Mountain-Pacific Quality Health

DUR PROGRAM NEWS

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The Drug Utilization Review (DUR) Program, administered by Mountain-Pacific through a contract with the Allied Health Services Bureau of the Montana Department of Public Health and Human Services, is the quality assurance body seeking to assure the quality of pharmaceutical care and to help provide rational, cost-effective medication therapy for Montana's Medicaid recipients.

Opioid-Induced Hyperalgesia

What is Opioid-Induced Hyperalgesia?

Opioids are an important pharmacologic treatment option used in the management of moderate to severe pain. Common considerations regarding the safety and efficacy of opioids include side effects, tolerance and addiction. Clinicians may be unaware of a resulting and relevant phenomenon of opioid use in which these medications may cause new or worsening pain. The resulting condition is known as opioid-induced hyperalgesia (OIH). The most researched theory behind the development of OIH is the neuroexcitatory model. Certain opioids and their metabolites agonize the N-methyl-D-aspartate (NMDA) receptor. This causes an influx of calcium which enhances neuron excitability. More active neurons allow more readily transmission of painful impulses initiated by substance P or other painful stimuli. Glutamate is the main intrinsic agonist of the NDMA receptor. Supporting this theory are studies showing relief of OIH after administration of NMDA receptor agonists.

Why is Awareness of Opioid-Induced Hyperalgesia Important?

In the clinical setting, patient reports of increased pain while taking opioids (a paradoxical effect) may be the result of OIH. Although true prevalence is unknown, awareness of this condition is important for effective assessment and identification of potential management strategies if it is suspected. The clinical evidence supporting OIH is well documented in animals. Human studies are primarily observational studies of patients exposed to long-term methadone maintenance treatment, however, some studies have also demonstrated the development of OIH in healthy volunteers exposed to the short-term use of opioids.

Clinical Presentation and Considerations

What is the clinical presentation of OIH?

In OIH, opioid exposure results in a paradoxical increased sensitivity to a painful stimulus. Most commonly, hyperalgesia (increased response to painful stimuli) and/or allodynia (painful response to normal stimuli) may be present in OIH. Pain may be in a different region and a different quality than the original presentation.

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For drug-specific prior authorization information, please contact the Medicaid Drug Prior Authorization Unit @ Mountain-Pacific 1-800-395-7961

How is OIH distinguished from other clinical conditions?

Distinguishing OIH from opioid tolerance, disease progression, opioid withdrawal, opioid addiction and pseudo-addiction can be difficult. In opioid tolerance, a prolonged opioid exposure results in requiring a larger dose of drug over time, which will ultimately improve pain. OIH is much like pain experienced during opioid withdrawal due the similar mechanism of action.

The following table highlights the most important distinguishing clinical features between OIH and other conditions:

Condition	Clinical Features	Onset	Response to Opioid Treatment
Opioid-induced hyperalgesia (OIH)	Paradoxical increase in pain associated with allodynia and hyperalgesia. Pain may occur at a different location and can be widespread. It is usually poor defined in terms of region/quality.	Abrupt or gradual	Pain worsens
Opioid tolerance	Persistent localized pain. May occur to therapeutic or side-effects.	Gradual	Pain improves
Disease progression	Gradually worsening pain despite opioid tx. May be present in other than original site.	Gradual	Pain improves
Opioid addiction	Behavior that includes impaired control and compulsive use of drug; continued use despite harm, and craving. Pain may or may not be present.	Gradual	Pain may improve, but aberrant behavior may worsen
Pseudo-addiction	Pain is under-treated, resulting in patients seeking opioids for pain relief. Usually mistaken for addiction. Pain presents at original site.	Variable	Pain improves
Opioid withdrawal	Acute phase with adrenergic sx i.e., tachycardia, hypertension, sweating. Flu-like sx with abdominal pain/ diarrhea may also be present. Pain sensitivity increases and pain location may extend beyond that of the pre-existing site.	Abrupt	Pain improves
Physical Dependence	State of adaptation with chronic opioid use, resulting in tolerance and physical withdrawal sx when the drug is abruptly stopped or dosage reduced. Pain presents at original site.	Gradual	Pain improves

Adapted from: Differential Diagnosis of Opioid-induced hyperalgesia. Continuing Education in Anaesthesia Critical Care & Pain, Volume 14, Issue 3, 1 June 2014, Pages 125–129, https://doi.org/10.1093/bjaceaccp/mkt045.

How is OIH distinguished from other clinical conditions?

When lack of opioid efficacy is reported, several options are available to diagnose OIH and manage the symptoms of OIH depending on patient-specific needs:

- *Increase the opioid dose and evaluate for efficacy*
  -If pain is reduced with the increased dose, this is suggestive of tolerance.
  - If pain worsens, this may be suggestive of OIH.

