Integrating Osteopathic Evaluation and Treatment in a Case of Opioid-Induced Hyperalgesia

Nicolette O. Rosendahl, DO

Abstract

This paper reviews a multimodal approach to the treatment of acute pain. Early recognition of systemic changes in pain indicators may be efficacious for the patient and practitioner to understand the subjective pain response. The application of osteopathic manipulative medicine may be beneficial during de-escalation therapy of opioid pain medication when the patient is experiencing symptoms consistent with opioid-induced hyperalgesia syndrome. Improved education and recognition of opioid-induced hyperalgesia can potentially improve medical management with the use of osteopathic manipulative treatment.

Background

Pain can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[1] A 2017 study in *The Journal of the American Medical Association* noted the incidence of prescription opioid medication prescriptions given at discharge after traumatic injury was 54.3% for moderate to severe trauma patients.[2] This initial prescription may be renewed when traumatic pain continues past the normal healing time of 3 months, as it meets the definition of persistent or chronic pain.[3] In the United States, there is an estimated 100 million people who have been diagnosed with chronic pain conditions in the last decade.[4] Opioid prescription practices for acute and chronic pain have come under intense review since the height of the epidemic in the early 2010s, leading the Centers for Disease Control and Prevention (CDC) to recommend that if opioids are used, they should be prescribed at the lowest effective dosage with justification to titrate to a dose above 90 MME daily.[5] In addition, non-opioid medications should be prescribed in combination with nonpharmacological treatment to optimize pain control.[5] Additional studies suggest osteopathic manipulative treatment (OMT) can be used as an efficacious adjunctive to pharmacologic pain management.[5,6,7]

This case illustrates how applying osteopathic manipulative medicine (OMM) improved a patient's subjective pain response during the de-escalation of opioid therapy. The patient is a 26-year old female presenting with opioid-induced hyperalgesia (OIH) syndrome after traumatic crush injury.

From the Good Samaritan Regional Medical Center, in Corvallis, Oregon.

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Correspondence address:

Nicolette O. Rosendahl, DO
Good Samaritan Regional Medical Center
3680 NW Samaritan Drive
Corvallis, OR 97330
(515) 805-0020
Nicolette.rosendahl@gmail.com

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Case Report

Initial Presentation

A previously healthy 26-year-old female presented to the emergency department after sustaining a full-body crush injury with subsequent prolonged entrapment before extraction.

The patient sustained the following injuries as evaluated in the initial emergency room assessment:

- Grade IV-V right hepatic lobe laceration
- Grade IV left renal laceration, with left renal artery occlusion
- Grade II right renal laceration
- Hemoperitoneum with abdominal aortic dissection at the level of T12-L1
- Right second and third posterior-medial rib fracture
- Right fourth anterior-lateral rib fracture
- Right fifth through eighth displaced rib fracture
- Non-displaced fracture of the right inferior-medial and superior pubic rami at the acetabular junction with fracture extending into the anterior right acetabular wall
- Avulsion fracture of the left anterior superior iliac spine

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Additional injuries sustained include the following:

- Right wrist laceration
- Bilateral pneumothorax left greater than right
- Bilateral lower lobe pulmonary emboli

Procedures included in the duration of the initial hospital admission including:

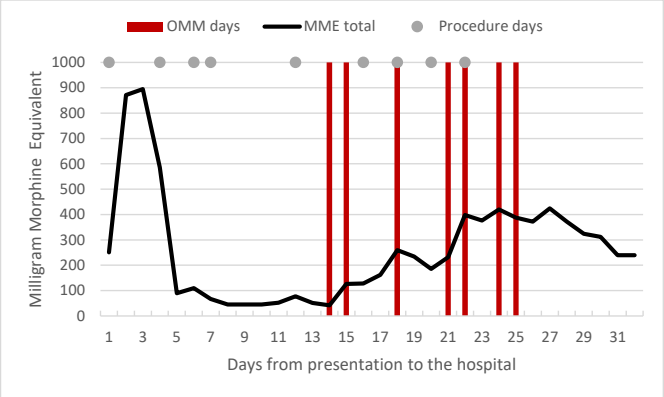
- Coil embolization of liver laceration
- Suture repair of wrist laceration
- Bilateral chest tubes for pneumothorax and effusion drainage
- Central venous and arterial access
- Right side thoracentesis on hospital days 4, 16, 18 and 22
- Continuous renal replacement therapy
- Paracentesis with a drainage catheter

