8 Specific clinical situations

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8.1 | Postoperative pain

One of the most common sources of acute pain is postoperative pain. A large amount of the evidence presented so far in this document is based on studies of pain relief in the postoperative setting. However, many of the management principles derived from these studies can be applied to the management of acute pain in general, as outlined in this and other sections that follow.

The treatment of postoperative pain in specific settings such as day-stay surgery will be discussed later in this chapter.

8.1.1 | Multimodal postoperative pain management

The concept of multimodal (or "balanced") analgesia has been advocated as being beneficial for the management of postoperative pain (Kehlet 1993 **NR**). This concept suggests that combinations of analgesics with different modes or sites of action can improve analgesia, reduce opioid requirements *("opioid-sparing effect"*) and thereby reduce adverse effects of opioids in the postoperative period (Gritsenko 2014 **NR**). This approach, by reducing the reliance on opioids in the postoperative setting, also offers opportunities to overcome current concerns about opioid use in pain management (Savarese 2017 **NR**). See also Sections 8.13. and 9.7. and for paediatric information Section 10.4.5.4.

As outlined in previous chapters, there is Level I evidence to support a large number of nonopioid analgesics, adjuvants and regional anaesthetic techniques as potential components of multimodal analgesia by fulfilling the above criteria: paracetamol, nsNSAIDs and coxibs, local anaesthetic techniques (local anaesthetic infiltration, peripheral nerve blocks and neuraxial blocks), systemic local anaesthetics, steroids, ketamine, alpha-2 agonists and alpha-2-delta ligands (Gabriel 2019 **NR**; Pitchon 2018 **NR**; Wick 2017 **NR**; Rosero 2014 **NR**).

In this context, depth of general anaesthesia (BIS 30–40 vs 45–60) had no effect on postoperative pain or opioid requirements (Law 2014 **Level II**, n=135, JS 4).

Comparative studies of solely opioid-based analgesia with multimodal approaches show benefits not only with regard to analgesia and patient satisfaction but also for other postoperative outcomes:

> After total knee joint arthroplasty (TKA), multimodal analgesia (including local anaesthetic infiltration, nsNSAIDs, tramadol and oxycodone) vs IV PCA hydromorphone alone resulted in lower pain scores, opioid-sparing, fewer adverse effects, higher satisfaction scores and earlier achievement of physical therapy milestones (Lamplot 2014 **Level II**, n=36, JS 3). For total hip and knee arthroplasty (THA/TKA), adding IV paracetamol to other techniques of analgesia reduces pain scores and opioid consumption (Yang 2017 **Level I** [PRISMA], 4 RCTs, n=865). After THA/TKA, 85.6% of patients received multimodal analgesia (Memtsoudis 2018 **Level III-2**, n=1,318,165). Addition of more modes of analgesia was associated with positive effects in a stepwise fashion; for THA patients, more than 2 modes of analgesia vs opioids only was associated with reduction of respiratory (OR 0.81; 95%CI 0.70 to 0.94) and gastrointestinal complications (OR 0.74; 95%CI 0.65 to 0.84), decreased opioid prescriptions (-18.5%; 95%CI -19.7% to -17.2%) and reduced LOS from median 3 to 2 d (-12.1%; 95%CI -12.8% to -11.5%). NSAIDS and coxibs had the most effect here. Multimodal analgesia has also been examined in adult OSA patients undergoing elective THA/TKA (Cozowicz 2019 **Level III-2**, n=181,182). Assessment of this higher perioperative risk population demonstrated a step-wise reduction in opioid dose, prescription and PCA use (26.6% in opioid only vs 19.2%, 13.7%, and 7.7%) with increasing modes of multimodal analgesia over 10 y (2006—2016). With regards to postoperative complications, there were significantly reduced odds for

postoperative mechanical ventilation (OR 0.23; 95%CI 0.16 to 0.32) and critical care admission (OR 0.60; 95%CI 0.48 to 0.75) with the addition of two or more non-opioid analgesic modes. Of note, the most commonly used components of multimodal analgesia included paracetamol, coxibs, nsNSAIDs, gabapentin or pregabalin, regional analgesia, ketamine and corticosteroids.

After spinal surgery, the use of multimodal analgesia (paracetamol, NSAIDs, gabapentin, S-ketamine, dexamethasone, ondansetron and epidural local anaesthetic infusion or IV PCA morphine) vs historical controls, reduced opioid consumption, nausea, sedation and dizziness and improved postoperative mobilisation (Mathiesen 2013 **Level III-3**, n=85). This was confirmed by a subsequent RCT in a similar setting (lumbar fusion), where pre- and postoperative multimodal analgesia (celecoxib, pregabalin, oxycodone CR and paracetamol) with IV PCA morphine vs IV PCA morphine alone reduced pain and disability (Oswestry Disability Index) without any difference in adverse effects (Kim 2016 **Level II**, n=80, JS 3).

After upper extremity orthopaedic surgery, multimodal analgesia (including NSAID and alpha-2-delta ligand) vs IV PCA opioid alone provided similar quality of analgesia with reduced incidence of opioid-related complications and greater patient satisfaction (Lee 2013b **Level II**, n=61, JS 3).

Introduction of a multimodal protocol for analgesia in laparoscopic sleeve gastrectomy (preoperative etoricoxib, intraoperative and postoperative paracetamol with optional postoperative tramadol) vs historic control (previous standard care) resulted in reduced opioid requirements, reduced adverse effects of opioids (8.8% vs 33%) with similar analgesic efficacy (Ng 2017 **Level III-3**, n=158). Similarly, adding paracetamol to PCEA (thoracic) for open gastrectomy in cancer patients improved pain control on coughing and reduced PCEA requirements (Kinoshita 2019 **Level II**, n=120, JS 3)

After cardiac surgery, multimodal analgesia (paracetamol, nsNSAID, dexamethasone, alpha-2-delta ligand and rescue morphine) vs paracetamol and morphine resulted in lower pain scores for the first 3 d, reduced PONV and a trend towards reduced complications (Rafiq 2014 **Level II**, n=180, JS 3).

In reconstructive pelvic surgery, a multimodal analgesic regimen (preoperative and postoperative celecoxib, gabapentin, intraoperative and postoperative IV and oral paracetamol and opioids prn) vs usual care (postoperative ibuprofen and opioids prn) resulted in reduced opioid requirements in hospital and after discharge (overall 195.5 MME [± 147.2] vs 304.0 MME [162.1]; 34.8% vs 10.6% no opioid use after discharge) with comparable pain relief and no difference in other outcomes (Reagan 2017 **Level II**, n=138, JS 2).. A multimodal bundle of standardised use of preoperative paracetamol, postoperative comfort education, simethicone, postoperative gum chewing, and abdominal binders reduced morphine requirements after Caesarean section by 61% (Burgess 2019 **Level III-1**, n=9,313). Furthermore, more women received less than 20 tablets of oxycodone at discharge (96.7% vs 26.3%).

After rhinoplasty, multimodal analgesia (pregabalin alone and combined with dexamethasone added to IV tramadol and diclofenac IM) vs IV PCA tramadol alone reduced pain scores, tramadol consumption, rescue opioid use and nausea (Demirhan 2013 **Level II**, n=60, JS 5).

An additional benefit of a multimodal approach to pain relief after THA/TKA (paracetamol, pregabalin and celecoxib or ketorolac) was a reduction in postoperative fever incidence (5 vs 25%) resulting in fewer patients undergoing tests (1.8 vs 9.8%) (Karam 2014 **Level III-3**, n=3,901).

A meta-analysis could not identify any RCTs comparing three non-opioids in the setting of postoperative analgesia after major surgery (Martinez 2017 **Level I** [NMA], 135 RCTs, n=13,287). Double combinations with the highest opioid sparing effects over 24 h were paracetamol/nefopam (-23.9 mg; 95%CI -40 to -7.7), paracetamol/NSAIDs (-22.8 mg; 95%CI -31.5

to -14) and an atypical opioid combined with a non-opioid tramadol/metamizole (tramadol being classified by the authors as a non-opioid) (-19.8 mg; 95%CI -35.4 to -4.2). In abdominal hysterectomy, an RCT comparing a triple combination of paracetamol, meloxicam and gabapentin vs the three double combinations was prematurely discontinued for futility, as interim analysis showed only a minimal chance of showing advantages (Gilron 2015 **Level II**, n=87 [terminated], JS 5). In the 8 armed OCTOPUS study, a triple combination of paracetamol, nefopam and ketoprofen (PCA morphine rescue in all groups) was compared to placebo, the non-opioids singly and as double combinations (Beloeil 2019 **Level II**, n=237 [of 1,000 required], JS 5). The study was discontinued early for logistical and ethical reasons, but showed superiority of the triple combination over some arms with reduced opioid requirements and pain intensity.

Preemptive or preventive pain psychoeducation is an underutilised component of multimodal analgesia despite data showing reduced pain intensity, analgesic use, LOS, return to ED, patient anxiety and possibly chronic postsurgical pain (Horn 2020 **Level IV SR**, 33 studies, n unspecified).

On the basis of the available evidence, multimodal analgesia regimens are therefore recommended in the management of postoperative pain, including in the setting of enhanced recovery after surgery (ERAS) (Dunkman 2018 **NR**; Beverly 2017a **NR**) and ambulatory surgery (Kaye 2019 **NR**; Prabhakar 2017 **NR**). A novel approach to introduce multimodal analgesia into routine clinical practice are Standardised Clinical Assessment and Management Plans (SCAMPs), providing an algorithmic approach to standardisation of postoperative analgesic care with the aim of increasing compliance with existing guidelines (Beverly 2017b **NR**).

Multimodal analgesia is the recommended approach in guidelines for the management of postoperative pain (Savoia 2010 **GL**; ANZCA 2013 **GL**; Chou 2016 **GL**) including guidelines specifically targeted at reduction of perioperative opioid use (Wu 2019 **GL**).

KEY MESSAGES

1. Multimodal analgesia compared to mainly opioid-based analgesia improves pain control and reduces opioid consumption ("opioid-sparing") and adverse effects (**S**) (**Level I** [NMA]).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ The concept of multimodal (or "balanced") analgesia suggests the use of combinations of analgesics with different mode or site of action (**S**).

8.1.2 | Procedure-specific postoperative pain management

In addition to the overall assessment of the efficacy of acute pain management, there is also a need for information on postoperative pain management that relates to the site of surgery and specific surgical procedures (Singla 2014 **NR**; Ward 2014 **NR**; Kehlet 2005 **NR**; Rowlingson 2003 **NR**).

This becomes obvious when considering that even a simple analgesic, like paracetamol, has different efficacy in different surgical settings; it is significantly less effective after orthopaedic surgery (RR [of achieving >50% maximal pain relief] 1.87; 95%CI 1.36 to 2.57) than after dental extraction (RR 3.77; 95%CI 2.80 to 5.07) (Gray 2005 reanalysing Barden 2004b **Level I**, 43 RCTs [paracetamol], n unspecified). Although calculation of NNTs requires the pooling of data from at least 500 patients to be credible (McQuay 2002 **NR**), pooling of data from different postoperative pain states may ignore the specific effects of a specific analgesic in a specific postoperative pain state (Joshi 2013 **NR**).

Furthermore, different surgical procedures cause different pain states (eg musculoskeletal vs visceral) of different severity in different locations. On POD 4 after ambulatory surgery, moderate (16.3%) to severe (12.1%) postoperative pain presented with procedure-specific variation; shoulder, anal and dental surgery was associated with the most intense pain (Vrancken 2018 **Level III-2**, n=1,123); preoperative pain intensity predicted postoperative pain intensity, but again related to the procedure performed. Similarly in another study, in addition to preoperative pain and patient derived expected pain, different types of surgery were the strongest predictor of moderate to severe pain 4 d after ambulatory surgery (Stessel 2017 **Level III-3**, n=1,118). Different surgical procedures influenced the wide range of IV PCA opioid requirements; open pancreatectomy had the highest (77 mg) and open hysterectomy the lowest requirements (34 mg) (Lin 2019a **Level III-2**, n=3,284). The paper presents a table/graph of all procedures and the respective IV PCA requirements. However, a large cohort study of postoperative patients reported those with worst pain (NRS > 6/10) on POD 1 included orthopaedic/trauma procedures on the extremities, while very high pain scores were also associated with so called "*minor*" surgery (eg appendectomy, cholecystectomy, hemorrhoidectomy and tonsillectomy) suggesting insufficient access to analgesia in this group (Gerbershagen 2013 **Level III-2**, n=50,523).

On the basis of these finding, postoperative pain requires a procedure-specific approach. The recognition of this need has led to the development of the PROSPECT (PROcedure-SPECific postoperative pain managemenT) initiative, which aims to provide procedure-specific evidence-based recommendations for the treatment of pain after a wide range of operations (Kehlet 2007 **NR**; Lee 2018 **NR**). Their guidelines can be found at the website of the European Society of Regional Anaesthesia & Pain Therapy (ESRA) which is supporting the PROSPECT initiative: https://esraeurope.org/prospect/. The revised methodology underlying this approach is accessible on the website and has been published (Joshi 2019b **NR**); it uses an evidence-based approach including meta-analysis of available procedure-specific data. Surgical factors contributing to postoperative pain are also considered (eg trocar size in laparoscopic cholecystectomy) (McCloy 2008 **Level I**, 13 RCTs, n=968).

Procedure-specific evidence for the following operations is currently available at the website with most of the underlying meta-analyses also published in the peer-reviewed literature; translated PDFs of the recommendations are available in severallanguages (Chinese, French, German, Japanese, Portuguese and Spanish):

- Abdominal hysterectomy;
- Caesarean section;
- Haemorrhoidectomy (Sammour 2017 **Level I** [QUOROM], 48 RCTs, n unspecified);
- Hernia repair (Joshi 2012 **Level I** [PRISMA], 79 RCTs, n unspecified);

- Laparoscopic cholecystectomy (Barazanchi 2018 **Level I** [PRISMA], 258 RCTs, n unspecified);
- Laparoscopic hysterectomy (Lirk 2019 **Level I** [PRISMA], 56 RCTs, n unspecified);
- Laparoscopic sleeve gastrectomy (Macfater 2019 **Level I** [PRISMA], 18 RCTs, n unspecified);
- Oncological breast surgery (Jacobs 2020 **Level I** [PRISMA], 9 SRs & 53 RCTs, n unspecified);
- Open colorectal surgery;
- Radical prostatectomy (Joshi 2015 **Level I** [PRISMA], 38 RCTs, n unspecified);
- Rotator cuff repair surgery (Toma 2019 **Level I** [PRISMA], 1 SR & 59 RCTs, n unspecified);
- Thoracotomy (Joshi 2008 **Level I**, 74 RCTs, n unspecified);
- Total hip arthroplasty (Fischer 2005 **Level I**, 55 RCTs, n unspecified);
- Total knee arthroplasty (Fischer 2008 **Level I**, 112 RCTs, n unspecified).

KEY MESSAGES

1. An analgesic may have different efficacy in different surgical settings (**U**) (**Level I**).
2. Different surgical procedures cause different pain states (eg musculoskeletal vs visceral) of different severity in different locations, thereby requiring a procedure-specific approach (**S**) (**Level III-2**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Pooling of data from different postoperative pain states may ignore the specific effects of a specific analgesic in a specific postoperative pain state (**U**).

8.1.3 | Acute rehabilitation after surgery, "fast-track" surgery and enhanced recovery after surgery (ERAS)

The concept of fast-track surgery is underpinned by a multimodal approach to the perioperative care of the patient (Nanavati 2014 **NR**; Kehlet 2008 **NR**; Wilmore 2001 **NR**). The approach uses combinations of perioperative interventions to facilitate the postoperative recovery involving a multidisciplinary team approach of surgeons, anaesthetists, nutritionists, physiotherapists and nurses. Management of the surgical stress response, perioperative fluids and pain are key factors of this approach (Kehlet 2011 **NR**).

Evidence-based approaches following these principles have resulted in a significantly reduced hospital stay for many operations without increasing, and often reducing, complications and readmissions. Evidence-based detailed protocols for enhanced recovery after surgery (ERAS) are published for multiple operations on the ERAS© Society's website: https://erassociety.org.

For example, application of an ERAS protocol to colorectal surgery results in reduced LOS (WMD -2.55 d; 95%CI -3.24 to -1.85) and complication rates (RR 0.53; 95%CI 0.44 to 0.64) (Varadhan 2010 **Level I**, 6 RCTs, n=452). However, it is of note that the number of individual ERAS elements employed ranged from 4 to 12, with a mean of 9 elements targeting perioperative care. The use of multiple components in enhanced recovery confirms previous findings that provision of good analgesia alone may have only minimal effects on speed and quality of postoperative recovery (Kehlet 1997 **NR**). This is not surprising given the numerous triggers of the injury response, of which acute pain is only one. This is confirmed in a systematic review of the role of pain management in recovery from colorectal surgery following ERAS protocols (Chemali 2017 **Level I** [PRISMA], 21 RCTs, n=1,261). It suggests that the modality for postoperative analgesia has no impact on the hospital LOS, pain, the time to the first bowel motion or nausea, although data are of limited quality. The authors suggest that as long as pain is reasonably well controlled, choice of the technique of pain management is of minor relevance.

Even thoracic epidural analgesia (TEA) use, with its superior analgesic effect and faster return of bowel function, does not shorten LOS or improve morbidity and mortality vs alternative analgesic techniques when used within an ERAS protocol for open abdominal surgery (Hughes 2014 **Level I** [PRISMA], 7 RCTs, n=378). This finding highlights the importance of other elements of these protocols. Similarly after laparoscopic colectomy, TEA significantly improves time to first bowel motion (WMD -0.62 d; 95%CI -1.11 to -0.12) and pain scores (WMD -1.23/10; 95%CI -2.4 to -0.07) but does not reduce LOS (WMD -0.47 d; 95%CI; -1.55 to 0.61) (Khan 2013 **Level I** [PRISMA], 6 RCTs, n=340).

The importance of the various elements of enhanced recovery protocols is well demonstrated in an analysis of the ERAS register for elective primary colorectal cancer resection (ERAS Compliance Group 2015 **Level IV**, n=2,352). Elements associated with shorter LOS were laparoscopic surgery (OR 0.83), increasing ERAS protocol compliance (OR 0.88), preoperative carbohydrate and fluid loading (OR 0.89) and total IV anaesthesia (OR 0.86). Here, epidural analgesia increased LOS (OR 1.07). While, risk of complications was reduced with restrictive perioperative IV fluids (OR 0.35), laparoscopic surgery (OR 0.68) and increasing ERAS protocol compliance (OR 0.69).

Other analgesic factors that reduced LOS after elective colorectal surgery including avoidance of oral opioids in the postoperative period (OR 0.39; 95%CI 0.18 to 0.84) and the use of shorter duration of epidural analgesia (OR 0.44; 95%CI 0.12 to 0.94) (Ahmed 2010 **Level IV**, n=231). Opioid-sparing analgesic techniques reduced postoperative ileus (Barletta 2011 **Level IV**, n=279; Barletta 2012 **NR**).

Overall, independent predictors of early recovery after open and laparoscopic colorectal surgery were enforced advancement of oral intake (normal diet at POD 1 to 3) and early

mobilisation (Vlug 2012 **Level III-2**, n=400). Effective analgesia facilitates these elements of ERAS protocols enabling early enteral feeding and mobilisation/ambulation. It follows that provision of analgesia by appropriate techniques remains an important component of these protocols (Kehlet 2011 **NR**; White 2007 **NR**; Kehlet 2003 **NR**). Therefore evidence-based and procedure-specific guidelines for pain management need to be incorporated in ERAS protocols for various operations; goals are not specifically low pain scores, but improved functionality and improved ambulation (Joshi 2019a **NR**).

In comparison to conventional care after breast reconstruction, following an ERAS pathway does not only reduce LOS, but also pain severity and reliance on opioid analgesia as measured by shortened IV PCA usage and reduced IV, oral and total opioid requirements (Tan 2019 **Level III-2 SR**, 10 studies, n=1,838). In an ambulatory setting, implementation of an ERAS protocol for mastectomy and breast reconstruction included multimodal analgesia (preoperative paracetamol, gabapentin; regional anaesthesia [PECS type 1 and 2 or PVB] and intraoperative dexamethasone and ondansetron) (Simpson 2019a **Level III-3**, n=437). Compared to historical controls prior to implementation of the ERAS protocol, patients in the ERAS group had lower highest pain scores (median 4/10 [IQR 2,6] vs 6/10 [IQR 4,7]), lower total opioid consumption in oral morphine equivalents (mean 111.4 mg [SD 46.0) vs 163.8 mg [SD 73.2]) and reduced PONV incidence (28% vs 50%).

