Pain after amputation

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Key points

• Good quality postoperative analgesia is essential for limb amputation.
• Pain management after amputation can be challenging due to the presence of mixed nociceptive and neuropathic pain.
• Thorough pain assessment is required to establish the aetiology of post-amputation pain.
• Prolonged analgesia via continuous perineural blockade provides optimal analgesia for early management of stump and phantom pain.
• Salmon Calcitonin and Memantine can be useful in the acute management of phantom limb pain.

Amputation of a limb is one of the oldest recorded surgical procedures. Traumatic amputation and use of a prosthesis is found written in Sanskrit texts dating from 1800 to 3500 BC. Today, amputation remains a commonly performed surgical procedure with ~5500 lower limb amputations carried out in England alone every year. Complications from peripheral vascular disease and diabetes are the leading medical causes of amputation although worldwide a vast number are as a consequence of trauma. Internationally, accurate numbers of limb amputations performed are very difficult to estimate as there is no recognized database or organization collecting this information.

Regardless of the indication for surgery, pain management after amputation is challenging. Amputation of a limb is one of the most severe pains in the human experience. This is attributable to the magnitude of the tissue injury involved and the varying loci of centres responsible for pain generation; comprising peripheral, spinal, and cortical regions. Pain after amputation involves nociceptive pain, due to bone and soft tissue injury, and neuropathic pain from direct neural trauma and central sensitization. This leads to a complicated, mixed, form of pain and a highly varied array of different postoperative pain syndromes. The burden of pain after amputation is therefore considerable, not just in the short term, but also in the years and decades after surgery. Severe post-amputation pains from phantom limbs have been recorded in survivors from World War II, some 50 yr after loss of a limb.

Pain management is often complicated in surgical amputees due to the presence of polypharmacy and severe co-morbidity including ischaemic heart disease and renal compromise. Furthermore, for these reasons, amputees remain a high-risk patient group with a 22% thirty-day mortality from emergency surgery. This article will discuss the different pain phenomena encountered after limb amputation and its management. This will include stump pain, acute phantom limb pain, and back pain. Different perioperative treatment modalities will be discussed aiming to inform practice in achieving optimal acute pain control and potentially preventing the chronicity of acute pain.

Pain following amputation

Acute pain management has been identified as a key priority in the management of patients undergoing amputation by a recent NCEPOD report. In achieving good quality analgesia it is important to strike a balance between effective pain control and excess morbidity as a result of interventional or pharmacotherapy. However, failure to optimize acute pain control not only leads to a detrimental pathophysiological stress response but impacts on a patient’s psychology, functional recovery and predisposes to chronic stump and phantom pain.

A number of different pain syndromes can present after amputation. These shall be discussed as stump pain, phantom pain, and mechanical pain. It should be borne in mind however that...
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each pain rarely exists in isolation and frequently contribute to one another. A full assessment must therefore be made of each patient to try and identify the predominant pain at the time.

Stump pain

The immediate aftermath of limb amputation in the first post-operative days is dominated by surgical wound pain. This pain is readily identifiable and confined to the surgical site. Surgical stump pain is often described as sharp, aching, and severe. It is primarily a nociceptive form of pain due to the extensive tissue trauma involved, however, the inevitable direct neural injury that occurs results in a significant neuropathic component to the presentation. This neuropathic component may be part of the reason for the relative analgesic failure seen if single modality, anti-nociceptive, pharmacotherapy is used.

In the absence of regional anaesthesia, the severity of the stump pain requires management with strong opioids as a baseline. Opioids used in isolation are however often insufficient and require to be taken in such quantities as to cause significant sedative side-effects. Consequently, adjuvant analgesics such as i.v. Ketamine are frequently required.

Acute stump pain would be expected to resolve in the first few weeks after amputation, however, ~10% of patients will go on to experience persistent stump pain3 although some studies quote a far higher incidence than this. The differential diagnosis for persistent stump pain is varied. It is therefore important to take a full history as well as visually inspecting, palpating, and performing sensory testing of the stump to identify any tender points, dysaesthetic areas and any possible pathology.

