12 February 2016
No. 3

# OPIOID INDUCED HYPERALGESIA

## A PAINFUL PARADOX

**KG Gordon**

Moderator: Dr R Hodgson

UNIVERSITY OF
KWAZULU-NATAL

INYUVESI
YAKWAZULU-NATALI

**School of Clinical Medicine**
**Discipline of Anaesthesiology and Critical Care**

## CONTENTS

# OPIOID INDUCED HYPERALGESIA

# A PAINFUL PARADOX

## INTRODUCTION

Global opioid consumption has increased fifty fold over the past twenty years. [1] This is likely due to a combination of the array of new synthetic opioids available for the management of both acute and chronic pain together with aggressive marketing strategies employed by the pharmaceutical industry; an aging world population with a new burden of chronic illness, greater patient access to opioid analgesics and changing prescription practices amongst physicians. [1-3]

Despite the fact that these drugs are controlled substances, their use and abuse in the United States of America (USA) is currently especially prolific. The Centres for Disease Control (CDC) have reported that enough prescription opioids were sold in the USA in 2010 to supply every American adult with 5mg of hydrocodone (Vicodin® - as taken by Dr. House) every 4 hours, for a month. [1] These narcotics, once solely employed for perioperative analgesia and palliative analgesia in cancer patients, are now being used by more and more patients over increasingly prolonged periods.

The more extensive use of opioids has led to a greater appreciation of side effects associated with chronic opioid use. Clinicians are familiar with side effects involving the gastrointestinal, skin, and central nervous system and the potential for dependence and addiction. However, the potential for an opioid to worsen rather than alleviate pain is not well recognised by clinicians outside pain clinics. Opioid induced hyperalgesia (OIH), acute opioid tolerance and opioid overuse pain syndrome (OOPS) are all relatively new concepts that have emerged in pain literature over the past 10 years to describe this phenomenon. [3-7]

This review will examine OIH more closely in order to more fully grasp the double edge sword that is opioid-induced hyperalgesia.

The aims are to:

- Describe the pathophysiology associated with OIH
- Review current management strategies for acute pain in the perioperative setting with a goal of opioid sparing or elimination in order to prevent OIH
- Review analgesic strategies for the chronic pain patient with established OIH both in the acute perioperative setting and in their long term management.

## DEFINITIONS

### Opioid Induced Hyperalgesia

OIH may be defined as the phenomenon of nociceptive sensitisation caused by exposure to opioids. [8] This sensitisation is distinct from the original pathology that caused pain; and is due to central and peripheral mechanisms within the nervous system that promote a pronociceptive state. [9] OIH occurs in the absence of opioid withdrawal or tolerance.

OIH is a clinical paradox: with pain perceived as worsening with the administration of increasing doses of opioids. [10] This increased sensitisation to pain may be accompanied by features of neuropathic pain; such as hyperalgesia and allodynia, either in the area of original pain or as a more indistinct generalised pain. [10]

A more specific consensus definition is required to facilitate research into this currently poorly understood condition. Unfortunately an accurate, well accepted definition remains elusive. [11] Basic science provides insights into the basic science of OIH but there are not only inter-individual variations within species but wide inter-species differences making extrapolation between species problematic. The perception of pain is measured in experimental animals by tolerance of nociceptive stimuli (tail clamp, hotplate).

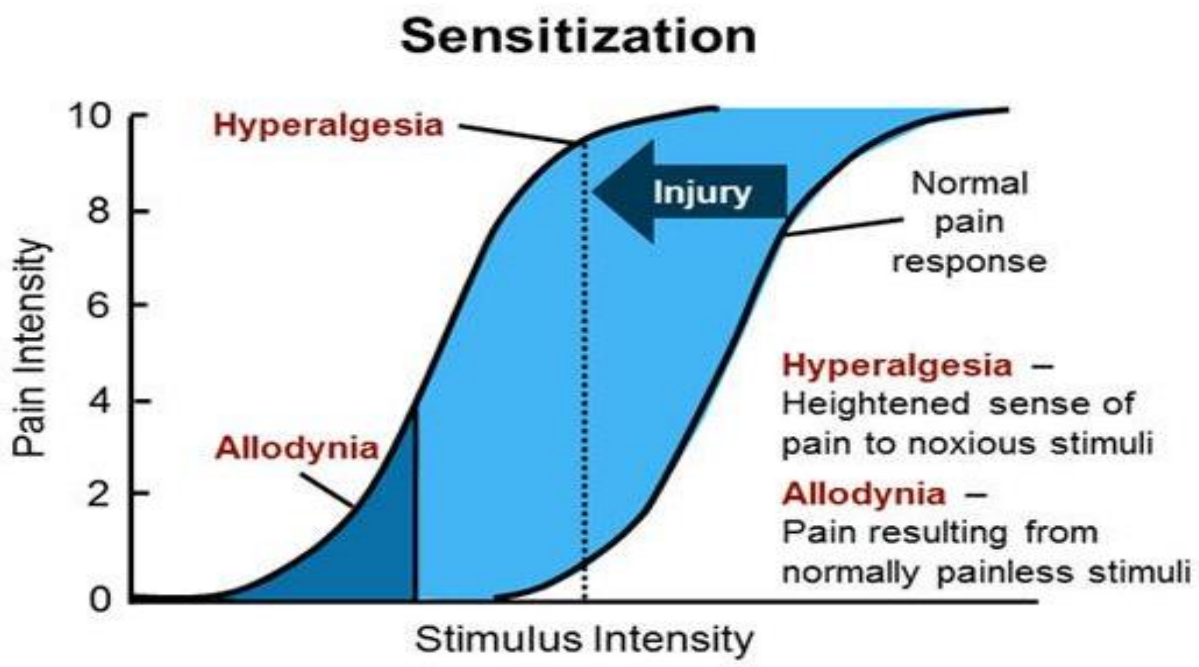
Experiments on human subjects use a combination of far less potent stimuli that are integrated in Quantitative Sensory Testing (QST) requiring expensive equipment with limited application outside academic medical centres. [12] A reduction in baseline pain threshold or tolerance after opioid exposure may be demonstrated by QST to define OIH. [11] The validity of QST has not been generally accepted making comparison of data and drawing of consensus conclusions difficult. [2]