KEY MESSAGES

1. Adherence to multimodal enhanced recovery protocols after surgery protocols reduces hospital length of stay, complication rates (**S**) (**Level I**), postoperative pain severity and opioid requirements (**N**) (**Level III-2 SR**)**.**

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Provision of appropriate analgesia is only one of several elements of enhanced recovery after surgery protocols (**S**).

☑ Analgesic techniques, which permit early mobilisation and early enteral feeding, in particular those that are opioid-sparing, may contribute to early recovery after surgery protocols (**S**).

8.1.4 | Risks of acute postoperative neuropathic pain

Neuropathic pain has been redefined as "*pain caused by a lesion or disease of the somatosensory nervous system*" (Jensen 2011 **NR**). Although neuropathic pain is often considered a chronic pain state, it can occur acutely. Acute causes of neuropathic pain can be iatrogenic, traumatic, inflammatory or infective (Gray 2008a **NR**). Nerve injury is a risk in many surgical procedures and may present as acute neuropathic pain postoperatively.

Screening questionnaires for neuropathic pain such as DN4, LANSS or painDETECT are widely used in the acute setting, but are only validated for chronic neuropathic pain (Schnabel 2018 **NR**). Therefore there is no diagnostic standard for acute neuropathic pain and an attempt has been made to develop diagnostic criteria in a three-step Delphi process among pain specialists (Searle 2012 **GL**). Besides the usual descriptors of neuropathic pain, the items "*difficult to manage pain*", "*poor response to opioids*" and "*good response to anti-neuropathics*" were suggested.

The incidence of acute neuropathic pain has been reported as 1 to 3%, based on patients referred to an APS, primarily after surgery or trauma (Hayes 2002 **Level IV**, n=4,888). The majority of these patients had persistent pain at 12 mth, suggesting that acute neuropathic pain is a risk factor for chronic pain. These qualitative results were confirmed subsequently (Beloeil 2017 **Level III-2**, n=593). Using a screening tool (DN-4), 5.6% (95% CI 3.6 to 8.3) screened positive on the day of surgery and 12.9% (95%CI 9.7 to 16.7) on POD 1. At phone follow-up 2 mth postsurgery, 33.3% of patients screened positively; acute positive screening was a risk factor for later positive screening (OR 4.2; 95%CI 2.2 to 8.1). Similarly, immediately after thoracotomy or video assisted thoracic surgery, 8% of patients scored positively on another screening tool for neuropathic pain (LANSS) and 22% 3 mth later; again acute positive was a risk factor for chronic positive results (RR 3.5; 95%CI 1.7 to 7.2) (Searle 2009 **Level III-2**, n=100).

The role of acute neuropathic pain as a component of postoperative pain is possibly underestimated; after sternotomy, 50% of patients had dysaesthesia in the early postoperative period, which was closely associated with severity of postoperative pain (Alston 2005 **Level IV**, n=50). After cancer surgery, a prospective study using the painDETECT screening tool identified acute neuropathic pain in 10% of cases in the first week postoperatively (Jain 2014 **Level IV**, n=300). In a general surgical population, the incidence was 3 to 4.2% (Sadler 2013 **Level IV**, n=165). Similarly, a high incidence of acute neuropathic pain in the lower limbs with lumbosacral plexus injury after pelvic trauma has been reported (Chiodo 2007 **Level IV**, n=78). In cohort studies, 6 to 13% of postoperative patients screened positive for acute neuropathic pain (Searle 2009 **Level III-2**, n=100).

Management of acute neuropathic pain is primarily based on extrapolation of data from the chronic neuropathic pain setting (see Sections 4.6 to 4.10). However, selection of a preferred treatment in the acute setting may be based on a faster onset of effect; tramadol, opioids and alpha-2-delta ligands are suggested (Macintyre 2015 **NR**; Dworkin 2010 **GL**). In two small series of acute neuropathic pain due to SCI, all patients responded positively to IV ketamine followed by oral ketamine (Kim 2013a **Level IV**, n=13) and salmon calcitonin (Humble 2011 **Level IV**, n=3).

There is some evidence that specific early analgesic interventions may reduce the development of chronic pain (often neuropathic pain) after some operations (eg thoracotomy, amputation). For more details, see Sections 1.4, 1.5, 8.1.5 and 8.1.6.

KEY MESSAGES

1. Positive screening for acute postoperative neuropathic pain is a risk factor for positive screening of chronic postsurgical neuropathic pain (**N**) (**Level III-2**).
2. Acute neuropathic pain occurs after trauma and surgery (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Treatment of acute neuropathic pain should follow guidelines for chronic neuropathic pain; ketamine, opioids (including tramadol and tapentadol in particular) and alpha-2-delta ligands may offer faster onset of effect than other treatment options (**U**).

8.1.5 | Acute postamputation pain syndromes

Following amputation of a limb, and also breast, tongue, teeth, genitalia, the eye and even inner organs such as the rectum, or a deafferentation injury such as brachial plexus avulsion (Ahmed 2014 **Level IV**, n=80; Boas 1993 **Level IV**, n=33; Bates 1991 **Level IV**, n=30; Andreotti 2014 **NR**), a number of phenomena can develop which require differentiation:

- *Residual limb pain (stump pain)* is pain localised to the site of amputation. It can be acute (usually nociceptive) or chronic (usually neuropathic) and is most common in the immediate postoperative period (Jensen 1985 **Level IV**, n=58; Nikolajsen 2001 **NR**). The overall incidence of residual limb pain is uncertain but the risk of early stump pain is increased by the presence of severe preamputation pain (Nikolajsen 1997 **Level IV**, n=56).
- *Phantom sensation* is defined as any sensory perception of the missing body part with the exclusion of pain. Almost all patients who have undergone amputation experience phantom sensations (Jensen 1983 **Level IV**, n=58). These sensations range from a vague awareness of the presence of the missing body part via associated paraesthesia, to complete sensation including size, shape, position, temperature and movement.
- *Phantom limb pain* is defined as any noxious sensory phenomenon in the missing body part. The estimated incidence of phantom limb pain is 30–85% after limb amputation and usually occurs in the distal portion of the missing limb (Jensen 1985 **Level IV**, n=58; Nikolajsen 2001 **NR**; Perkins 2000 **NR**). Pain may be early, 75% of patients will report phantom pain within the first few days after amputation (Nikolajsen 1997 **Level IV**, n=56), or delayed in onset. The pain is typically intermittent and diminishes with time after amputation. Factors that may be predictive of postamputation phantom pain are the severity of preamputation pain, the degree of postoperative stump pain, and chemotherapy or radiotherapy (see also Sections 1.4. and 1.5.). If preamputation pain was present, phantom pain might resemble that pain in character and localisation (Katz 1990 **Level IV**, n=68). The intensity of preamputation pain and acute postoperative pain were strong predictors of the intensity of chronic pain after amputation (Hanley 2007 **Level III-3**, n=57). Preoperative passive coping strategies, in particular catastrophising, were other strong predictors of phantom limb pain 6 mth later (Richardson 2007 **Level III-3**, n=59). Reduction of chronic phantom limb pain intensity by peripheral nerve blocks suggests that afferent input from the periphery plays a role in maintaining phantom limb pain (Buch 2019 **Level II EH**, n=12 [crossover], JS 5).

There is a strong correlation between phantom limb and residual limb or site pain, and they may be inter-related (Kooijman 2000 **Level IV**, n=124; Jensen 1983 **Level IV**, n=58). All three of the above phenomena can coexist (Nikolajsen 1997 **Level IV**, n=56).

A survey identified the high incidence of these pain syndromes after amputation; only 14.8% were pain-free, 74.5% had phantom limb pain, 45.2% residual limb pain and 35.5% a combination of both (Kern 2009 **Level IV**, n=537).

Phantom breast pain has also been described; however, the incidence was low in the range of 7% at 6 wk and 1% at 2 y (Dijkstra 2007 **Level III-3**, n=82). Phantom sensations are more common; reported in 19% of patients more than 5 y after surgery (Peuckmann 2009 **Level IV**, n=2,000).

Predictive factors of phantom limb pain were longstanding preoperative chronic pain, subacute postoperative pain as well as psychological factors (depression and anxiety) (Larbig 2019 **Level IV**, n=52). Preoperative state anxiety is a risk factor for acute residual and phantom limb pain (Raichle 2015 **Level IV**, n=69).

8.1.5.1 | Prevention of phantom limb pain

Evidence for the benefit of epidural analgesia in the prevention of all phantom limb pain is inconclusive (Halbert 2002 **Level III-2 SR**, 3 studies [epidural], n=106). However, perioperative (pre, intra and postoperative) epidural analgesia reduced the incidence of severe phantom limb pain (NNT 5.8; 95%CI 3.2 to 28.6) (Gehling 2003 **Level III-2 SR**, 9 studies, n=836). In a subsequent systematic review, chronic pain is reduced by epidural analgesia at 6 mth in 3 of 7 studies, however with poor study quality (von Plato 2018 **Level IV SR** [PRISMA], 9 RCTs & 10 studies, n=949).

Epidurally administered calcitonin reduced the incidence of chronic phantom limb pain, allodynia and hyperalgesia at 6 and 12 mth in diabetic patients undergoing lower limb amputation (Yousef 2017 **Level II**, n=60, JS 5).

In a small observational study, the overall incidence of long term phantom limb pain was similar in regional analgesia recipients given IV ketamine (bolus dose followed by an infusion, started prior to skin incision and continued for 72 h) vs no ketamine; however the incidence of severe phantom limb pain was reduced in the ketamine group (Dertwinkel 2002 **Level III-3**, n=28). An RCT was inadequately powered to show a difference with IV ketamine vs controls in the incidence of phantom limb pain at 6 mth after amputation (47% vs 71%; p=0.28) (Hayes 2004 **Level II**, n=45, JS 4). Perioperative ketamine/bupivacaine given by the epidural route showed no preventive effect vs epidural saline/bupivacaine (Wilson 2008 **Level II**, n=53, JS 5).

Perioperative gabapentin was ineffective in reducing incidence and severity of phantom limb pain vs placebo (Nikolajsen 2006 **Level II**, n=46, JS 5). Valproic acid for the duration of the hospital stay after amputation had no preventive effect on phantom limb pain vs placebo (Buchheit 2019b **Level II**, n=128, JS 5).

Infusions of local anaesthetics via peripheral nerve sheath catheters, usually inserted by the surgeon at the time of amputation, show no benefit in preventing phantom pain or residual limb pain (McCormick 2014 **Level I**, 2 RCTs [perineural], n=151; Bosanquet 2015 **Level III-2 SR** [PRISMA], 2 RCTs & 5 studies, n=416; von Plato 2018 **Level IV SR** [PRISMA], 2 RCTs & 8 studies [CPNB], n=949) (2 RCTs overlap [between all 3 SR] & 5 studies overlap Bosanquet 2015 with von Plato 2018). In the latter systematic review, acute postoperative opioid requirements are reduced (SMD -0.59; 95%CI -1.10 to -0.07) without any other positive outcomes.

Common peroneal nerve to tibial nerve coaptation and collagen nerve wrapping vs traction neurectomy only for transfemoral amputation resulted in less neuroma formation and phantom limb pain respectively at 2 mth (0% vs 36.3% and 0% vs 54.5%) and at 6 mth (0% vs 54.5% and 0% vs 63.6%) (Economides 2016 **Level III-2**, n=17). Furthermore, pain scores at 6 mth were lower (0.75/10 vs 5.6/10) and more patients were walking with a prosthesis (67% vs 9%).

8.1.5.2 | Therapy for phantom limb pain

A survey in 1980 identified over 50 different therapies used for the treatment of phantom limb pain (Sherman 1980 **NR**), suggesting limited evidence for effective treatments. Not a lot of progress has been made since then (Urits 2019 **NR**; Collins 2018 **NR**).

Pharmacological treatment

With regard to pharmacological treatment, most conclusions are based on studies limited by their small sample size (Alviar 2016 **Level III-1 SR** [Cochrane], 14 studies, n=269). Oral and IV morphine are effective in the short term (2 RCTs, n=43) as are the NMDA-antagonists ketamine (2 RCTs) and dextromethorphan (1 RCT). Gabapentin also has an analgesic effect (MD -1.16/10; 95%CI -1.94 to -0.38) (2 RCTs, n=43). An earlier meta-analysis of gabapentin specifically in this setting included a third RCT that showed no benefit (Nikolajsen 2006 **Level II**, n=46, JS 5) which therefore weakens this conclusion (Abbass 2012 **Level I**, 3 RCTs, n=89).

Amitriptyline may be ineffective in acute phantom limb pain management (1 RCT, n=39) as well as botulinum toxin A (1 RCT, n=14) (Alviar 2016 **Level III-1 SR** [Cochrane], 14 studies, n=269).

For memantine no effect is shown in the overarching systematic review (4 RCTs and 2 studies, n=81) (Alviar 2016 **Level III-1 SR** [Cochrane], 14 studies, n=269). Although an overlapping memantine specific systematic review reports use immediately after amputation reduces phantom limb pain (1 RCT, n=19; 3 studies, n=5), but lacks efficacy in established chronic phantom limb pain (4 RCTs, n=75) (Loy 2016 **Level IV SR** [PRISMA], 5 RCTs & 3 studies, n=99) (4 RCTs overlap).

In acute phantom limb pain, IV (and likely SC) salmon calcitonin (within 7 d of amputation) was more effective than placebo (Alviar 2016 **Level III-1 SR** [Cochrane], 1 RCT: Jaeger 1992 **Level II**, n=21 [cross over], JS 3; Bornemann-Cimenti 2017 **CR**; Turek 2012 **CR**). However, it was not effective for chronic phantom limb pain (Alviar 2016 **Level III-1 SR** [Cochrane], 1 RCT: Eichenberger 2008 **Level II**, n=20 [cross over], JS 5).

Systemic lignocaine (1 RCT, n=31) may be ineffective, while contralateral myofascial injection of bupivacaine (administered once) may reduced phantom limb pain in a very small study (1 RCT, n=8 [cross-over]) (Alviar 2016 **Level III-1 SR** [Cochrane], 14 studies, n=269).

A subsequent systematic review reports similar results in a less thorough way (McCormick 2014 **Level III-1 SR**, 27 RCTs & 1 study, n=807 [& multiple CRs]). With regard to morphine an additional RCT (n=12) confirms long term benefits (with a slow-release preparation). An RCT excluded from the Cochrane review above due to its complex study design is incorrectly interpreted by this systematic review; the RCT shows that amitriptyline as well as tramadol provided good control of phantom limb pain (Wilder-Smith 2005 **Level II**, n=94 [cross-over], JS 4).

Neurostimulation

Neurostimulation has some effect in case series for the treatment of phantom limb pain in the form of spinal cord (McAuley 2013 **Level IV**, n=12) and peripheral nerve stimulation (Rauck 2014 **Level IV**, n=16). Percutaneous peripheral nerve stimulation resulted in more patients achieving ≥50% reduction in neuropathic postamputation pain after 4 weeks vs placebo (58% vs 14%) (Gilmore 2019 **Level II**, n=28, JS 5). Transcranial magnetic stimulation is also reviewed for treatment of phantom limb pain and non-painful phantom sensations (Nardone 2019 **Level IV SR**, 18 studies, n unspecified). However, a systematic review concludes that there /are currently no robust and reliable data on efficacy and safety of any neurostimulation in the setting of postamputation pain (Corbett 2018 **Level IV SR**, 7 RCTs & 69 studies, n unspecified); spinal cord stimulation specifically shows mixed results with some weak evidence for benefit (Aiyer 2017 **Level III-3** [PRISMA], 12 studies, n=115)..

Surgery

Targeted muscle reinnervation, originally developed to improve prosthetic tolerance and bioprosthetic outcomes, has been used for the treatment of residual and phantom limb pain (Bowen 2017 **NR**). It may even have preventive effects on both types of pain if performed at the time of amputation (Valerio 2019 **Level III-2**, n=489).

Nonpharmacological treatment

A systematic review of RCTs excluded low quality RCTs (Batsford 2017 **Level I** [PRISMA], 12 RCTs, n=135). The 5 high to moderate quality RCTs show:

- Inconclusive evidence for an effect on phantom limb pain by electromagnetically shielding limb liner (2 RCTs, n=91);
- Graded motor imagery to reduce phantom limb pain and improve function at 6 mth (1 RCT, n=9);
- A single session of mirror therapy to be ineffective (1 RCT, n=15);
- Hypnosis to reduce phantom limb pain in the short-term vs waitlist control (1 RCT, n=20).

However, nonpharmacological treatment options for phantom limb pain based on concepts of cortical reorganisation are widely discussed (Aternali 2019 **NR**; Andoh 2018 **NR**). All studies of mirror therapy, motor imagery, and virtual feedback show an effect on intensity of phantom limb pain in amputees; however the evidence is weak, as the studies included are of limited quality (Herrador Colmenero 2018 **Level III-3 SR** [PRISMA], 6 RCTs & 6 studies, n in range of 5 to 41) (2 RCTs overlap with Batsford 2017). Mirror therapy specifically shows a short-term beneficial effect in 3/4 RCTs vs controls and similar effects to TENS in 1 RCT and the authors regard the evidence as weak and insufficient to support its current use as a "*first-intention*" treatment for phantom limb (Barbin 2016 **Level IV SR** [PRISMA], 5 RCTS & 15 studies, n=258). An RCT published subsequent to the systematic review showed that graded motor imagery for 6 wk was superior to routine physiotherapy in reducing intensity of phantom limb pain and interference with function (Limakatso 2019 **Level II**, n=21, JS 3).

These findings are supported by even weaker evidence in the form of case reports excluded from the systematic review above. Maladaptive changes in cortical organisation were reversed during mirror treatment, which over 4 wk resulted in an average decrease of phantom limb pain intensity of 27% (Foell 2014 **Level IV**, n=13); mirror therapy was also effective if self-administered at the home of patients (Darnall 2012 **Level IV**, n=40). Use of a hand prosthesis with somatosensory feedback on grip strength reduced phantom limb pain (Dietrich 2012 **Level IV**, n=8). Illusory touch was another effective approach in this context (Schmalzl 2013 **Level IV**, n=6).

A technique not included in the systematic review is sensory discrimination training, which was associated with reduced phantom limb pain and cortical reorganisation (Flor 2001 **Level II**, n=10, JS 2).

There are only case series and reports describing a beneficial effect on phantom limb pain by use of virtual or augmented reality treatments (Dunn 2017a **Level IV SR**, 8 studies, n=45).

A systematic review of TENS in the treatment of phantom limb pain found no studies (Johnson 2015 **Level I** [Cochrane], 0 RCTs, n=0). However, a subsequent RCT of TENS vs mirror therapy found both were equally effective at reducing pain scores from baseline (Barbin 2016 **Level I** [PRISMA], 1 RCT: Tilak 2016 **Level II**, n=25, JS 3).

KEY MESSAGES

1. Morphine, gabapentin, ketamine and dextromethorphan reduce phantom limb pain compared to placebo (**U**) (**Level I** [Cochrane Review]).
2. Calcitonin reduces phantom limb pain in the acute (<7 days post amputation) but not the chronic setting (**U**) (**Level I** [Cochrane Review]).
3. Continuous regional block via nerve sheath catheters provides postoperative analgesia after amputation but has no preventive effect on phantom limb pain (**U**) (**Level I**).
4. Treatments aiming at cortical reorganisation such as mirror therapy (**W**) (**Level IV SR**), sensory discrimination training and motor imagery may reduce chronic phantom limb pain (**W**) (**Level III-2 SR**).
5. Perioperative epidural analgesia reduces the incidence of severe phantom limb pain (**U**) (**Level III-2 SR**).
6. Anxiety may be a predictor of phantom limb pain (**N**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Perioperative ketamine may prevent severe phantom limb pain (**U**).

8.1.6 | Other postoperative pain syndromes

Increasing evidence for the development of postoperative chronic pain syndromes has led to the more detailed study of some of them. In the latest revised version of the International Classification of Diseases (ICD-11), accepted by the WHO, "chronic postsurgical and posttraumatic pain" is a new classification (Schug 2019 **GL**); a range of postsurgical pain syndromes are listed (eg chronic pain after thoracotomy, breast surgery, herniotomy, hysterectomy).

The progression from acute to chronic pain and specific early analgesic interventions to reduce the incidence of chronic pain after some operations are discussed in Sections 1.4 and 1.5.