Some potential causes of persistent stump pain are listed in Table 1:

- Infection
- Arterial insufficiency
- Osteomyelitis
- Bone spur
- Haematoma
- Insufficient myoplasty covering
- Poorly fitting prosthesis

If a stump infection is suspected it must be treated early and aggressively. Baseline investigations include white cell count, CRP, and wound cultures. X-ray, magnetic resonance imaging (MRI), or bone scan may be required if osteomyelitis is suspected. Prolonged antibiotic treatment is often required. If a stump infection is not controlled, early serious systemic sepsis requires surgical debridement or revision of a stump to a higher level.

Stump neuroma

After a nerve has been severed, an intense immune-cell mediated inflammatory reaction is observed. This of itself causes pain and peripheral sensitization but also initiates a process by which free endings of unmyelinated A-delta and C-fibres sprout to form a tangled end at the cut surface of the nerve bundle. Neuro- mas display altered sodium channel function with reduced activation thresholds and spontaneous firing. This leads to unprovoked pain and contact sensitivity in the region of the neuroma. There is a close association between the presence and severity of stump neuroma pain and phantom limb pain.

Neuromas take time to develop and are not usually seen in the first few weeks after amputation. Features suggestive of neuroma formation include a focal point of pain at the stump, spontaneous pain, and localized sensory changes.

Heterotopic ossification

This is a phenomenon rarely considered as a cause for acute or persistent stump pain. It has only been characterized recently due to the upsurge in patients suffering traumatic amputation in military conflict. Heterotopic ossification essentially involves the deposition of calcium in the soft tissues of the stump. The incidence is unknown in medical amputees but has been found in up to 63% of patients after traumatic amputation.4 Interestingly, the presence of traumatic brain injury significantly increases the risk of heterotopic ossification.

There is no definitive means of preventing heterotopic ossification. Some centres have used a bisphosphonate (such as Eti- dronate) to prevent heterotopic ossification but good evidence for this practice is lacking. Non-steroidal anti-inflammatory medication may be helpful but this class of drug is frequently contra-indicated in many amputees. COX-2 inhibitors may offer a slightly safer alternative although, again, there is no good evidence to support routine use of these drugs in this circumstance.

In the sub-acute or chronic setting, a patient presenting with persistent stump pain should have this diagnosis considered and investigated by way of an X-ray of the stump. There are no well described, definitive, treatments for this condition. Heterotopic ossification can be managed conservatively in many cases but further surgery may be indicated if ossification is severe.

Management of acute stump pain

Systemic opioids delivered via patient controlled analgesia (PCA) are commonly used for post-amputation pain management in the acute phase. This can provide reasonably satisfactory analgesia and has a number of advantageous features including ease of titration, reliable systemic delivery, minimal invasive- ness, and relatively low associated morbidity. Morphine is com- monly used however there is no good evidence to indicate it is superior to any other opioid in the circumstance. The patients’ clinical condition or past experience may make another opioid more preferable, e.g. fentanyl may be more appropriate if there is significant renal impairment (eGFR <30 ml min⁻¹ 1.73 m⁻²).

Acute stump pain, in the absence of other pathology, would normally be expected to have subsided by the time of discharge from hospital such that strong opioids were no longer required. If stump pain is still severe enough to require strong opioids at the point of discharge, continuing causative factors or pathology
should be sought and referral made to Out-patient Pain Services for follow-up and monitoring of analgesia.

Other pharmacological modalities are often used in the management of acute stump pain. Ketamine given via a low-dose continuous i.v. infusion at up to 15 mg h$^{-1}$ is often helpful. Gaba-pentimoids are frequently utilized and present a rational choice due to their effect on nociceptive as well as neuropathic pain. Pregabalin is a good choice due to its superior pharmacokinetic profile with more reliable enteric absorption, faster onset, and relatively low incidence of side-effects. A starting dose of 25–75 mg per day is recommended depending on renal function and clinical condition.

The gold standard for management of post-amputation acute stump pain is regional anaesthesia. This can be accomplished either with central neuraxial blockade, usually via an epidural infusion, or peripheral nerve block. It should be noted that there is no good evidence to indicate that commencing central neuraxial or perineural blockade for a prolonged period before operation confers any advantage in terms of minimizing acute, or chronic, stump or phantom pain. Preoperative regional anaesthesia is only clearly indicated in cases of severe, treatment refractory, ischaemic pain before re-vascularization or amputation. In this circumstance regional anaesthesia is highly effective in controlling pain, alleviating distress, decreasing opioid related morbidity and even improving peripheral perfusion.

