Opioid Induced Hyperalgesia (OIH)

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Purpose

The purpose of this course is to discuss the phenomenon of opioid induced hyperalgesia (OIH) and to explore healthcare recommendations, and treatment options available on this topic. Additionally clinical evidence on OIH has observed in several patient studies, exposure to long term opioid treatment may have a reduced clinical efficacy. The reduction in clinical efficacy can facilitate nociception, thereby counteracting the opioid's analgesic effect (Fishbain, Cole, Lewis, Gao, and Rosomoff, 2009).

Objectives

1. Understand the financial cost associated with pain Caused by surgery, injuries, and diseases.
2. Define chronic pain.
3. Summarize what medications fall under the category Opioids.
4. Understand the definition and Causes of Opioid-induced hyperalgesia (OIH).
5. Describe the patients presenting symptoms of Opioid-induced hyperalgesia (OIH).
6. Describe the healthcare challenges associated in treating patients with OIH

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Introduction

Parselis-Kelly, Cook, and Kaufman (2008) reports that pain is the most common reason that people seek medical attention. Pain is can also be associated with a wide range of surgical procedures, injuries, and diseases. According to the American Academy of Pain and Medicine Millions of individuals suffer from acute or chronic pain every year and the effects of pain exact a tremendous cost on our country in health care costs, rehabilitation and lost worker productivity, as well as the emotional and financial burden it places on patients and their families. In addition, the Institute of Medicine (2011) reports that pain is a significant public health problem that costs society at least $560-$635 billion annually, an amount equal to about $2,000.00 for everyone living in the U.S. This includes the total incremental cost of health care due to pain ranging from $261 to $300 billion and $297-$336 billion due to lost productivity (based on days of work missed, hours of work lost, and lower wages).

Chronic Pain

While acute pain is a normal sensation triggered in the nervous system to alert you to possible injury and the need to take care of yourself, chronic pain is different. Chronic pain persists. Pain signals keep firing in the nervous system for weeks, months, even years. There may have been an initial injury, a sprained back, serious infection, or there may be an ongoing cause of pain for example; arthritis, cancer, ear infection, but some people suffer chronic pain in the absence of any past injury or evidence of body damage. Many chronic pain conditions affect older adults. Common chronic pain complaints include headache, low back pain, cancer pain,

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arthritis pain, neurogenic pain (pain resulting from damage to the peripheral nerves or to the central nervous system itself) National Institute of Neurological Disorders and Stroke: Pain in America (2016). Management of chronic pain with medications such as opioids is a common strategy, but chronic pain can persist or worsen despite aggressive opioid therapy.

According to the National Institute of Health (NIH) (2014) opioids are medications that relieve pain. Opioids reduce the intensity of pain signals reaching the brain and affect those brain areas controlling emotion, which diminishes the effects of a painful stimulus. The medications that falls under the classification of Opioids are as follows:

Phenanthrene Opioids	**Nonphenanthrene Opioids**
Codeine, and related drugs	Piperidine derivatives:
Hydrocodone (e.g., Vicodin)	Fentanyl
Hydromorphone	Meperidine
Morphine (e.g., Kadian, Avinza)	Sufentanil
Oxycodone (e.g., OxyContin, Percocet)	**Other:**
Oxymorphone	Buprenorphine
	Methadone
	Tramadol

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Hydrocodone medication classifications are the most commonly prescribed for a variety of painful conditions. Morphine is often used before and after surgical procedures to alleviate severe pain. Codeine, is often prescribed for mild pain. When individuals continue to have chronic or persistent pain despite opioid treatment a health care provider may introduce a diagnosis of Opioid-induced hyperalgesia (OIH).

Definition and Causes of OIH

OIH first was described in the peer-reviewed literature in 1943 (Andrews, 1943). OIH has garnered increasing attention over the past two decades because numerous of patients were presenting with a persistent or increase in chronic pain despite aggressive opioid therapy. OIH can be defined as a state of nociceptive sensitization caused by exposure to opioids. The condition is characterized by a paradoxical response whereby a patient receiving opioids for the treatment of pain could actually become more sensitive to certain painful stimuli (Fallon, and Colvin, 2008). In other words somewhat paradoxically, opioid therapy aiming at alleviating pain may render patients more sensitive to pain and potentially may aggravate their pre-existing pain (Varney, and Bebarta, 2013).

Causes of OIH occurs when a patients consumes opioids chronically resulting in a paradoxical response of increased pain. OIH appears to be a distinct, definable, and characteristic phenomenon that could explain by loss of opioid efficacy in some patients. OIH is difficult to diagnose and is often under recognized, and therapies are unconventional. Health care provider should also keep in mind that OIH can be difficult to diagnose and it differs distinctly from

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tolerance, addiction, dependence, and disease progression. As previously mentioned the type of pain that a patient may experience may be the same as the underlying pain or might be different from the original underlying pain. OIH appears to be a distinct, definable, and characteristic phenomenon that could explain loss of opioid efficacy in some patients.