- *Reduce or discontinue the opioid and evaluate for OIH*
  -A reduction in the dose may lessen hyperalgesia and improve pain scores.

- *Opioid rotation to a different structural class of opioid.* Studies have shown a greater incidence of OIH with specific opioids from the phenanthrene class (except oxymorphone), i.e., codeine, hydrocodone, hydromorphone, morphine, oxycodone. Fentanyl, buprenorphine, and methadone* are commonly used in opioid switching. An initial reduction in the dose of the new opioid by 25-50% must be calculated to account for incomplete cross tolerance.

- *Adjunctive treatment with, or switching to, a medication with NMDA receptor antagonist* properties (i.e., tramadol or low-dose methadone in rare clinical situations).

- *Adjunctive treatment with other opioid-sparing medications*, i.e., antidepressants, anticonvulsants, and NSAIDs.

- *Incorporation of non-pharmacological interventions* into the treatment plan, i.e., physical/psychological/interventional therapies.

OIH has been well documented in clinical studies, however additional research is necessary to further better understand the development and clinical significance of OIH. Currently, the cautious use of opioids in the treatment of non-malignant cancer pain may be the best prevention.

*Note: Montana Medicaid has implemented stringent Prior Authorization criteria for the use of methadone in non-malignant pain due to safety concerns.

Resources:

Continuing Education in Anaesthesia Critical Care & Pain, Volume 14, Issue 3, 1 June 2014, Pages 125–129, https://doi.org/10.1093/bjaceaccp/mkt045. Accessed 8/17/2017.
http://www.mascc.org/assets/documents/pain_Opioid_Induced_Hyperalgesia.pdf. Accessed 8/17/2017.
http://www.medicalmedia.co.il/publications/articledetails.aspx?artid=5395&sheetid=370 . Accessed 8/21/2017.
https://www.uspharmacist.com/article/opioid-induced-hyperalgesia-an-emerging-treatment-challenge. Accessed 8/17/2017.

Important Web Sites

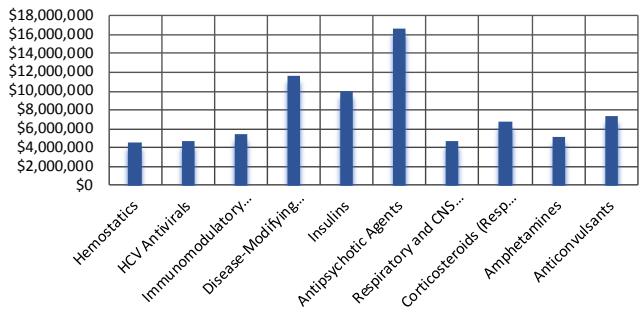
Complete CDC Guideline for Prescribing Opioids in Chronic Pain
http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

CDC Clinical Tools for Prescribing Opioids for Chronic Pain
http://www.cdc.gov/drugoverdose/prescribing/resources.html

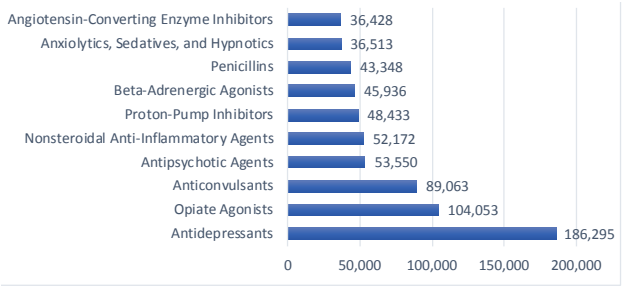
Montana Prescription Drug Registry
http://boards.bsd.dli.mt.gov/pha/pha-mpdr

Montana Medicaid Top Therapeutic Classes YTD 2017

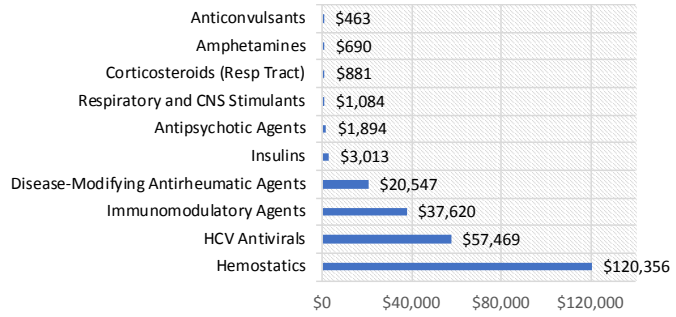
By total Claims Cost*



By number of Claims



*Average Cost Per Patient Detail



Montana Medicaid Preferred Drug List is available at: http://medicaidprovider.mt.gov/Portals/68/docs/pharmacy/2017/9817PDLFinal.pdf

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