**Epidural analgesia**

This has been the most widely discussed and researched technique for post-amputation analgesia. For management of stump pain, epidural analgesia can be effective and versatile offering a number of advantages over systemic pharmacological techniques. For example, epidural analgesia can be started before operation to provide analgesia for ischaemic pain; can be converted to provide anaesthesia for surgery and continued after operation.

Opioid related morbidity, particularly respiratory complications, can be minimized with central neuraxial blockade but there has been no consistent or clear advantage demonstrated to date on preventing chronic pain, including phantom pain, with the use of epidural analgesia for amputation. This is somewhat surprising but methodological problems with the design of many studies, particularly the early discontinuation of epidural analgesia after operation, is important in interpreting the validity of these findings.

Although epidural analgesia can be very effective for the management of acute surgical pain, there are limitations to the technique in this patient group. Specifically, many vascular patients require therapeutic anti-coagulation thus either contra-indicating or substantially increasing the risk of epidural haematoma. Furthermore, epidural analgesia can have a failure rate approaching 10%; the potential for infection is higher with prolonged use of epidural blockade particularly in the diabetic population and adequate critical care facilities, staffing and monitoring are required. Consequently, resources may not be available in many hospitals to deliver epidural analgesia safely to this high-risk patient group.

**Perineural blockade**

Perineural blockade has been a major advance in pain management after amputation. The introduction of ultrasound guided neural blockade has made this technique more reliable particularly when identifying nerve supply to a non-viable limb or after traumatic amputation. Perineural blockade has been effectively utilized by the Armed forces for many years because continuous peripheral nerve block provides a relatively simple and highly effective means of providing prolonged, good quality analgesia, with low monitoring requirements that is virtually free of systemic side-effects.

When instituting regional anaesthesia for the lower limb, the relevant nerves should be blocked depending on the level of amputation. For below knee amputation a sciatic nerve block is sufficient while for above knee amputation, both the femoral and sciatic nerves should be targeted. Ideally, nerve blocks should be instituted immediately before surgery in addition to either general or central neuraxial anaesthesia. Anaesthetic placement of a perineural catheter may not be possible in all circumstances in which case a surgically placed sciatic catheter should be sought to be sited under direct vision providing there are no significant concerns regarding on-going local infection.

For postoperative analgesia perineural blockade can be initiated with a bolus dose and continued with elastomeric pumps delivering local anaesthetic at up to 10 ml h$^{-1}$. Ropivacaine is a good choice due to low cardiotoxicity; an important consideration particularly if two nerve catheters are placed. A typical perineural infusion lasts 40 h and is often discontinued at this point once the elastomeric pump runs out. For management of wound pain, this is too early as nociceptive pain is still maximal inside the first 72 h. Perineural blockade should be extended beyond 72 h whenever possible. Experience at our hospital indicates that perineural blockade can be continued safely to 80 h or more before discontinuing. This technique provides excellent analgesia in the first crucial days after amputation with low associated morbidity, results in minimal systemic opioid requirements and has a very low incidence of catheter related infections.

**Phantom limb pain**

Phantom limb pain is the most widely known post-amputation pain syndrome. The first written record of phantom limb pain dates to 1462 when Ambrose Paré, a French surgeon, reported the phenomenon in his book Treatise on Surgerie. It is a phenomenon that has largely remained a medical curiosity over the centuries as it defied satisfactory explanation and effective treatments remained elusive. It is only in recent years that we are gaining a clearer insight into this problem and how to manage it.

Phantom limb pain occurs in up to 80% of amputees. At least 75% of patients who develop phantom pain do so within the first week after amputation. The natural history of phantom pain is then variable. Many patients will show gradual improvement of phantom pain within the first year and some will resolve completely. Many patients however will have phantom pain for life.

Like other chronic post-surgical pain syndromes there are no definitive predisposing factors but some circumstances do make the chances of developing phantom pain higher. These are listed in Table 2.