After presentation, the patient was stabilized and admitted to the intensive care unit for mechanical ventilation and sedation. The patient was extubated after five days on the ventilator. After several days awake, complaints of increasing abdominal distention were reported. Imaging revealed bowel hyperemia and stool impaction for one week which was quickly remedied. The patient had been on an average of 330 milligram morphine equivalent (MME) a day since admission, including sedation opioids. Physical therapy was initiated for mobilization 9 days after the accident, which was admittedly slow due to the extensive injuries. The patient was transferred from the intensive care unit 2 weeks after admission, at which point the osteopathic inpatient consult service was asked to assess and treat the patient for uncontrolled pain in various body regions and anasarca. After an osteopathic structural evaluation deemed the patient appropriate, the patient was evaluated and treated with OMT in 7 sessions during their initial admission. After 20 days in the hospital, pain medication was switched from as-needed intravenous to all parenteral formulations, which lead to an increase in use temporarily. Given the response to OMM, they were advised to follow up in the outpatient setting to continue progress in recovery.

First Outpatient Period

The patient was discharged to a skilled nursing facility after 32 days in the hospital. Pain medication at that time included a combination of transdermal, scheduled, and as needed parenteral opiates, which equaled a maximum of 240 daily MME. General surgery evaluated the patient, as well as orthopedics, and occupational medicine shortly after discharge. At each visit, the patient reported persistent back pain and chest wall pain with worsening of pain with deep breathing. Follow up evaluation in the osteopathic outpatient clinic never occurred due to insurance coordination.

Figure 1: Inpatient daily MME and OMT with procedure days



Second Inpatient Admission

Approximately 58 days after their injury, the patient was admitted to the hospital for intravenous pain medication. The admitting diagnosis was severe uncontrolled nausea and vomiting attributed to an allergic reaction to their first dose of Cymbalta, prescribed for mood. The care plan for the previous 2 weeks had also included trying to decrease oral opioid dosing from every 3 to every 5 hours, and replacing the transdermal opiate every 48 hours instead of 72 hours, but this was met with limited success. Daily, the patient was still taking up to a maximum of 220 MME.

Since the previous discharge, the patient admitted the overall pain level improved minimally. Reports of generalized pain not always associated with the areas of previous trauma were noted. Depressed mood with increased pain intensity had limited the patient's ability to complete physical therapy, as any touch was reported as painful. On admission, based on reported pain and lack of improvement, all pain medications were changed to oral morphine given concern for opioid-induced hyperalgesia (OIH). The patient agreed to an informal plan to decrease dosing by 20% as a taper to ease symptoms. Given concern for OIH, the maximum dose was set at 90 MME a day. OMT was again consulted to help with pain management and mindfulness-based stress reduction. The patient was discharged home after making significant progress with physical and occupational therapy efforts. The second hospitalization was 11 days in the hospital; and 68 days post initial injury. By discharge, she was taking 60 MME daily.

Start Of Second Outpatient Period

Approximately 2 weeks after discharge and 78 days after the initial accident, the patient presented to the outpatient osteopathic clinic. Reports of pain in the right rib cage and low back made breathing deeply difficult. Nausea attributed to pain medications and constipation that improved with taper were also reported. Orthopedics and psychiatry continued to see the patient concurrently.

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The patient was seen and treated in the outpatient OMM clinic twice before treatment was suspended due to unforeseen circumstances. Usage of opioids had tapered down to 45 MME daily. The patient returned for OMM evaluation 164 days after the accident, and was doing well with mobility and return to work status. Opioid use at this visit was reported as 15 MME a day with plans for continued treatment with taper.

Past Medical History

The patient was reportedly healthy and working as a graduate student. One prior injury was reported, a wrist laceration several years prior which required suture closure. Additionally, the patient reported "a few" motor vehicle accidents without a significant injury requiring medical attention. Dental history included wisdom teeth removal and retainer as a teenager. The patient denied medical or environmental allergies, and had no history of illicit drug use, but admitted to the occasional use of alcohol before the accident.