### Pain threshold

Pain threshold is defined as the lowest stimulation intensity at which pain is first experienced. [12] This intensity of the stimulus may be measured – in units of pressure with mechanical stimulus or temperature with thermal stimulus – and thus compared with subsequent applications of the stimulus in experimental testing.

### Pain Tolerance

Pain tolerance is a measure of the maximum pain perceived from a given stimulus before an individual must seek relief. [12] As with pain threshold, pain tolerance may be measured numerically using various painful stimuli. Pain threshold and pain tolerance are recognised as two distinct and separate entities with two different underlying psychophysical mechanisms. [2]




**Hyperalgesia**
Hyperalgesia is an increased response to a noxious stimulus that is normally experienced as painful. The level of pain experienced is greater than that normally in keeping with the level of stimulus.

**Allodynia**
Allodynia is the perception of a non-noxious stimulus as painful.

**Hyperpathia**
Hyperpathia is the pain experienced following exposure to a noxious stimulus. The pain response outlasts the stimulus duration and may spread beyond the site of stimulus application.

**Opioid Tolerance**
Opioid tolerance is distinct from OIH, but may appear clinically similar: with pain despite opioid administration. Tolerance occurs with prolonged exposure to the drug and subsequent right shift of the normal dose- response curve of the agent. [8] This state develops due to opioid receptor changes and down regulation at a more peripheral level. Tolerance may present in the acute or chronic setting with either a rapid or a gradual loss of potency and efficacy of the drug. [1]

While OIH and tolerance may present in a similar fashion, their clinical management may distinguish them: increased doses of opioid will induce analgesia in the case of tolerance, but worsen OIH. [8] It should however be borne in mind, that tolerance and OIH may co-exist – this presents a management conundrum.

**Opioid Overuse Pain Syndrome**
Opioid overuse pain syndrome (OOPS) is recently proposed term to encompass the clinical syndrome encountered with opioid non-responders or high dose requiring patients. [1]

This group of patients may be further categorised into the following underlying pathologies:

- Opioid induced hyperalgesia
- Opioid abusers and addicts
- Opioid tolerant (Pseudo-addiction)
- Misdirected use of opioids as mood modulators. [1-3]

These patients should be reviewed by a pain specialist with the aim of gradual withdrawal of opioids and institution of other psychiatric and analgesic regimes. [1]

## HISTORY OF OPIOID INDUCED HYPERALGESIA (OIH)

Opiates are among the first drugs employed by early healers. Their use predates modern history with records of these agents found in relics from Ancient Mesopotamia, Greece and Egypt. Yet the paradox of opioid-induced hyperalgesia has only been appreciated relatively recently. Albutt and later Rossbach described the consequences of opiate dependence in the latter half of the nineteenth century. [4] Both noted that the narcotics, after chronic use, produced a clinical effect that differed significantly to the expected analgesia and sedation: restlessness, hyperesthesia and neuralgia were noted. [4]

Andrews was the first to formally describe this phenomenon and coined the term in a 1943 paper on opioid-induced hyperalgesia in recovering opioid addicts. [3, 13] Much of this early work was done on methadone addicts, with limited other patient populations exposed to chronic opioids during this time period. [3, 13] Subsequently it was viewed as something of a curiosity: a fascinating pharmacological concept, but of little clinical relevance in the field of pain management. [2]

It took the introduction of remifentanil onto the market in the 1990's along with the advent of a prescription drug abuse problem to create a renewed interest in this field. [13, 16] Remifentanil, with its' promisingly short context sensitive half-life was mired by the acute opioid tolerance and opioid-induced hyperalgesia that developed in its wake. Here was a clinically relevant extension of the previously essentially academic problem. [12, 16]

As a result we have seen an increasing interest into the development and prevention of OIH in the acute perioperative setting over the past twenty years. OIH's impact on the field of chronic pain is also emerging as an area of interest in more recent literature. [3, 14-16]

Despite the recent interest in OIH, understanding of the condition is still limited. While numerous clinical and preclinical studies have demonstrated the existence of OIH and its clinical relevance, further studies are still required. [2, 4, 5] Studies should address the pathophysiology and neurobiology underlying OIH and clinical techniques to prevent and manage OIH need to be proposed and validated.

