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Opioid-Induced Hyperalgesia Tolerance and Chronic Postsurgical Pain: A Dilemma Complicating Postoperative Pain Management

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Stem Case and Key Questions Content

A 48 y/o male with history of Crohn's disease and past substance abuse is scheduled for exploratory laparotomy and total colectomy. He has chronic abdominal pain with baseline pain scores averaging 7-8/10. He has history of lower extremity deep venous thrombosis for which he takes coumadin 5 mg qhs. His pain regimen includes oxycodone CR 20 mg PO tid, gabapentin 600 mg PO tid and amitriptyline 25 mg PO qhs. He has had multiple abdominal surgeries in the past with severe postoperative pain.

During his visit to the anesthesia perioperative medicine clinic, he expresses concerns regarding management of his postoperative pain. He states that even very high doses of pain medication do not alleviate his pain.

What would you tell this patient in preparation for his surgery? What are your goals and expectations for this patient?

The day of surgery he mentions that he forgot to take his morning dose of oxycodone CR. He is anxious and concerned about his pain management. He discontinued coumadin 5 days ago and preoperative labs show a normalized INR.

What are some of the different perioperative options for pain management in this patient?

A T10-11 epidural is placed preoperatively. A 5 cc test dose of lidocaine with epinephrine 1:200,000 is administered. The patient's hemodynamics remains stable without the presence of a sympathectomy. An appropriate dermatomal distribution is identified from the T7 to T12 level. A general anesthetic with intravenous induction is conducted. The patient's surgery lasts approximately 8 hours. He is extubated and brought to the PACU. He appears comfortable and is transferred to the surgical floor.

During acute pain service rounds on POD#1, it was noted that the patient's coumadin therapy was inadvertently reinitiated that evening. Morning labs showed an increase of INR from 1.2 to 1.7. The surgical service requests anticoagulation therapy because of patient's history of recurrent deep venous thrombosis.

Are you concerned? Will you keep or remove the epidural catheter? If you decide to remove it, would you remove it with his INR of 1.7?

The acute pain service decides to remove the epidural catheter. Approximately 3 hours after the epidural has been removed, he is found to be hypertensive and tachycardic. He reports severe

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pain. Over the next few hours, the patient is given escalating doses of potent opioids and continues to complain of excruciating pain.

Why is the patient not responding to the administered narcotics? Is this patient demonstrating opioid-induced hyperalgesia (OIH) or tolerance? Are some patients more prone to developing OIH, tolerance or chronic post-surgical pain? How is OIH diagnosed? Do opioid medications have different risk profiles? How would you manage opioid non-responsiveness?
After several adjustments to the patient's pain regimen, he appears comfortable. When asked to rate his pain on a scale from 0 to 10, he rates it a 20. The patient is somnolent but verbally arousable. His respiratory rate and pulse oximetry are within normal range.

Would you increase or decrease the opioid dosage? What other measures can be used to assess pain?
On POD #4, in preparation for transitioning to PO pain medication, the surgical service requests a consultation regarding an oral pain regimen for this patient.

What would you recommend? Are there any additional considerations for a patient with a history of substance abuse? What type of outpatient management is required for this patient?

Model Discussion Content
Introduction
The treatment of acute postoperative pain continues to be an ongoing challenge. In a random sample of 250 adults who underwent a surgical procedure, 80% of the patients reported having acute postoperative pain and 86% reported moderate to severe pain after surgery (1).
Some patients are more vulnerable and at higher risk for developing severe acute postoperative pain. Such individuals should be identified at risk for treatment. Acute postoperative pain management remains a major challenge for physicians. Inadequate treatment of acute and perioperative pain can have a devastating impact on patients and can lead to chronic postsurgical pain if not treated. Pain can burden patients in multiple domains: socioeconomic, psychological and qualitative.

Anesthesiologists have a crucial role in the perioperative management of pain. Anesthetic technique can influence the development of acute postoperative pain, chronic postsurgical pain, opioid-induced hyperalgesia and opioid tolerance. Opioids are conventionally thought of as the first line of treatment for pain. The USA appears to be the main consumer of opioids accounting for 56% of morphine and 81% of oxycodone global usage (2). Growing evidence has shown that opioids may have a negative impact on postoperative pain.