Patient Presentation

Mao (2002) illustrates that one of the chief problems in properly diagnosing OIH is the condition's close resemblance to opioid tolerance. Tolerance and OIH share the characteristic of reduced analgesic response to the opioid dose (patients continue to complain of pain due to tolerance), and they likely share many of the same cellular mechanisms. Tolerance can be overcome by increasing the opioid dose, whereas the same increase in a patient with OIH results in worsened pain. Additionally, tolerance tends to develop slowly over time, whereas the increased pain resulting from opioid treatment in the OIH patient occurs relatively quickly. Often, OIH differs from tolerance in that the pain intensity is stronger than initially reported (Lee et.al.; Raffa, and Pergolizzi, 2011).

Health care provider should also try to rule out untreated pain. If opioid therapy is suboptimal, increasing the dose should lead to pain relief; if OIH is present, the opposite should occur. **For an accurate diagnosis of OIH, the pain must resolve once treatment with the offending opioid is discontinued.** Li, and Clark (2002) clearly indicates that health care providers should also pay close attention to hyperalgesia resulting from opioid withdrawal, because this is also a well-documented phenomenon. It is also important to note that pain

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resolution from opioid discontinuation in OIH will not be immediate and will require patience. This poses its own challenges for both the health care provider and patient when diagnosing OIH.

Patients who have opioid induced hyperalgesia may present with:

a. Worsening pain over time in spite of, and because of, increases in opioid dose
b. Increased sensitivity to painful and non-painful stimuli.
c. Worsening pain despite increasing doses of opioids.
d. Decreased pain threshold.
e. Nociceptive sensitization
f. Pain that becomes more spread out, extending beyond the area of usual pain (harder to pinpoint).

When a patient is examined they may complain of pain from ordinary non-painful stimuli, such as stroking skin with cotton or light pressure. When a patient has OIH they patient develop an increased sensitization to pain that may be unlike their original pain.

Treatment

Health care provider should first rule out OIH by temporally reducing opioids prior to being a treatment option. If when the opioids are reduced the patient experiences less pain a diagnosis of OIH may been made. There are a number of treatment options from which a medical health care provider can choose. Provided that the initial painful injury or tissue damage has resolved and the pain persists in spite of, and because of, opioid treatment, the most

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straightforward approach is to gradually reduce, and discontinue the offending opioid. Gradual reduction of opioid may minimize adverse withdrawal effects. It should be noted that hyperalgesia may likely worsen early in the discontinuation process Hooten, Mantilla, Sandroni, and Townsend (2010).

Silverman (2009) illustrates that reducing and discontinuing opioids may presents a challenging ethical situation in which the clinician may have difficulty convincing the patient that the medication prescribed to treat pain may have been causing or worsening the pain and that the pain may get worse still before it ultimately resolves. If legitimate pain persists and some amount of analgesia with opioids is required, other strategies beyond total opioid discontinuation should be explored. Patients experiencing OIH may obtain relief by reducing the opioid dose Lee et. al., (2011).

Studies to date have demonstrated that switching from one structural class of opioids to another has been an effective option for mitigating OIH. Additionally other studies have demonstrated that OIH is more strongly associated with opioids from the phenanthrene class (Table 1) Lee et.al., (2011). Titration of the phenanthrene opioid and conversion to another may provide resolution of OIH. Lee et. al., (2011) further illustrates that Codeine, hydromorphone, and morphine are structurally similar opioids that undergo glucuronidation as part of their metabolism. Glucuronidation is a detoxification pathway that occur in the liver in which glucuronic acid is unite with other toxins. Glucuronic acid is a carboxylic acid derived from the glucose, the basic form of sugar in the human body. It is formed when glucose interacts with

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oxygen and creates a slightly different structure, through a process known as oxidation. This acid's main function is to combine with toxins and eliminate them from the body.

Conclusion

Tompkins, and Campbell, (2011) illustrates that although evidence is not entirely consistent, OIH in humans appears to pose a significant clinical challenge in acute, chronic, and cancer pain settings. Further research remains to be done before OIH can be clearly understood because the exact cellular mechanism and signaling pathways responsible for this phenomenon are not defined. Currently there are a number of ongoing clinical studies for further research on how to diagnose OIH. Further research must be done to determine the key responsible receptors and mechanisms present in OIH. The future aspiration of health care providers will be to bring more answers to the mechanisms of OIH and open the field for better treatments with the goal of pain reduction and increased quality of life for patients.

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