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The challenges of postoperative pain

Inadequate postoperative pain control is a frequent reason for patients to contact their GP after discharge from hospital. Postoperative pain impairs recovery and rehabilitation, and should be treated with judiciously prescribed analgesics and, when necessary, referral to pain medicine specialists.

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The possibility of experiencing pain is usually the worst fear of patients facing surgery. Postoperative pain causes deleterious physiological and psychological effects leading to prolonged recovery and hospitalisation.[1] Furthermore, acute pain limits functional rehabilitation and may develop into chronic pain.[2]

Although pain-free surgery is not a reality, with the evolution of medicine postoperative pain is now better understood and managed. Advances in pain medicine have led to major developments in postoperative analgesia, including:

- the formation of acute pain services
- the development of the concept of multimodal analgesia
- the utilisation of patient-controlled and regional analgesia techniques.

What is postoperative pain?

Pain is defined by the International Association for the Study of Pain as an 'unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'.[3] It is therefore not only the trauma of surgery but also the physiological and psychological make-up of the patient that determines how pain is felt.

A surgical incision is a tissue injury that activates specific nociceptors.[4] It is associated with a release of inflammatory mediators resulting in peripheral sensitisation, which is manifested by hyperalgesia and allodynia (increased sensitivity to painful and nonpainful stimuli). Intense and ongoing peripheral nociceptive input will then increase the excitability of neurons in the spinal cord and

IN SUMMARY

- **Patients with postoperative pain most often present to their GPs rather than returning to the hospital, particularly after ambulatory surgery and with current trends for early discharge.**
- **Appropriate analgesics should be provided to such patients and any treatable causes of postoperative pain should be identified.**
- **Acute pain can progress to chronic pain, so should be adequately managed to prevent this occurring.**
- **Psychological, behavioural, environmental and social factors influence pain and may contribute to the progression from acute to chronic pain.**
- **Patients exhibiting hyperalgesia, opioid tolerance and/or addictive behaviour (including aberrant medication taking) should be identified and, if necessary, referred to pain specialists.**

lead to central sensitisation.[4]

Neuropathic pain is associated with injury or disease of the peripheral or central nervous systems, for example, nerve injury during surgery. This can result in changes such as hyperexcitability of damaged peripheral nerves, central sensitisation and reorganisation of synaptic connections in the spinal cord.[5]

Pain management in the hospital setting

Increasingly, hospitals are providing acute pain services comprised of nursing and medical staff (usually anaesthetists or pain medicine specialists) dedicated to pain management and supplying patients with information and staff with education. These services supervise advanced 'multimodal' analgesic techniques and set the goals for effective and appropriate pain management. This approach aims to facilitate rapid recovery and return of the patient to full function, thereby reducing morbidity and allowing early discharge from hospital.[6]

The current concept of multimodal (or balanced) analgesia suggests the use of multiple medications with different mechanisms of action to improve analgesia and reduce medication doses, and therefore their adverse effects.[6] This is particularly useful if these techniques are opioid sparing.

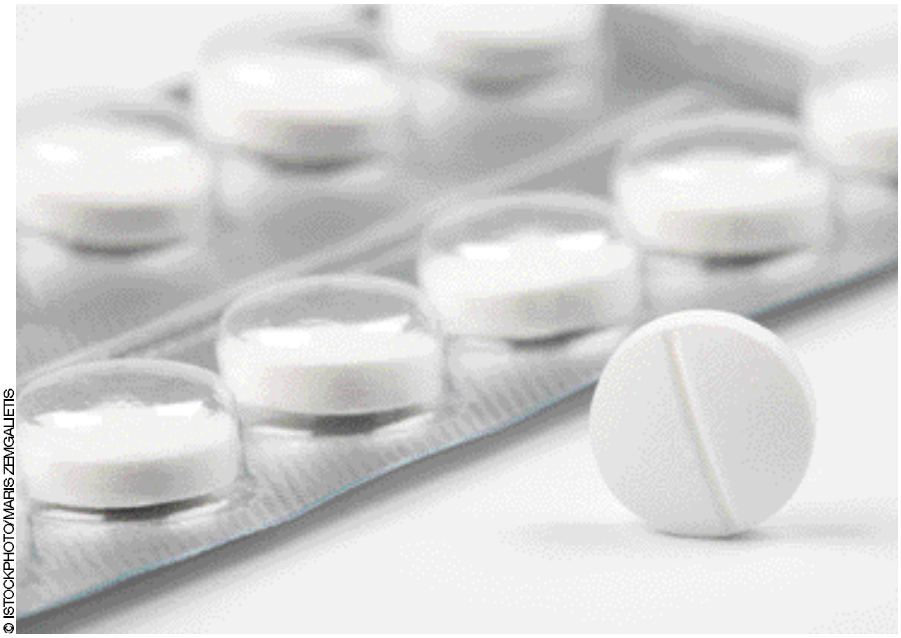
Modalities used include:

- background medication with non-opioids, such as paracetamol and/or NSAIDs (including COX-2 inhibitors)
- opioids administered by patient-controlled analgesia for titration to effect
- adjuvants, such as ketamine and pregabalin
- local anaesthetic infiltration
- regional catheter techniques (in the epidural space or near peripheral nerves).

To facilitate rehabilitation and early discharge from hospital, patients are switched early to oral analgesics, including oral opioids titrated to effect and to reduce adverse effects (in particular sedation).

Postoperative pain assessment after hospital discharge

Patients are most often discharged from hospital on oral analgesics, usually with detailed instructions and a limited (five day) supply of medication. Importantly, the exact analgesic medications and doses prescribed on discharge should be specified, with clear instructions to the patient on their use. This will provide useful information when assessing and managing a patient's pain issues. A guide to postoperative pain management in general practice is given in the box on page 32.



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When seeing a patient after discharge, treatable causes of pain should be identified and therapy directed to the cause of pain. The presence of surgical complications, such as haematoma, dehiscence or infection needing further immediate investigation, should be excluded. Regional anaesthesia techniques provide good anaesthesia and analgesia but carry inherent risks. Extremely rare but serious complications, such as meningitis or epidural abscess, can occur after hospital discharge in patients with epidural catheters. New symptoms of severe back pain, weakness, increasing numbness or loss of sensation in the legs, or loss of bladder or bowel control in a patient after epidural analgesia warrant immediate hospital referral for further investigation.[7]

Headaches following a dural puncture for spinal anaesthesia occur with an incidence of about 1%. They are classically postural in nature and more common in patients under the age of 50 years and in the parturient. Non-opioid and opioid analgesics may provide temporary relief. About 90% of cases improve spontaneously within 10 days.[8]

Postoperative pain management in general practice

Patient presents with pain after surgery

- Exclude any treatable cause or surgical or anaesthetic complication
- Assess for a neuropathic component of the pain.

If obvious nociceptive pain, i.e. ongoing postoperative pain, is present

- Use paracetamol 1 g four times a day in all patients
- If pain is not relieved by paracetamol and there are no contraindications, use an NSAID to its maximum daily dose. Contraindications include the presence or history of gastrointestinal ulcers, renal impairment, other nephrotoxic medications, bleeding risk or aspirin-sensitive asthma
- Use celecoxib 200 to 400 mg a day if any risk factors for NSAID use are present but consider that renal risk factors are similar to those for NSAIDs; if there is an increased risk or past history of gastrointestinal ulcer, co-medicate with a proton pump inhibitor
- If pain is not relieved by non-opioids, offer immediate-release opioids at doses titrated against pain, but limited by sedation; allow two to six doses a day to be taken only as needed. Doses should be at the lower end of the range in older patients:
  - tramadol 50 to 100 mg
  - oxycodone 5 to 20 mg
  - morphine 5 to 20 mg
- If there are ongoing opioid requirements for obvious pain and no aberrant medication-related behaviour, convert about 50% of daily opioid requirements to sustained-release preparations
- Reduce dose of opioid gradually as pain improves; watch for aberrant behaviour and maintain firm boundaries with regard to dose increase. Organise review by pain medicine specialist if opioid requirements continue.

If neuropathic pain or mixed nociceptive and neuropathic pain are present, consider using adjuvants

- Tricyclic antidepressants or serotonin noradrenaline reuptake inhibitors (off-label uses):
  - amitriptyline 5 to 10 mg at night, then increase dose as tolerated
  - nortriptyline 5 to 10 mg at night, then increase dose as tolerated
  - duloxetine 30 to 60 mg a day
  - venlafaxine (modified release) 25 to 37.5 mg a day
- Anticonvulsants:
  - gabapentin initially 300 mg three times a day, then increase dose as tolerated to a maximum of 1200 mg three times a day
  - pregabalin initially 75 mg twice a day, then increase dose as tolerated to a maximum of 300 mg twice a day
  - other anticonvulsants such as carbamazepine, phenytoin, sodium valproate or clonazepam (off-label use) may also be used, but there is no good supportive evidence for their use in peripheral neuropathic pain and they have increased adverse effects

Consider referral

- Consider urgent referral to a pain medicine specialist if the patient has any of the following:
  - persistent, in particular neuropathic, pain
  - pain poorly responsive to opioids with dose escalation
  - features of aberrant medication-related behaviour.

