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# A New Paradigm: Prevention of Central Sensitization in Pain Management through Minimizing Opioid Exposure

*Pamela Bolyanatz*

## Abstract

Current exacerbations of chronic pain cannot be understood in isolation from how past incidents impact pain and its experience. Patients who frequent the Emergency Room or hospital for a pain crisis or intensification of their pain without new findings on X-rays or scans are often seen as ‘drug seekers.’ Yet, to the patient the pain is agonizing, and the suffering real. It is this type of patient that prompted an ongoing improvement project in our local hospital, our Multiple Visit Patient Complex Care Program. The goal was to determine the similarities between this type of ‘complex’ patient—who frequents the hospital despite no new radiographic change—and other patients. Understanding this ‘complex’ pattern in terms of central intractable pain can change the trajectory of treatment. Results of our program described here reveal that a better understanding of central pain and central sensitization can result in better patient care.

**Keywords:** opioids, central sensitization, central intractable pain, trauma, multi-modal pain management

## 1. Introduction: the costs of misdiagnosing pain

Patient complaints of pain can befuddle even the most experienced healthcare provider. The seeming lack of an organic origin, along with multiple exacerbating affective and cognitive variables can result in stopgap measures and incomplete or inaccurate diagnoses. The costs of this approach to treatment can be significant.

Broadly speaking, misdiagnoses or inadequate contribute to overall runaway healthcare costs. The cost of pain care is exorbitant already; inaccurate diagnoses can result in money spent for the wrong treatment: ‘The annual cost of pain was greater than the annual costs in 2010 dollars of heart disease (\$309 billion), cancer (\$243 billion), and diabetes (\$188 billion) and nearly 30% higher than the combined cost of cancer and diabetes’ [1].

For individual patients who do not receive an accurate diagnosis of their pain, there is a risk of a redundancy of testing that can result in increased exposure to radiation, risk of further misdiagnosis, and mistreatment. The primary risk to the patient, however, is the development of debility, immobility, and isolation.

The reasons for inadequate pain diagnoses are sometimes attributed to the patients themselves. Many times, patients are labeled as ‘drug seekers’ when they

come to the Emergency Department complaining of pain. If patients are presumed to be drug seekers, and if opiates are the easy default treatment for pain, this combination can easily lead to a resistance, even if not entirely conscious—on the part of healthcare staff to assume that the pain is overstated, or perhaps even utterly absent. The ready use of opiates, then, does have to be seen as a contributing problem to pain misdiagnoses. This predisposition has its own set of costs.

For example, patients may have neurobiological anomalies, in which there is an anxiety, fear, and pain matrix in the prefrontal cortex and amygdala. This is influenced by neurotransmitters and glial cell activation, which can lead to pervasive inflammation and central sensitivity. It is paramount that hospitals utilize non-opioid and multi-modal treatments after surgeries to reduce opioid exposure of the brain. The exposure of the insula and the limbic area of the brain to morphine or hydromorphone begins the cascade of blocking endogenous opioid production.

In fact, ~20% of patients complaining of pain have likely used illicit substances, and may be found to have psychiatric or opioid use disorders that are not accurately diagnosed and miss proper treatment with medical-assisted drug therapy. Sporadic follow-up, and missed opportunities to begin treatment due to the health care providers judgment and stigma, can lead to becoming stuck in the same cycle [2].

Ultimately, it is vital to determine a patient’s full history. Displays of judgment that evoke a patient’s sense of being stigmatized will more likely lead to an improper diagnosis and treatment by the healthcare team. If a treatment is not effective, then understanding the options to reassess and change the course of treatment become necessary. Opioid administration guidelines have been slowly changing since 2005 with the concept of ‘not every increase in pain should be met with a higher dose of narcotics (opioids)’ [3]. Further research into hormonal, dietary, and other natural or integrative methods of the treatment of pain is increasingly necessary, especially as the costs of opioid use for misdiagnosed pain become more widely known.

**2. Current practices in pain treatment**

Today healthcare providers are working to lower opioid use in their own way, some in systemized fashion, while other just draw a line in their practice and hope that patients’ pain improves, and/or that the patients get tired of asking for medication. But the use of opioids, especially, in pain management today is a complex landscape.