Review Of Systems

Over multiple visits, the patent admitted to persistent nausea with intermittent vomiting, abdominal pain, and constipation, as well as chest wall pain and shortness of breath. They denied headaches, fevers, or chills.

Physical Examination

Initial hospital evaluation, the first evaluation

Osteopathic structural exam findings included: T12 extended, side bent and rotated left; L5 flexed, side bent and rotated left; Lumbosacral compression; Left sacroiliac compression; Pelvic and abdominal diaphragm exhalation somatic dysfunction with median arcuate ligament restriction.

First hospital admission, final hospital evaluation, 7th evaluation

Osteopathic structural exam findings included: Atlanto-occipital joint extended, side bent right and rotated left; T10 extended, side bent and rotated right; T12 extended, side bent and rotated left; Lumbosacral compression; Right rib 8-10 exhalation and abdominal diaphragm exhalation somatic dysfunction.

Second hospital admission, initial evaluation, 8th evaluation

Osteopathic structural exam findings included: Atlanto-occipital joint flexed, side bent right and rotated left; Cervical-thoracic junction compression; T10 flexed, side bent and rotated left; Lumbosacral compression; L2-4 neutral, side bent right and rotated left; Posterior peritoneum restriction and psoas spasm right greater than left; Right backward sacral torsion on a left oblique axis; Pelvic diaphragm exhalation somatic dysfunction; Right carpal compression; Right rib 4-7 exhalation and abdominal diaphragm exhalation somatic dysfunction.

Second hospital admission, final hospital evaluation, 11th evaluation

Osteopathic structural exam findings included: Inferior vertical strain and lateral flux; Cervical-thoracic junction compression; T1 flexed, side bent and rotated right; Lumbosacral compression; Left forward sacral torsion on a left oblique axis; Right serratus posterior superior spasm; Right radial-ulnar ligament restriction; Radial-ulnar interosseous strain and abdominal diaphragm exhalation somatic dysfunction.

Outpatient evaluation, 13th evaluation

Osteopathic structural exam findings included: T12 flexed, side bent and rotated left; L2 flexed, side bent and rotated left; L3-4 extended, side bent and rotated left; Lumbosacral compression; Left forward sacral torsion on a left oblique axis; Right rib 12 inhalation; Left rib 9 inhalation; Bilateral first rib inhalation and abdominal diaphragm inhalation somatic dysfunction.

Assessment

The patient is a 26-year old female with injuries consistent with crush injury and significant somatic dysfunctions of the thoracic, lumbar, sacrum, pelvis, ribs, and abdomen, which were contributing to generalized pain. The progression of pain was out of proportion to physical examination with anticipatory symptoms, as indicated during their second admission, which was consistent with hyperalgesia. There was likely a component of dependence, tolerance, and hyperalgesia. They were also dealing with the symptoms of PTSD and the psychosomatic component.

Treatment

Osteopathic manipulative treatment was applied to the above areas utilizing balanced ligamentous tension (BLT), myofascial release (MFR), osteopathy in the cranial field (OCF), articulatory (ART) and visceral techniques. Over the 90-day lookback period, the patient was treated 14-times with an average of 6 regions being treated at each visit.

During treatments, the limited abdominal and pelvic diaphragm motion was significant with decreased respiratory muscle compliance. There was dyssynchronous motion of ribs due to the right-sided rib fractures. Diaphragmatic crural restriction and psoas muscle spasm were attributed to a possible viscerosomatic reflex as the body responded to the atrophy and hypertrophy of the renal system. Compression and restriction of the posterior peritoneal structures were due to non-physiologic diaphragm motion. The decreased sacral motion likely contributed to constipation, increased sympa-