## PATHOPHYSIOLOGY

Endogenous opioids act via binding to one of four opioid receptors:

- Mu-opioid peptide receptor (MOP)
- Delta-opioid peptide receptor (DOP)
- Kappa-opioid peptide receptor (KOP)
- Nociception/orphanin FQ peptide receptor (NOP). [8]

These receptors are distributed throughout the central and peripheral nervous system. When bound and activated these G-protein coupled receptors cause closure of voltage gated calcium channels and simultaneous potassium efflux. Subsequently neuronal hyperpolarization occurs and an anti-nociceptive state is generated. [8]

Different opioid molecules found in the various natural and synthetic opioids have varying affinities for each of the different receptor subtypes. [5, 7, 8] Opioid tolerance develops chiefly at one sort of receptor with chronic exposure to an agent; and is thus potentially amenable to management with opioid rotation techniques. [4, 8]

This traditionally held view of opioid receptor physiology fails to describe the paradoxical pro-nociceptive state observed in OIH. More recent research has highlighted a number of mechanisms that may start to explain OIH. Most of these mechanisms are postulates and more work is underway in this sphere. [4, 5, 7, 8] It seems likely that OIH is a multifactorial phenomenon with central and peripheral processes contributing to the clinical picture of OIH. [4, 7]

It appears that OIH is produced via various central mechanisms including:

- **NMDA receptor activation**
  This mechanism is central to most work in understanding the pathophysiology of this phenomenon. Both acute and chronic opioid exposure increases activity in the central glutaminergic system. Down regulation of glutamate transporters within the spinal cord with subsequent elevated glutamate levels and increased NMDA receptor occupancy and activation have been shown to induce spinal neuron sensitisation. [4, 7, 8] NMDA receptor antagonists have thus been identified to play an important role in the prevention and management of OIH. [4, 7, 8]

  Chronic opioid administration has also been demonstrated to mediate neurotoxicity via the NMDA receptors in the anterior horn cells of the spinal cord. [4] Apoptotic changes occur within the central and peripheral pain pathways with loss of modulation and increased sensitisation. [4, 7]

- **Increased spinal dynorphins activation**
  Dynorphins are naturally occurring opioid peptides that increase in the face of chronic exogenous opioid peptide exposure. [4, 7, 8] Increased dynorphins levels at spinal cord level stimulate the release of excitatory agents including cholecystokinin (CCK) and calcitonin gene-related peptide (CGRP). These in turn generate a pronociceptive environment with central sensitisation. [7, 8]

- **Enhanced descending facilitation**
  It is well established that nociceptive transmission in the peripheral nervous system and spinal cord may be modulated by descending inhibitory or excitatory input from the brain itself. The rostral ventral medulla (RVM) and periaqueductal grey matter of

the brainstem are two areas that have been identified as significant sources of input for this facilitation. [7, 8] Both of these areas are rich in opioid receptors.

It has been illustrated that central opioid receptor activation in these areas can in turn mediate descending excitatory pathways. [7, 8] This descending facilitation effectively sensitises the spinal and peripheral afferents, promoting ascending nociceptive input and a hyper-algesic state. [4-8] Research subjects with spinal cord lesions and thus lacking the necessary descending pathways do not exhibit the increase in neuro-excitatory transmitters and sensitisation. [4]

These changes in neuroplasticity are commonly encountered in chronic pain states in isolation. The addition of chronic opioid therapy seems to amplify this phenomenon. This mechanism requires chronic exposure to central opioids to develop, and does not fully describe the acute OIH seen in the perioperative period with the use of remifentanil and related agents.

- **Altered opioid receptor responsiveness**
  This is another proposed mechanism that chiefly describes OIH in the patient with chronic opioid exposure. It demonstrates that long term opioid use causes a switch from the normal G-protein linked inhibitory receptor to a different excitatory-coupled mechanism. [7, 8] This alteration in function occurs through an alteration in cell membrane structure with glycolipid complex substitution. [7, 8] This excitatory activity appears to contribute to OIH and tolerance. This explains the thought process behind managing OIH with small doses of opioid antagonists.

OIH may also be induced via certain peripheral mechanisms:

- **Peripheral opioid receptor changes**
  Studies have demonstrated that opioids need not reach the central nervous system in order to generate OIH. Peripheral opioid receptors can undergo similar changes in structure and function as those described previously and lead to clinically relevant OIH. [4, 7, 8]

- **Serotonin receptor activation**
  The activation of 5HT2 and 5HT3 receptors in patients receiving chronic opioid analgesia has also been implicated in the development of OIH. [4] Despite the fact that centrally serotonin is generally implicated in descending modulation to inhibit a pro-nociceptive state; preclinical studies have shown that serotonin antagonists such as Odansetron may be helpful in the management of OIH. [7, 8]

- **Calcium channel changes**
  Calcium regulated intracellular protein kinase C has been identified as a possible link between chronic opioid exposure and OIH. [4, 7] The specifics remain to be defined.