Persistence of postoperative pain

Acute pain (such as postoperative pain) is pain of recent onset and limited duration caused by tissue injury, while chronic pain commonly persists beyond the time of healing. Studies have shown that acute postoperative pain can persist as chronic pain, thus showing the need to prevent the progression from acute to chronic.[2,9]

To prevent acute pain becoming chronic, the cause of and reason for the occurrence of the pain should be understood. Although the reason why some people develop chronic pain after surgery while others do not is still a mystery, risk factors for progression of pain have been identified and this has helped the development of strategies to reduce its incidence.

Factors that determine if a patient is at risk of developing chronic pain include genotype, medical history, past experiences of and beliefs about pain and its meaning, and psychosocial circumstances. Medical factors, such as the types of surgery and anaesthesia received, perioperative analgesia and treatments given, also have an effect.[2,9]

Pain that persists beyond the time of recovery frequently has a neuropathic element. Certain operations carry an increased risk of nerve injury, putting patients at risk of developing chronic pain. With an incidence of chronic pain of up to 60%, such operations include, but are not limited to, amputations (with up to an 80% risk of phantom limb pain), thoracotomies, mastectomies, cholecystectomies and hernia repairs.[2,9]

Analgesic options for the management of postoperative pain

A summary of the analgesic drugs used in general practice to treat patients with acute pain is given in the Table.

Paracetamol

Paracetamol is the most widely used analgesic drug worldwide for all pain. It is

continued

Table. Analgesic drugs used in general practice

Drug	Route	Standard dosage
Paracetamol	Orally	Two 500 mg tablets every four hours
NSAIDs		
Ibuprofen	Orally	Two 200 mg tablets three or four times a day
Diclofenac	Orally Rectally	25 to 50 mg two to three times a day 25 to 50 mg two to three times a day
Naproxen	Orally	Initially 500 mg, then 250 mg every six to eight hours
Celecoxib*	Orally	200 mg a day, twice a day in acute pain
Immediate-release opioids (titrate dose for acute pain relief and against adverse effects, primarily sedation)		
Tramadol	Orally	50 to 100 mg two to four times a day to a maximum of 400 mg a day
Oxycodone	Orally	5 mg every four to six hours to a maximum of 400 mg a day
Morphine – tablets – solution	 Orally Orally	 10 to 30 mg every four to six hours 5 to 20 mg every four hours
Hydromorphone	Orally	2 to 4 mg every four hours
Adjuvants for neuropathic pain		
Gabapentin	Orally	Initially 300 mg three times a day; may increase to a maximum of 3600 mg a day
Pregabalin	Orally	Initially 75 mg twice a day; may increase to 150 mg twice a day after three to seven days; may increase to a maximum of 300 mg twice a day after another seven days
Amitriptyline†	Orally	5 to 25 mg at night
Nortriptyline†	Orally	25 mg three to four times a day
Duloxetine†	Orally	60 mg a day
Venlafaxine,† modified release	Orally	25 to 37.5 mg a day
Slow-release opioids (not used in acute pain; only used in highly selected patients with increased opioid requirements and only for a limited duration if improving function and rehabilitation)		
Tramadol, sustained release	Orally	100 to 200 mg twice a day to a maximum of 400 mg a day
Oxycodone, controlled release	Orally	Usual starting dose 10 mg twice a day; may titrate to more than 80 mg a day only in highly selected patients
Morphine – controlled release tablets – controlled release solution – sustained release capsules – modified release capsules	 Orally Orally Orally Orally	 Initially 10 to 20 mg every 12 hours; may administer every eight hours; may increase dose at 48-hour intervals Initially 20 mg sachet (reconstituted in 10 mL of water) every 12 hours; may increase dose at 48-hour intervals 20 mg every 12 hours or 40 mg every 24 hours Initially 30 mg a day; may increase dose in 30 to 50% increments
Hydromorphone, modified release	Orally	8 mg a day
Buprenorphine patches	Trans-dermal	Initially 5 µg an hour; titrate at three-day intervals or longer as needed by replacing or adding patches (maximum two concurrent patches); replace patch every seven days
Fentanyl patches	Trans-dermal	Initially 12 to 25 µg an hour; may titrate up or down by 12 or 25 µg an hour every three days; replace patch every 72 hours