There is no clear difference in the incidence of phantom pain between the sexes and psychological factors such as depression.

### Table 2 Risk factors for developing phantom limb pain

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<td>Severe preoperative pain</td>
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<td>Bilateral amputation</td>
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<td>Stump pain</td>
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<td>Repeated limb surgeries</td>
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<td>Increasing age</td>
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or anxiety are not predictive. It is important to note however that patients with significant psychological risk factors do tend to report more severe phantom pain with higher levels of disability and reliance on medication.

Phantom limb pain is typically felt in the distal extremity of the absent limb. Pain characteristics vary but are often described as being cramping, burning, or shooting in nature. It is not uncommon to observe that if a patient experiences severe pain in a limb before operation then the same pain will be experienced after removal of that limb. Phantom pains are usually episodic occurring in short bouts ranging from a few seconds to many hours. It is the minority of patients who have severe and unremitting phantom pain.

Patients may report other phenomenon from the missing limb such as tingling or itching. These non-painful phenomena are termed phantom sensations. Patients should be informed that these are normal and reassurance is provided. The phantom limb may also be felt to be in a different position, shape or size to the missing limb. Telescoping, where sensation from a missing extremity migrates in perceived position towards the stump, can occur but this is usually a finding in more established cases.

Pathophysiology

The precise mechanisms underlying phantom limb pain have been difficult to accurately elucidate. This is likely to reflect the fact that anatomically different pain centres can be involved in producing the phenomenon with one or more loci contributing at any one time. There are however three key areas that are implicated in phantom pain.

Peripheral nerves

Many patients presenting for amputation will already have a damaged and sensitized peripheral nervous system due to ischaemia. Further neural injury from surgical trauma leads to an inflammatory reaction and the release of pro-nociceptive factors such as cytokines, prostaglandins, and substance P. These factors cause a decrease in activation thresholds from nociceptors and spontaneous discharge leading to further sensitization. These changes occur in afferent nociceptive pathways emanating from the absent limb.

It is likely that during the early postoperative phase it is the intensity of the afferent peripheral nociceptive stimulus that initiates phantom pain and results in the changes seen subsequently upstream in the central nervous system (CNS). Neurona formation is frequently cited as being the cause of phantom pain. While this may be true in the sub-acute or chronic phase, within the first week of amputation when the majority of phantom pains first present, a neuroma would not have had time to develop so cannot be responsible for acute phantom pain.

Spinal cord

The intense nociceptive barrage from the peripheral nervous system has a profound effect on pain pathways at the spinal cord. At this level the dorsal root ganglion is an important site as afferent pain signals can be substantially modified, either attenuated or enhanced. The N-methyl-D-aspartate receptor seems to be particularly important in this process for both modifying nociceptive signals and facilitating CNS plasticity. Specifically, the NMDA receptor is involved in the phenotypic switch and cross sprouting that occurs in afferent nerve fibres after amputation. This results in afferent non-painful stimuli being felt as painful and the widening of receptive fields from one neural pathway resulting in sensitivity extending beyond the dermatomal distribution of one nerve.

Somatosensory cortex

Considerable attention has been focused on the somatosensory cortex as a source of phantom limb pain. It has long been suspected that cortical structures were implicated in the generation of phantom limb pain however it has not been until the introduction of functional MRI scanning that this has been confirmed. The cortical changes after amputation are complex but not unique to phantom pain. Similar cortical reorganization is also seen in cases of Complex Regional Pain Syndrome and lower back pain.

In essence the cortical changes involve a compensatory migration into the representation of the absent limb from adjacent regions of the somatosensory cortex. This can be inferred clinically as patients with upper limb amputation can experience exacerbations of phantom pain on touching their face or, in the lower limb, experience phantom pain with a full bladder.

Prevention and treatment

Many therapies have been studied over the decades for phantom pain and are too numerous to cover in detail within the scope of this article. Only the most pertinent and promising interventional and pharmacological treatments are discussed. The use of strong opioids in this circumstance does require special mention. It must be emphasized that strong opioids have a very limited role in the management of either acute or chronic phantom limb pain. Strong opioids initiated to manage wound pain should not be continued without very good reason and with proven efficacy on a case-by-case basis for the management of phantom pain.