- **Genetic factors**
  There is mounting evidence that genetics influence pain threshold, tolerance, response to analgesia and OIH. The Catechol-O-methyltransferase (COMT) enzyme is one of the identified genetic components that contribute to pain perception. [4] Three possible genetic polymorphisms of the enzyme exist, with resultant various breakdown rates of synaptic neurotransmitters, including those involved in nociception and modulation and sensitisation. [4]

- **Activation of pronociceptive substances**
  There has also been research into the manner in which OIH may be linked to the activation of peripherally acting pronociceptive substances including substance P, nitric oxide and numerous cytokines and chemokines. [4, 7, 8] Research regarding specifics is ongoing.

## CLINICAL FEATURES

OIH may present as allodynia, hyperalgesia or both in the clinical setting. [8] Pain experienced is typically described as more diffuse than expected by the underlying injury. It often manifests in areas beyond the original tissue damage. It will also worsen with ongoing opioid use. [4, 5, 8, 9]

It may be difficult to distinguish clinically between OIH, opioid tolerance and underlying disease progression. The following table illustrates the subtleties that may help in identifying each entity.

**Table to distinguish between OIH and other clinically similar syndromes** [8]

| Entity | Clinical Picture | Onset | Response to Opioids |
|---|---|---|---|
| OIH | Allodynia<br>Hyperalgesia<br>Diffuse, poorly localised site of pain | Acute or gradual | Worsening pain |
| Opioid tolerance | Persistent localised pain | Gradual | Analgesia at higher doses |
| Disease Progression | Worsening pain<br>Localised but may extend beyond original injury | Gradual | Analgesia |
| Opioid addiction | Psychological compulsion to consume drug<br>Pain may or may not be present | Gradual | Analgesia |
| Opioid withdrawal | Adrenergic symptoms<br>Pain if present worsens, hyperalgesia | Acute | Analgesia |

As mentioned earlier, Quantitative sensory testing (QST) is the current tool employed in pain research to diagnose and quantify OIH. It is a standardised pain assessment tool that involves the application of predetermined stimuli, in a controlled environment with uniform instructions and evaluation protocols. Basic principles used in these protocols employ ie. the application of a mechanical stimulus through the application of a monofilament at progressively increasing pressures to a test subject to establish a baseline pain threshold and then compare this baseline threshold to levels identified after opioid usage. QST thus allows the clinician to assess peripheral and central pain perception and processing indirectly. [8, 17]

## PRECLINICAL EVIDENCE

Much research has been done in murine models to establish the existence of OIH and elucidate the mechanisms that cause it. [5] OIH has been established to exist as an entity in animal studies. [4-8]The current multifactorial model of the neurobiology of OIH is due to accumulation of preclinical evidence, which continues. [5]

OIH has been identified in laboratory animals exposed to morphine, fentanyl, remifentanil and heroin. [5] OIH has been shown to develop in chronic opioid usage and in the acute perioperative setting. [5, 7] Opioids administered peripherally and intrathecally have both been implicated in the development of OIH in the preclinical setting. [5]

## CLINICAL EVIDENCE

Over the past 20 years many observational, cross-sectional and prospective controlled trials have examined OIH and its clinical implications in humans. [4 – 7] Early clinical evidence in this field was chiefly based on observational data from opioid addicts on methadone therapy. [5] Newer research has focused on the development of OIH in chronic opioid users with non-cancer pain; in the acute perioperative setting and in healthy volunteers exposed to opioids for the purpose of experimental testing. [4 – 6]

It should be borne in mind that this research represents four vastly different categories of patient, and not all of the findings regarding OIH may be generalizable between all groups. For example few prospective studies amongst patients with chronic non-cancer pain initiated on opioid therapy have demonstrated the existence of OIH in humans after a month of morphine therapy. [7] Whereas healthy volunteers exposed to acute opioid therapy demonstrated OIH with thermal stimuli only. [5, 7] The presence of pain significantly influences response to opioids with tolerance and OIH developing less frequently with ongoing, particularly nociceptive, pain.

Much work is currently underway to establish exactly which opioids are capable of generating OIH, at which doses, over which time periods. Techniques for managing established OIH are also being examined, as are preventive strategies and protective agents. Further detail with regards to clinical evidence will be examined in more detail in the rest of this review.

## PROBLEMS WITH THE EVIDENCE

The lack of a universal definition of OIH means that continuity across the research and pain literature is limited.

QST is a useful tool in describing pain perception, but requires rigorous standardisation in terms of environment, instruction and evaluation that confines this modality to academic pain clinics. Uniformity in testing between different studies and investigators is difficult, thus comparisons of the literature in meaningful reviews or meta-analyses are lacking.

Further confounders that may colour the evidence and limit meaningful comparisons include modality of pain stimulus; type, dose and route of opioid administered and patient category receiving the drug. [5 – 8] The potential for over-lap with opioid tolerance is another big problem in this field of research.