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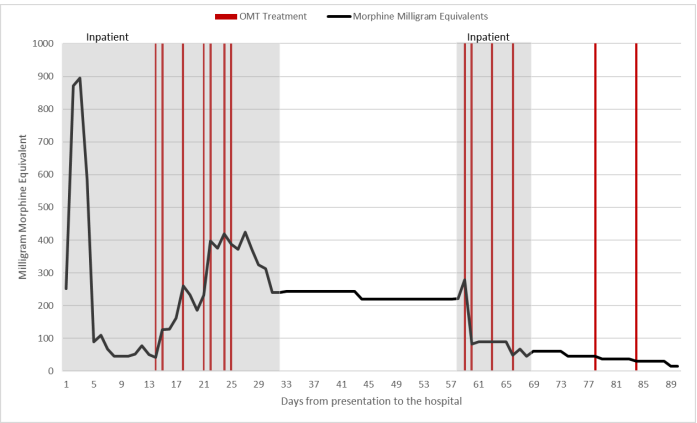
thetic tone, and ineffective lymphatic and venous return of the lower extremities, resulting in significant anasarca. Recurrent leftward rotation of the lumbar spine was evident as the patient became more mobile and may have been a response of the postural muscle imbalance from the trauma as they recovered.

In addition to OMM, the patient was receiving opioid medication as well as Gabapentin and acetaminophen for their pain.

Patient Response To Treatment

Immediately after each treatment the patient reported improvement in anxiety, ease with breathing and decreased pain. Response to treatment was difficult to track during the first admission due to repeated procedures and increasing opioid medication. However, with the second admission, after each treatment, the patient reported improvement in whole body pain and utilized less as-needed medications. Understanding the neuropsychology around chronic pain motivated the patient to continue with opioid taper. With a combination of OMM and pharmaceuticals, there was an overall decrease from a maximum prescription of 240MME to 60MME, and eventually 15MME daily over a three-month period.

Figure 2: Daily Milligram Morphine Equivalents and OMT treatment in the course of the opioid taper. The areas of shading indicate treatment in which the patient was hospitalized and may include intravenous medications.



Discussion

Opioid induced hyperalgesia (OIH) is a diagnosis that can be easily overlooked, but is critical when dealing with chronic and persistent pain. The pathophysiology of OIH is still being explored and is hypothesized to be a consequence of repeated exposure to opioid medications, which utilize the mu receptors, coupled with a neuroplastic change in the central and peripheral pronociceptive pathways.[1,3,8] A brief review of the physiology of pain, as a physical and sensory experience, will help the clinician understand the role of opioid use in the development and resolution of OIH, as well as help guide the clinician's future treatment of acute to chronic pain.

Clinicians' understanding of when acute pain from trauma transitions into chronic or persistent pain while using opioids will help with the understanding of hyperalgesia and tolerance.[9] Hyperalgesia can be defined as an increased pain from a stimulus that normally provokes pain, resulting in a suprathreshold stimulation.[1] This is different from tolerance, which is defined as "the capacity of the body to endure or become less responsive to a substance or a physiological insult, especially with repeated use or exposure."[10] Both OIH and tolerance present with escalating use of opioid medication. Such as in this case, clinicians should consider OIH with increasing doses of opiates with lack of improvement in pain and in the absence of disease progression.[3]

Pain is initially registered through the peripheral nervous system, which is composed of the somatic, visceral and vascular systems, and is conducted through afferent neurons. These afferent neurons are further subdivided into four types of fibers, each with a unique receptor origin and effective stimulus for activation.

The large fiber system travels from the dorsal column-medial lemniscus system and cerebellar system up to the thalamus for conduction into the sensory cortex. These A-alpha and A-beta fibers provide sensory discrimination and proprioception to modulate the nociceptive sytem.[11] This large fiber system also acts as an inhibitor of the small fiber system through the dorsal horn to prevent transmission into the spinal cord tracks. This is known as the "gate-control theory" of pain modulation and can help dampen the sensation of pain initially.[12] However, with excessive stimulation, it can act as a generator of pain perception.

The small fiber system is made up of A-delta and C-fibers that are referred to as the primary afferent nociceptors (PANs), and are found in all areas of the body except the brain, liver and lung parenchyma.[11] These fibers often require tissue damage before activation, acting as a protection system by modulating the perceptions from touch into pain.[11] These fibers are unique in that they will increase their sensitivity to a stimulus, unlike large fibers, which can adapt to the stimulus. There are five separate pathways through which these small fibers project ascending nociceptive information to the cerebral cortex to activate the "general adaptive response."[13] These pathways can trigger changes in the autonomic and neuroendocrine systems, leading to a more systemic response to the stimulus.