8.1.6.1 | Post-thoracotomy pain syndrome

Post-thoracotomy pain syndrome is one of the most common chronic pain states. The incidence of chronic pain after thoracotomy was 57% at 3 mth (95%CI 51 to 64) (17 studies, n=1,439) and 47% at 6 mth (95%CI 39 to 56) (15 studies, n=1,354) (Bayman 2014 **Level IV SR**, 17 studies, n=1,439). The average severity of pain at these time points was respectively 30/100 (95%CI 26 to 35) and 32/100 (95%CI 17 to 46). Quality of life (QoL) was reduced in the SF-36 domains of physical functioning, bodily pain and vitality (Kinney 2012 **Level IV**, n=110).

Pathophysiology

Post-thoracotomy pain syndrome is thought to be caused primarily by trauma to intercostal nerves and most patients relate their pain directly to the site of surgery (Karmakar 2004 **NR**). Neurophysiological assessments (QST) have revealed that patients with post-thoracotomy pain, but also pain-free patients after thoracotomy, show increased thresholds suggesting nerve injury in both groups (Wildgaard 2009 **NR**). However, only the patients in pain show increased sensitivity to heat and cold and hyperaesthesia; this suggests that nerve injury by itself is not a predictor for post-thoractomy pain syndrome and other factors need to be present. Increased or decreased sensitivity and allodynia were reported more by patients with chronic post-thoracotomy pain at 6 and 12 mth; between the 6 and 12 mth assessments, pain resolved in some patients but developed in others (Hetmann 2017 **Level IV**, n=170). Furthermore, sensory dysfunction on the nonoperated side was found in patients with post-thoracotomy pain, while such "*mirror-image sensory dysfunction*" was not accompanied by mirror pain (Werner 2013 **Level IV**, n=28). However, myofascial pain syndromes as a consequence of thoracotomy have also been described (Hamada 2000 **Level IV**, n=27).

Predictive factors

As with other postsurgical pain syndromes, poorly controlled acute postoperative pain was a strong predictor of chronic post-thoracotomy pain (Niraj 2017 **Level IV**, n=504). Other risk factors were diagnosis of cancer and preceding chronic pain (Shanthanna 2016 **Level III-3**, n=106). Similar findings of chronic preoperative and severe acute postoperative pain were confirmed in other studies (Kampe 2017 **Level III-2**, n=174; Wang 2017a **Level III-2**, n=298). A further study identified preoperative pain as the major predictor of chronic pain (OR 6.97; 95%CI 2.40 to 20.21) while finding dispositional optimism was a protective factor (OR 0.36; 95%CI 0.14 to 0.96) (Hetmann 2015 **Level IV**, n=170). Surgical approach is relevant where video-assisted thoracoscopic surgery (VATS) vs open thoracic surgery has reduced risk of post-thoracotomy pain (adjusted OR 0.33; 95%CI 0.13 to 0.86) and neuropathic pain (adjusted OR 0.18; 95%CI 0.04 to 0.85), but VATS still carries a significant risk (35% incidence) (Shanthanna 2016 **Level III-3**, n=106); this was confirmed in another study (VATS 13.3% vs thoracotomy 32.2%) (Wang 2017a **Level III-2**, n=298).

Preventive strategies

Following open thoracotomy (7 RCTs, n=499), epidural anaesthesia reduces the incidence of CPSP three to 18 mth following surgery vs systemic analgesia (OR 0.52; 95%CI 0.32 to 0.84) (NNT 7) (Weinstein 2018 **Level I** [Cochrane], 63 RCTs, n=3,027). A subsequent RCT is in line with these results (Khoronenko 2018 **Level II**, n=300, JS 3), while a single bolus perioperative PVB had no protective effect (Li 2018b **Level II**, n=56, JS 5).

Cryoanalgesia provides pain relief superior to other techniques only in 6 of 12 RCTs in the immediate postoperative period but increased the incidence of post-thoracotomy pain in 4 of 4 RCTs evaluating this outcome (Khanbhai 2014 **Level I**, 12 RCTs, n unspecified).

Magnesium (IV bolus and 24 h postoperative infusion) may have a preventive effect on chronic neuropathic pain after thoracotomy (Ghezel-Ahmadi 2019 **Level III-2**, n=100).

Treatment

Detailed reviews of treatments for acute and chronic pain after thoracotomy have been published (Doan 2014 **NR**; Romero 2013 **NR**).

8.1.6.2 | Post-mastectomy pain syndrome

Chronic pain after mastectomy is common (Kokosis 2019 **NR**). A consensus document on suggested diagnostic criteria has been published suggesting the following: *"Postmastectomy pain syndrome is pain that occurs after any breast surgery; is of at least moderate severity; possesses neuropathic qualities; is located in the ipsilateral breast/chest wall, axilla, and/or arm; lasts at least 6 months; occurs at least 50% of the time; and may be exacerbated by movements of the shoulder girdle."* (Waltho 2016 **NR**).

In epidemiological studies, an overall prevalence of 29.8% has been found (Wang 2018c **Level IV SR**, 30 studies [postmastectomy], n=3,746). In this context, it is of interest that the same systematic review found an incidence of chronic pain after radiotherapy of 27.3% (Wang 2018c **Level IV SR**, 41 studies, n=15,019).

Phantom breast pain has also been described; however, the incidence was low in the range of 7% at 6 wk and 1% at 2 y (Dijkstra 2007 **Level III-3**, n=82). Phantom sensations are more common; reported in 19% of patients >5 y after surgery (Peuckmann 2009 **Level IV**, n=2,000). Postmastectomy pain syndrome has a negative effect on many domains of quality of life (Meijuan 2013 **Level IV**, n=225).

Pathophysiology

Sensory testing (thermal thresholds, cold allodynia and temporal summation of repetitive stimulation) showed that postmastectomy pain is often a neuropathic pain condition (Vilholm 2009 **Level III-2**, n=82); in line with this, 64% of patients after mastectomy describe sensory disturbances with an increased risk of chronic pain (Meijuan 2013 **Level IV**, n=225).

Predictive factors

Significant predictors for the development of postmastectomy chronic pain were younger age (Meijuan 2013 **Level IV**, n=225) and radiotherapy (Henderson 2014 **Level III-2**, n=272; Peuckmann 2009 **Level IV**, n=2,000). Other risk factors were higher postoperative pain scores and inclusion of major reconstructive surgery (Chang 2009 **Level IV**). Psychosocial factors including catastrophising, somatisation, anxiety (OR 1.63; 95% CI 1.23 to 2.40) (Nishimura 2017 **Level IV**, n=64) and sleep disturbance were significant predictors (Belfer 2013 **Level IV**, n=611). Type of surgery, axillary node dissection, surgical complication, recurrence, tumour size and, contrary to above findings, radiation and chemotherapy were not significantly associated with postmastectomy chronic pain. Immediate breast reconstruction (implant or pedicled flap) does not increase

postmastectomy pain vs mastectomy alone (Henderson 2014 **Level III-2**, n=272). In contrast, a subsequent study (prevalence of postmastectomy pain 57.3%) identified the risk factors of postdischarge chemotherapy (OR 2.52; 95%CI 1.13 to 5.82) and postdischarge radiation (OR 3.39; 95%CI 1.24 to 10.41), while reconfirming the importance of severe acute pain (OR 5.39; 95%CI 2.03 to 15.54) and even moderate acute pain (OR 5.31; 95%CI 1.99 to 15.30) (Habib 2019 **Level IV**, n=124).

Preventive strategies

PVB reduces postmastectomy pain syndrome at 3 to 12 mth vs systemic analgesia (OR 0.43; 95%CI 0.28 to 0.68) (NNT 5) (Weinstein 2018 **Level I** [Cochrane], 18 RCTs [breast surgery], n=1,297). A subsequent RCT has confirmed these findings of reduced chronic postmastectomy pain with PVB use at 3 mth (OR 0.51; 95%CI 0.28 to 0.94) and at 6 mth (OR 0.48; 95%CI 0.25 to 0.94) (Qian 2019 **Level II**, n=184, JS 5).

Lidocaine IV infusion vs placebo reduces the risk of chronic postmastectomy pain (OR 0.29; 95%CI 0.18 to 0.48) (Bailey 2018 **Level I** [PRISMA], 6 RCTs, n=420).

Following mastectomy, 10 d treatment with venlafaxine commencing preoperatively was associated with significantly lower burning and stabbing pain after 6 mth (Amr 2010 **Level II**, n=150, JS=3). A 4 wk course of memantine (5-20 mg/d;started 2 wk before surgery) reduced pain intensity,neuropathic analgesia requirements and improved emotional state at 3 mth vs placebo (Morel 2016 **Level II**, n=43, JS 5).

Perioperative use of gabapentin or mexiletine after mastectomy reduced the incidence of neuropathic pain at 6 mth postoperatively, from 25% in the placebo to 5% in both treatment groups (Fassoulaki 2002 **Level II**, n=75, JS 4). Similar protective results were reported by the same group by the use of a eutectic mixture of local anaesthetics alone (Fassoulaki 2000 **Level II**, n=46, JS 4) or in combination with gabapentin (Fassoulaki 2005 **Level II**, n=50, JS 5).

Treatment

For treatment of chronic postmastectomy pain, amitriptyline (1 RCT, n=15 [crossover]), venlafaxine (1 RCT, n=13 [crossover]), topical capsaicin (0.075%) (1 RCT, n=23) and autologous fat grafting into the scar area (2 studies [Level III-2], n=209) are effective, while levetiracetam (1 RCT, n=27) is ineffective (Larsson 2017 **Level III-2 SR**, 4 RCTs & 2 studies, n=277).

8.1.6.3 | Post-herniotomy pain syndrome

At 6 mth after herniotomy, 12.4% had “moderate/severe” pain (Aasvang 2010 **Level IV**, n=442) and 16.0% had substantial pain-related functional impairment (Bischoff 2012 **Level III-3**, n=244).

Pathophysiology

This syndrome is thought to be mainly neuropathic pain as a result of nerve injury. This assumption was confirmed in a study that showed that all patients with chronic postherniotomy pain had features of neuropathic pain (Aasvang 2008 **Level IV**, n=46). Ejaculatory pain is a feature of this syndrome and occurs in around 2.5% of patients after herniotomy (Aasvang 2007b **Level IV**, n=10).

Predictive factors

The following risk factors were identified: preoperative Activity Assessment Scale score, preoperative pain to tonic heat stimulation, 30-d postoperative pain intensity and sensory dysfunction in the groin at 6 mth (nerve damage). An attempt to predict risk also identified open vs laparoscopic herniotomy as an additional intraoperative risk factor (OR 0.45; 95%CI 0.23 to 0.87). Furthermore, a genetic risk factor may exist as a homozygous single nucleotide polymorphism in the TNF-α gene was associated with an increased risk of neuropathic pain after

herniotomy (Kalliomaki 2016 **Level III-2**, n=200). Another study suggests that functional variations in COMT and GCH1 may predict to some extent impairment due to chronic pain after herniotomy (Belfer 2015 **Level III-2**, n=429).

Very young age may be a protective factor as hernia repair in children <3 mth age did not lead to chronic pain in adulthood (Aasvang 2007a **Level IV**, n=651).

Preventive strategies

Deliberate neurectomy (of the ilioinguinal nerve) for inguinal hernia repair reduced the incidence of CPSP (from 21–6%) in one RCT (Malekpour 2008 **Level II**, n=100, JS 4) and in another study (Smeds 2010 **Level III-2**, n=525), while an earlier nonrandomised multicentre prospective study found this increased CPSP risk (Alfieri 2006 **Level III-2**, n=973). Intraoperative nerve identification of the iliohypogastric, ilioinguinal and genitofemoral nerves did not reduce the risk of development of sensory loss or postherniotomy pain syndrome vs nonidentification (Bischoff 2012 **Level III-3**, n=244).

Mesh removal and selective neurectomy of macroscopically injured nerves reduced impairment in patients with postherniorrhaphy pain syndrome (Aasvang 2009 **Level III-3**, n=21).

Treatment

Evidence-based consensus guidelines for prevention and management of postoperative chronic pain following inguinal hernia surgery have been published (Alfieri 2011 **GL**). Recommended approaches include to identify and preserve all three inguinal nerves and to perform elective resection of a suspected injured nerve. Patients with a postherniotomy pain syndrome not responding to other pain management treatment should be offered surgical treatment (including all three nerves) after at least 1 y from the previous hernia repair.

8.1.6.4 | Post-hysterectomy pain syndrome

The incidence of chronic post-hysterectomy pain was 27.7% at 3 mth (Han 2017 **Level IV**, n=870), 32% at 4 mth and 15.7% at 6 mths (Sng 2018 **Level IV**, n=216), in line with previous data (Brandsborg 2012 **NR**). Incidence at 5 y was 17.1% in another study (Pinto 2018 **Level III-2**, n=170).

Predictive factors

In most women pain was present preoperatively; at a 1 to 2 y follow-up, pain was reported as a new symptom in 1 to 15% of patients (Brandsborg 2008 **NR**). In an initial small prospective survey postoperative pain intensity, as well as preoperative nonpelvic pain, were associated with the presence of pain 4 mth after surgery (Brandsborg 2009 **Level III-3**, n=90). For pain reported 1 y after surgery, risk factors were preoperative pelvic and nonpelvic pain and previous Caesarean section; there was no difference found between vaginal or abdominal hysterectomy or the type of incision for abdominal hysterectomy (Brandsborg 2007 **Level IV**, n=1,299). Preoperative pain sensitisation (cutaneous and vaginal hypersensitivity) is associated with acute pain after hysterectomy; but only preoperative brush-evoked allodynia was associated with chronic pain at 4 mth postoperatively (Brandsborg 2011 **Level IV**, n=90). Subsequent more detailed analyses confirmed most of these risk factors for pain at 4 mth: preoperative lower abdominal pain (OR 8.55), postoperative itching at 24 h (OR 3.33) and severe pain in PACU (OR 1.39) (Sng 2018 **Level IV**, n=216); presurgical anxiety (OR 1.18), emotional representation of the surgical disease (OR 1.21), pain catastrophising (OR 1.143), acute postsurgical pain intensity (OR 1.21) and frequency (OR 3.00) and postsurgical anxiety (OR 1.182), as well as preoperative depression, pre-existing pelvic pain and sexual dissatisfaction (Han 2017 **Level IV**, n=870).

Preventive strategies

Patients given perioperative gabapentin and a postoperative ropivacaine wound catheter infusion had lower opioid requirements after surgery and less pain 1 mth later vs placebo, although there was no difference in pain scores for the first 7 d postoperatively (Fassoulaki 2007 **Level II**, n=60, JS 5). Perioperative pregabalin (150 mg 3 times/d for 5 d) reduced postoperative opioid requirements, but had no effect on any pain outcome at 3 mth (Fassoulaki 2012 **Level II**, n=80, JS 5).

Spinal anaesthesia in comparison with general anaesthesia reduced the risk of chronic postsurgical pain after hysterectomy (OR 0.42; 95%CI 0.21 to 0.85) (Brandsborg 2007 **Level IV**, n=1,299). Propofol-based general anaesthesia vs sevoflurane-based anaesthesia reduced the incidence (17.5 vs 52.5%; p<0.01) and severity of posthysterectomy pain (0.78/10 ±0.55 vs 2.23/10 ±0.73; p<0.01) at 3 mth postoperatively (Ogurlu 2014 **Level II**, n=80, JS 5).

KEY MESSAGES

1. Following thoracotomy, epidural analgesia reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
2. Following breast cancer surgery, paravertebral block (**S**) (**Level I** [Cochrane Review]) and lidocaine IV infusions reduce the incidence of chronic postsurgical pain (**N**) (**Level I** PRISMA]).
3. Cryoanalgesia of the intercostal nerves at the time of thoracotomy results in no improvement in acute pain, but an increase in chronic pain (**U**) (**Level I**).
4. Video-assisted thoracoscopic surgery versus open thoracic surgery resulted in a reduced rate of chronic post-thoracotomy pain (**N**) (**Level III-3**).
5. Post-thoracotomy, post-mastectomy, post-herniotomy and post-hysterectomy pain syndromes occur frequently (**S**) (**Level IV**) and psychological factors (eg anxiety, catastrophising), chronic preoperative pain and severe acute postoperative pain are consistently reported risk factors for these pain syndromes (**N**) (**Level IV**).

8.1.7 | Ambulatory or short-stay surgery

Ever increasing numbers of surgical procedure are now performed on an ambulatory or short-stay basis, here defined as hospital LOS <24 h. Adequate postoperative pain management is often the limiting factor when determining whether a patient can have surgery performed as a day-stay procedure.

Provision of effective analgesia after ambulatory surgery remains poor. In two Swedish nationwide surveys of ambulatory surgery, pain was the most common problem at follow-up after discharge in a mixed (Segerdahl 2008b **Level IV**, n=92 [hospitals]) and a paediatric population (Segerdahl 2008a **Level IV**). Another survey from a single institution found that at 3 and 4 d after day-stay surgery, 10 and 9% of patients respectively reported moderate to severe pain (Greengrass 2005 **Level IV**). Even after cataract surgery in an ambulatory setting, ocular pain was reported by 10% of patients at 24 h, 9% at 7 d and 7% at 6 wk (Porela-Tiihonen 2013 **Level IV**, n=201). Similarly, a French survey identified variable quality and a lack of standardisation of postoperative analgesia provision after ambulatory surgery across 221 randomly selected health care facilities (Aubrun 2019 **Level IV**, n=7,382).

After paediatric adenotonsillectomy, 52% patients had pain >5/10 at POD 3 (33% had nausea) and 30% at 7 d (Stanko 2013 **Level IV**, n=100). Pain scores during the first 24 h were slightly increased for day-stay tonsillectomy vs overnight inpatient stay, although maximal pain scores at 24 h and 7 d were unchanged (Norrington 2013 **Level III-2**, n=60). Differences in parental attitudes, understanding and access to medications, nausea or fear of adverse effects may explain some of these differences. Barriers have been summarised as parental, child, medication and system factors (Dorkham 2014 **NR**). Neither supplying a discharge medication package (Hegarty 2013 **Level II**, n=200, JS 2) nor nurse telephone follow-up improved pain relief after ambulatory tonsillectomy (Paquette 2013 **Level II**, n=45, JS 2). An audit of children found that pain reports were significantly higher at home than in hospital (Shum 2012 **Level IV**, n=200). Pain scores, functional limitation and analgesic use are greater after tonsillectomy than after inguinal hernia repair or orchidopexy in children discharged from ambulatory surgery, with the majority requiring at least one analgesic medication for 7 d after surgery and more than half of the patients requiring visits to a general practitioner (Stewart 2012 **Level IV**, n=105).

The best predictive factor of postoperative pain after ambulatory surgery is the presence of preoperative pain; other factors include high expectations of postoperative pain, anticipation of pain by clinicians, younger age, and surgery type (particularly orthopaedic, dental, inguinal hernia, anal, scrotal, and tendon/fascia surgeries) (Gramke 2009 **Level IV**, n=648). Not all of these factors could be confirmed in a subsequent modelling attempt, which identified preoperative pain, patient derived expected pain, and different types of surgery as the strongest predictors of moderate to severe pain 4 d after ambulatory surgery (Stessel 2017 **Level III-3**, n=1,118). Younger age and orthopaedic surgery were risk factors for severe postoperative pain in wk 1 after ambulatory surgery and high pain scores predicted more severe nausea for POD 1 to 5 (Odom-Forren 2015 **Level IV**, n=248). On POD 4 after ambulatory surgery, moderate (16.3%) to severe (12.1%) postoperative pain presented with procedure-specific variation; shoulder, anal and dental surgery was associated with the most intense pain (Vrancken 2018 **Level III-2**, n=1,123); preoperative pain intensity predicted postoperative pain intensity, but again related to procedure performed.

8.1.7.1 | Adverse effects of pain and principles of management

Inadequate analgesia delays patient discharge; pain was the most common cause of delayed recovery affecting 24% of patients (Pavlin 2002 **Level IV**, n=150). Uncontrolled pain is also associated with nausea and vomiting, extending the patient's stay in the recovery room (Eriksson 1996 **Level III-1**, n=90; Michaloliakou 1996 **Level III-1**, n=49) and is likely to continue after hospital discharge (Odom-Forren 2015 **Level IV**, n=248). The most common reason for unplanned hospital admission across 14 day-stay surgical units in Finland was unrelieved pain (Mattila 2009 **Level III-2**, n=7,915). The readmission rate was 5.4% in ambulatory surgery cases with nearly half related to inadequate pain management and half of these potentially avoidable with appropriate management (Herbst 2017 **Level IV**, n=28,674). Inadequate pain management may cause sleep disturbance and limit early mobilisation, which may be crucial for early return to normal function and work (Strassels 2002 **Level IV**, n=30).