The small sample sizes also make many of these studies underpowered.

## OIH AND ACUTE PAIN

The development of OIH in the acute setting in terms of the perioperative period has been described. A recent meta-analysis my Fletcher et al examined 27 studies including 1494 patients whom developed OIH after exposure to intraoperative opioids. [16] This review confirmed that OIH does occur in the acute setting, with patients receiving high-dose intraoperative opioid experiencing significantly increased pain in the postoperative period. [16] Pain threshold was noted to be most reduced during the first hour postoperatively when compared to baseline and lowered for a 24 hour period post-surgery. [16] Additionally more opioid – morphine – was consumed during the first day post operatively with subsequent increased nausea, vomiting and sedation. [4, 16]

The development of OIH has been reviewed with regards to:

- **Opioid type**
  Though animal studies and chronic pain studies have illustrated the development of OIH in the presence of multiple different opioids; OIH in the acute setting can only be definitively linked to remifentanil. [12, 16] While there is less evidence reviewing the use of fentanyl and sufentanil compared to remifentanil, the limited data available displays no clinically relevant OIH. [16]
  One study has actually illustrated the superiority of sufentanil over remifentanil in the prevention of OIH. [18] Another study has estimated the prevalence of OIH after peri-operative remifentanil use at approximately 16%. [19]

- **Route of administration**
  OIH has the potential to develop regardless of route of administration. The intravenous route has been implicated in most studies, potentially because this is the chief route that the primary offending agent – remifentanil – is administered. [16]

- **Cumulative dose**
  Fletcher et al were unable to definitively identify a cut-off remifentanil cumulative dose, infusion rate or target effect site concentration above which OIH develops. [16] Other reviews suggest a cut-off of 0.1mcg/kg/minute or an effect site concentration of 2.7ng/ml. [12]
  Though no specific cumulative dose has been identified, the principle exists that the larger the dose employed, the higher the chance of OIH in the perioperative period. [2, 4 -9, 12, 16]

- **Duration of exposure**
  It has been postulated that longer duration of exposure to intra-operative remifentanil regardless of cumulative dose can contribute to OIH. Limited data exist

to evaluate this point. Investigators have shown that clinically relevant OIH may develop in as short a period as 30 minutes. [4]

- **Technique of withdrawal**
  The abrupt cessation of a remifentanil infusion versus a more controlled decline in infusion rate has also been suggested to play a role in OIH. No studies have formally investigated this issue as a primary outcome. Further investigation is needed on this point in the future.

- **Identifying the patient at risk for OIH**
  The potential to identify at risk patients for OIH and attempt to limit or even avoid perioperative opioid is appealing, but currently not clinically feasible. As expressed earlier genetics may play a role in the evolution of OIH. Research has illustrated that patients with specific COMT enzyme genotypes are more likely to experience OIH, yet routine screening is not warranted in daily practice. [5] Sex also appears to play a role in OIH development, with female sex being identified as a risk factor. [10, 14] Personality traits and psychiatric illness – specifically depression - have also been demonstrated to contribute. [4]

## OIH AND CHRONIC PAIN

OIH may occur in patients with chronic pain in one or more ways. Firstly, hyperalgesia and increased perioperative pain are recognised risk factors for the development of chronic pain. [20] In a recent study intra-operative remifentanil usage has been implicated in the emergence of chronic thoracic pain following cardiac surgery. [21]

Secondly, patients with chronic non-cancer pain may develop OIH with chronic opioid maintenance therapy. [4, 22] Studies have indicated that OIH may develop relatively quickly with demonstrable hyperalgesia present within a month of therapy initiation in opioid-naïve patients. [14, 22]

As with the field of acute pain, no precise cut-offs in terms of dosage or duration of treatment have been recognised. However, the principle that the higher the dose and the longer the course of opioid, the higher the risk of OIH, stands firm. [14, 22] Unlike the perioperative setting, where remifentanil exclusively seems a problem, numerous causative agents have been identified in this area. Hydromorphone, morphine, fentanyl, methadone and codeine have all been implicated. [2, 4, 14, 22]

Finally, patients with established OIH – such as a chronic pain patient on opioids – presenting for surgery poses another challenge to the anaesthetist. This is a subset of patients where little literature and subsequent guidance currently exists.