* Used off label for acute pain; † Used off label for all pain.

exclusively an analgesic and antipyretic. Unlike NSAIDs, it does not inhibit peripheral cyclo-oxygenase activity and does not cause gastrointestinal ulceration or bleeding.[10]

Hypersensitivity to paracetamol is very uncommon and at the suggested therapeutic dosage of 4 g a day, it has minimal adverse effects. However, if taken in excessive doses, paracetamol can cause fatal liver damage. There is a debate about whether precautions are necessary in those patients with pre-existing liver disease or malnourishment.

Nonsteroidal anti-inflammatory drugs

NSAIDs are the second-line treatment for mild to moderate acute pain. Their analgesic and anti-inflammatory actions are explained by their mechanism of action, that is the inhibition of cyclo-oxygenase. Thereby, their effects are inherently linked to their adverse effects, namely gastric and duodenal ulceration, renal impairment, cardiovascular complications and induction of asthma in sensitive patients.[10] In addition, the use of NSAIDs may lead to prolonged bleeding time, increasing perioperative blood loss.

The selective COX-2 inhibitors such as celecoxib and parecoxib have advantages with regard to their lower risk of adverse effects. However, the possibility of renal impairment in the perioperative period remains and is a major contraindication for the use of COX-2 inhibitors in such situations.[11]

Tramadol

Tramadol as an atypical centrally acting analgesic is another good option for the management of postoperative pain. The analgesic effect of tramadol is partially mediated via opioid receptor effects and partially via reuptake inhibition of noradrenaline and serotonin at nerve terminals. As a result, it carries a lower risk of adverse effects such as respiratory depression, constipation and the potential for abuse than other opioids.[12]

continued

Tramadol should not be used in patients taking the monoamine oxidase inhibitor (MAOI) class of antidepressants and should be used with caution in those at increased risk of seizures or taking tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs). The mechanism of action of tramadol on noradrenaline and serotonin, which is similar to that of TCAs, may explain its efficacy in treating neuropathic pain.[13]

Opioids

Opioids such as hydromorphone, morphine and oxycodone remain the mainstay analgesics for use in moderate to severe acute pain. Interindividual opioid requirements vary greatly; therefore, opioid dose is best titrated in the acute setting with immediate-release opioids given at doses as needed to suit each patient.

Slow-release and transdermal (buprenorphine and fentanyl) opioid preparations have a slow onset of effect and should not be used in acute pain situations; transdermal fentanyl is contraindicated in acute pain. However, slow-release and transdermal preparations may be useful in providing background analgesia in carefully selected cases of persistent pain or in patients with high opioid requirements. Often patients requiring these preparations need advice from a pain medicine specialist.

Adjuvant analgesics (co-analgesics) for the management of postoperative pain

The Latin word *adjuvans* means to help, particularly to reach a goal. Adjuvant analgesics enhance the effects of classic analgesics, particularly in complex settings such as in patients with neuropathic pain, pre-existing chronic pain, long-term opioid usage with tolerance or poor responsiveness to opioids. They are commonly initiated by pain medicine specialists; some are not suitable or not available in the GP setting.

N-methyl-D-aspartic acid receptor antagonists

N-methyl-D-aspartic acid (NMDA) receptor antagonists may not only prevent the development of wind-up or central sensitisation, but may also downregulate hyperexcitability after sensitisation has taken place.[14] The neurotransmitter glutamate binds to this receptor. There is evidence for NMDA receptor involvement in many types of pain, including inflammatory, postoperative, neuropathic and ischaemic.

Ketamine is the most common NMDA

receptor antagonist in clinical use. It was initially developed as a dissociative anaesthetic agent. Low-dose ketamine is often added to opioid analgesic regimens to reduce the requirement for use of opioids, to manage opioid-tolerant patients and to manage patients with neuropathic and ischaemic pain. Such low doses of ketamine are rarely associated with psychomimetic side effects (such as nightmares and hallucinations), which, if they do occur, may be reduced with the use of benzodiazepines.