Perineural blockade

Perineural blockade provides excellent analgesia for surgical stump pain and in doing so can attenuate peripheral and central sensitization that may either prevent, or at least minimize, the impact of phantom pain. Many studies looking at the use of regional anaesthesia in the prevention of phantom limb pain discontinue neural blockade within 48 h of surgery. When considering that stump pain and the inflammatory process is still at its peak at this time, as stated previously, it is clear this is far too soon to discontinue therapy.

An interesting study by Borghi et al. demonstrated a very significant reduction in the incidence of phantom limb pain with the use of prolonged perineural blockade. They reported only a 2% incidence of phantom pain by continuing neural blockade for up to 80 days after amputation. Prolonging perineural blockade to this extent is unlikely to be feasible in most hospitals but enhancing existing practice is possible.

In our hospital, continuous perineural blockade is commenced perioperatively with 400 ml of Ropivacaine 0.2% infused via an elastomeric pump at 10 ml h⁻¹ if a single catheter is used or 5 ml h⁻¹ per catheter if two infusions are required for above knee amputations. Perineural blockade is continued for a minimum of 80 h after amputation to get a patient beyond the crucial first days of maximal pain in order to minimize sensitization. Local experience indicates this is probably the single most important technique for acute pain management after amputation and is crucial in decreasing the likelihood of developing significant phantom limb pain.
Pharmacological treatment

Tricyclic antidepressants

This family of medication is frequently utilized in the management of neuropathic pain, however, they have little role in the acute management of phantom limb pain. Tricyclic antidepressants are of limited utility as they are frequently contra-indicated in surgical amputees due to patients’ concurrent co-morbidities; the analgesic effect is of slow onset, of poor efficacy and side-effects frequently preclude dose titration.

Gabapentinoids

Gabapentinoids are agonists at the alpha-2-delta subunit of voltage dependent calcium channels and GABA_α receptors in the CNS. This class of medication is increasingly recognized for its anti-nociceptive and anti-neuropathic effects. Gabapentinoids are an integral part of many enhanced recovery pathways for their opioid sparing effects and there is increasing evidence they can help prevent the development of chronic post-surgical pain.

Gabapentinoids have a good safety profile, few drug interactions, are well tolerated and have efficacy in both neuropathic and nociceptive pain. With regard to phantom limb pain the majority of published evidence only examines the use of Gabapentin in chronic, established, cases. Only one study by Nikoljsen et al. examined early postoperative use of Gabapentin after amputation but did not find any benefit for stump or phantom pain. No studies to this time have been done examining Pregabalin in this context. Although there is no conclusive evidence, a Cochrane review identified a ‘trend towards benefit’ from Gabapentin in the management of phantom pain. 

Increasingly compelling evidence is emerging regarding the use of Gabapentin, and Pregabalin in particular, for preventing chronic post-surgical pain. Combining these two strands of evidence indicates that it is reasonable to initiate therapy with a Gabapentinoid perioperatively, as the clinical condition allows, continuing after operation for as long as felt to be clinically necessary.

Salmon calcitonin

Salmon calcitonin is a neuropeptide with a novel analgesic action. Its exact mechanism of action is not well defined but it is postulated to be due to a combination of altered β-endorphin production, inhibition of prostaglandin and cytokine production and modulation of central serotonergic pathways. It is only available in parenteral form in the UK.

Salmon calcitonin has been found to have analgesic efficacy in a diverse range of pain disorders including pain from spinal cord injury and vertebral fractures. It was however first serendipitously found to have an analgesic action on phantom limb pain in a number of early case reports. A small study by Jaeger confirmed the benefits of a short treatment course of salmon calcitonin on phantom limb pain the effects of which were still evident on follow-up 1 yr later. Unlike many therapeutic agents in pain management salmon calcitonin, when successful, abolished phantom limb pain.

Despite these promising early results, salmon calcitonin has seldom been studied and is infrequently utilized in acute pain management. Due to its good safety profile, low incidence of side-effects, and efficacy it should be considered for early treatment of acute phantom limb pain. A dose of 100 IU per day given subcutaneously as a treatment course for 5–7 days should be considered for acute presentations.