## PREVENTION OF OIH

Various strategies have been proposed to prevent the development of OIH. Most of the available literature explores the acute perioperative setting. Limited research has reviewed the prevention of OIH in the chronic pain setting. It appears that prevention is more effective than management – once established, OIH is a challenge to treat. [16]

Proposed pharmacotherapies to prevent OIH include:

- **Opioid choice and limitation of dose**
  This technique – limiting intra-operative use of remifentanil and reducing the cumulative dose administered is widely recommended. [4, 8, 16] Research is currently ongoing to establish optimum infusion levels and maximum safe doses. [12] Steps to limit opioid use include the use of multimodal analgesia: simple analgesics, regional nerve blocks and neuroleptics. The use of target controlled infusions compared to continuous infusions for the administration of remifentanil in an attempt to limit opioid dose and prevent postoperative OIH has been evaluated and showed no significant difference in terms of OIH. [16]

- **Pre-treatment with morphine**
  The pre-emptive administration of morphine in patients undergoing surgical procedures requiring prolonged remifentanil infusions has been described as a means to prevent OIH and acute tolerance. [23] The theory that two alternative agonists with slightly different opioid receptor binding preferences and duration of action could limit OIH has unfortunately proved untrue with no clinical significant difference in pain scores or opioid requirements in the first 24 hours post operatively. [23]

- **Ketamine**
  Much work has gone into evaluating NMDA receptor antagonists in the prevention of remifentanil induced OIH. Ketamine in particular has garnered much attention and some conflicting evidence. [24, 25] Early work suggested that low dose ketamine – an initial bolus of 0.5mg/kg administered prior to remifentanil infusion, followed by a continuous infusion of 2mcg/kg/minute could prevent OIH. [4, 8, 24] It has also shown to be helpful in controlling perioperative pain in chronic opioid users and impede the development of opioid tolerance in this group. [4]

  However, a more recent meta-analysis by Liu which reviewed 14 prospective randomised control trials and 623 patients undergoing a variety of surgeries with remifentanil-based analgesia failed to illustrate a statistically significant reduction in postoperative pain scores, overall analgesic requirements or time to first morphine bolus postoperatively. [25] Despite the lack of statistical significance, there was a trend to reduced OIH in the presence of ketamine. [25]

  In the face of this controversy, many authorities in the field continue to recommend the use of low dose ketamine (<0.3mg/kg bolus / <0.3mg/kg/hr). At these low doses significant side effects are rare, but profound analgesia may reduce opioid requirements and modulate the development of acute tolerance. [6, 8, 26] More research is required to definitively answer this question.

- **Nitrous oxide**
  Another NMDA antagonist and analgesic, nitrous oxide has been explored in limited work. Fletcher et al in their 2012 meta-analysis on OIH were unable to test its impact on remifentanil-induced OIH due to insufficient numbers. [16]

- **Magnesium**
  Magnesium was reviewed along with ketamine in Liu's meta-analysis of NMDA antagonism and the prevention of OIH. As with ketamine, there was no statistically significant reduction in OIH in the magnesium group. [25] The dosage regime used was a 50mg/kg bolus of magnesium sulphate followed by a continuous infusion of 10mg/kg/hr. [25]

- **Dextromethorphan**
  Dextromethorphan is another NMDA antagonist used chiefly as an anti-tussive. Interest surrounding its use in the prevention and management of OIH has waned after several large studies have failed to show significant effects. [4]

- **Propofol**
  The use of propofol as opposed to sevoflurane, desflurane or halothane in the maintenance of anaesthesia on patients receiving remifentanil infusions has been shown to be protective. [16, 27] Patients receiving propofol administered using target controlled infusions (TCI) using the Schnider model demonstrated significantly lower post-operative pain scores and opioid consumption in the perioperative period than those maintained on sevoflurane in a study by Shin et al. [27]

- **Paracetomol**
  Paracetomol has been demonstrated to be effective in preventing remifentanil induced OIH when administered as a 1g intravenous loading dose prior to induction of anaesthesia. [28]

- **NSAIDs**
  COX-2 Inhibitors, particularly Parecoxib have also generated interest as potential preventive agents. Prostaglandins play a central role in the modulation of nociceptive processing. Through their inhibition with the COX-2 inhibitors, the pro-nociceptive state that develops in OIH may be limited. [4, 8]

- **Naloxone**
  An interesting view on the prevention of OIH entails the co-administration of an opioid agonist and an ultra-low infusion of an antagonist: naloxone. The rationale behind this co-administration is due to naloxone's high affinity for the mu-opioid receptor implicated in remifentanil-induced OIH. Antagonism of this receptor and specifically its binding to the C-terminal of this mu-receptor is considered the cause of an observed enhancement of opioid analgesia and the prevention of OIH. [4, 29]

  Infusions of 0.25mcg/kg/hr of naloxone administered during the operative period have been linked to reduced opioid consumption postoperatively and fewer opioid related side effects including nausea and vomiting, but has not shown a statistically significant reduction in pain scores. [29]

Psychological interventions have also been proposed. [8] Cognitive behavioural therapy and management of associated mood disorders have been shown to be effective in the prevention of other chronic pain states. [8] This knowledge may transfer to OIH.

## MANAGEMENT TECHNIQUES

The management of established OIH is time consuming and difficult. Perhaps the most important aspect is establishing a diagnosis and differentiating OIH from opioid tolerance. [8] The administration of an increased dose of opioid will induce analgesia in the tolerant patient but worsen the pain in OIH. [4, 8] Alternatively, and reducing or discontinuing the opioid will improve analgesia in OIH but worsen tolerance. [4, 8] This system is imperfect – we should be striving to alleviate pain, not use it as a diagnostic test – yet this is what is currently available.