Central PANs are responsible for the release of pro-inflammatory neuropeptides and excitatory amino acids (EAA) when activated. Glutamate is an EAA that will activate the alpha-amion-3-hydroxy-5-methyl-4-isoxazolepropioic acid (AMPA) located in the dorsal horn. After repeated stimulation, enough neuropeptides are released

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from the PAN to activate the peptide-receptor complex (PRC), which is internalized into the post synaptic neuron.[14] The PRC interacts with the cell to start the process of phosphorylation of the AMPA and N-methyl-d-aspartate (NMDA) receptors. This potentiation of the dorsal horn cells contributes to central sensitization through neuronal plasticity.[15]

This local damage and inflammation contributes to a feed-forward allostatic process by release of proinflammatory cytokines, which enhance the release of prostaglandin (PGE2) and cytokines.[11] As the tissues react, there is a potential for potentiation of the PANs, resulting in an area of somatic dysfunction and to potentially create a hyperalgesic response.

With this understanding of the physiology of pain in mind, the following three models elaborate on the facilitation of pain, including the development of a centralized response, and the role of somatic dysfunction in the development of hyperalgesia. In the first model, Dr. Richard Van Buskirk proposed a nociceptive model of input that may cause facilitation within the spinal segments through two mechanisms, including a centrifugal and centripetal action.[16] The centrifugal action occurs with the peripheral release of neurotransmitters at free nerve endings, resulting in release of substance P in a localized inflammatory response. This then results in a decreased threshold for sensitivity to the area of concern, as well as a central hypothalamic-pituitary-axis (HPA) stimulation.[16,17]

This release of proinflammatory cytokines also results in the production of nitrous oxide and an influx of calcium ions through the NMDA receptors, which have been demonstrated to increase spinal facilitation as well.[17] The centripetal action occurs with spinal cord reflex stimulation with facilitation of segments and connective tissue reorganization, as well as stimulation of the HPA axis, resulting in pain and further changes to the body via the autonomic and somatic motor system.[16]

As local tissues react to these proinflammatory cytokines and tissue damage, the development of somatic dysfunction occurs. In this next model, Irvin Korr and JS Denslow describe the neurophysiological basis of somatic dysfunction by showing that facilitated spinal segments associated with osteopathic "lesions" had a lower reflex threshold to produce an efferent response.[18] Stimulation to these areas around these facilitated segments could reproduce the excitatory response similar to direct stimulation to that area or "secondary hyperalgesia".[11,19] This finding is significant in understanding that facilitated segments, under repeated strain or trauma, can result in pain beyond the area of initial injury and can further exacerbate the patient's pain response if they were experiencing OIH.

The final model explored here is the osteopathic model of pain which identifies the cascade of unique determinates of the pain experience. These include the social environment, behaviors and musculoskeletal-immune-neurological-endocrine system (MINE) dysregulation.[20] The MINE system can be dysregulated in a multitude of ways, which can contribute to a prolonged pain experience. Immune system dysregulation can occur over time, resulting in an imbalance of Th1 and Th2 cytokines. This can lead to the body's difficulty or inability to respond to increased stressors.[20] Such an imbalance can be seen with the addition of sleep disturbances, depression, decreased activity level, and an increased focus on the pain as an identity.

In the presented case, because of the extreme external forces applied to the body, there was a significant amount of somatic dysfunction and spinal facilitation resulting in a delay in finding a balance point with the body's ability to structurally adapt.[21] The peripheral and central sensitization of pain increased as a consequence of intensification in nociceptive and neural responses to pain which resulted in hyperalgesia or central facilitation.[19] The body's response to pain may have been heightened due to this central sensitization, which was exacerbated by ever-increasing opioid use. In addition, the MINE system dysregulation created another layer of body experiences and stress for the patient to process. This case highlights an important use of OMT through recognition of physical changes in the body and an understanding of the underlying pathophysiology of pain.