More complex surgery continues to be performed on an ambulatory or short-stay basis and therefore the analgesic drugs and techniques required are similar to those used for inpatient pain relief. Multimodal analgesia is recommended in this setting (Schug 2015 **NR**; Elvir-Lazo 2010 **NR**) and seen as an essential part of enhanced recovery in ambulatory surgery settings (Kaye 2019 **NR**). Preoperative implementation of multimodal analgesia (various regimens including paracetamol, gabapentin and celecoxib) for ambulatory breast surgery reduced pain scores and opioid requirements vs no preoperative use and to IV paracetamol alone (Barker 2018 **Level III-3**, n=560).

See also relevant sections of this document:

- Systemically administered analgesic drugs (Chapter 4);
- Regionally and locally administered analgesics drugs (Chapter 4);
- Regional and other local analgesia techniques (Chapter 5);
- Postoperative pain (Chapter 8);
- Paediatric issues (Chapter 10).

8.1.7.2 | Systemic analgesia

Paracetamol, nonselective NSAIDs and coxibs

Following outpatient surgery, ibuprofen (1,200 mg/d) or celecoxib (400 mg/d) for 4 d vs placebo reduced the need for breakthrough analgesia in the early postdischarge period leading to improved patient satisfaction and quality of recovery (White 2011 **Level II**, n=180, JS 4). A study in minor oral surgery demonstrated equivalent benefit of celecoxib 400 mg to diclofenac 50mg over placebo for VAS scores and opioid consumption, and while acetaminophen had a similar effect it was not manifest until 5 and 6 h post administration (Hanzawa 2018 **Level II**, n=128, JS 4).

For ambulatory laparoscopic cholecystectomy, parecoxib preoperatively (30 min prior to surgery) vs postoperatively or placebo was associated with less pain and analgesic requirements for up to 24 h leading to shorter times to attain PACU and hospital discharge criteria (Shuying 2014 **Level II**, n=120, JS 4). However, for minor day-stay gynaecological surgery, paracetamol or parecoxib, either alone or in combination, did not produce a clinically significant impact on pain in the first 24 h after surgery vs placebo (Mohamad 2014 **Level II**, n=240, JS 4).

In children undergoing ambulatory inguinal hernia repair under general anaesthesia with caudal bupivacaine, rectal diclofenac provided longer duration of analgesia vs rectal paracetamol or placebo (Nnaji 2017 **Level II**, n=90, JS 4).

After ambulatory surgery, the combination of paracetamol/metamizole vs paracetamol/ibuprofen provided similar acute postoperative pain control at home including comparable patient satisfaction levels (Stessel 2019 **Level II**, n=200, JS 5).

Conventional and atypical opioids (alone or in combination)

Paracetamol/tramadol provided similar analgesia to tramadol alone after ambulatory hand surgery and resulted in a reduced rate of adverse effects (Rawal 2011 **Level II**, n=80, JS 5). Paracetamol/tramadol was also superior to combination paracetamol/codeine with better analgesia, fewer adverse effects and higher patient satisfaction in a mixed day-stay surgical population (Alfano 2011 **Level II**, n=122, JS 2). Paracetamol/codeine provided similar analgesia but with more discontination due to adverse effects vs paracetamol/ibuprofen after day-stay breast surgery (Mitchell 2012 **Level II**, n=145, JS 5).

Morphine vs hydromorphone in patients having ambulatory (including laparoscopic) surgery showed no difference in analgesic efficacy or side effects (Shanthanna 2019 **Level II**, n=402, JS 5). Similarly after pregnancy termination, intraoperative administration of IV oxycodone (0.06 mg/kg and 0.08 mg/kg) vs IV fentanyl (2 mcg/kg) resulted in no clinically relevant difference in pain score at 30 min (Xie 2017 **Level II**, n=120, JS 2); statistically the higher dose oxycodone group had the lowest pain scores.

For ambulatory surgery, the use of intraoperative methadone (0.15 mg/kg IBW) resulted in similar pain control and adverse effects vs conventional prn dosing of short acting opioids (eg fentanyl, hydromorphone) (Komen 2019 **Level II**, n=66, JS 3). Although the authors report reduced postoperative requirements for other opioids, the potential risks of methadone administration (OIVI, QT prolongation), particularly in an ambulatory setting, were not discussed (Dunn 2018a **Level IV**, n=1,478).

Systemic adjuvant medications

IV dexamethasone 0.1 mg/kg in an ambulatory gynaecological surgery population improved Quality of Recovery score (QoR-40) and reduced opioid consumption in the first 24 h postoperatively vs dexamethasone 0.05 mg/kg or placebo (De Oliveira 2011 **Level II**, n=120, JS 5). Similarly in a paediatric setting, the addition of systemic dexamethasone (0.5 mg/kg; 10 mg maximum) to caudal blocks for day-stay orchidopexy improved and extended postoperative analgesia (Hong 2010 **Level II**, n=77, JS 5). After ambulatory knee arthroscopy, IV betamethasone (8 mg) vs placebo increased the number of patients with no or minor pain at POD 2 (67 vs 44%) (Segelman 2016 **Level II**, n=74, JS 5).

IV dexmedetomidine (0.5 mcg/kg) intraoperatively vs placebo after ambulatory ureteroscopy and ureteric stenting improved pain control at 1 h and on POD 1 to 3 (at rest and on movement) and return to daily activities (Shariffuddin 2018 **Level II**, n=60, JS 5). For outpatient gynaecological diagnostic laparoscopy, dexmedetomidine (0.5 mcg/kg) vs fentanyl (0.5 mcg/kg) on induction reduced postoperative pain severity, rescue analgesic requirements and PONV (Techanivate 2012 **Level II**, n=40, JS 4).

Nebulised dexmedetomidine/ketamine (1 mcg/kg and 1 mg/kg) preoperatively in the setting of outpatient dental surgery was superior to either ketamine (2 mg/kg) or dexmedetomidine (2 mcg/kg) alone with regard to preoperative sedation and recovery and superior to ketamine alone for postoperative analgesia (Zanaty 2015 **Level II**, n=60, JS 4).

IV lidocaine infusion intraoperatively until 30 min after arrival in PACU vs placebo for ambulatory laparoscopic sterilisation had no effect on postoperative pain and opioid requirements, increased requirement of PONV rescue, but resulted in earlier readiness for discharge (Dewinter 2016 **Level II**, n=80, JS 5).

8.1.7.3 | Local anaesthesia techniques

Certain local and regional techniques offer specific benefits to patients after day-stay or short-stay surgery. There has been increasing interest in the use of single dose ("single injection") as

well as continuous peripheral nerve block (CPNB) in patients discharged home (Ardon 2019 **NR**; Schug 2015 **NR**). See also Section 5.8.

Local and peritoneal infiltration

After day-stay hernia repair, wound infiltration with levobupivacaine provided analgesia for 24 h (Ausems 2007 **Level II**, n=120, JS 5) and with bupivacaine reduced pain and tramadol requirements in the first 4 h (Qureshi 2016 **Level II**, n=80, JS 3). However, after day-stay laparoscopic gynaecological surgery, wound infiltration did not significantly reduce pain or opioid requirements (Fong 2001 **Level II**, n=100, JS 5).

After ambulatory hallux valgus repair, mid foot infiltration vs sciatic nerve block provided similar analgesia, but infiltration permitted earlier ambulation (Adam 2012 **Level II**, n=40, JS 3).

Three systematic reviews of local anaesthetic interventions for day-stay laparoscopic cholecystectomy have been performed with significant overlap of included RCTs; the two Cochrane reviews highlight the very low quality of the included RCTs. Local anaesthetic infiltration provides superior analgesic benefit vs placebo in 6 of 8 RCTs, with preincisional infiltration being superior to postincisional administration (Ahn 2011 **Level I**, 8 RCTs [local infiltration], n unspecified). Pain intensity is lower with local anaesthetic infiltration vs placebo at 4 to 8 h (MD -1.33/10; 95%CI -1.54 to -1.12) (13 RCTs, n=806) and 9 to 24 h (MD -0.36/10; 95%CI -0.53 to -0.20) (12 RCTs, n=756) (Loizides 2014 **Level I** [Cochrane], 19 RCTs, n=1,263). Intraperitoneal local anaesthetic is beneficial in 7 of 9 RCTs, with one of the two negative RCTs using local anaesthesia at the end of the procedure (Ahn 2011 **Level I**, 9 RCTs [intraperitoneal], n unspecified). Local anaesthetic is more effective when applied before the commencement of pneumoperitoneum and use of aerosolised local anaesthetic is more effective than simple instillation. Two RCTs showed the combination of incisional and intraperitoneal local anaesthesia is more effective than either intervention alone. Intraperitoneal local anaesthetic vs placebo lowers pain intensity at 4 to 8 h (MD -0.99/10; 95%CI -1.10 to -0.88) (32 RCTs, n=2,020) and at 9 to 24 h (MD -0.53/10; 95%CI -0.62 to -0.44) (29 RCTs, n=1,787) (Gurusamy 2014 **Level I** [Cochrane], 48 RCTs, n=2,849).

After laparoscopic cholecystectomy, same day discharge readiness criteria were achieved after intraincisional ropivacaine in 31% patients, intraperitoneal ropivacaine in 48%, and after combined intraincisional and intraperitoneal ropivacaine in 89% patients (Kaushal-Deep 2019 **Level II**, n=191, JS 5).

Intraperitoneal instillation of local anaesthetic at gynaecological laparoscopy reduced pain scores for up to 6 h postoperatively (Marks 2012 **Level I**, 7 RCTs, n=478). Intraperitoneal local anaesthetic also reduces shoulder tip pain within 24 h of ambulatory gynaecological laparoscopy (OR 0.23; 95%CI 0.06 to 0.93) (2 RCTs, n=157) (Kaloo 2019 **Level I** [Cochrane], 32 RCTs, n=3,284).

Single injection peripheral nerve block

PNBs are useful in ambulatory surgery as they provide site-specific anaesthesia with prolonged analgesia and minimal haemodynamic changes (Salinas 2014 **NR**).

The decision to discharge ambulatory patients following PNB with long-acting local anaesthesia is controversial due to the potential risk of harm to an insensate limb. A prospective study demonstrated that long-acting PNBs were safe and that patients could be discharged with an insensate limb (Klein 2002 **Level IV**, n=1,119 [upper] & 1,263 [lower extremity blocks]). Therefore, provided patients are given verbal and written information regarding the risks as well as appropriate follow-up, it would seem reasonable to discharge these patients with the benefit of prolonged analgesia. Patients may suffer intense pain following resolution of a PNB, although it maximises pain relief in the first 12 to 24 h (Chung 1997 **Level IV**, n=10,008). After outpatient shoulder arthroscopy with single injection interscalene block, 15% of

patients experienced severe pain at home in the first 3 d and 5% contacted their general practitioner for analgesia issues (Trompeter 2010 **Level IV**, n=109). After wrist fracture surgery, patients who received a single injection brachial plexus block were 3 times more likely to require medical attention for pain management within 48 h vs GA (Sunderland 2016 **Level IV**, n=419). These studies illustrate a major concern with the use of single injection PNBs, in particular in the ambulatory setting, of 'rebound' pain after the regional block wears off (Lavand'homme 2018 **NR**).

Ilioinguinal and iliohypogastric block

Ambulatory herniorrhaphy performed under ilioinguinal and iliohypogastric nerve block led to superior pain relief, less morbidity, less urinary retention and cost advantages (Ding 1995 **Level II**, n=30, JS 4). The analgesic benefit with bupivacaine lasted around 6 h (Toivonen 2001 **Level II**, n=100, JS 3). For open inguinal hernia surgery, US-guided ilioinguinal and iliohypogastric blocks with bupivacaine vs saline reduced pain scores at rest and on movement in the PACU, although opioid consumption and time to discharge did not differ (Baerentzen 2012 **Level II**, n=60, JS 5).

For paediatric information, see Section 10.6.2.3.

Transversus abdominis plane blocks (TAPB)

After day-stay laparoscopic cholecystectomy, TAPB with ropivacaine vs placebo reduced opioid requirements for 2 h and pain on coughing, but not at rest, for up to 4 h (Petersen 2012 **Level II**, n=80, JS 5).

After day-stay inguinal hernia repair, local infiltration and TAPB vs local infiltration for surgical anaesthesia alone reduced the need for intraoperative rescue analgesia (36 vs 8%) and improved postoperative pain scores for 12 h (Milone 2013 **Level II**, n=150, JS 3). When blind ilioinguinal/iliohypogastric nerve blocks were compared to US-guided TAPB for day-stay open inguinal hernia surgery, there was a small reduction in pain at rest (but not on movement) in the TAPB group for up to 24 h (Aveline 2011 **Level II**, n=273, JS 5). There was also a modest reduction in postoperative oral morphine requirement over the first 2 d. The primary outcome for this study was pain at 6 mth, where no difference was found.

For paediatric information, see Section 10.6.2.3.

Paravertebral block (PVB)

For inguinal herniorrhaphy, PVB vs general anaesthesia/systemic analgesia (4 RCTS, n=268) or neuraxial anaesthesia (6 RCTs, n=377) reduced PONV, although pain outcomes and hospital LOS were similar (Law 2015 **Level I** [PRISMA], 14 RCTs, n unspecified). PVBs provided better analgesia than more distal nerve blocks (2 RCTs [ilioinguinal block], n=140; 1 RCT [TAPB], n=60). Successful use after outpatient lithotripsy has also been reported (Jamieson 2007 **Level IV**, n=2).

After ambulatory breast augmentation, PVB was superior to direct surgical infiltration with ropivacaine with regard to pain scores and requirements for rescue analgesia (Gardiner 2012 **Level II**, n=40, JS 3). However, comparing PVB to general anaesthesia for minor breast surgery in a day-care setting, the benefits were small and may not justify the increased risk (Terheggen 2002 **Level II**, n=30, JS 3). After PVB performed for ambulatory breast surgery, complications included hypotension and/or bradycardia in 2.2%, LAST in 0.17%, and pneumothorax requiring only conservative management in 0.26% (Kelly 2018b **Level IV**, n=1,322).

Newer blocks, such as erector spinae plane blocks (ESPB) may prove suitable alternatives to PVB for abdominal and thoracic surgery (Hannig 2018 **Level IV**, n=3).

For paediatric information, see Section 10.6.2.3.

Upper and lower limb blocks

Adductor canal blocks (ACBs) offer potential for improved analgesia without significant motor block for ambulatory arthroscopic knee surgery. For simple arthroscopic procedures, ACBs

reduced pain scores modestly to 8 h and opioid consumption up to 24 h (4 RCTs, n=247); however, no benefit was demonstrated after anterior cruciate ligament repair from either ACB vs placebo (3 RCTs, n=135) or ACB vs FNB (3 RCTs, n=308) (Sehmbi 2019 **Level I** [PRISMA], 10 RCTs, n=716).

Interscalene (Bishop 2006 **Level IV**, n=299; Faryniarz 2006 **Level IV**, n=133) and supraclavicular (Liu 2010 **Level IV**, n=1,169) plexus blocks provided safe and effective analgesia after ambulatory shoulder surgery. For hand and wrist surgery, infraclavicular nerve blocks with propofol sedation vs general anaesthesia followed by local anaesthetic wound infiltration resulted in less postoperative pain, less nausea, earlier ambulation and earlier hospital discharge (Hadzic 2004 **Level II**, n=52, JS 3). US-guided PNBs with ropivacaine can be added to brachial plexus anaesthesia with lignocaine to prolong analgesia after hand surgery, while avoiding significant motor block (Dufeu 2014 **Level IV**, n=125). For day-stay hand surgery (trapeziectomy) performed under an axillary plexus block, distal nerve blocks (radial and median nerve) with levobupivacaine 0.125% vs systemic analgesia provided superior pain relief on POD 1 with reduced opioid requirements and PONV incidence (Rodriguez Prieto 2018 **Level II**, n=52, JS 4).

For ambulatory shoulder surgery, using 20 vs 40 mL of mepivacaine 1.5%/bupivacaine 0.5% for US-guided interscalene blocks resulted in similar analgesia and patient satisfaction, but 20 mL had lower incidence of hoarseness and provided better hand grip strength (Maalouf 2016 **Level II**, n=154, JS 4). For major day-stay arthroscopic shoulder surgery, the anterior suprascapular block was non-inferior to the interscalene block and preserved best pulmonary function (Auyong 2018 **Level II**, n=189, JS 5).

Pelvic plexus block

Pelvic plexus block provided better intra and postoperative analgesia than periprostatic nerve block for ambulatory transrectal US-guided prostate biopsy (Cantiello 2012 **Level II**, n=180, JS 3).

Gynaecological paracervical block

In awake patients, paracervical local anaesthesia for cervical dilatation and uterine intervention reduces intraoperative pain vs placebo (10 RCTs), but fails to show a benefit over sedation (6 RCTs) or other local anaesthesia techniques for postoperative pain (Tangsiriwatthana 2013 **Level I** [Cochrane], 26 RCTs, n=2,790). Overall, no recommendations regarding benefits could be made.

Specifically, for ambulatory hysteroscopy, paracervical block (SMD -1.28/10; 95%CI -2.22 to -0.35 [vs placebo]) provides superior analgesia vs intracervical injection of LA (SMD -0.36/10; 95%CI -0.61 to -0.10 [vs placebo]) (Cooper 2010 **Level I**, 20 RCTs, n unspecified); transcervical and topical application of LA has no analgesic effect.

Adjuvants to single injection peripheral nerve block

Buprenorphine

Buprenorphine added to local anaesthetic for brachial plexus and intraoral blocks increased the duration of analgesia vs local anaesthetic alone (Kumar 2013 **Level II**, n=100, JS 3; Modi 2009 **Level II**, n=50, JS 3; Candido 2001 **Level II**, n=40, JS 5). However, with infragluteal sciatic block for foot and ankle surgery, when buprenorphine was either added to bupivacaine or given IM, there was only a modest analgesic benefit, with increased vomiting in the groups receiving buprenorphine (Candido 2010 **Level II**, n=103, JS 5).

Dexamethasone

Caudal dexamethasone improved the quality and duration of caudal epidural ropivacaine analgesia in a paediatric day-stay orchidopexy population (Kim 2014a **Level II**, n=80, JS 5). In the setting of paediatric day-care hernia repair, IV dexamethasone (0.5 mg/kg) also increased duration of caudal levobupivacaine analgesia (800 vs 520 min) and improved pain control on POD 1 and 2 (Murni Sari Ahmad 2015 **Level II**, n=64, JS 5).

For arthroscopic ambulatory shoulder surgery, both systemic and perineural dexamethasone (10 mg) prolonged interscalene block with 0.5% ropivacaine, with both dexamethasone groups requiring less analgesics in the first 48 h vs placebo (Desmet 2013 **Level II**, n=150, JS 5). When dexamethasone 4 mg was added to interscalene ropivacaine for shoulder arthroscopy, median duration of analgesia was longer than systemic administration (18 h vs 14 h), which was similar to placebo (Kawanishi 2014 **Level II**, n=39, JS 3). However, a subsequent RCT found only a minor prolongation of duration of interscalene block for ambulatory arthroscopic shoulder surgery with perineural vs systemic dexamethasone, which might not be clinically relevant (Holland 2018 **Level II**, n=280, JS 5); there was no difference between doses of 4 and 8 mg.

For more details, see Section 4.12.2.

Dexmedetomidine

When added to caudal ropivacaine for paediatric day-stay patients undergoing lower abdominal and perineal surgery, dexmedetomidine (0.5 to 1.5 mcg/kg) prolongs analgesia with minor prolongation of motor block, time to void and sedation, without increased hypotension or delay in hospital discharge (Bharti 2014 **Level II**, n=80, JS 5). For paediatric day-stay orchidopexy, addition of dexmedetomidine (1 mcg/kg) to caudal ropivacaine prolonged time to first analgesic request (Cho 2015a **Level II**, n=80, JS 4).

For more details, see Section 4.9.2.2

Ketamine

A systematic review of ketamine 0.25 to 0.5 mg/kg added to caudal local anaesthetic prolongs analgesia (time to first request) by a median difference of 5.6 h, without prolonged motor block (Schnabel 2011 **Level I** [PRISMA], 13 RCTs, n=884). Of the 13 RCTs, 9 were in the ambulatory paediatric population. Although many adverse effects were more frequent in the ketamine group, there was no significant difference to placebo. However, concerns of local neurotoxicity *in vitro* continue to limit the use of neuraxial ketamine, in particular when combined with lignocaine (Werdehausen 2011 **NR**).