Once a diagnosis of OIH has been established, a variety of management options exist:

- **Opioid dose reduction**
  Though perhaps a counter-intuitive step in the management of pain, a reduction in the dose of opioid has been illustrated to reduce OIH and improve pain scores. [4, 5, 8] A dose reduction by as much as 50% has been proposed and observed to improve outcome. [5] This dose reduction may be used in isolation or in conjunction with other opioid limiting techniques including multimodal analgesic programmes. [8]

- **Opioid rotation**
  Different classes of opioids exist – phenanthrenes, phenylheptylamines and phenylpiperidines. Chronic use of one class may result in OIH and tolerance, the intermittent rotation of drugs may limit this as cross-tolerance between classes is limited. [8] The substitution to methadone with its weak NMDA antagonism, serotonin and noradrenalin re-uptake inhibition and long half-life has shown particular promise. [4, 5, 8] Its use has been limited by its side effect profile and drug interactions. [4, 5, 8]

- **Opioid antagonists and partial agonists**
  Buprenorphine, with its agonism at the mu-receptor and kappa-receptor antagonism has been shown to mitigate the effects of OIH – probably by blocking spinal dynorphins kappa-receptor interaction. [4, 5, 8] It is a versatile drug that may be administered in an out-patient setting and therefore very useful for chronic pain patients with OIH.

  The use opioid antagonists - in the form of naloxone - are documented in the short term management of OIH. [29] Chronic therapy for OIH combines naloxone with buprenorphine – a partial agonist – in the drug suboxone. [30] Studies have shown the drug to be effective in the management of chronic pain patients with OIH. It appears preferable to the use of buprenorphine or methadone alone in terms of analgesia and side effect profile. [4, 30]

- **NMDA Antagonists**
  NMDA antagonists – particularly ketamine - have been investigated for both the prevention and management of OIH and acute opioid tolerance, and appear to be the drugs of choice to administer in the setting of acute postoperative OIH. [4, 5, 8] Their rapid onset of action will provide immediate relief and begin to mitigate the effects of OIH and tolerance.

  However, this short half-life and associated side effects limit ketamine's utility in the management of OIH in the chronic pain setting. [8] The use of oral ketamine has been described for problem cases: a mean effective dose of 200mg for the poorly

bio-available preparation has been suggested, with 6hrly dosing intervals. [8] Dextromethorphan has also been investigated – its NMDA antagonism together with a more favourable side effect profile appeared a better choice – however results have proved disappointing. [4, 5, 8]

- **Gabapentin**
  Gabapentin – a GABA analogue – has an established role in the management of chronic neuropathic pain. Preclinical studies and some case reports suggest that it may also be useful in the management of OIH. [31] Through the agent's inhibitory action on spinal cord calcium channels and spinal interleukins, OIH's pronociceptive state may be countered. [31] Further research is required in this domain.

- **Alpha 2 Adrenergic Agonists**
  Alpha 2 adrenergic agonists clonidine and dexmedetomidine have been illustrated to attenuate the effect of OIH. [4, 5] These drugs, used frequently in both the management of acute and chronic pain should be considered in the management of OIH, though specific treatment regimens need further investigation. [4, 5]

- **Non-pharmacological interventions**
  There is a role for non-pharmacological interventions in the chronic setting as with all patients experiencing chronic pain. Cognitive behavioural therapy, physical therapy and even spinal cord stimulators have been used in conjunction with pharmacological techniques. [4, 8]

## CONCLUSION

In conclusion, OIH remains a fascinating pharmacological phenomenon that we as clinicians are only starting to fully appreciate. We should be sensitive to this phenomenon in the management of both acute pain in the perioperative setting specifically when employing remifentanil-based techniques and also in chronic pain clinic in patients on long term morphine.

A pre-emptive approach to the prevention of OIH should be adopted through:

- Avoiding or limiting opioid use where possible
- Use of a multimodal analgesic approach
- NMDA antagonist usage
- Propofol TCI when employing Remifentanil analgesia.

Management of established OIH should occur in conjunction with a pain specialist and should include:

- Use of alternative multimodal analgesic strategies including NMDA antagonists, gabapentinoids, alpha 2 agonists and non-pharmacological interventions
- Opioid reduction and rotation
- Opioid antagonists and partial agonists.

Ongoing research in this expanding field should also begin to yield interesting developments and provide more definitive guidelines over the next few years.