Preoperative Pain Management
Perioperative management of pain begins preoperatively. A pain prevention plan should be created that focuses on multimodal therapy, pain education, and assessment. Scoring systems have been developed to help providers identify patients at risk for developing severe postoperative pain (3).

Pain education is an important component in the perioperative management of pain. One of the

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major sources of pre-surgical anxiety for patients is the apprehension of experiencing postoperative pain. There should be an emphasis on patient targeted goals in the treatment of pain. Patients must be educated about multimodal analgesia which decreases opioid-related adverse events, length of hospital stay, and cost. Options regarding different analgesic agents should be discussed with patients, considering past experience if applicable. Regional techniques such as epidural or peripheral nerve blocks/catheters may be discussed. Postoperative pain assessment should include the conventional visual analogue score (VAS), but more emphasis should be placed on recovery of function, early ambulation, and recovery of bowel and bladder function.

The perioperative management of pain for patients with a history of chronic pain or of substance abuse adds additional challenges. These patients tend to have a high tolerance to opioids and may experience severe postoperative pain. Those with a history of substance abuse can be at risk for relapse. According to the Model Policy for the Use of Controlled Substances for the Treatment of Pain, the management of pain in patients with a history of substance abuse may require extra care, monitoring, and documentation or consultation with an expert (4).
Opioid-induced hyperalgesia (OIH), Opioid Tolerance and Chronic Postsurgical Pain
Chronic opioid exposure can lead to opioid tolerance or opioid-induced hyperalgesia postoperatively. Clinical differentiation between them can be challenging.

Opioid tolerance is a physiological process in which a progressive lack of response to opioids requires an increase in dose to produce the same effect. There is a shift to the right of the dose-response curve. The lack of response is overcome by increasing the dose. Pharmacokinetic changes occur which include up-regulation of the metabolic process responsible for elimination of the drug. Pharmacodynamic changes include down-regulation of the opioid receptor or desensitization. The opioid receptor is linked to a G-protein, when activated, leads to a decrease in cyclic Adenosine 3, 5-monophosphate (cAMP) which inhibits Na and Ca influx. But over time, changes in G-protein function can lead desensitization and development of opioid tolerance.

Opioid-induced hyperalgesia (OIH) is a paradoxical response to opioids. Patients experience a worsening of pain with administration of opioids.

Risk Factors for Opioid Induced Hyperalgesia
Why some patients develop OIH and others do not is not completely understood. Some of the animal models have indicated that effect of a sex difference. Female rats develop OIH faster and for a longer duration than male rats after exposure to morphine (5). Genetic predisposition may be a factor. Polymorphism in catecho-O-methyltransferase (COMT) gene may predispose patients to the development of OIH (6). Patients with high levels of anxiety about postoperative pain may be more susceptible to OIH (7).

Mechanism of Action for Opioid-Induced Hyperalgesia
The exact mechanism of opioid-induced hyperalgesia (OIH) is unknown. Some of the proposed mechanisms include involvement of the central glutaminergic system, spinal dynorphins, descending facilitation, genetic influence, and enhanced response to nociceptive neurotransmitters (8).

The central glutaminergic system involves the excitatory neurotransmitter glutamate and

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activation of the N-methyl-D aspartate (NMDA) receptor. Prolonged exposure to morphine was shown to cause neurotoxicity by inducing NMDA receptor-mediated cell death in the dorsal horn (9). Prolonged exposure to μ-receptor agonists has been shown to increase levels of spinal dynorphins which can increase the release of excitatory neuropeptides (10). Activation of the descending facilitation from the rostral ventromedial medulla can activate spinal nociceptive processing and increase excitatory neuropeptides (11). Genetic variability of catechol-O-methyltransferase (COMT) may affect central pain processing (6).

OIH differs from opioid tolerance in that an increase in dose worsens pain. Pain is improved by lowering opioid dosage. Performing quantitative sensory testing (QST) before administration of opioids and at regular intervals may assist in the clinical diagnosis (12).