Pain and the treatment or management of pain is a widely debated subject. It is typically not a favorite topic of most providers; many feel they were not trained to care for the wide variety of pain complaints and some throw their hands up in frustration at the myriad of complaints they hear. Some providers have changed their office policy to include a blanket statement, “I do not prescribe narcotics.” The reason for this policy, gleaned through many conversations with providers, is that they prefer to avoid the many ‘headaches’ from the ‘drug seekers.’ Case Study 1 illustrates this problem.

**Case Study 1**

A patient arrives at the Emergency Department with no external presenting problems, but she describes her internal pain as, ‘I feel like I am going to break apart.’ She had undergone surgery 1 week prior, a straightforward laparoscopic cholecystectomy, but she is sure there is an infection or something worse inside. The staff in the Emergency Room see her often for her anxiety; they have other patients with ‘true’ emergencies in the rooms next door. Should she receive opioids for her pain? She and others like her struggle with feelings of anxiety, fear, pain and often come to the Emergency Department for relief. On a daily basis, patients with chronic pain feel their pain in a way that is difficult to express to others. Their previous experiences of anxiety, trauma, chronic disease, and previous treatment with opioids influence their current situation.

But medical providers are not the only piece of the puzzle. National pharmacy chains have placed restrictions of 7 days for the first prescription of opioids, regardless of whether the patient is opioid naïve or opioid tolerant. This can have unintended outcomes, exemplified by Case Study 2:

**Case Study 2**

A postoperative patient changed pharmacies shortly after surgery. He was able to receive the first 7 days of medication, but while the pharmacy was waiting for a phone call to complete his authorization, he did not have access to his regularly prescribed medication. This contributed to a pain crisis and he was hospitalized for 3 days. With his regular opioid medication dosage, the admission could have been prevented. The patient was not misusing his medication; he was affected by a ruling that was put in place to safeguard opioid medication from getting in to the hands of those who do not need a large quantity of opioid medication (from Ref. [3]).

Many state surgical organizations are taking notice of the overprescribing on the part of their members in the past. A not uncommon unintended consequence of this practice has been for post-operative patients, historically, to take a few oral pain relievers, and then the rest of the bottle of hydrocodone (Norco™, Vicodin) or oxycodone (Percocet™) sits in the medicine cupboard for many years. The result is that many household opioid supplies allow patients to self- and over-medicate in ways that “fly under the radar” of healthcare personnel. Case Study 3 is one such instance:

**Case Study 3**

A patient arrived at the Emergency Room in clear distress from her new onset pneumonia. She was experiencing significant chest discomfort, and asked for pain medications since her hydrocodone with acetaminophen 7.5/325 mg was not working; the patient felt that something stronger was needed, and so insisted on a stronger dose. Emergency Room providers do not routinely administer opioids for pneumonia, so she left the hospital against medical advice, frustrated that her pain was not controlled. She eventually returned due to her worsening pneumonia symptoms, which resulted in hospitalization.