## REFERENCES


1. Opioid overuse pain syndrome (OOPS): The story of opioids, Prometheus unbound. Mehendale AW, Goldman MP, Mehendale RP. Journal of Opioid Management 2013 Nov-Dec; 9(6): 421-438
2. Opioid-Induced Hyperalgesia: Clinically Relevant or Extraneous Research Phenomenon? Tompkins DA, Campbell CM. Curr Pain Headache Rep 2011; 15:129–136
3. Prescription opioid abuse, pain and addiction: Clinical issues and implications. Ling W, Moony L, Hillhouse M.Drug and Alcohol Review. 2011 May;30 300–305
4. A Comprehensive Review of Opioid-Induced Hyperalgesia. Lee M, Silverman S, Hansen H, Patel V, Manchikanti L. Pain Physician 2011; 14:145-161
5. Opioid-induced Hyperalgesia in Humans: Molecular Mechanisms and Clinical Considerations. Chu LF, Angst MS, Clark D. Clin J Pain 2008 July-Aug; 24(6):479-496
6. Opioid-induced hyperalgesia: pain hurts? Konopka KH, Van Wijhe M. BJA. 2010; 105(5): 555-557
7. Opioid-induced hyperalgesia: a clinical challenge. Colvin LA, Fallon MT. BJA. 2010; 104(2): 125-127
8. Opioid induced hyperalgesia. Velayudhan A, Bellingham G, Morley-Forster P. CEACCP. 2014; 14(3): 125- 129
9. Opioid-induced Hyperalgesia: An emerging treatment challenge. Bottemiller S. US Pharmacist 2012 June; 16: 1-5
10. Analgesic tolerance without demonstrable opioid-induced hyperalgesia: a double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain. Chu LF, et al. Pain Feb 2012; 28(2): 1- 10
11. Complications of Long-Term Opioid Therapy for Management of Chronic Pain: the Paradox of Opioid-Induced Hyperalgesia. Brush DE. J. Med. Toxicol. 2012; 8:387–392
12. Intraoperative use of remifentanil and opioid induced hyperalgesia/ acute opioid tolerance: a systematic review. Kim S, Stoicea N, Soghomonyan S, Bergese SD. Frontiers in Pharmacology. 2014 May; 108(5): 1-9
13. Opioid induced Hyperalgesia in Anaesthetic settings. Lee HS, Yeomans DC. Korean J Anesthesiol 2014 November; 67(5): 299-304
14. Opioid induced hyperalgesia in the chronic pain patient and the mitigating effects of gabapentin. Stoicea N, et al. Frontiers in Pharmacology. 2015 May; 104(6): 1-6
15. What do we know about opioid induced hyperalgesia? Chen LL, J Com. 2014 Mar; 21(3): 169-175
16. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Fletcher D, Martinez V. BJA 2014 May; 112(6): 991-1004
17. Quantitative sensory testing in measurement of neuropathic pain phenomena and other sensory abnormalities. Backonja MM, et al. Clin J Pain 2009 Sep; 25(7): 641-647
18. Influence of peri-operative opioid on postoperative pain after major abdominal surgery: sufentanil TCI versus remifentanil TCI. A randomized, controlled study. Derrode N, et al. BJA 2003; 91(6): 842-849
19. Cohort study of remifentanil-induced hyperalgesia in postoperative patients. Ma JF, Huang ZL, Li J, H SJ, Lian QQ Zhonghua Yi Xue Za Zhi 2011; 91: 977–979
20. Postoperative hyperalgesia: its clinical importance and relevance. Wilder-Smith OH, Arendt-Nielsen L. Anaesthesiology 2006; 104: 601-607

21. Remifentanil during cardiac surgery is associated with chronic thoracic pain one year after sternotomy. Van Gulik L, et al. BJA 2012 July; 100: 1-7
22. A Negative Correlation Between Hyperalgesia and Analgesia in Patients with Chronic Radicular Pain: Is Hydromorphone Therapy a Double-Edged Sword? Suzan E, Eisenberg E, Treister R. Pain Physician 2013; 16:65-76
23. Pre-treatment with morphine does not prevent the development of remifentanil-induced hyperalgesia. McDonnell C, et al. Can J Anaesth. 2008 Dec; 55(12): 813-819
24. Remifentanil-induced Postoperative Hyperalgesia and Its Prevention with Small-dose Ketamine. Joly V, et al. Anesthesiology 2005; 103:147–55
25. The efficacy of NMDA receptor antagonists for preventing remifentanil-induced increase in post-operative pain and analgesic requirements: a meta-analysis. Liu Y, Zheng Y, Gu X, Ma Z. Minerva 2012; 78(6): 653-667
26. Prevention of opioid-induced hyperalgesia in surgical patients: does it really matter? Martinez V, Fletcher D. BJA 2012; 109(3): 302-304
27. Maintenance anaesthetics during remifentanil-based anaesthesia might affect postoperative pain control after breast cancer surgery. Shin SW, et al. BJA 2010 Sep; 105 (5): 661–7
28. A Comparison of Ketamine and Paracetamol for Preventing Remifentanil Induced Hyperalgesia in Patients Undergoing Total Abdominal Hysterectomy. Yalcin N, et al. Int Jour Med Sci. 2012; 9(5):327-333
29. Naloxone infusion and post-hysterectomy morphine consumption: a double-blind, placebo-controlled study. Movafegh A, et al. Acta Anaesthesiol Scand 2012; 56**:** 1241–1249
30. Buprenorphine–Naloxone Therapy in Pain Management. Chen KY, Chen LC, Mao J. Anesthesiology 2014; 120:1262- 1274
31. Opioid-induced hyperalgesia in chronic pain patients and the mitigating effects of gabapentin. Stoicea N, et al. Frontiers in Pharm. 2015 May; 104(6):1-6