Management of Opioid Induced Hyperalgesia and Opioid Tolerance
Opioid-induced hyperalgesia and opioid tolerance are two distinct phenomena that result in postoperative pain that is difficult to control. The initial response by most practitioners is to escalate the opioid dose. If no response is observed, opioid-induced hyperalgesia should be considered. A reduction of opioid dosing should be initiated. The mechanism of action and treatment options for opioid-induced hyperalgesia and opioid tolerance are summarized in Table 1.

Chronic Postsurgical Pain Syndrome
Chronic Postsurgical Pain Syndrome (CPSP) was reported in 1998 in the United Kingdom. The etiology of pain in 40% of the chronic pain population was determined to be postsurgical in origin (13). The International Association for the Study of Pain (IASP) defines CPSP as pain that persists for at least 2 months after a surgical intervention (14). There is a strong positive correlation between the severity of acute postoperative pain and the development of CPSP (15). Risk factors have been identified for CPSP (Table 2) (16-20). Among them are repeated surgical interventions, lengthy surgical time, and surgery in an area already traumatized (16). Predictive patient factors include female gender, younger age, and preoperative anxiety (17). Obesity is a risk factor with the underlying mechanism associated with a pro-inflammatory state (18). Anesthetic technique has also been implicated in CPSP. Retrospective data from hysterectomies and c-sections have shown a risk reduction of 50% with spinal anesthesia versus general anesthesia (19, 20).

Intraoperative Management
For patients with a history of chronic pain requiring opioid therapy, a multimodal approach and introduction of adjunct therapy (Table 3) intraoperatively may improve postoperative pain control and reduce the risk of developing OIH and opioid tolerance.

Methadone has been used for treatment of chronic neuropathic and cancer pain. Its utilization for acute pain and the perioperative period has been minimal. Patient-controlled analgesia (PCA) has been the foundation for the management of acute and perioperative pain. Although PCA is superior to nurse-administered analgesia, PCA has its limitations. There are many misapprehensions regarding the onset, duration and metabolism of methadone making it less attractive for the acute pain setting. The myth that methadone has a slow onset of action, that duration of analgesia is shorter than elimination half-life, and that its highly variable clearance and interactions with other drugs makes it unattractive for use in acute or perioperative settings has been disproven (21). The use of methadone has several advantages over the

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conventionally available narcotics used for acute pain. It is a mu receptor agonist that contains an NMDA antagonism property, which has been implicated in and can counteract OIH (22, 23). It also inhibits reuptake of serotonin and norepinephrine (SSNRI), which has additional analgesic benefits.

The initial studies on the use of methadone perioperatively were introduced by Gourlay et al (24). In a double-blind randomized trial comparing postoperative analgesia after perioperative loading doses of methadone or morphine, the mean duration of pain relief between methadone (20.7 +/- 20.2h) and morphine (6.3 +/-3.0h) was statistically significant (25). In a prospective study of patients undergoing thoracolumbar spine surgery, patients were randomized to receive either methadone before surgical incision or a sufentanil loading dose followed by a sufentanil infusion. Perioperative treatment with a single intravenous bolus of methadone was superior and improved postoperative pain (26).

Methadone is rapidly growing as a first-line treatment in cancer and neuropathic pain (27, 28). The potential benefits include its duration of action and incomplete cross-tolerance with opioid rotation. It may, however, be associated with respiratory depression, sedation and prolongation of QT.

Buprenorphine is a partial μ receptor agonist, opioid receptor like-1 (ORL-1) agonist, and kappa antagonist. It may prevent OIH through its kappa antagonist activity. Spinal dynorphin is a kappa receptor agonist which is known to release excitatory neurotransmitters (8). Cyclooxygenase inhibitors may prevent OIH by inhibiting of prostaglandin production, which facilitates the release of excitatory neurotransmitters along with peripheral and central sensitization (29).

Ketamine is beneficial intraoperatively to reduce OIH and opioid-induced tolerance (30). It is an antagonist of the NMDA receptor.
Dexmedetomidine is an alpha 2 receptor agonist that may prevent OIH. Its agonistic property at the alpha 2 receptor in the spinal cord and locus ceruleus produces analgesia and sedation without respiratory depression. The addition of dexmedetomidine to morphine PCA resulted in less fewer morphine-induced side effects and a 29% reduction in opioid consumption compared to morphine PCA alone (31).