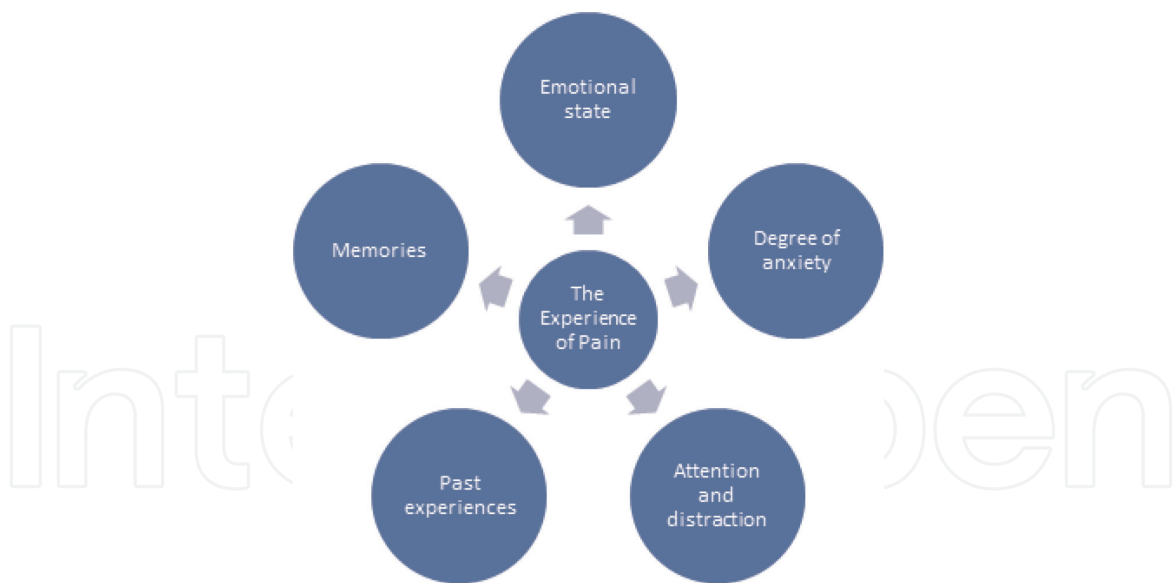
3. Factors that affect the experience of pain

Ossipov et al. [4] found the experience of pain to be influenced by emotions and experiences. Painful experiences accompanied by intense emotions, such as wartime injuries, or co-occurring mental health disorders play a role in the body’s own endogenous inhibitory system in heightening the pain perception.

Pain perception and modulation are important concepts to understand within pain management and its treatment, as in **Figure 1**.

The following is not an exhaustive list of some of the complexities of the experience of pain; they are offered to show that today’s pain management provider must be something of a jack-of-all-trades in order to understand the nature and treatment of pain.

- *Multiple medications are often utilized in the management of pain.* Antidepressants, anti-inflammatories, and bowel medications are all important parts of the picture. Some are finding that topical treatments can be effective in the treatment of pain. It can be a burden to maintain a working knowledge of the plethora of available options, in order to be able to utilize the most effective pain medications, especially if one is not a pain specialist.
- *There are not enough pain specialists.* There is a disparity between the number of pain specialists and the number of patients in pain. Pain patients sense, not



**Figure 1.**  
*Factors influencing the pain experience [4].*

surprisingly, that their needs are viewed as of secondary importance when they perceive that their sense of urgency is not matched by healthcare team.

- *Patient pain care guidelines do not have individual complex patients in mind.* It is a constant challenge to maintain a targeted therapy for a patient and stay within the morphine milligrams guidelines as set by national and state guidelines. Some states have even prepared guidelines for Emergency Rooms that generalize treatments rather than allow for individual treatments of pain [5].
- *Patient frustration can be high.* Maintaining the provider-patient relationship can be difficult if the non-opioid medications do not work, and the only thing that helps is the opioid pain relievers [6]. The real struggle comes when the opioids are ineffective or requests for more and more opioids occur, especially if a provider is not aware of other options for pain control or even the true diagnosis of the patient. This is exacerbated by the fact that if opioids are overused, the diagnostic picture can become clouded due to suspicion.
- *Patient expectations are based on past history.* Often, when a patient comes to the Emergency Room and has a history of being on chronic opioids, the opioids become the focus of the visit. The struggle begins: the patient feels they deserve more, since their home medications (including, sometimes, that leftover hydrocodone or oxycodone) do not work. For her part, the provider does not want to give opioids, given the growing awareness of opioid-related problems, especially now that providers receive scorecards with their opioid prescribing measured.
- *Surgical delay can limit choices for the orthopedic patient.* Current guidelines for knee replacement are to ‘proceed with total joint replacement after **all** other modalities have failed’ [7]. This delay may increase the use of opioids since many patients struggle with limited mobility, and perhaps severe pain for many months or years, until they have qualified for the replacement. Ironically, a predisposition to leap to opioids is often done in order to delay the surgery. Recovery is often delayed due to the muscle atrophy of older patients,



and these patients often need higher doses of medications to be able to tolerate movement.