For more details, see Section 4.6.2.1

Continuous peripheral nerve block

Continuous peripheral nerve blocks (CPNBs) after ambulatory surgery vs single injection blocks reduce pain at rest and during movement and opioid requirements for the first 24 h, but not consistently sustained beyond this time frame (Saporito 2017 **Level I** [PRISMA], 5 RCTS, n=160); the quality and size of the RCTs limits the strength of these conclusions.

Upper and lower limb CPNB

CPNB using perineural catheters and continuous infusions of local anaesthetic led to sustained postoperative analgesia (Zaric 2004 **Level II**, n=63, JS 5; Ilfeld 2002b **Level II**, n=30, JS 5; Ilfeld 2002a **Level II**, n=30, JS 5), was opioid-sparing (Ilfeld 2003 **Level II**, n=25, JS 5; Ilfeld 2002b **Level II**, n=30, JS 5; Ilfeld 2002a **Level II**, n=30, JS 5) and resulted in less sleep disturbance (Ilfeld 2002b **Level II**, n=30, JS 5; Ilfeld 2002a **Level II**, n=30, JS 5) and improved rehabilitation (Capdevila 1999 **Level II**, n=56, JS 2).

Patients achieved discharge criteria significantly earlier in a number of settings approaching short-stay discharge times: after total shoulder arthroplasty with use of continuous interscalene blocks (21 vs 51 h) (Ilfeld 2006 **Level II**, n=29, JS 5); after hip arthroplasty with use of continuous lumbar plexus block (29 vs 52 h) (Ilfeld 2008a **Level II**, n=47, JS 5); and after total knee arthroplasty with the use of continuous FNBs (25 vs 71 h) (Ilfeld 2008b **Level II**, n=50, JS 5). Adductor canal catheters allowed discharge on POD 1 after knee arthroplasty in 12% of patients in one series (Hanson 2016 **Level IV**, n=512). These benefits have the potential to reduce hospital costs (Ilfeld 2007 **Level III-3**, n=20). Similar benefits have been observed with a range of CPNBs in a predominantly paediatric population (Gurnaney 2014 **Level IV**, n=1,285).

A 2 d interscalene infusion at home after shoulder surgery vs a single injection interscalene block, was opioid-sparing and improved pain relief, sleep and patient satisfaction (Salviz 2013 **Level II**, n=70, JS 4; Mariano 2009 **Level II**, n=32, JS 5). Furthermore at day 7, fewer patients had an NRS > 4 (26% v. 83%), suggesting a sustained analgesic benefit. Similarly, after arthroscopic rotator cuff repair, continuous (3 d of 0.125% bupivacaine at 5 mL/h plus a patient-controlled bolus of 5 mL/h) vs single injection interscalene block provided better analgesia with better sleep pattern and reduced opioid requirements (Malik 2016 **Level II**, n=92, JS 4). Patient-controlled bolus added to continuous infusion of ropivacaine improved analgesia and function more than a continuous infusion and even more so vs IV morphine PCA (Capdevila 2006 **Level II**, n=86, JS 4).

Continuous popliteal sciatic nerve block for foot and ankle surgery has a high success rate and a low rate of complications, with a catheter dislocation rate of 0.2% (Borgeat 2006 **Level IV**, n=1,001). Compared to inpatients, ambulatory sciatic popliteal catheters were not associated with increased pain, complications or healthcare interventions in outpatients, allowing a significant reduction in healthcare costs (Saporito 2014 **Level II**, n=120, JS 4). For day-case hallux valgus surgery, placing the tip under US-guidance of the sciatic nerve catheter medial to the tibial nerve vs between the tibial and peroneal components provides equivalent analgesia with reduced insensate limb and foot drop and was therefore advantageous in an ambulatory setting (Ambrosoli 2016 **Level II**, n=84, JS 3).

Paravertebral CPNB

Continuous PVB after short-stay mastectomy with 0.4% ropivacaine vs saline at 5 mL/h for 3 d demonstrated improved pain scores and less pain-induced physical and emotional dysfunction for the infusion duration (Ilfeld 2014 **Level II**, n=60, JS 5). Adding a continuous infusion to maintain the PVB after a single injection block for outpatient breast cancer surgery did not add further benefits (Buckenmaier 2010 **Level II**, n=94, JS 5).

Safety and management of CPNB in an ambulatory setting

The safety and efficacy of CPNBs in an ambulatory setting has been confirmed in adult (Nye 2013 **Level IV**, n=281; Fredrickson 2008 **Level IV**, n=300; Swenson 2006 **Level IV**, n=620) and paediatric patients (Gurnaney 2014 **Level IV**, n=1,285; Ludot 2008 **Level IV**, n=47; Ganesh 2007 **Level IV**, n=226 [catheters]).

Inadvertent intravascular catheter placement needs to be excluded prior to patient discharge using a test dose of local anaesthetic and adrenaline (epinephrine) (Rawal 2002 **NR**). Patients and their carers should be given extensive oral and written instructions about management, adverse effects and care of the local anaesthetic catheter, and have 24 h telephone access to an anaesthesiologist during the postoperative period while CNPB is in use (Swenson 2006 **Level IV**, n=620) as 30% of patients make unscheduled phone calls regarding catheter infusions despite been given adequate written and verbal instructions (Ilfeld 2002a **Level IV**, n=30). A review of outpatients with CPNB (including popliteal fossa, fascia iliaca and interscalene) showed that 4.2% required assistance by the anaesthesiologist after discharge from hospital for problems relating to issues such as patient education, inadequate analgesia and equipment malfunction; only one patient was unable to remove their catheter (Swenson 2006 **Level IV**, n=620), although patients may have significant anxiety about catheter removal at home (Ilfeld 2004 **Level IV**, n=24). While patient satisfaction is high, failure of brachial plexus catheters within 72 h of insertion in the ambulatory setting may be as high as 26% for supraclavicular and 19% for infraclavicular approaches (Ahsan 2014 **Level IV**, n=207). In another series, approximately one third of patients with brachial plexus catheters (continued for an average of 4 d) experienced adverse effects or required additional healthcare intervention (King 2019 **Level IV**, n=501).

Detailed narrative reviews of the use of CPNBs for ambulatory surgery have been published (Jones 2019b **NR**; Salinas 2014 **NR**; Ilfeld 2011 **NR**).

8.1.7.4 | Nonpharmacological techniques

Nonpharmacological techniques such as TENS, acupuncture, hypnosis, US, laser and cryoanalgesia have also been used in the treatment of acute pain management after ambulatory surgery. Pressure on acupoints decreased pain following knee arthroscopy (Felhendler 1996 **Level II**, n=44, JS 3). TENS resulted in a significant, but clinically trivial reduction of pain after endometrial biopsy vs placebo TENS (Yilmazer 2012 **Level II**, n=65, JS 1). Continuous-flow cold therapy has been shown to be effective following outpatient anterior cruciate ligament reconstruction, also reducing analgesic requirements (Barber 1998 **Level II**, n=100, JS 1).

An educational intervention (individualised education using written and verbal information as well as two telephone support calls before and after surgery) vs usual care improves multiple measures of pain intensity and function on POD 2 (Sawhney 2017 **Level II**, n=82, JS 5). An empathic patient-centered interview vs standard care prior to ambulatory general surgery resulted in lower levels of pain, preoperative anxiety and higher levels of daily activity and satisfaction with the information received (Pereira 2016 **Level II**, n=104, JS 1).

8.1.7.5 | Procedure-specific pain management after ambulatory surgery

Ambulatory arthroscopic anterior cruciate ligament reconstruction

A systematic review finds that arthroscopic anterior cruciate ligament (ACL) reconstruction preformed as an outpatient vs an inpatient procedure resulted in similar or better outcomes with regard to pain, satisfaction, knee function, strength and complications (Ferrari 2017 **Level III-3 SR** [PRISMA], 2 RCTs & 5 studies, n=407); included studies were of low methodological quality. In the same setting, there was no more postoperative discomfort in outpatients vs inpatients and outpatients had less difficulty sleeping, were less often woken by pain during the first postoperative night and more often walked regularly on POD 1 (Lefevre 2015 **Level III-1**, n=133).

A systematic review of analgesic approaches to ambulatory arthroscopic ACL reconstruction finds regional nerve blocks and intra-articular LA injections equally effective analgesic techniques (Secrist 2016 **Level III-2** [PRISMA], 77 studies, n unspecified). Gabapentin, zolpidem, ketorolac, and ibuprofen have opioid sparing effects and cryotherapy-compression (10 studies) as well as early mobilisation are effective non-pharmacological approaches. There is no support for the routine use of FNBs in this setting (Vorobeichik 2019 **Level I** [PRISMA], 8 RCTs, n=716) and ACB is not superior to FNB (Sehmbi 2019 **Level I** [PRISMA], 10 RCTs, n=714), while use of LIA reduces pain intensity and opioid requirements with minimal complications (Yung 2019 **Level I** [PRISMA], 11 RCTs, n=515).

Procedure-specific guidelines for pain management after ambulatory arthroscopic ACL reconstruction have been published (Abdallah 2019 **GL**).

Ambulatory shoulder arthroscopy

After ambulatory shoulder arthroscopy, interscalene nerve blocks (ISBs) are the most effective approach to pain management (Warrender 2017 **Level I** [PRISMA], 40 RCTs, n unspecified); increasing LA concentrations, continuous infusions, and patient-controlled methods are effective strategies to improve analgesia. Duration of the analgesic effect can be extended by adding dexamethasone, clonidine, intrabursal oxycodone, and magnesium. Preoperative oral pregabalin and coxibs improve analgesia and patient satisfaction.

8.1.7.6 | Discharge analgesia

A survey of day-surgery practices in 100 hospitals in 8 European countries reported take-home analgesics were provided as a "*tablet-package*" by 69% or as prescription by 80% of hospitals (Stomberg 2013 **Level IV**). Strong opioids on discharge were given or prescribed by 59% of units. Written instructions about management of pain were provided by 69% of units.

Early discharge after day-stay surgery with a prescription of opioids or NSAIDs carries an increased risk of subsequent long term use of these analgesics. In a population of 391,139 opioid-naïve patients aged >65 y having short-stay surgery, patients receiving an opioid prescription within the 7 d after surgery were more likely to become long term opioid users within 1 y in comparison to those without a prescription (OR 1.44; 95%CI 1.39 to 1.50) (Alam 2012 **Level III-2**, n=391,139). Discharge NSAID prescriptions were also more likely to be associated with persistent use (OR 3.74; 95%CI 3.27 to 4.28).

Implementation of multimodal analgesia pathways for same-day thyroid, parathyroid, and parotid surgery (adherence increased from 0% to 87% from 2015 to 2017) resulted in a dramatic reduction of opioid prescription on discharge (OR 0.13; 95%CI 0.04 to 0.44) (Militsakh 2018 **Level III-3**, n=528). After ambulatory surgical procedures, there was a wide range of amounts of opioids prescribed; only 28% of prescribed opioids were taken and suggestions for more appropriate prescribing are made (Hill 2017 **Level IV**, n=642). An educational intervention based on estimated opioid requirements for specific outpatient procedures resulted in decreased prescribing rates without increasing patients' refill requirements (Hill 2018b **Level IV**, n=224).

The importance of opioid stewardship specifically in the ambulatory surgery setting has been emphasised (Roth 2018 **NR**).

For more details, see Section 8.13 and for paediatric information, see Section 10.4.5.

KEY MESSAGES

1. Wound infiltration and intraperitoneal instillation with local anaesthetics for short-stay laparoscopic cholecystectomy has good analgesic efficacy, in particular when combined and administered prior to trocar insertion and at commencement of pneumoperitoneum respectively (**S**) (**Level I** [Cochrane Review]).
2. Intraperitoneal instillation with local anaesthetic provides good analgesia for up to 6 hours after short-stay gynaecological laparoscopy (**U**) (**Level I**) and reduces shoulder tip pain for 24 h (**N**) (**Level I** [Cochrane Review]).
3. Ketamine added to caudal local anaesthetic for paediatric day-stay surgery prolongs analgesia, but not motor block (**U**) (**Level I** [PRISMA]); however, concerns regarding neurotoxicity remain.
4. Continuous peripheral nerve blocks after short-stay surgery provide extended analgesia for at least 24 h, leading to reduced opioid requirements (**S**) (**Level I** [PRISMA]), earlier achievement of discharge criteria, less sleep disturbance and improved early rehabilitation (**S**) (**Level II**).
5. Paravertebral block improves pain-related outcomes after short-stay hernia repair (**S**) (**Level I** [PRISMA]) and major breast surgery (**U**) (**Level II**).
6. After ambulatory anterior cruciate ligament repair, analgesia is superior with local infiltration anaesthesia versus femoral nerve blocks and adductor canal blocks; multimodal systemic analgesia, early mobilisation and cooling/compression are also supported (**N**) (**Level I** [PRISMA]).
7. After ambulatory shoulder arthroscopy, interscalene nerve block is superior to other peripheral nerve blocks; adjuvants to increase block duration and systemic multimodal analgesia are also supported (**N**) (**Level I** [PRISMA]).
8. Gynaecological paracervical block provides superior analgesia to intracervical and transcervical block and topical local anaesthetic administration (the latter both without analgesic effect) for ambulatory hysteroscopy (**N**) (**Level I**).
9. Dexamethasone added to local anaesthetics in peripheral nerve blocks and for caudal analgesia or given systemically prolongs duration of analgesia after short-stay surgery (**S**) (**Level I**).
10. Single injection peripheral nerve blocks with long-acting local anaesthetics provide long-lasting postoperative analgesia after short-stay surgery (**S**) (**Level II**).
11. Infiltration of the wound with local anaesthetic provides effective and long-lasting analgesia after many short-stay procedures (**U**) (**Level II**).
12. In the short-stay surgery setting, anti-inflammatories (nonselective NSAIDs, coxibs and dexamethasone) and paracetamol contribute to reduced pain and improved recovery (**U**) (**Level II**).
13. Buprenorphine or dexmedetomidine added to local anaesthetics for peripheral nerve blocks prolong duration of analgesia after short-stay surgery (**U**) (**Level II**).

14. Anterior cruciate ligament repair performed as a short-stay procedure in comparison to an inpatient setting achieves comparable quality of pain relief and better outcomes (**N**) (**Level III-3 SR**).
15. Pain relief after short-stay surgery remains poor (**U**) (**Level IV**) and is a common cause of unplanned re-presentation (**U**) (**Level III-3**).
16. Continuous peripheral nerve blocks have been shown to be safe at home after short stay surgery, if adequate resources and patient education are provided (**U**) (**Level IV**).
17. Predictive factors of severe pain after short-stay surgery are preoperative pain, high expectation of postoperative pain, younger age and certain types of surgery (in particular orthopaedic surgery) (**N**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Preoperative patient-centered education (verbal and written) and telephone follow-ups may improve anxiety, pain and functional outcomes and patient satisfaction after ambulatory surgery (**N**).

8.1.8 | Cranial neurosurgery

There is a widespread belief that intracranial surgery does not result in much patient discomfort and pain. However, surveys have shown that patients have significant pain in the early phase after intracranial surgery; the incidence of acute post craniotomy pain varies from 27% (de Oliveira Ribeiro Mdo 2013 **Level IV**, n=91) to 80% of patients (Gottschalk 2007 **Level IV**, n=187; Nemergut 2007 **NR**). These findings are in line with other studies that found incidences of 56% moderate and 25% severe pain (Thibault 2007 **Level IV**, n=299) and of 87% pain overall in the first 24 h (NRS 1 to 3, 32%; 4 to 7, 44%; 8 to 10, 11%) despite conventional pain management (Mordhorst 2010 **Level IV**, n=256). In a paediatric population, 35% of patients had moderate to severe pain in the immediate postoperative setting but this reduced to 8% at POD 1 (Bronco 2014 **Level IV**, n=206). Similarly, 42% of children had at least one episode of pain ≥3/10 in the first 72 h after craniotomy (Teo 2011 **Level IV**, n=52).

However, the pain is not as severe as after other surgical procedures such as extracranial maxillary/mandibular surgery or lumbar surgery (Klimek 2006 **Level III-2**, n=649; Dunbar 1999 **Level III-2**, n=99). The findings that the pain is more severe after an infratentorial rather than a supratentorial approach (Gottschalk 2007 **Level IV**, n=187) are disputed by another study (Irefin 2003 **Level III-2**, n=128). Noncraniotomy neurosurgery, for example trans-sphenoidal surgery, seems to be associated with very limited pain and minimal morphine requirements (Flynn 2006 **Level IV**, n=877).

It is noteworthy that craniotomy can lead to significant chronic headache, defined as postcraniotomy headache by the International Headache Society (Headache Classification Committee 2018 **GL**). At 6 mth after supratentorial craniotomy for aneurysm repair, 40% of patients reported headache, of whom 10.7% had acute and 29.3% chronic headache (Rocha-Filho 2008 **Level IV**, n=79). A review of the issues related to postcraniotomy headache has been published (Molnar 2014 **NR**).

The management of postoperative pain after intracranial surgery is often poor. The problems of postcraniotomy analgesia were analysed in a survey of UK neurosurgical centres (Roberts 2005 **Level IV**, n=23 [centres]); the principal analgesic was IM codeine, only 3 of 23 centres used morphine and only one used PCA. Pain was only assessed in 57% of cases. Similar data are reported in a survey of Canadian neurosurgeons, with 59% describing codeine as their first-line opioid (Hassouneh 2011 **Level IV**, n=103 [neurosurgeons responding]). This practice has changed little since 1995, when IM codeine was the primary analgesic used by 97% of centres (Stoneham 1995 **Level IV**, n=110 [neuroanaesthetists responding]).

Concerns about the adverse effects of opioids and their ability to interfere with recovery and neurological assessment contribute to this, as well as the concern that opioid-induced respiratory depression will lead to hypercarbia and increased intracranial pressure (Nemergut 2007 **NR**). Similarly, there is a concern that NSAIDs could interfere with haemostasis and increase intracranial bleeding. Furthermore, there is poor evidence on which to base protocols for the assessment and treatment of pain after cranial surgery (Nemergut 2007 **NR**); the limited number of trials are heterogeneous and have many weaknesses in study design and methodology. The question remains as to whether all craniotomies are the same with regard to analgesic requirements.

8.1.8.1 | Treatment of acute postoperative pain after cranial neurosurgery

A systematic review of pain treatments after craniotomy identified scalp infiltration/block, opioids and diclofenac as some evidence-based approaches, but could not make firm

recommendations due to limited data (Tsaousi 2017 **Level I** [PRISMA], 19 RCTs, n=1,805 [limited search period January 2011 to April 2016]).

Paracetamol

A trial comparing paracetamol alone with paracetamol/tramadol or paracetamol/nalbuphine was stopped early as paracetamol alone gave ineffective pain relief in most patients (Verchere 2002 **Level II**, n=64, JS 5). Another case series found that oral paracetamol only reduced pain effectively in 27% of patients post supratentorial craniotomy (Nair 2011 **Level IV**, n=43).

Nonselective NSAIDs

Ketoprofen was more effective than paracetamol in reducing PCA opioid requirements after craniotomy, but with minimal benefits in regard to pain scores and no change in adverse effects (Tanskanen 1999 **Level II**, n=45, JS 4). Similarly, diclofenac was superior to placebo and comparable to another nonopioid analgesic, flupirtine, for pain post craniotomy (Yadav 2014 **Level II**, n=390, JS 2). Preoperative single dose PO diclofenac 100 mg resulted in improved analgesia and reduced opioid requirement up to 5 d postoperatively (Molnar 2015 **Level II**, n=200, JS 4). A single-centre, retrospective cohort study over 5 y identified an association between the development of postoperative haematoma and the use of aspirin or nsNSAIDs (Palmer 1994 **Level IV**, n=71 [haematomas] in n=6,668 [neurosurgical operations]).

Coxibs

There was no benefit with a single dose of IV parecoxib (40 mg given at the end of the case) over the first 24 h postoperatively with regard to pain scores, morphine use and analgesia-related adverse effects in one study (Williams 2011 **Level II,** n=100, JS 5), although another study showed limited benefit over the first 6 h postoperatively (Jones 2009 **Level II**, n=82, JS 5).

Opioids

IV PCA morphine (with or without ondansetron) was superior to placebo after infratentorial craniotomy (Jellish 2006 **Level II**, n=120, JS 5). Morphine was also more effective than codeine following craniotomy; this was found for IM prn administration of both compounds (Goldsack 1996 **Level II**, n=40, JS 3), but also in a comparison of PCA morphine with IM codeine (Sudheer 2007 **Level II**, n=60, JS 3). PCA morphine provided better analgesia than PCA tramadol (Sudheer 2007 **Level II**, n=60, JS 3). PCA fentanyl was more effective than IV fentanyl prn and did not increase the risk of adverse effects after craniotomy, although more fentanyl was used in the PCA group (Jalili 2012 **Level II**, n=80, JS 5; Morad 2009 **Level II**, n=79, JS 2).