Regional techniques (Table 4) can be considered a part of a multimodal approach in the treatment of postoperative pain. Thoracic epidural anesthesia is a cornerstone for perioperative management after major thoracic and abdominal surgery. Advantages include not only analgesia but a decrease in perioperative cardiovascular events and improved intestinal motility (32). Contraindications to epidural analgesia include patient refusal and coagulopathy. The American Society of Regional Anesthesia (ASRA) has developed guidelines for the placement of single shot or indwelling catheters and removal of indwelling catheters (Table 5) (33). Controversy exists regarding the conservative nature of the recommendations. In a series of 4365 patients undergoing hip and knee replacement surgery, there was uncomplicated removal of epidural catheters despite INRs ranging from 1.5 to 5.9. Removal of the epidural catheters was timed during initiation of warfarin therapy (34). Warfarin inhibits protein C and factors II, VII, IX, and X. According to the authors, during initiation of warfarin therapy, the INR is initially dependent on levels of factor V11, as it has the shortest half-life. Vitamin K and factors II and X have a longer half life and remain adequate, even though an increase in INR is detected during

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the first 48 hr. For effective anticoagulation, these factors must be decreased.
The ASRA Consensus Guidelines recommend that for patients undergoing peripheral nerve and deep plexus block the guidelines for neuraxial techniques apply. Transversus abdominis plane blocks (TAP) and paravertebral blocks are peripheral nerve blocks that can be utilized for postoperative pain management.

The TAP block was initially introduced in 2000 as a blind approach with local anesthetic injection into the lumbar triangle of petit. Ultrasound-guided and surgically assisted approaches have been described. The TAP is created by the fascial layer between the transverse abdominis muscle and the internal oblique muscle. The anterior rami of spinal nerves T7-L1 travel between these layers and are responsible for innervations of the anterior abdominal wall. The TAP block has been described for postoperative pain relief for several abdominal procedures (35). It can be considered for patients undergoing abdominal surgery who are not candidates for epidural analgesia because of coagulopathies. It is a technically non challenging procedure but some complications have been reported such as liver lacerations.

Paravertebral blocks have been described for breast and thoracic surgery but less frequently used for abdominal surgery. They can be incorporated as a part of a multimodal approach in the treatment of postoperative abdominal pain (36).

Postoperative Pain Management:
Chronic pain is two to six times greater among patients with a history of substance abuse. Patients with a history of substance abuse will need opioids because adjunct therapy alone is not sufficient.

Although the potential is there for addiction, some suggest that pain appears to provide a protective action against the rewarding effects of opiates. In animal studies using the conditioned place preference paradigm, morphine was less rewarding in the presence of pain. Pain may lower the risk rather than increase the risk of opiate addiction.
Many physicians feel that prescribing opioids to patients with a history of substance abuse and chronic pain would feed a habit and encourage dependence. A survey conducted by the Pain and Policy Group, University of Wisconsin among state medical board members compared responses from 1991, 1997, and 2004. On state medical boards, 75% of members are physicians, 20% are members of the public, and 5% are other health professionals. State board members are still skeptical on prescribing opioids for non-cancer pain. A minority of board members considered it illegal to prescribe opioids to patients with a history of substance abuse (37), even though DEA law and the federation model policy permit their use. According to the model policy, the Board considers the inappropriate treatment of pain to be a departure from standards of practice and will investigate such allegations (4). In the survey, 18% of respondents reported addiction as synonymous with physical dependence or tolerance. This misconception has potentially profound clinical implications as these views are held by members of the board that determine physicians' breach of professional conduct.
Pain relief is a fundamental human right, even in patients with a history of substance abuse. The pain in patients with a history of chronic opioid or substance abuse can be challenging to manage, but incorporating a multimodal approach may improve outcome. A multidisciplinary approach is recommended including pharmacological and non-pharmacological treatment options. Seeking consultation with experts in the field is highly recommended.

