inflammatory cytokines (16, 17)
- Essential oils have been implemented in preventing overactivation of inflammatory pathways and decreasing allodynia (18)

### Progression

- 23% of patients who initially screen negative for neuropathic pain shown to develop pain at 6 or 12 months after injury (19)
- The delayed development of CNP is not well understood (19)
- Delayed presentation of CNP may be linked to time required for neuroma development (19)
- Long-term follow-up is essential for patients who have suffered CNS injury (19)

### Sensitization

- Role of sensitization in the pathogenesis of CNP is unclear (20)
- Central sensitization involves structures in the anterior cingulate cortex (ACC), hippocampus, and amygdala (21)
- A study showed that following SCI patients experience central sensitization compared to controls but not compared to their own baselines (20)
- Varied dosages of opioid medication regimens do not appear to impact sensitization to pain or pressure post-SCI (20)

## Diagnosis

- Diagnosis is difficult, especially given delay in symptom onset (weeks to years)
- Detailed history and physical examination should help differentiate central and peripheral etiologies
- International Association for the Study of Pain diagnostic criteria require a history of CNS injury (22)

- Imaging should be used to confirm history of stroke, SCI, MS, and other CNS lesions (22)
- Pain and somatosensory changes must be distributed in body region affected by CNS injury (22)
- Initial pain may be predominantly musculoskeletal, neuropathic pain becomes more prevalent over time (5)

## Pharmacologic Treatment Modalities

### First-Line Agents

- First-line interventions are similar to those used for peripheral neuropathy and include gabapentinoids, tricyclic antidepressants, SSRIs, and SNRIs (23)
  - The efficacy of these first-line agents is highly individual-dependent
  - These agents should be titrated to achieve clinically significant pain relief for each individual patient and account for comorbidities (i.e., depression)
  - Patients with CNP may exhibit deficits in physical and cognitive function secondary to the original CNS injury with decreased tolerance for medications that cause sedation, dizziness, and ataxia (23)
  - Since combination therapy is frequently required to achieve clinically meaningful pain relief, prescribers must be aware of drug interactions and polypharmacy
- **Gabapentin**
  - Shown to be variably effective in post-SCI CNP at a dose of at least 1,800 mg/d (24)
  - Typical starting dose of 300 mg daily
  - Incremental increase by 300 mg every 4–7 days initially to a dosing of 3 times daily
- **Pregabalin**
  - Two randomized controlled trials have shown pregabalin to be effective for post-SCI CNP at a mean dosage of 410–460 mg/d (25, 26)
  - Shown to be variably efficacious in CPSP (27)
  - Typical starting dose of 75 mg twice daily
  - Incremental increase by 75 mg after 4–7 days to goal of 300 mg/d

- **Lamotrigine**
  - Shown to be effective in CPSP and in some forms of post-SCI CNP at mean dosages of 200–400 mg/d (28)
  - Typical starting dose of 25 mg/d for 2 weeks
  - Incremental weekly increase by 25 mg twice daily to goal of at least 100 mg twice daily
- **Amitriptyline**
  - Shown to be effective for CPSP at a dose of at least 75 mg/d (29)
  - Suggested to be variably effective in post-SCI pain with high dosages (up to 150 mg/d) proving effective in patients with comorbid depression (30)
  - Typical starting dose of 10–25 mg at bedtime
  - Incremental increase every 4–7 days to goal of 100 mg at bedtime
- **Duloxetine**
  - Shown to be effective in MS-related CNP at a dose of 60 mg/d (31)
  - Typical starting dose of 20–40 mg once daily
  - Incremental increase weekly by same dosage to goal of 60 mg/d

## Opioids

- Use of opioids for neuropathic pain control is not recommended given known risks associated with this drug class
  - Case reports indicate that some patients with refractory CNP secondary to CNS malignancy have achieved adequate pain control with combinations of high-dose oxycodone, methadone, and gabapentin (23)
  - Only one-third of patients with CNP experience up to a 50% decrease in pain with current pain regimens that implement opioids (32)
  - Opioids moderate pain through mu receptor pathways, but have been shown to increase neuropathic pain by increasing expression of toll-like receptor 4 (TLR4) (32)

## Cannabinoids

- Use of cannabinoids has proven efficacious in patients with CNP secondary to MS (33)