IM codeine 60 mg was more effective than IM tramadol 50 mg or 75 mg (Jeffrey 1999 **Level II**, n=75, JS 5). However, the addition of tramadol 100 mg twice daily to a paracetamol and morphine or oxycodone analgesic regimen improved analgesia and reduced opioid requirements vs placebo (Rahimi 2010 **Level II**, n=50, JS 2).

The intraoperative use of remifentanil may result in increased pain and/or increased analgesia requirements postoperatively (see Section 4.3.1.5). This was found vs both fentanyl (Gelb 2003 **Level II**, n=91, JS 4) and sufentanil (Gerlach 2003 **Level II**, n=36, JS 3).

Local anaesthetic scalp block

A meta-analysis found that regional scalp block improved pain scores up to 12 h postoperatively and reduced opioid requirements until 24 h postoperatively vs placebo block (Guilfoyle 2013 **Level I** [PRISMA], 7 studies, n=325). An RCT performed after this meta-analysis confirmed not only better analgesia after aneurysm clipping, but also improved outcome (reduced PCA consumption, requirement for a postoperative antihypertensive agent and PONV incidence) with scalp block (0.75% levobupivacaine) vs placebo (Hwang 2015 **Level II**, n=52, JS 5). Preemptive scalp block vs block at the end of surgery provided improved analgesia up to 6 h postoperatively and

reduced number of patients requiring opioid and median opioid consumption up to 24 h postoperatively (Song 2015 **Level II**, n=52, JS 3). Scalp blocks have also been used in children following craniosynostosis repair (Pardey Bracho 2014 **Level IV**, n=32).

Systemic adjuvant medications

Dexmedetomidine given intraoperatively for craniotomy provides superior analgesia in PACU and up to 12 h postoperatively vs placebo (2 RCTs, n=128) and remifentanil (1 RCT, n=139) (Tsaousi 2017 **Level I** [PRISMA], 19 RCTs, n=1,805). It also reduces opioid requirements up to 24 h postoperatively, with inconclusive evidence on effects on PONV and increased risk of delayed recovery. Clonidine did not improve analgesia after supratentorial craniotomy (Stapelfeldt 2005 **Level II**, n=34, JS 3).

Gabapentin improved postoperative analgesia and reduced opioid consumption, but increased sedation and delayed extubation (by 12 min) vs phenytoin perioperatively for supratentorial craniotomy (Ture 2009 **Level II**, n=80, JS 2). This was contradicted by a later study, which was however inadequately powered with pain relief only as a secondary outcome (Misra 2013 **Level II**, n=79, JS 4). Pregabalin showed marginal benefit for postoperative analgesia and reduced number of patients requiring opioids for up to 48 h (Shimony 2016 **Level II**, n=100, JS 4).

Non-pharmacological techniques

Transcutaneous electric acupuncture stimulation (TEAS) may improve postoperative analgesia and reduce opioid requirements; however, studies were of poor quality with a high risk of bias (2 RCTs, n=176) (Tsaousi 2017 **Level I** [PRISMA], 19 RCTs, n=1,805).

Cryotherapy (cold bags and ice gel packs) improved pain control along with eyelid oedema and facial ecchymosis after craniotomy (Shin 2009 **Level II**, n=97, JS 3).

KEY MESSAGES

1. Local anaesthetic infiltration of the scalp provides early analgesia after craniotomy and reduces opioid requirements (**S**) (**Level I** [PRISMA]).
2. Intraoperative dexmedetomidine provides early analgesia after craniotomy and reduces opioid requirements compared to placebo or remifentanil (**S**) (**Level I** [PRISMA]).
3. Morphine is more effective than codeine and tramadol for pain relief after craniotomy (**U**) (**Level II**).
4. Craniotomy leads to significant pain in the early postoperative period (**U**) (**Level IV**), which is however not as severe as pain from other surgical interventions (**U**) (**Level III-2**).
5. Craniotomy can lead to significant chronic headache (**U**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Acute pain following craniotomy is underestimated and often poorly treated (**U**).

8.1.9 | Spinal surgery

A considerable number of patients presenting for surgery on the spine have pre-existing persistent and/or acute pain and some may be on long term analgesic medications. Therefore, managing acute postoperative pain can be more difficult with an increased risk of persistent postoperative pain.

8.1.9.1 | Type of Anaesthesia

Propofol/fentanyl TIVA versus desflurane/fentanyl anaesthesia resulted in a minor not clinically meaningful reduction of postoperative pain, but also reduces opioid requirement up to 48 h post spinal surgery (Lin 2019b **Level II**, n=60, JS 4).

8.1.9.2 | Systemic anlgesics

Use of IV paracetamol vs placebo is associated with better analgesia postoperatively, although an opioid-sparing effect was not demonstrated (Cakan 2008 **Level II**, n=40, JS 4).

NSAIDs

Consistent with general postoperative data, nsNSAIDs have demonstrated analgesic benefit and are opioid-sparing in spinal surgery (Zhang 2017 **Level I** [PRISMA], 8 RCTs, n=408).

A meta-analysis of retrospective studies of spinal fusion concluded that the use of normal doses of nsNSAIDs or coxibs for <14 d postoperatively was not associated with increased non-union (Li 2011 **Level III-3 SR**, 5 studies, n=1,403). However, high-dose ketorolac (>120 mg/d) was associated with increased rates of nonunion (RR 2.9; 95%CI 1.5 to 5.4).

Opioids

Single IV doses of methadone given at the start of spine surgery provided improved pain control and reduced analgesic requirements up to 72 h postoperatively (Murphy 2017b **Level II**, n=150, JS 5; Gottschalk 2011 **Level II**, n=29, JS 5). Although no significant adverse effects were noted in these RCTs, caution is advised re potential OIVI (37%), hypoxaemia (80%) and QTc prolongation (59%) in a case series of spinal surgery patients, of whom 72% were taking opioids preoperatively (Dunn 2018a **Level IV**, n=1,478).

8.1.9.3 | Systemic adjuvant medications

Alpha-2-delta ligands (gabapentin and pregabalin)

Both gabapentin and pregabalin given preoperatively reduced postoperative pain and opioid requirements up to 48 h post spinal surgery vs placebo (Liu 2017a **Level I** [PRISMA], 16 RCTs, n=1,112). Although heterogenous in dosing and timing, in all of the RCTs gabapentin or pregabalin was given 1 to 2 h preoperatively as a single dose and then continued in some up to POD 3. Two RCTs examined variable doses suggesting that the maximal benefit of gabapentin is achieved with 600 mg (Liu 2017a **Level I** [PRISMA] 1 RCT: Pandey 2005 **Level II**, n=100, JS 5) to 900 mg (Liu 2017a **Level I** [PRISMA], 1 RCT: Khan 2011 **Level II**, n=175, JS 5) with no further benefit in larger doses.

Long term benefits of perioperative gabapentin or pregabalin use beyond the acute postoperative period after lumbar spine surgery were found in three RCTs. After lumbar discectomy, pain intensity was reduced and functional outcome improved at 3 mth with perioperative pregabalin administration (Khurana 2014 **Level II**, n=90, JS 4; Burke 2010 **Level II**, n=40, JS 5) and quality of life was improved at 3 mth, but not at 1 y (Gianesello 2012 **Level II**, n=60, JS 5). In one of these studies, 75 mg pregabalin every 8 h for 7 d was more effective than 300 mg gabapentin administered in the same way (Khurana 2014 **Level II**, n=90, JS 4).

Alpha-2 agonists

IV dexmedetomidine used intraoperatively (14 RCTs) and intra- and postoperatively for 24 h (1 RCT) in spinal surgery reduces postoperative pain at 2 h (3 RCTs, n=237) and analgesic requirements at 12 h (2 RCTs,n=149) and 48 h, but not 24 h (3 RCTs, n=380) (Tsaousi 2018 **Level I** [PRISMA], 15 RCTs, n=913).

Antidepressants

Use of duloxetine 60 mg given preoperatively for spinal surgery and 24 h postoperatively had contradictory effects on pain scores in 2 RCTs, but reduced opioid requirements up to 48 h postoperatively (Attia 2017 **Level II**, n=60, JS 5; Bedin 2017 **Level II**, n=57, JS 3).

Corticosteroids

IV corticosteroids given intraoperatively for spinal surgery reduce pain up to 48 h postoperatively, as well as nausea and length of stay (Wang 2018b **Level I** [PRISMA], 8 RCTs, n=918).

Epidural corticosteroids (triamcinolone, methylprednisolone or dexamethasone) applied by the surgeons intraoperatively for microdiscectomy or laminectomy reduce pain at 24 h and 1 mth postoperatively as well as opioid requirements and hospital LOS vs placebo (Wilson-Smith 2018 **Level I** [PRISMA], 17 RCTs, n=1,727; Arirachakaran 2018 **Level I** [PRISMA], 12 RCTs, n=1,006) (10 RCTs overlap). The effects on opioid requirements are more pronounced after open laminectomy vs microdiscectomy (Arirachakaran 2018 **Level I** [PRISMA], 12 RCTs, n=1,006). There is no difference in complications in these two systematic reviews and a further meta-analysis looking specifically for complications also found no increase in overall complication (RR 1.94; 95%CI 0.72 to 5.26) or infectious complication rates (RR 4.6; 95%CI 0.8 to 28.0) (Akinduro 2015 **Level III-2 SR**, 16 RCTs & 1 study, n=1,933).

Systemic lidocaine

A perioperative IV lidocaine infusion reduced pain scores and postoperative opioid requirements after complex spinal surgery (Farag 2013 **Level II**, n=116, JS 5), microdiscectomy (Kim 2014c **Level II**, n=51, JS 5) and spinal fusion (Ibrahim 2018 **Level II**, n=44, JS 4). The latter study showed a clinically insignificant pain reduction even at 3 mth; in this RCT, one participant had a convulsion after the loading dose of lignocaine (2mg/kg). However, a more recent RCT in spinal fusion showed none of these benefits (Dewinter 2017 **Level II**, n=70, JS 5).

Ketamine

Ketamine as an adjuvant to PCA fentanyl after lumbar spinal surgery decreased fentanyl requirements, but increased nausea with no other benefits (Song 2013 **Level II**, n=50, JS 5). In children undergoing spinal fusion, there was no benefit of perioperative ketamine continued until POD 3 (Pestieau 2014 **Level II**, n=50, JS 5).

Ketamine may have a special role in patients who are opioid tolerant prior to back surgery (Boenigk 2019 **Level II**, n=122, JS 5; Nielsen 2017 **Level II**, n=147, JS 5; Loftus 2010 **Level II**, n=101, JS 4). Here perioperative ketamine resulted in significantly reduced opioid requirements up to 6 wk postoperatively with limited benefit on pain intensity in the immediate postoperative period. However, there was pain reduction as well as functional benefit seen at 6 wk (Loftus 2010 **Level II**, n=101, JS 4) and 6 mth follow-up (Nielsen 2017 **Level II**, n=147, JS 5).

Magnesium

A perioperative magnesium infusion reduced pain scores and analgesic requirements and improved patient satisfaction (Levaux 2003 **Level II**, n=24, JS 5). However, this might be due to reduction of OIH associated with perioperative remifentanil infusion rather than an additional analgesic benefit.

Muscle Relaxants

Chlorzoxazone, a centrally acting muscles relaxant, used after spine surgery did not improve rest or movement pain (Nielsen 2016 **Level II**, n=110, JS 5).

8.1.9.4 | Neuraxial analgesia

IT morphine vs systemic opioids after spinal surgery results in reduced pain scores and postoperative opioid consumption during the first 24 h in the IT morphine group; however, with a higher rate of pruritus and respiratory depression only occurring in the IT morphine group (Pendi 2017 **Level I**, 8 RCTs, n=393).

Patient-controlled epidural analgesia with opioid and/or local anaesthetic vs IV PCA results in clinically irrelevant improvements of analgesia in the first 2 postoperative days with a higher incidence of pruritus and paraesthesia (Tian 2015 **Level I**, 8 RCT, n=405). A subsequent RCT in posterior spinal fusion showed analgesic benefits with reduced opioid requirement for up to 3 days and increased patient satisfaction (Park 2016 **Level II**, n=94, JS 3). Similarly, in children undergoing thoraco-lumbar spinal surgery, epidural analgesia reduced pain for up to 72 h postoperatively vs systemic analgesia (Guay 2019 **Level I** [Cochrane], 7 RCTs, n=249).

8.1.9.5 | Peripheral regional analgesia

Local infiltration analgesia (LIA) reduces pain at 1 h (but not at 12 and 24 h) postoperatively and analgesic requirement vs placebo infiltration (Perera 2017 **Level I** [PRISMA], 11 RCTs, n=438). Preemptive infiltration with local anaesthetic provided additional benefits vs infiltration at wound closure; addition of steroid did not improve analgesic efficacy (Gurbet 2008 **Level II**, n=100, JS 1; Ersayli 2006 **Level II**, n=75, JS 3).

Continuous infusion of local anaesthetics (ropivacaine) after posterior spinal fusion surgery through wound catheters did not show any further benefit when added to systemic multimodal analgesia (Greze 2017 **Level II**, n=39, JS 5).

8.1.9.6. | Non-pharmacological techniques

Acupuncture used postoperatively after spinal surgery reduces pain without reduction of opioid requirement in the first 24 h postoperatively (Cho 2015b **Level I** [PRISMA], 5 RCTs, n=480).

Cognitive Behavioural Therapy (CBT) preoperatively (total 9 h group sessions) improved mobilisation in the early postoperative period after lumbar fusion and reduced analgesic requirements without changing pain scores suggesting improved coping skills (Rolving 2016 **Level II**, n=96, JS 3); however, there was no longer a benefit at 1 y follow-up (Rolving 2015 **Level II**, n=90, JS 3).

KEY MESSAGES

1. Epidural analgesia compared to systemic analgesia after spinal surgery in children improves pain up to 72 hours postoperatively (**N**) (**Level I**[Cochrane Review]).
2. Perioperative use of gabapentin or pregabalin improves analgesia and reduces opioid requirements after spinal surgery (**S**) (**Level I** [PRISMA]).
3. NSAIDs provide analgesic benefits as well as opioid-sparing effects after spinal surgery (**S**) (**Level I** [PRISMA]).
4. Intravenous dexmedetomidine improves early postoperative analgesia and reduces analgesic requirement up to 48 hours after spinal surgery (**N**) (**Level I** [PRISMA]).
5. Intravenous corticosteroids improve analgesia and reduce nausea and length of stay after spinal surgery (**N**) (**Level I** [PRISMA]).
6. Epidural steroid application intraoperatively by the surgeon provides analgesic benefit up to 24 hours and reduces length of stay after spinal surgery(**N**) (**Level I** [PRISMA]).
7. Perioperative pregabalin improves functional outcome after laminectomy at 3 months (**U**) (**Level II**).
8. Local infiltration anaesthesia improves analgesia and reduces opioid requirements after spinal surgery; this benefit is enhanced with preincision infiltration compared to infiltration at wound closure (**U**) (**Level II**).
9. Perioperative systemic lidocaine infusion improves analgesia and reduces opioid requirements after spinal surgery (**W**) (**Level II**).
10. NSAID use for less than 14 days does not increase the risk of nonunion after spinal fusion, except with high-dose ketorolac (**U**) (**Level III-3**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Acute pain management following spinal surgery is often complicated by preoperative chronic pain and long term medication use (**U**).

8.2 | Acute pain following spinal cord injury

Acute pain following spinal cord injury (SCI) is common, with over 90% of patients experiencing pain in the first 2 wk following injury (Siddall 1999 **Level IV**, n=100). Acute pain may also develop during the rehabilitation phase due to intercurrent disease (eg renal calculus) or exacerbation of a chronic pain syndrome.

Pain associated with SCI usually falls into two main categories: neuropathic pain, either at or below the level of the injury, and nociceptive pain, from somatic and visceral structures (Bryce 2012 **GL**). Neuropathic pain associated with a lesion or disease of the central somatosensory nervous system is termed central neuropathic pain (Jensen 2011 **GL**). Phantom pain and complex regional pain syndromes may also develop in patients with SCI.

Table 8.1 | Taxonomy of acute pain associated with spinal cord injury pain

Pain type	Pain subtype	Examples of primary pain source or pathology
Neuropathic pain	At level	Cauda equina compression, nerve root compression, spinal cord compression
	Below level	Spinal cord compression or ischaemia
	Other	Trigeminal neuralgia, diabetic neuropathy
Nociceptive pain	Somatic	Musculoskeletal pain (eg vertebral fracture, muscle spasms, overuse syndromes) Procedure-related pain (eg pressure sore dressings)
	Visceral	Renal calculus, pain due to bowel impaction
Other		Complex regional pain syndrome

*Source: Based on the International Spinal Cord Injury Pain Classification (Bryce 2012 **GL**).*

8.2.1 | Treatment of acute neuropathic pain after spinal cord injury

There are only case series specifically examining the treatment of acute neuropathic pain following SCI.

Three patients with acute neuropathic pain following SCI were administered SC calcitonin 100 IU in addition to other medications with improved pain relief in each person and reduced analgesic requirements (Humble 2011 **Level IV**).

Thirteen patients with acute neuropathic SCI pain received IV ketamine (50 mg over 2 h, twice daily for several days followed by 50 mg orally for up to 3 mth) with a mean pain reduction of 75% at the time of treatment cessation (mean 17 d) with further benefit over the subsequent months (Kim 2013a **Level IV**).

Treatment of acute neuropathic pain must therefore be based on evidence from studies of chronic central neuropathic pain and other neuropathic pain syndromes (see below). An algorithm for the treatment of pain in patients with SCI has been promulgated (Siddall 2006 **GL**).

8.2.2 | Treatment of chronic neuropathic pain after spinal cord injury

Clinical practice guidelines have been published which make a number of recommendations for the treatment of chronic neuropathic pain after SCI (Guy 2016 **GL**). These guidelines recommend:

First line: pregabalin, gabapentin and amitriptyline;

Second line: tramadol and lamotrigine (in incomplete SCI);

Third line: Transcranial direct current stimulation (tDCS) alone and combined with visual illusion;

Fourth line: TENS, oxycodone and dorsal root entry zone lesions.

Further information based on results from individual studies and other systematic reviews is described below.

8.2.2.1 | Conventional and atypical opioids

Under experimental conditions, IV alfentanil decreased central pain following SCI vs placebo or ketamine (Eide 1995 **Level II EH**, n=9, JS 5). IV morphine decreased tactile allodynia but had no effect on other neuropathic pain components in SCI and poststroke patients (Attal 2002 **Level II EH**, n=21, JS 5). Tramadol was effective for the treatment of neuropathic pain after SCI but the incidence of adverse effects was high (Norrbrink 2009 **Level II**, n=35, JS 4). A review of animal studies is concerning here as it shows that high doses of opioids in the acute (<14 d) period following SCI may be associated with impaired locomotor recovery and increased risk of the development of pain and infection (Woller 2013 **BS**). Although these findings have not been verified in clinical studies, they suggest the need for caution in administering high doses of opioids in the acute period post injury.

8.2.2.2 | Ketamine

Ketamine infusion decreased acute (see above) and chronic neuropathic pain in SCI patients. IV Ketamine is superior to placebo and comparable to IV lignocaine and IV alfentanil in the treatment of pain after SCI (Teasell 2010 **Level I**, 2 RCTs [ketamine], n=19).

8.2.2.3 | Membrane stabilisers

There is good evidence to support the effectiveness of lidocaine and mexiletine, when data from neuropathic pain studies done in a variety of conditions including neuropathic SCI pain are grouped together (Challapalli 2005 **Level I** [Cochrane], 30 RCTs, n=750). However, the effects in SCI specifically are mixed. IV lidocaine reduced neuropathic pain in SCI (Finnerup 2005a **Level II**, n=24, JS 5) and reduced spontaneous pain and brush allodynia in central pain (Challapalli 2005 **Level I** [Cochrane], 1 RCTs: Attal 2000 **Level II**, n=16, JS 4). Other trials have found that lidocaine reduced pain >50% in only one of ten SCI patients (Challapalli 2005 **Level I** [Cochrane], 1 RCT: Kvarnstrom 2004 **Level II**, n=10, JS 5) and that mexiletine was ineffective (Challapalli 2005 **Level I** [Cochrane], 1 RCT: Chiou-Tan 1996 **Level II**, n=11, JS 2). Lidocaine is most effective in the treatment of neuropathic pain due to peripheral nerve lesions (Kalso 1998 **Level I**, 17 studies, n=450).