- *An increasingly obese population has implications for pain management.* Obesity becomes a post-operative barrier to surgery due to lack of mobility. Physical therapy pain can be more intense and last longer if movement has been difficult for a patient.

The list of considerations entailed in understanding the nature of pain and subsequent pain management could go on. Patients with debilitating illnesses who have had to retire early may be less mobile and so more susceptible to pain—post-operative or other. Clinical observations reveal that back pain and spinal stenosis can leave a patient with weak proximal thigh muscles and the inability to walk more than 30–40 feet, while daily headaches can lead to the inability to leave the home for weeks at a time. Prolonged chronic pain and discomfort often leads to disability.

Disability from pain is increasing. Clinically, patients become more and more deconditioned. They often ambulate or walk less, lose muscle mass, and may become discouraged and often depressed. Some eat lower-quality food, as in the case of a 50-year-old patient who told me that she orders from a mobile app at home and has her food delivered to her, since she cannot drive or stand to cook. Her diet is fast food almost exclusively. This leads to isolation and emotional ‘sadness’ as described by many patients. Many of the pain patients in my practice state, ‘I want to be a good parent (or son, daughter, wife, husband), but I hurt too much.’ The psychological and cognitive dysfunction persist.

#### **4. The missing link: central intractable pain**

As if the complexities of pain management just addressed were not enough, there are the important differences in types of pain, not just differences in patients. Patients with fibromyalgia, chronic fatigue, and small fiber neuropathy suffer from a category of pain known as central intractable pain (CIP)—a type of pain that does not respond to opioids and is, in fact, a type of pain for which the use of opioids has been detrimental [8, 9].

Understanding CIP is vital for diagnosis, and for treatment modalities. Joshi [10] describes the etiology of CIP in terms of brain stimulation due to trauma or injury. NMDA and glutamate are released, and, due to glutamate excitability, glial cells are released. These glial cells are irritated and inflamed, and cytokines release cytotoxins. These cytotoxins are neurotoxins, are pervasive throughout the body, and cause damage to nerves from inflammation. Sensory nerve fibers are specifically targeted. It is important to stress here it is believed that the patient’s subjective experience of events as emotionally traumatic in triggering this physiological response that results in cytotoxins’ attack on sensory nerve fibers.

There are other variables that can compound and exacerbate this process. There are genes that have been found to be involved in the amplification of pain and may indicate an increased risk of chronic pain development [11]. In addition, there are environmental influences. Previous emotional trauma, sexual abuse, medical influenced trauma, previous stigma from the LGBTQ or other gender related or minority stress inducers has been thought to amplify pain perception. The Substance Abuse and Mental Health Services Administration (SAMSHA) have developed Trauma-informed care education for health care providers for these populations [12].

Treatment is typically a multi-faceted approach to minimize sensitization; there are a number of ways that this can be affected:

1. Prevent the exposure to opioids.
2. Minimize the wind up phenomena. Defined as stimulation of pain nerve fibers to the extent that the fibers are altered and produce neuropathic pain.
3. Setting the expectation for patients prior to painful experiences. Information and education of patients and providers has proven to lower patients' pain scores after surgery.
4. The use of oral Naloxone™ has been on the rise in the recent past due to the research surrounding the stimulation of the midbrain periaqueductal grey (PAG) region. Outputs from the PAG to the medulla reduce pain by activating an endogenous opioidergic pain inhibitory system [13].
5. Lidocaine has been used for over 50 years as a local anesthetic; now it is assisting with less exposure to opioid medications due to its anti-inflammatory and analgesic properties. Postoperative infusions at a low dose have effectively lowered opioid requirements, decreased post-operative nausea, and enhanced the return of bowel function [14].
6. Hormone replacement has been shown to indicate that various hormones regulate the hypothalamic-pituitary-adrenal axis, which, when activated cause persistent pain. Multiple hormones are implicated here, including cortisol and pregnenolone. Dr. Forrest Tennant has developed a protocol for patients who have Ehlers Danlos syndrome and arachnoiditis, which replaces hormones to assist with pain control [15].
7. Dr. Jay Joshi [10] has worked diligently to determine an appropriate plan for individual patients who struggle with CIP, using a treatment plan that relies on ketamine, which has the following benefits:
  - Increase in cerebral blood flow
  - Resetting of the mu receptor
  - Reduction of hypersensitivity
  - Reversal, in some cases, of post-traumatic stress disorder (PTSD)
  - NMDA receptors mediation
  - It serves as a potent neuro-anti-inflammatory agent