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Table 1: Mechanism of Action and Treatment Options for OIH and Opioid tolerance		
Causes of opioid non-responsiveness	Mechanism of Action	Treatment Options
Opioid tolerance	1. Shift to the right of the dose-response curve 2. Possible down regulation of receptors	Increased opioid dosage
Opioid-induced hyperalgesia	1. Central glutaminergic system; activation of dorsal horn NMDA 2. Inactivation of μ-receptor 3. Enhanced response to nociceptive neurotransmitters 4. Spinal dynorphin release 5. Genetic polymorphism of COMT	1. Decrease opioid dosage 2.Discontinue opioid 3. Opioid rotation 4. NMDA receptor modulators

*NMDA = N-methyl-D aspartate, COMT = Catechol-O-methyltransferase, OIH = opioid-induced hyperalgesia

Table 2: Risk Factors for Developing Chronic Postsurgical Pain	
Surgical	1. Repeated surgical intervention 2. Lengthy surgical time 3. Surgery in previously traumatized area
Patient	1. Preexisting pain 2. Female gender 3. Young age 4. Obesity 5. Preoperative anxiety/catastrophize
Anesthesia	1.General versus regional techniques

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Table 3: Intraoperative Adjunct Therapy			
Medication	Dose	Mechanism of Action	Possible Side Effects
IV Methadone	2.5-5mg q 8-12hr	μ receptor agonist, N-methyl-D-aspartate (NMDA) receptor antagonist	Respiratory depression, sedation, prolonged QT
IV Buprenorphine	300 mcg q6-8h	Partial μ receptor agonist ORL-1 agonist Kappa receptor antagonist	Respiratory depression, sedation
IV Ibuprofen	400-800mg q 6hr	Inhibits cyclooxygenase	Renal insufficiency, Platelet inhibition, GI upset
IV Acetaminophen	1g q 6hr	Unknown	Hepatic toxicity
IV Ketamine	0.5mg/kg bolus prior to incision 0.5mg/kg/hr infusion	NMDA receptor antagonist	Psychomimetic
IV Dexmedetomidine	0.5-2 mcg/kg bolus prior to incision 0.2-0.7mcg/kg/hr infusion	Alpha 2 agonist	Hypotension, Bradycardia, Sedation

*IV = intravenous, GI = gastrointestinal

Table 4: Regional Techniques for Abdominal Surgery		
Regional Techniques for Abdominal Procedures	Indications	Contraindications
Epidural analgesia	1. Provides analgesia to somatic and visceral organs.	1. Patient refusal 2. Coagulopathy 3. Infection at site
Transversus abdominis plane block (TAP)	1. Provides analgesia to skin and muscles of the anterior abdominal wall in lower abdomen 2. Epidural contraindicated	1. Patient refusal 2. Infection at site
Subcostal block	1. Provides analgesia to skin and muscles of the anterior abdominal wall in upper abdomen 2. Epidural contraindicated	1. Patient refusal 2. Infection at site
Paravertebral block	1.Provides analgesia to somatic and visceral organs	1. Patient refusal 2. Coagulopathy 3. Infection at site

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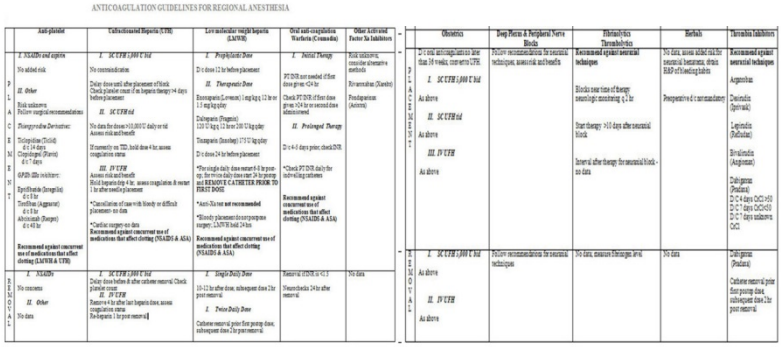
Table 5: American Society of Regional Anesthesia Anticoagulation Guidelines for Regional Anesthesia (33)



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