8.2.2.4 | Antidepressants

There is lack of evidence to support the effectiveness of antidepressants (amitriptyline, duloxetine, venlafaxine and trazadone) in people with neuropathic SCI pain, except in those with

co-existing depression (Mehta 2016 **Level I**, 5 RCTs, n=295). There are no studies of SSRIs in the treatment of central neuropathic pain (Finnerup 2005b **Level I**, 0 RCTs [SSRIs], n=0). An RCT of amitriptyline vs lamotrigine found that both medications were effective in reducing neuropathic SCI pain, with no difference between the two medications (Agarwal 2017 **Level II**, n=147, JS 3).

8.2.2.5 | Anticonvulsants

Alpha-2-delta ligands (gabapentin and pregabalin) are effective for the treatment of neuropathic pain after SCI (Mehta 2016 **Level I**, 10 RCTs, n=567).

Lamotrigine reduced spontaneous and evoked pain in patients with incomplete SCI (Finnerup 2002 **Level II**, n=30, JS 5). Valproate was ineffective in the treatment of SCI pain (Drewes 1994 **Level II**, n=20, JS 3).

8.2.2.6 | Cannabinoids

The cannabinoid dronabinol did not reduce pain intensity in people with chronic neuropathic SCI pain (Rintala 2010 **Level II**, n=7, JS 5). Inhalation of vaporized cannabis (delta 9-THC) vs placebo reduced neuropathic SCI pain over an 8 h period ($NNT_{30\%}$ 4 [95%CI 2.1 to 25.3] for 2.9% and $NNT_{30\%}$ 3 [95%CI 1.6 to 4.2] for 6.7%) although with dose-dependent psychoactive side effects (Wilsey 2016 **Level II EH**, n=42 [crossover], JS 4).

8.2.2.7 | Intravenous anaesthetics

An IV bolus of low-dose propofol reduced the intensity of central neuropathic pain and allodynia for up to 1 h in approximately 50% of patients (Canavero 2004 **Level II**, n=21, JS 4).

8.2.2.8 | Botulinum toxin

SC injection of botulinum toxin type A (200 U total) into the painful area in people with neuropathic SCI pain reduced pain intensity when measured at 4 and 8 wk (VAS -18.6 16.8 and -21.3 26.8 respectively) following injection (Han 2016 **Level II,** n=40, JS 5).

8.2.2.9 | Baclofen

IT baclofen had an analgesic effect in patients with spinal cord lesions and reduced spasticity (Kumru 2018 **Level II**, n=13, JS 4).

8.2.2.10 | Palmitoylethanolamide (PEA)

Ultramicronised palmitoylethanolamide (PEA) for 12 wk had no analgesic or other effect on neuropathic pain after spinal cord injury (Andresen 2016 **Level II**, n=73, JS 5).

8.2.2.11 | Nonpharmacological treatments

There is currently insufficient evidence to support the effectiveness of TENS, acupuncture, self-hypnosis or cognitive behavioural therapy for chronic pain in SCI (Boldt 2014 **Level I** [Cochrane], 16 RCTs, n=616).

A systematic review found transcranial direct current stimulation (tDCS) reduces chronic neuropathic SCI pain immediately post treatment, but not at follow-up (Mehta 2015 **Level I**, 4 RCTs, n=57). A more recent RCT found that significant improvements up to 4 wk post treatment with tDCS could be demonstrated if the initial 5 d of treatment was followed by a second 10 d period of treatment 3 mth later (Thibaut 2017 **Level II,** n=9, JS 3).

Repetitive transcranial magnetic stimulation (rTMS) of the prefrontal cortex was found to result in a significant reduction in neuropathic SCI pain, but this was only maintained for one day following treatment (Nardone 2017 **Level II**, n=12, JS 2).

Virtual reality techniques to create leg illusions demonstrated a modest and non-significant reduction in pain intensity (Pozeg 2017 **Level II**, n=20, JS 2). Virtual walking resulted in a greater reduction in pain intensity than virtual wheeling, but the pre to post change was not significant (Jordan 2016 **Level IV**, n=50).

Breathing controlled electric stimulation has an immediate analgesic effect on chronic neuropathic SCI pain, with no augmentation when combined with tDCS (Li 2018a **Level III-2**, n=12).

8.2.3 | Treatment of nociceptive and visceral pain after spinal cord injury

There is no specific evidence to guide the treatment of acute nociceptive and visceral pain in SCI patients. Treatment is therefore based on evidence from other studies of nociceptive and visceral pain and is usually directed at treating the specific underlying cause of the pain.

KEY MESSAGES

1. Alpha-2-delta ligands (gabapentin/pregabalin) are effective in the treatment of neuropathic pain following spinal cord injury (**S**) (**Level I**).
2. Antidepressants (amitriptyline, duloxetine and venlafaxine) are effective in the treatment of neuropathic pain following spinal cord injury but only in those with co-morbid depression (**N**) (**Level I**).
3. Intravenous opioids, ketamine ((**U**) (**Level I**), lidocaine and tramadol are effective in the treatment of neuropathic pain following spinal cord injury (**U**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Treatment of acute spinal cord injury pain is largely based on evidence from studies of other neuropathic and nociceptive pain syndromes (**U**).

☑ There is currently insufficient evidence to support non-pharmacological treatments (TENS, acupuncture, self-hypnosis or cognitive behavioural therapy) for spinal cord injury pain (**N**).

8.3 | Chest trauma (Rib fractures)

Rib fractures occur in approximately 10% of multi-trauma patients (Flagel 2005 **Level IV**, n=732,823; Ziegler 1994 **Level IV**, n=7,147). This is also a common injury in the elderly population, often with serious consequences (Christie 2019 **NR**). There are multiple complications associated with rib fractures such as pneumonia, aspiration, atelectasis and acute respiratory distress syndrome (Witt 2017 **NR**). The prevention of such complications relies on high quality analgesia and aggressive physical rehabilitation. General recommendations are to implement a protocolised bundled clinical pathway (Witt 2017 **GL**).

8.3.1 | Paracetamol

A single dose of IV paracetamol 1 g vs IV morphine (0.1 mg/kg) had similar analgesic effects and adverse event rates (Esmailian 2015 **Level II**, n=54, JS 5).

8.3.2 | NSAIDS

Regular IV ibuprofen reduced pain scores over the 7 d study period and IV morphine requirements on d 3 to 7 vs control (Bayouth 2013 **Level III-3**, n=42). Regular IV ketorolac reduced the incidence of rib fracture related pneumonia vs control (Yang 2011 **Level III-3**, n=619).

8.3.3 | Adjuvant medications

IV ketamine infusions (0.1-0.15 mcg/kg/hr) reduced pain scores and opioid requirements (Carver 2019 **Level II**, n=91, JS 5; Walters 2018 **Level III-3**, n=30). There were no other benefits with regard to outcome.

IV dexmedetomidine (1 mcg/kg loading followed by 0.5mcg/kg/h infusion) was inferior to thoracic epidural analgesia in terms of pain and sedation scores (Mahmoud 2016 **Level II**, n=58, JS 2).

Regular gabapentin (300mg) provided no benefit in terms of pain scores, opioid requirement and adverse events (Moskowitz 2018 **Level II**, n=40, JS 5).

Lignocaine patches (5%) showed no difference vs placebo with regard to pain scores, opioid consumption, LOS or adverse outcomes (Ingalls 2010 **Level II**, n=58, JS 5). Another study showed a reduction in pain scores, but no effect on morphine consumption or adverse events (Zink 2011 **Level III-3,** n= 58). A further study showed no benefit in the first 4 d, but then reduced pain scores from the fifth day, reduced opioid requirements and LOS (Cheng 2016 **Level II**, n=44, JS 3).

8.3.4 | Epidural analgesia

Thoracic epidural analgesia vs systemic IV analgesia (5 RCTs & 6 studies, n=1,057) improves pain scores (4 RCTs) (Peek 2019 **Level III-2 SR** [PRISMA], 8 RCTs & 11 studies, n=2,081). There was no significant difference in secondary outcomes such as hospital LOS (4 RCTs, n=130 & 4 studies, n=523), ICU LOS (4 RCTs, n=118 & 4 studies, n=501), duration of mechanical ventilation (3 RCTs, n=94 & 1 study, n=165) and pulmonary complications (widely variable rates) (4 RCTs, n=126 & 6 studies, n=907). Thoracic epidural analgesia achieves similar pain scores vs continuous intercostal (1 RCT, n=60 & 1 study n=169) and vs paravertebral blocks (1 RCT, n=30 & 2 studies, n=1,224), with no difference in hospital LOS, ICU LOS, duration of mechanical ventilation and pulmonary complications (0 to 13.3%) (2 or 3 studies each outcome: 6 studies, n=1,045). Dexmedetomidine/bupivacaine via thoracic epidural catheters improved pain scores slightly vs bupivacaine alone (Agamohammdi 2018 **Level II**, n=64, JS 2).

8.3.5 | Peripheral regional analgesia

Continuous paravertebral and intercostal blocks are effective regional analgesia techniques providing analgesia superior to IV systemic analgesia (1 study [PVB], n=54; 1 study [ICB], n=90) and equivalent to thoracic epidural analgesia (see above) (Peek 2019 **Level III-2 SR** [PRISMA], 8 RCTs & 11 studies, n=2,081).

Interpleural blocks did not provide analgesia superior to placebo blocks (Short 1996 **Level II**, n=16, JS 5) and were inferior to epidural analgesia (Luchette 1994 **Level IV**, n=19).

Serratus anterior blocks (Iotti 2019 **Level IV**, n=3; Jadon 2017 **Level IV**, n=6; Camacho 2019 **CR**; Fu 2017 **CR**) and erector spinae plane blocks (ESPB) (Luftig 2018 **Level IV**, n=3; Nandhakumar 2018 **Level IV**, n=2; Hamilton 2017 **CR**) are described as effective analgesic options after rib fractures. ESPBs reduced pre to post insertion pain scores in patients with up to seven or more rib fractures (Adhikary 2019 **Level IV**, n=79).

8.3.6 | Surgical fixation

Surgical fixation vs non-surgical treatment in patients with three or more fractured ribs reduces duration of ventilation (Level I, 3 RCTs; Level III-2 SR, 1 RCT & 4 studies), need for tracheostomy (Level I [Cochrane], 2 RCTs; Level III-2 SR, 1 RCT & 6 studies) and intensive care LOS (Level I, 3 RCTs; Level III-2 SR, 1 RCT & 2 studies), pneumonia (Level I [Cochrane], 3 RCTs; Level III-2 SR, 2 RCTs & 6 studies), hospital LOS (Level I, 2 RCTs; Level III-2 SR, 1 RCT & 6 studies) and mortality (OR 0.28; 95%CI 0.08 to 0.92) (Level III-2, 3 studies); pain and opioid requirements were not assessed (Cataneo 2015 **Level I** [Cochrane], 3 RCTs, n=123; Schuurmans 2017 **Level I**, 3 RCTs, n=123 [all 3 RCTs overlap]; Liu 2019c **Level III-2 SR** [PRISMA], 2 RCTs and 12 studies, n=839 [1 RCT overlap]). There was contradictory information on hospital costs; significant reduction (Level I, 2 RCTs) and significant increase (Level III-2, 3 studies) respectively.

8.3.7 | Non-pharmacological therapy

TENS was superior to regular naproxen (275 mg tds) in terms of pain scores for up to 3 d (Oncel 2002 **Level II**, n=100, JS 4). Acupuncture vs sham acupuncture on top of background ibuprofen reduced pain on deep breathing and coughing for up to 6 h on each of 3 d of treatment (Ho 2014 **Level II**, n=58, JS 4).

KEY MESSAGES

1. Surgical fixation in patients with 3 or more fractured ribs improves outcome with regard to incidence of pneumonia and need for tracheostomy (**N**) (**Level I** [Cochrane Review]), duration of ventilation, ICU and hospital stay (**N**) (**Level I**) and mortality (**N**) (**Level III-2 SR**).
2. Continuous thoracic epidural analgesia and continuous intercostal and paravertebral blocks provide similar analgesia and are superior to intravenous opioids for rib fracture related pain (**N**) (**Level I** [PRISMA]).
3. Systemic NSAIDs and ketamine are efficacious analgesic adjuvants for rib fracture related pain (**N**) (**Level III-3**)

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Emerging regional techniques such as serratus anterior and erector spinae plane blocks (single shot and continuous infusion) are supported by case series and could be considered for rib fracture analgesic management (**N**).

☑ Chest trauma with rib fractures carries a high risk of potentially life-threatening complications; excellent analgesia and aggressive physical rehabilitation, ideally provided in a protocolised clinical pathway, can improve outcome (**N**)

8.4 | Acute pain after hip (neck of femur) fractures

Hip fractures occur in 199 to 240/100 000 people per year in Australia and New Zealand (AIHW 2018b **Level IV**; HQSC 2018 **Level IV**) and cause significant morbidity and mortality largely due to patient age (mean age 84 y), cognitive impairment (39%) and pre-existing co-morbidities (majority ASA 3 or above) (ANZFHR 2018 **Level IV**, n=9,408). Three mth following a hip fracture, mortality is 10%, and although 71-76% of people have returned home, only 23-26% will have achieved pre-injury mobility.

Pain is a significant feature of a hip fracture, causing discomfort and distress to the person and family, thus satisfactory analgesia is a critical aspect of care. Risk factors for severe post-operative pain in the immediate post-operative period include level of education, cognitive function, preoperative delirium and depression (Radinovic 2014 **Level III-2**, n=344).

Delirium following hip fracture is common (24% of patients) (Yang 2017 **Level III-2 SR**, 24 studies, n=5,364) and is associated with increased 1 y mortality (Ruggiero 2017 **Level III-2**, n=514; Mitchell 2017 **Level III-2**, n=27,888). Risk factors for developing postoperative delirium are older age, pre-admission aged care facility residency, multiple co-morbidities, pre-existing cognitive impairment and morphine use (Yang 2017 **Level III-2 SR**, 24 studies, n=5,364; Smith 2017b **Level III-2 SR**, 32 studies, n=6,704) (17 studies overlap). Effective analgesia provision is an important factor to reduce the risk of delirium (ANZFHR Steering Group 2014 **GL**).

Surgical intervention is often the most effective form of analgesia and is one of the main drivers to timely access to surgery (ANZFHR Steering Group 2014 **GL**). Arthroplasty techniques are associated with less pain and opioid requirements than internal fixation, dynamic hip screw or intramedullary nail (A'Court 2017 **Level III-2**, n=357; Salpakoski 2016 **Level III-2**, n=136). Hemiarthroplasties performed with cement (Ng 2014 **Level III-2**, n=197) and minimally invasive anterior approach (Pala 2016 **Level III-2**, n=89) have less post-operative pain than non-cemented or posterolateral approach hemiarthroplasties.

Guidelines to direct care of hip fracture patients are published (ANZFHR Steering Group 2014 **GL**); integrated orthogeriatric care, utilisation of care bundles and adherence to clinical care standards improves outcomes in hip fracture patients (ACSQHC 2016 **GL**).

8.4.1 | Nerve Blocks

In 2017, on average 36% of patients in New Zealand and 66% of patients in Australia received a nerve block before hip fracture surgery, whilst overall 78% had a nerve block during admission (ANZFHR 2018 **Level IV**, n=9,408). No major complications due to peripheral nerve blocks for hip fractures have been reported in the literature (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760).

8.4.1.1 | Pain Relief

Peripheral nerve blocks (pooled data) decrease pain at rest and movement within 30 min of block placement (SMD -1.41; 95% CI -2.14 to -0.67 [equivalent to -3.4/10]) (8 RCTs, n=373) vs systemic analgesia (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760). Femoral nerve blocks (FNB) (Hartmann 2017 **Level I**, 2 RCTs, n=84) and fascia iliaca compartment blocks (FICB) (Steenberg 2018 **Level I**, 11 RCTs, n=1,062) performed before positioning lead to less pain and shorten time to performing spinal anaesthesia vs IV opioids alone.

When performed in the emergency department or on admission, FICB (Hong 2019 **Level I** [PRISMA], 11 RCTs, n=937; Steenberg 2018 **Level I**, 11 RCTs, n=1,062) (8 RCTs overlap), FNB (Riddell 2016 **Level I**, 7 RCTs, n=224) or 3-in-1 blocks (4 RCTs, n=199) (Ritcey 2016 **Level I** [PRISMA], 9 RCTs, n=547) are

superior to systemic opioids in reducing pain on movement, decrease preoperative opioid requirements and lengthen time to rescue analgesia. These findings are consistent even in patients with dementia (Unneby 2017 **Level II,** n=266, JS 2).

Nerve blocks decrease pain at rest 6 to 8 h after surgery and reduce pain at rest, opioid requirements, time to first mobilisation and lead to higher patient satisfaction up to 24 h after surgery (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760). There is no reduction in pain on movement 6 to 8 and 24 h after surgery, or pain on rest or movement 48 to 72 h after surgery.

Single injection PNBs and CPNBs (pooled data) are equivalent in effect 24 h after surgery (4 RCTs, n=195); CPNBs do not improve pain on movement or at rest 48 h (5 RCTs, n=335) and 72 h (2 RCTs, n=140) after surgery (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760). However, CPNBs vs systemic analgesia reduced postoperative pain, opioid requirements, opioid adverse effects, time to mobilisation and resulted in more frequent discharge home (Arsoy 2017a **Level III-3**, n=265; Arsoy 2017b **Level III-3**, n=29; Morrison 2016 **Level II**, n=161; JS 5).

8.4.1.2 | Prevention of other complications

Moderate quality evidence demonstrates that PNBs (pooled data) reduce the risk of pneumonia vs systemic analgesia (RR 0.41; 95%CI 0.19 to 0.89) (NNT 7) (3 RCTs, n=131) (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760). PNBs do not decrease the risk of acute confusional states, acute myocardial infarction/ischaemia or 6 mth mortality; although evidence was low to very low quality. FICB led to better abbreviated mental test scores following hip fracture surgery vs systemic analgesia (Odor 2017 **Level III-2**, n=959).

8.4.1.3 | Nerve Block Technique

There is no evidence for superiority of a particular nerve block or its insertion technique (Steenberg 2018 **Level I**, 11 RCTs, n=1,062; Riddell 2016 **Level I**, 7 RCTs, n=224; Ritcey 2016 **Level I**, 9 RCTs, n=547) (significant overlap of all 3 SRs). US guided 3-in-1 blocks and landmark guided FICBs are equivalent for pain reduction at 30 and 60 min after intervention (Reavley 2015 **Level II**, n=178, JS 3). Nerve stimulator guided FNB reduced pain scores and opioid requirements more than landmark guided FIC blocks, but the reduction (-0.9/10) was felt not to be clinically significant (Newman 2013 **Level II**, n=107, JS 3).

8.4.1.4 | High volume local anaesthesia infiltration

High volume, low concentration (75 mL containing 200 mg ropivacaine [0.266 %]) local anaesthetic fracture, capsular and tissue infiltration followed by post-operative boluses (20 mL containing 100 mg ropivacaine [0.5%]) via surgically placed catheter did not reduce postoperative pain or opioid consumption vs placebo (Bech 2018 **Level II**, n=74, JS 5).

Periarticular infiltration with bupivacaine (50 mL of 0.25%) followed by liposomal bupivacaine (20 mL diluted into 40 mL) did not result in significantly better pain control or less opioid requirements vs no local anaesthetic infiltration (Hutchinson 2019 **Level III-2**, n=178). However, LOS was lower by 1.1 d and patients were more likely to be ambulatory on discharge (82% vs 69%) if they had received high volume local anaesthetic infiltration.

8.4.2 | Systemic analgesia

Generally, post-operative analgesia administered on a regular time-based regime leads to less pain vs prn regimens (Di Filippo 2015 **Level III-2**, n=131). Choice and dose of analgesia should be age appropriate with close monitoring for associated side effects (ANZFHR Steering Group 2014 **GL**).