Early identification of central pain syndromes prevents the central sensitization and brain reorganization. Functional MRIs show cortical reorganization: psychologic interaction with pain and stress that causes areas in the brain to become hyperactive to a stimulus, including brain mapping and biofeedback [16]. CIP, then, often has its origins in supratentorial factors, and failure to take these factors seriously can result in opioid overuse.

## **5. The multiple visit patient complex care program**

The hospital-based team approach to helping multiple-visit patients has been successful at my suburban hospital for the past 3 years. Recent data indicates the use

of individualized care plans by a Complex Care team has helped reduce readmissions by 36%.<sup>1</sup> The goal is to assist the patient to find proper outpatient treatment, so that a readmission to the Emergency Room becomes less necessary. The goals of the care plans include providing appropriate symptom management, as well as reducing the opioids that are prescribed during the Emergency Room visit, and at discharge. Other techniques include giving a welcome letter to a patient that frequently uses the Emergency Room. The goals of the letter are to (1) alert patients to the program; (2) introduce the Complex Care team; (3) offer to help patients obtain a primary care physician; and in accordance with the Center for Disease Control Guidelines; (4) state clearly that we will not always treat their pain with opioids, but will use a multimodal approach when they present for treatment. These specific strategies have reduced the readmission rate by 60–70% during a more specific period of study.

Identification and diagnosis is paramount to optimizing treatment strategies and symptom management. Patients who frequent the Emergency Room can be misunderstood with characteristics that are not always identified early in their pain treatment. This can place the patient at risk for over-medication syndromes, over-utilization of the healthcare system, and developing central sensitization.

Retrospectively, identification of complex patients who have symptoms that correlate to those identified as CIP has been ongoing. Recognizing CIP has resulted in revised treatment plans for patients. Case Study 4 describes one such instance of the importance of recognizing CIP.

**Case Study 4**

A patient experienced a significant traumatic event when she was young. She developed low back pain and abdominal pain, although the imaging for both were not significant enough to pinpoint the cause for the pain. She had multiple medical procedures and work-ups, and because she complained of severe pain even after other medications, opioids were begun. Over the years, the dosages were increased, but they were not effective. The pain continued despite the subsequent overuse of the opioids. She eventually had multiple admissions to the hospital without a cause for the pain identified.

After being treated for opioid addiction, the patient was introduced to the concept of ketamine treatment for desensitization for central pain. After a series of ketamine infusions, the central sensitization subsided. The patient was able to use significantly less opioids, with much greater relief of the pain. She has now learned to identify the triggers of her pain exacerbations, and has been able to be active and care for her family.

Informal conversations with colleagues at other institutions suggest that our suburban hospital is not the only facility to have concerns about patients similar to the one described above. Recognizing that many pain patients have a type of central sensitization—chronic pain that is out of control—can both reduce pain that is activated by a physical response to a past stressor—and the repeated exposure to opioids.

The case studies below represent how recognizing the role of CIP in supratentorial pain can reduce reliance upon opioids and subsequent opioid-related addiction problems. Some of the implications found in the cases below include non-opioid pain management, the use of postoperative lidocaine, and desensitization with ketamine. This is consistent with the prevention of opioid exposure as the new paradigm, and the need to implement innovative treatments.

<sup>1</sup>Source: unpublished data from 2015 to 2017 (Delnor Hospital, Geneva, Illinois, USA).