This patient presented a unique but not uncommon challenge for the osteopathic care team, who are often consulted in the hospital for uncontrolled pain after all pain medication options have been exhausted. While osteopathic treatment is often considered as a complementary treatment, it is important to understand that osteopathic physicians are conventional providers who can provide rational and comprehensive care while considering the whole-patient.[22] Osteopathic physicians are trained to look at the whole body and assess for areas of somatic dysfunction that may be causing continued or recurrent disease or pain. In this patient's case, the recurrent pleural effusions were attributed to the injuries sustained to their right chest and ribcage. The lymphatic congestion and fluid stagnation was attributed to a lack of physiologic motion, which is understood to perpetuate the pathophysiology of pain. The motion of the ribs was seen as key to the movement of fluid, but also the motion of the thoracic diaphragm and the liver, which lays inferior to this structure. As the body responded to the trauma of the liver and ribcage, a dichotomy

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formed between the healing properties of the influx of fluid and the stagnation of fluid, which caused worsening pain, somatic dysfunction, and diseased state. Moreover, this case illustrates how common side effects of opioid medications, and treatment of these side effects with further medications, such as constipation and the use of stool softeners, may be avoided.[23] Early recognition of sacral, pelvic, and thoracic diaphragm restriction and continued treatment to these areas likely helped with alleviating constipation alongside the standard pharmacological agents for management.

Objectively, while no significant statistical results can be concluded from the data, in this case, loose associations can be considered. With each treatment, there was a relative stagnation or decrease in the daily MME after treatment and non-procedure days. The change of daily MME was considered with procedure days as well, given the likelihood of pain increasing with invasive procedures. With the timing of OMM, it was not always practical to treat on the same day, which left larger periods between treatments.

Furthermore, during the two separate hospitalizations, the patient reported subjective feelings of improvement after OMM treatments. The patient's feelings are important to recognize regarding the social and behavioral response to pain. The conscious awareness of the patient goes beyond sensation and includes emotions and suffering, which is highly individualized in regards to how they may overcome the dysregulation.[20]

In summary, the early recognition of hyperalgesia, tolerance, and dependence by the medical care team during the second hospitalization, as well as the use of OMM consult and treatment, led to a significant decrease in opiate use and overall pain as reported by the patient. While the fifth vital sign, pain, is often reported as a numeric scale by the patient, in this case a more accurate description of the location and sensation of pain likely guided all members of the treatment team that the patient's pain was not just worsening, but morphing into hyperalgesia.

With OIH, limited studies have shown that the pain response may improve with de-escalation of dosing, supplementing with NMDA receptor modulators, or opioid rotation to methadone.[3,9,24] When considering de-escalation, osteopathic physicians may consider OMM essential, as the potential for pain and allodynia also comes from the body's initial response to the trauma in the form of somatic dysfunction. An area for future research would be to better describe pain so that early recognition of hyperalgesia can be made with more precision.

As osteopathic physicians, we had the ability to work with the patient on describing pain during evaluation and treatment, utilizing feedback to guide treatments. Although not a unique approach, something has to be said for listening to the patient and trusting findings during a complete osteopathic physical and structural examination.

Conclusion

This case report emphasizes the need for vigilance during pain management due to trauma for prevention of both tolerance and hyperalgesia. Osteopathic manipulation can be used as an adjunctive treatment to de-escalate the usage of opioid medication. It not only helps the patient with the fight or flight response, but also helps with regulating the mu receptors, creating a state of balance in the system and helping to mitigate the effects of fluid stagnation. In addition, certain OMM techniques create an 'endocannabinoid' response that assists the patient in weaning off pain medication.

Early recognition of opioid-induced hyperalgesia in this case allowed actionable changes to treatment plans, including standard of care treatment with de-escalation of opioid medication, and the addition of osteopathic manipulative medicine.

For clinicians, this case is important to be able to recognize that acute trauma necessitates adequate pain control, but chronic pain requires mindfully knowing how and when to taper pain medications. This decrease in medication should be met with a multimodal approach to continued care based on patient feedback, as well as knowledge of the physiologic effects of opioid medications. OMM is an effective tool in management of hyperalgesia. In addition, active management of any post-traumatic stress syndrome by working with support groups in addition to physical therapy and occupational therapy will assist a patient in their recovery. As clinicians, we cannot forget the "whole-person approach" and we must "find the health" as did Dr. Still. With a mind, body, and spirit focus, this patient has proven a success story for recovery from OIH.

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