Antidepressants

TCAs inhibit the reuptake of the monoamine neurotransmitters noradrenaline and serotonin into nerve terminals and modulate pain sensation via descending inhibitory pathways in the spinal cord. Of those TCAs used for chronic pain, amitriptyline has been most widely studied; however, nortriptyline can be used as an alternative.[15] Side effects result from their anticholinergic actions and sedation is reasonably common.

The serotonin noradrenaline reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine, are increasingly used to manage patients with postoperative pain. They are most suited to use in patients with neuropathic pain and chronic pain states, although patients may need to be assessed by pain medicine specialists.

The use of both TCAs and SNRIs to treat patients with pain is off label.

Anticonvulsants

Gabapentin and pregabalin are two anticonvulsants that are becoming more frequently used as first-line treatment for neuropathic pain because of their good efficacy, but even more so because of their low incidence of adverse effects.[16] These drugs have been shown to successfully treat patients with a wide range of neuropathic pain conditions and may offer some protection from progression to chronic pain.

However, these drugs are costly and are not listed on the PBS for the treatment of neuropathic pain. This limits their use in the general practice setting, but treatment with gabapentin or pregabalin is increasingly initiated by pain medicine specialists who will regularly titrate the dose accordingly.

Anticonvulsants such as carbamazepine (evidence of efficacy based mainly in trigeminal neuralgia), phenytoin, sodium valproate and clonazepam are also used to manage postoperative pain (used off label), although they have more severe side effects and the data on their efficacy are not as good as for gabapentin and pregabalin.

Problems with opioid use

Tolerance

Tolerance to a drug results in a lesser effect from the same dose of medication, or the need for progressively larger doses to maintain the same effect. In patients with pain, true tolerance rarely limits the effectiveness of opioids.[17]

Dependence

Physical dependence is a physiological adaptation to a drug characterised by the emergence of a withdrawal syndrome if the drug is abruptly stopped, reduced in dose or antagonised. Dependence is common with opioid use beyond 10 days' duration, but can be easily overcome by tapering opioid doses. This approach of gradual, not abrupt, discontinuation of opioid treatment should be used to withdraw postoperative patients from opioid use.

Opioid-induced hyperalgesia

Opioids can actually worsen pain by causing opioid-induced hyperalgesia. This is one of the reasons why patients taking long-term high-dose opioids increase their dose and yet pain continues to worsen over time. In such a situation, gradual reduction of opioid dose may surprisingly lead to better pain relief or at least no worsening of pain but fewer side effects such as constipation, drowsiness or nausea.[17]

Abuse and aberrant medication-related behaviour

Addiction is a pattern of drug use characterised by aberrant drug-taking behaviours and the compulsive use of a substance in order to experience its psychic effects or to avoid the effects of its absence. Users continue to take the drug despite the risk of physical, psychological or social harm to themselves.

Aberrant medication-related behaviour is commonly linked to abuse of opioids or is at least a clue to predict an emerging problem during opioid therapy.[18] It is often a big problem in the management of patients after surgery and trauma. Major behavioural patterns of this condition are concurrent abuse of alcohol or illicit drugs, non-sanctioned dose escalations, medication and/or prescription loss, injecting of oral formulations, selling or stealing drugs, forging prescriptions and deteriorating function.

If such aberrant behaviour is detected, it should be addressed in a conversation with the patient to establish clear ground rules about the use of opioids. It might be useful to use a written treatment agreement with the patient, even at the start of any long-term opioid exposure. Ongoing problems should lead to consideration of a referral to a pain medicine and/or addiction medicine service, depending on the specific aberrant behaviour demonstrated.

Establishment of long-term treatment with opioids, which can easily develop out of short-term use for acute pain, requires careful regular reviews and for the patient to adhere to well-established rules.[19,20] Involvement of a pain medicine specialist is also recommended.

Conclusion

Often patients will present to their GPs with ongoing pain after surgery. This may still be acute pain and surgical causes should be excluded and analgesics given for ongoing management of the pain.

Pain is an individual and subjective experience, and is not only influenced by physiological factors but also by psychological, behavioural, environmental and social factors. These factors influence pain perception and therapy, and can contribute to the transition from acute to chronic pain. Therefore, persistent postoperative pain needs to be considered as a complication of surgery and should be investigated and diagnosed. Often such pain is neuropathic in origin, and if treatment is unsuccessful then patients should be referred to a pain medicine specialist. MT

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