**Case Study 5**

A patient with significant head pain sought diagnosis for her pain at multiple facilities without a definite diagnosis. All headache abortive efforts failed, and all multimodal management failed to relieve the pain. The patient was placed on intravenous meperidine and over the course of many years, the dosage was raised to a high dose. This was effective for a short time, but then the high dose began to fail in efficacy. Re-interpretation of her pain in terms of CIP etiology has resulted in conversations about stressors in her social life, and a reduction of opioids.

**Case Study 6**

A patient had a cervical spinal cord stimulator placed, but it failed almost immediately, worsening her pain. Struggles with anxiety and debility have contributed to a clinical diagnosis of depression. Treatment for depression has resulted in less frequent PTSD responses to an earlier-life trauma. As a result, her pain is not managed with less reliance on opioids.

**Case Study 7**

A patient has progressive neuropathy, although the reason is unclear. Initially she presented with the inability to sit up long enough to go to her primary care physician's office, which suggested significant psychological overlay. Opioids were escalated, and her ability to sit comfortably and walk easily did improve. Care conferences ensued and biopsies, along with neurologic medication were used without improvement. Finally, the recognition that CIP might, at least in part, have had a role in the patient's symptoms resulted in fewer symptoms and a consequent reduction of opioids.

**6. Conclusion and recommendations**

The management of pain by health care providers and pain specialists has a new contour: identify the patients with CIP in a timely manner, then identify treatments and methods to find sustained relief with limited or no use of opioids.

A patient's previous history of PTSD, anxiety (general anxiety disorder, post-partum depression, etc.), chronic pain, or substance use disorder matters when it comes to differential diagnoses. It is vital that health care providers realize the ramifications of co-existing psychological and neurologic impact when planning for surgery or other pain-producing procedures.

What might be routine and typical surgery/procedure from the perspective of a surgeon could be different to the brain, neurotransmitters, and the other aspects of a patient's neuroanatomy. It is crucial that patients' prior history be considered, and a plan put in place to assist the patient in coping. Pre-surgical education and planning, along with collaboration between anesthesia or social work colleagues can have a long-term positive effect. It may be beneficial to place a temporary nerve block, low dose lidocaine, or bupivacaine (either short acting or long-acting) in order to block the ascending nociceptors from sending the pain signal through the descending pain pathway. The future of pain management must be the prevention of pain pathway activation. This will lower the exposure to opioids and prevent future substance use disorder.

Of note, physical therapy is very beneficial to a large subset of patients. Specialized concepts have been developed by physiatrists' (also called physical medicine and rehabilitation specialists) to assist patients with chronic pain, known as an integrative comprehensive pain management program (CPMP). This program revealed significant improvement through the administration of a battery of observed functional tests (BOFT) to patients with chronic pain who were attending the CPMP [13].

Activity can be the best treatment for most pain. Exercise and stretching of muscles, and desensitization of scar tissue leads to healing. Part of the CPMP is cognitive therapy, psychological, neurological, and pain education. It is clear that improving outcomes in chronic pain management occur when the patient understands the influence the mind and the body play in pain perception.

The FDA and other research opportunities should be supported to continue to find more methods of pain blockade and prevention of pain at the site of surgery. Kaiser Permanente and other hospitals around the United States have been adopting the enhanced recovery after surgery (ERAS) concept. There is a full protocol of management of the patient, but the basic tenet is to block the pain to speed recovery with very little or no opioids.

Lowering opioid exposure is paramount and should be supported and rewarded with funding and research grants. Health care and surgeries with minimal or no opioids are possible now, and need to be utilized immediately. Minimizing opioid exposure is the mandate at this time, there are available options presently, and more research dollars should be committed to new ways to block the perception of pain. Finally, patients should be educated about the options and choose hospitals and providers who utilize the most up-to-date resources.

Education of the next generation of providers needs to be clear in the direction and potential options for preventing disability and preventing overuse syndromes, early identification and the importance of prevention of the central sensitization and CIP.

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## **Conflict of interest**

No conflict of interest to declare.

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### **Author details**

Pamela Bolyanatz  
Northwestern Medicine Delnor Hospital, Geneva, Illinois, USA

\*Address all correspondence to: [pamela.bolyanatz@nm.org](mailto:pamela.bolyanatz@nm.org)

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