Clonidine

Clonidine is an agonist at α2-adrenoreceptors which are primarily located in the CNS and are involved in central control of the cardiovascular system. α2-Adrenoreceptors are also expressed on macrophages at the site of inflammation where they have a role in the expression of pro-inflammatory cytokines. Perineural clonidine has been found to prolong and enhance regional anaesthesia and reduce mechanical hypersensitivity after nerve injury.

There are no well conducted studies specifically examining the use of clonidine as an adjuvant to perineural blockade for amputation. Extrapolating the best evidence available and clinical experience indicates that the addition of clonidine to a continuous perineural infusion at a dose of between 10 and 20 μg h⁻¹ after amputation can be safe and effective. In our practice, perineural clonidine is reserved for patients whose block has not been complete or who are judged to be very high risk of severe stump or phantom pain.

NMDA antagonists

Ketamine is the most widely used NMDA antagonist. It has specific anti-neuropathic, anti-nociceptive and anti-hyperalgesic properties. It is commonly used perioperatively for amputation surgery but it does not prevent the development of phantom limb pain. Rather, Ketamine can decrease the severity of phantom pain experienced. I.V. Ketamine is probably the best means of administration as it ensures reliable systemic delivery (oral Ketamine has a bio-availability of only 20–40%), minimizes side-effects and ensures continuous blockade of the NMDA receptor in the crucial early postoperative period.

Memantine is another NMDA antagonist that is seldom considered in pain management. It has different binding characteristics at the NMDA receptor compared with Ketamine and, crucially, is relatively free of the psychotrophic effects that frequently limit the use of Ketamine. Memantine has no active metabolites, is renally excreted and preferentially accumulates in the CNS where it has a half-life of 80 h. All these properties are advantageous in treating pain in amputees.

Memantine has been studied when given perineurally and orally. The conclusions reached from these studies and in subsequent reviews dismissed Memantine on the grounds of lack of statistical significance in treating phantom pain. Crucially, Memantine did display considerable clinical significance in these studies and the evidence available needs to be re-evaluated with this in mind. Local experience indicates Memantine is generally well tolerated and efficacious in the management of phantom pain.

Back pain

Back pain is a very common yet under recognized and seldom studied post-amputation pain problem. Back pain can arise de novo after amputation or pre-exist and be exacerbated by loss of a limb. Back pain may also occur as a result of prolonged bed rest after surgery but is more frequently encountered during the early rehabilitation phase during weight bearing on a prosthesis. Considerable bio-mechanical changes occur in the lower back and pelvis as a result of altered weight and force distribution and different muscle utilization.

Assessment of the clinical characteristics of back pain is essential to exclude any specific spinal or disc pathology. Following exclusion of spinal pathology, e.g. disc herniation or discitis, treatment can proceed on empirical grounds with attention paid to adequate prosthetic fitting and physiotherapy.

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Pharmacological management should comprise simple analgesics, anti-inflammatories (where clinically appropriate), middle strength opioids, and non-benzodiazepine-based neuromuscular blocking agents. TENS machines and acupuncture are also useful in this setting. Strong opioids should be avoided if at all possible.

**Conclusion**

Post-amputation pain management remains a challenging area of clinical practice. A wide variety of pain problems present after operation which need careful clinical assessment to differentiate. Despite considerable advances in surgical and anaesthetic practices, pain related morbidity remains high after amputation.

The evidence base for optimal analgesic management is incomplete but it is wrong to use this reason as a basis for persevering with conventional treatment strategies that have proved ineffective. Best evidence, clinical experience, and pragmatism all indicate prolonged perineural blockade is the best analgesic technique post-amputation to attenuate both nociceptive and neuropathic pain. Continuation of perineural blockade for a minimum of 72 h post-amputation is essential in achieving this goal.

A multi-disciplinary, multi-modal approach to pain management must be emphasized comprising assessment and engagement in pain control from all team members involved in the care of amputees. Early treatment of acute phantom limb pain with novel analgesic agents such as salmon calcitonin and Memantine may offer the best chance of success to prevent chronicity alongside active physical and rehabilitation therapy.

**MCQs**

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to BJA Education.

**References**