- Dosing, relative proportion of cannabidiol and tetrahydrocannabinol, and form of administration are highly variable, no formal recommendations are available

## Infusions

- **Methylprednisolone**
  - A derivative of hydrocortisone and prednisolone, is a corticosteroid known to interfere with mediators of the inflammatory response (34)
  - Can be given at higher doses than prednisone as an intravenous infusion for severe inflammation (34)
  - A small study in China found that over 90% of patients with post-SCI CNP receiving a daily methylprednisolone infusion for 1 week experienced allodynia relief exceeding 50% (34)
    - These effects persisted during the 3-month follow-up; however, the data are underwhelming as the study was not placebo-controlled (34)
- **Baclofen**
  - A gamma-aminobutyric acid (GABA) analog that acts by activating GABA receptors (35)
  - A small placebo-controlled study found that intrathecal baclofen significantly decreases post-SCI CNP (35)
  - Ability of baclofen to decrease spasticity gives it potential as an acute intervention (35)
  - Endorsed by patients to improve function and decrease interference of chronic pain on daily life (35)
- **Ziconotide**
  - An omega-conotoxin analog that blocks neuronal N-type voltage-sensitive calcium channels (36)
  - A small study found that 70% of patients with post-SCI CNP experienced greater than 40% pain score reduction following intrathecal ziconotide injection (36)
  - Analgesic effect is persistent, allowing patients to opt for placement of implanted ziconotide pumps (36)
  - Further research is needed to evaluate both efficacy and toxicity of this drug

## Non-Pharmacologic Treatment Modalities

### Transcranial Magnetic Stimulation (TMS)

- TMS is a noninvasive form of brain stimulation that uses magnetic fields to stimulate specific areas of the brain (37)
- Thought to induce effects via manipulation of blood flow and neurotransmitter release (37)
- Has been successfully implemented in treatment of fibromyalgia, complex regional pain syndrome, and peripheral neuropathic pain (37)
- A randomized study found that TMS of the posterior superior insula induced analgesia and activation of the anterior cingulate cortex had an anxiolytic effect in patients with CPSP and post-SCI CNP (37)

### Transcranial Direct Current Stimulation (tDCS)

- An alternative to TMS that uses constant, direct low current to stimulate specific areas of the brain to modulate neuronal activity (21)
- There is evidence that tDCS directed at the primary motor cortex (M1) can achieve local and distant pain reduction (21)
- A randomized controlled study found that patients who underwent repeated stimulation with tDCS experienced significant pain reduction that persisted during follow-up (21)
- Effect of tDCS on pain is delayed, suggesting that pain reduction is a result of changes in cortical plasticity rather than immediate excitability (21)
- Treatment with tDCS requires an optimized protocol with repeated stimulation sessions (21)

### Breathing-Controlled Electrical Stimulation (BreEStim)

- BreEStim is a novel technique for treatment of neuropathic pain that modulates the autonomic system (38–40)
- BreEStim targets the pain-neuromatrix central autonomic network (PNM-CAN), which has been shown to be partially responsible for modulating pain (38–40)
- Activation of the PNM-CAN is quantified based on heartrate variability
- A small randomized controlled trial found that BreEStim was effective in decreasing post-SCI pain (31)

## Exercise

- Patients with CNP commonly experience a major decrease in quality of life due to not only pain but also a decrease in overall motor and sensory function
- A study conducted in mice found that exercise dampens microglial cell proliferation following spinal cord injury (11)
- A placebo-controlled study of post-SCI CNP patients found that exercise consisting of wheelchair propulsion resulted in subjective decreases of neuropathic pain on a numerical rating scale and an improvement of mood (42,43)
- EEG recordings of patients post-wheelchair exercise showed increased central peak alpha frequencies, correlating with a decrease in neuropathic pain (42,43)

## Conclusion

- CNP is a chronic pain condition resulting from injury to the central and specifically the somatosensory nervous system.
- Treatment of CNP is challenging, and patients should be educated that the goal is clinically meaningful pain relief rather than complete resolution of pain.
- Multimodal analgesia has been shown to be more effective than monotherapy and can be combined with advanced neuromodulation techniques such as TMS, tDCS, and BreEStim.
- Patients with refractory pain can benefit from referral to a multidisciplinary pain management team.

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