8.4.2.1 | Paracetamol

Regular paracetamol should be prescribed every 6 h unless contra-indicated (ANZFHR Steering Group 2014 **GL**); dose adjustments should be considered (older age, malnutrition, low body weight) (see Section 4.1.3.). When compared to oral paracetamol, patients administered IV paracetamol had lower pain scores, less opioid use and shorter hospital LOS (Sanzone 2016 **Level III-3 SR**, n=332). Paracetamol prescribed on discharge is not associated with increased 6 mth mortality, falls or hospital readmission (Harstedt 2016 **Level III-2**, n=272)

8.4.2.2 | NSAIDs

Development of acute kidney injury (AKI) following hip fracture surgery ranges from 11 to 24% and is associated with higher mortality. Risk factors for developing AKI include male sex, older age, number of co-morbid conditions, antihypertensives (particularly ACE-inhibitors and ATRA2-antagonists), pre-existing renal impairment, hypalbuminaemia and obesity (Shin 2018 **Level III-2**, n=481; Porter 2017 **Level III-2**, n=2,959; Hong 2017 **Level III-2**, n=450; Pedersen 2017 **Level III-2**, n=13,529; Pedersen 2016 **Level III-2**, n=13,259). NSAIDs are not an independent risk factor for developing AKI in hip fracture patients (Hong 2017 **Level III-2**, n=450; Pedersen 2016 **Level III-2**, n=13,259). In the largest population-based study, NSAIDs were prescribed to 12.3% of patients who developed AKI vs 14.2% of patients who did not (Pedersen 2016 **Level III-2**, n=13,259).

Caution should be exercised when considering NSAIDs in hip fracture patients, due to the predominantly older population with co-existent disease; however time limited use of NSAIDs may be clinically appropriate and relatively safe for short term use in patients with preserved renal function (Hong 2017 **Level III-2**, n=450; ANZFHR Steering Group 2014 **GL**). A retrospective analysis using data from 2003 to 2016 looking at transfusion risk for hip fractures found a small increase in risk of transfusion with preoperative NSAID use within 90 d of surgery (RR 1.07; 95%CI 1.04 to 1.10) (Glassou 2019 **Level III-2**, n=74,791). There is insufficient evidence to conclude whether NSAIDs are associated with other complications in hip fracture patients or to compare analgesic regimes with and without NSAIDs.

8.4.2.3 | Conventional and atypical opioids

Additional opioids should be offered if non-opioids alone do not provide sufficient pain relief (ANZFHR Steering Group 2014 **GL**). Ninety-five percent of hip fracture patients receive opioids during their admission (Lindestrand 2015 **Level IV**, n=416). Opioid analgesia is part of standard systemic analgesia in the majority of studies (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760). Continuous IV morphine infusion (0.01 mg/kg/h) provides similar pain scores and rescue analgesia requirements as regular paracetamol, but was associated with more complications requiring cessation (Di Filippo 2015 **Level III-2**, n=131). Compared to other patients, hip fracture patients with dementia and cognitive impairment receive less opioid analgesia (Moschinski 2017 **Level I** [PRISMA], 17 RCTs, n=4,249; Jensen-Dahm 2016 **Level III-2**, n=1,507). High prevalence of renal impairment (11-24%) and association of morphine use with increased risk of postoperative delirium in hip fracture patients (OR 3.01; 95%CI 1.30 to 6.94) would suggest that if opioids are required, those not relying on renal elimination should be used in this cohort (Yang 2017 **Level III-3 SR**, 24 studies, n=5,364).

Pre-existing chronic opioid use occurs in approximately 1 in 4 hip fracture patients (Lindestrand 2015 **Level IV**, n=416) and is associated with increased risk of hip fracture (RR 1.54; 95%CI 1.34 to 1.77) (Ping 2017 **Level I**, 10 RCTs, n=697,011).

Eighty-one percent of hip fracture patients are discharged on opioids with 30% still on prescribed opioids 6 mth later (Lindestrand 2015 **Level IV**, n=416). Pre-existing opioid use and osteoporosis were the most significant factors associated with continued use at 6 mth. Conflicting evidence exists regarding opioids and mortality in hip fracture patients. One study found that discharge opioids were associated with an increased risk (OR 2.95; 95%CI 1.19 to 7.34) of mortality within 6 mth of surgery (Harstedt 2016 **Level III-2**, n=272), whereas another study found that opioids were not associated with increased risk at 30 d, 6 mth or 1 y (Lindestrand 2015 **Level IV**, n=416).

Tramadol

Following hip fracture surgery, patients prescribed tramadol on discharge had an increased risk of hospital readmission (OR 2.84) within 6 mth due to falls (Harstedt 2016 **Level III-2**, n=272). There is insufficient evidence to compare perioperative analgesic regimes with and without tramadol.

8.4.2.4 | Acupuncture

Auricular acupressure performed during prehospital transport led to better pain relief after hip fracture (Barker 2006 **Level II**, n=38, JS 5).

KEY MESSAGES

1. Lower limb nerve blocks with local anaesthetics reduce pain, analgesia requirements and lengthen time to rescue analgesia in hip fracture patients compared to systemic analgesia; there is no advantage of a specific nerve block, insertion technique or continuous versus single injection administration (**S**) (**Level I** [Cochrane Review]).
2. Lower limb nerve blocks decrease the risk of pneumonia in hip fracture patients, but do not decrease the risk of delirium, myocardial infarction/ischaemia or mortality (**N**) (**Level I** [Cochrane Review]).
3. Morphine should be avoided due to increased risk of delirium in hip fracture patients, who have a high prevalence of renal impairment (**N**) (**Level III-3 SR**).
4. Arthroplasty techniques in hip fracture patients are associated with less pain and opioid requirements than non-arthroplasty techniques (**N**) (**Level III-2**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Integrated orthogeriatric care, utilisation of care bundles and adherence to clinical care standards improve outcomes in hip fracture patients (**N**).

8.5 | Acute burns injury pain

Acute pain following burns injury can be nociceptive and/or neuropathic in nature (Nelson 2019 **NR**; Gray 2008a **NR**) and may be constant (background pain), intermittent or procedure-related. Itch can also be a significant symptom (for details see Section 10.9.2.3). The multifaceted character of burns injury pain requires a broad-based assessment tool for clinical application and research, which is currently not available (Mahar 2012 **Level I**, 25 RCTs, n≈800).

Burns pain is often undertreated, particularly in the elderly (Choiniere 2001 **NR**). However, effective pain management after acute burns injury is essential, not only for humanitarian and psychological reasons but also to facilitate procedures such as dressing changes and physiotherapy and possibly to minimise the development of chronic pain, which is reported in 18–58% of burns patients (Browne 2011 **Level IV**, n=492; Dauber 2002 **Level IV**, n=358; Choiniere 1989 **NR**).

More severe acute pain following burns injury leads to a greater risk of post-traumatic stress disorder (McGhee 2011 **Level IV**, n=113; Browne 2011 **Level IV**, n=492). Increased early use of opioids in children with burns injury reduces post-traumatic stress symptoms up to 4 y after the injury (Sheridan 2014 **Level III-3**, n=147 [paediatric]).

There is limited evidence for the management of pain in burns injury, and treatment continues to be largely based on evidence from several randomised clinical trials, case reports and case series, or data extrapolated from other relevant areas of pain medicine. The use of a highly protocolised pain management flowchart may be helpful in improving the pain experience (Yang 2013 **Level III-3**, n=107).

For paediatric information, see also Section 10.9.2.

8.5.1 | Management of background nociceptive pain

Immediately after the injury, simple measures such as cooling (Davies 1982 **NR**), covering and immobilising the burn may provide analgesia (Allison 2004a **GL**; Gallagher 2000b **NR**; Kinsella 1991 **NR**). Cooling under running tap water for ≥20 min or the application of a wet towel (ANZBA 2014 **GL**) is supported by porcine data (Rajan 2009 **BS**) and is useful up to 3 h post initial burn injury. Temporary burns dressings such as thin film plastic “cling” wrap (or clean sheets if unavailable) reduce pain caused by contact and draft; they should not be applied circumferentially as swelling is inherent (ANZBA 2014 **GL**; Allison 2004a **GL**).

In the initial presentation of severe burn, analgesia is best achieved by titration of IV opioids. Absorption of IM and SC opioids may be unreliable in the presence of hypovolaemia and vasoconstriction associated with burns (Kinsella 2008 **NR**). PCA with morphine is effective for burns pain in adults (Choiniere 1992 **Level II**, n=24, JS 4; Lin 2019c **Level IV**, n=23) and children (Gaukroger 1991 **Level IV**, n=11).

The addition of dexmedetomidine to an IV PCA (0.5 mcg/kg dexmedetomidine loading 10 min before induction, then 200 mcg to 100 mcg sufentanil per IV PCA bolus) vs IV PCA sufentanil only reduced rest and dynamic pain as well as opioid consumption slightly and improved recovery scores in the first 24 h after burns surgery (Jiang 2019 **Level II**, n=60, JS 5); however, the bolus dose of sufentanil was quite low and therefore this may have biased towards a positive response in the combination group.

Conversion to oral opioids is possible once normal gastrointestinal function has returned; even severe burns injury does not affect gastric emptying or the absorption of oral paracetamol (Hu 1993 **Level III-2 PK**, n=30).

Morphine doses do not require adjustment in burns injury, as its pharmacokinetics are unchanged in burns patients (Kinsella 2008 **NR**; Perreault 2001 **PK**).

In the ICU, intrathecal (IT) infusion of morphine has been reported as a method to control burns pain and thereby avoiding the adverse effects of systemic opioids (Zuehl 2018 **CR**).

8.5.2 | Management of acute neuropathic pain and hyperalgesia

Animal and human volunteer studies in burns injury have shown that secondary hyperalgesia develops around the injured site. In addition, burns injury results in damage to cutaneous nociceptors and conducting neurons that may lead to acute neuropathic pain. There is growing evidence that the addition of antihyperalgesic agents is an important part of multimodal treatment of burn injury pain. This is also relevant in view of the development of pruritus in the context of burns injury. Evidence based guidelines for post-burn pruritus recommend cetirizine and cimetidine as first line and loratadine as second line peripherally acting agents, gabapentin as a first line centrally acting agent, and laser therapy and pressure garments as possible nonpharmacological interventions (Goutos 2010 **GL**). Combination therapy is commonly used and should be implemented in a judicious stepwise fashion that includes peripherally acting, centrally acting and nonpharmacological interventions early.

Gabapentin reduced pain and opioid consumption following acute burns injury (Cuignet 2007 **Level III-3**, n=20) and reduced neuropathic pain descriptors in a small case series (Gray 2008b **Level IV**, n=6).

Pregabalin reduced pain in outpatient burns patients (Wong 2010 **Level IV**, n=24) and reduced "hot" and "sharp" pain as well as itch and procedural pain in severe burns injury (Gray 2011 **Level II**, n=90, JS 5).

Parenteral methylprednisolone or ketorolac reduced secondary hyperalgesia surrounding an experimental burns injury in human volunteers; however further clinical research is required prior to recommending these agents (Stubhaug 2007 **Level II**, n=12, JS 5).

There is also evidence in a burns injury model in human volunteers for beneficial effects of ketamine (McGuinness 2011 **Level I EH**, 4 RCTs, n=67) and dextromethorphan (Ilkjaer 1997 **Level II EH**, n=24, JS 3). Although ketamine is effective as an analgesic and reduces secondary hyperalgesia without relevant adverse effects, the limitations of the studies (no clinical studies, heterogeneity of results, small study size) preclude any definitive recommendations on clinical use of ketamine in a burns setting (McGuinness 2011 **Level I EH**, 4 RCTs, n=67).

8.5.3 | Management of procedural pain

Treatment and rehabilitative procedures for burns patients may be associated with frequent and prolonged periods of pain. It was previously reported that up to 84% of burns patients experience extreme and intense pain during therapeutic procedures (Ashburn 1995 **NR**). Analgesic strategies have more recently improved, but managing procedural pain remains a significant and ongoing challenge that requires a balance of pharmacological and nonpharmacological approaches.

8.5.3.1 | Opioids

Opioid therapy is the mainstay of analgesia for burns procedures. However, very high doses may be required (Linneman 2000 **Level IV**, n=55) and opioid-related sedation and respiratory depression may develop when the pain stimulus decreases following the procedure.

Short-acting opioids such as fentanyl (Prakash 2004 **Level II**, n=60, JS 4) or alfentanil (Sim 1996 **Level IV**) administered via PCA or target-controlled IV infusions (Gallagher 2000a **Level IV**, n=10) successfully provide analgesia during burns dressing changes. IN fentanyl was a viable alternative

to oral morphine in children for burns dressings (Borland 2005 **Level II**, n=28, JS 4). In adults, there was no difference in pain scores or rescue analgesic requirements between IN fentanyl and oral morphine for burns dressings (total surface less than 26%) (Finn 2004 **Level II**, n=26, JS 5). Oral transmucosal fentanyl provided similar analgesia to oral oxycodone (Sharar 2002 **Level II**, n=20, JS 4) and hydromorphone (Sharar 1998 **Level II**, n=14, JS 4) with a similar adverse-effect profile in children and adolescents. See also Section 10.9.4.

8.5.3.2 | Adjuvant medications

N_2O, ketamine and IV lidocaine infusions (Jonsson 1991 **Level IV**, n=7) have also been used to provide analgesia for burns procedures (see Sections 4.5.1, 4.6.1 and 4.4.1). However, efficacy of IV lidocaine for procedural pain could not be confirmed in an RCT (Wasiak 2011 **Level II**, n=45, JS 5) and a subsequent Cochrane review found no further trials (Wasiak 2014a **Level I** [Cochrane], 1 RCT, n=45; see above).

A systematic review of ketamine in volunteers with a burns injury model has been discussed above (McGuinness 2011 **Level I EH**, 4 RCTs, n=67). PCA with a ketamine/midazolam mixture was effective and well tolerated when used for analgesia and sedation during burns dressings (MacPherson 2008 **Level IV**, n=44). In children aged 12 to 36 mth with major burns requiring deep sedation for dressings, a propofol/remifentanil infusion was as effective as a propofol/ketamine infusion, but had a faster recovery (Seol 2015 **Level II**, n=50, JS 5). Oral ketamine/midazolam may provide superior pain reduction vs an oral midazolam/paracetamol/codeine combination for burns dressing changes in children aged 1 to 5 y (Norambuena 2013 **Level III-1**, n=60). IM ketamine/tramadol/ dexmedetomidine was found to be more effective than IM ketamine/tramadol/midazolam or IM ketamine alone in adult burns patients (Zor 2010 **Level III-1**, n=24). In contrast, there was no difference in the pain experience between three groups receiving ketamine/midazolam, ketamine/dexmedetomidine or ketamine alone in the same setting (Gunduz 2011 **Level II**, n=90, JS 3). Oral ketamine was better than oral dexmedetomidine for pain reduction during dressing changes in adult burns patients (Kundra 2013 **Level II**, n=30, JS 4).

The heterogeneous nature of the studies and the lack of pain outcome data in a meta-analysis of dexmedetomidine in burns patients mean no conclusions can be drawn as to its effect on burn pain (Asmussen 2013 **Level I**, 4 studies, n=266). Only improved sedation is identified.

Sedation and anxiolysis as an adjunct to analgesia can improve pain relief. This has been shown for lorazepam combined with morphine (Patterson 1997 **Level II**, n=79, JS 5). However, a retrospective case series of patients receiving midazolam for dressing changes did not demonstrate a reduction in overall pain or opioid use during the hospital admission (Bidwell 2013 **Level III-2**, n=36). Patient-controlled sedation with propofol may also be effective (Coimbra 2003 **Level IV**, n=20). A propofol/ketamine combination resulted in less “restlessness” during burns dressing changes vs a propofol/fentanyl combination, with no difference in emergence phenomena (Tosun 2008 **Level II**, n=32, JS 5).

Inhaled methoxyflurane may be helpful for dressing changes for burns patients in an ambulatory setting but further evidence is required prior to recommending routine use (Wasiak 2014b **Level IV**, n=15).

Topical analgesic techniques, such as lidocaine as a cream (Brofeldt 1989 **Level IV**, n=30) or a spray (Desai 2014 **Level II**, n=29, JS 5) or morphine-infused silver sulfadiazine cream (Long 2001 **Level IV**, n=4) may be effective; however a topical gel dressing containing morphine was not more effective than other gel dressing in reducing burns injury pain in the ED (Welling 2007 **Level II**, n=59, JS 5). The use of biosynthetic dressings is associated with a reduction in pain during dressing changes and a decrease in time to healing (Wasiak 2013 **Level I** [Cochrane], 30 RCTs of various dressings, n unspecified). The use of a soft silicone wound contact layer on split thickness skin grafts

reduced pain on dressing changes in comparison to conventional dressings (Patton 2013 **Level II**, n=43, JS 2).

Puerarin, a Chinese herb extract, was found to be analgesic and anti-inflammatory for dressing changes;however the control group received no analgesia (Zhang 2013b **Level II**, n=32, JS 5).

8.5.4 | Regional analgesia for donor site pain management

Traditionally, regional analgesia is often avoided in burns patients due to the high incidence of bacteraemia and bacterial colonisation. However, recent research suggests that well-selected patients may benefit from regional analgesia for donor site pain management.

US-guided local anaesthetic block of the lateral femoral cutaneous nerve in 16 consecutive patients resulted in no pain 4 h after surgery at the donor site (lateral thigh) (Shteynberg 2013 **Level IV**, n=16); however longer-term effects of this intervention are not known. Fascia iliaca compartment block reduced dynamic, but not rest pain, at the skin donor site and injection of local anaesthetic through the catheter placed in the compartment reduced pain at the first dressing change on d 3 following surgery (Cuignet 2005 **Level II**, n=81, JS 3).

8.5.5 | Nonpharmacological pain management

Numerous non-pharmacological techniques have been described to assist in reducing the pain and suffering of procedures necessary in burns management

Distraction techniques of virtual reality and hypnosis have the most beneficial effects on reducing procedural pain, however with high heterogeneity of study effects (Scheffler 2018 **Level I** [PRISMA], 21 RCT, n=660). Stratified analysis suggest that relaxation alone is insufficient to reduce procedural pain. Hypnosis provides benefit in pain and anxiety reduction but not medication use for pain of burn wound care (Provencal 2018 **Level I** [PRISMA], 6 RCTs, n=234) (4 RCTs overlap); however, the conclusion states that it may be premature to make hypnosis a general clinical recommendation in the burn injured population. Indeed, a subsequent RCT found that hypnosis had no benefit in pain reduction (Chester 2018 **Level II**, n=64, JS 5).

Virtual reality reduces pain intensity, time spent thinking about pain and unpleasantness (Luo 2019 **Level I** [PRISMA], 13 RCTs, n=362; Scheffler 2018 **Level I** [PRISMA], 21 RCT, n=660) (4 RCTs overlap). VR techniques in combination with pharmacological measures reduce the pain experience during dressing changes and physiotherapy in children (Morris 2009 **Level IV SR**, 9 studies, n=152) (6 RCTs overlap). Providing a VR service requires significant physical and staffing resources (Markus 2009 **Level IV**, n=10). Simply watching television during burns care may be as effective as VR techniques in reducing pain scores (van Twillert 2007 **Level III-3**, n=19) and use of commercially available video games may be another option (Parry 2012 **Level III-2**, n=24).

Music interventions are helpful for pain alleviation, anxiety relief and heart rate reduction (Li 2017b **Level I** [PRISMA], 17 RCTs, n=804).

Aroma therapy may reduce pain, anxiety and improve sleep quality, but the low quality of trials with regard to randomisation and bias does not permit a conclusion (Choi 2018 **Level I** [PRISMA], 4 RCTs, n=248).

Transcranial direct current stimulation (Hosseini Amiri 2016 **Level II**, n=60, JS 1) and whole body vibration reduce pain and/or anxiety (Ray 2017 **Level II**, n=31, JS 3).

KEY MESSAGES

1. The use of biosynthetic dressings is associated with a decrease in time to healing and a reduction in pain during burns dressings changes (**U**) (**Level I** [Cochrane Review]).
2. Virtual reality distraction, augmented reality techniques and multimodal distraction methods reduce pain and unpleasantness during burns dressings (**S**) (**Level I** [PRISMA]).
3. Music interventions are helpful in reducing pain, anxiety and heart rate in burns patients (**N**) (**Level I** [PRISMA])
4. Opioids, particularly via PCA, are effective in burns pain, including procedural pain (**U**) (**Level II**).
5. Pregabalin reduces pain following acute burns injury (**U**) (**Level II**).
6. Sedation and anxiolysis with lorazepam improves procedural pain relief in acute burns injury (**U**) (**Level II**).
7. Regional analgesia reduces donor site pain in selected burns patients (**U**) (**Level II**).
8. Gabapentin reduces pain and opioid consumption following acute burns injury (**U**) (**Level III-3**).
9. PCA with ketamine and midazolam mixture provides effective analgesia and sedation for burns dressings (**U**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Acute pain following burns injury can be nociceptive and/or neuropathic in nature and may be constant (background pain), intermittent or procedure-related (**U**).

☑ Acute pain following burns injury requires aggressive multimodal and multidisciplinary treatment and may benefit from protocolised management approaches (**S**). This is particularly important as severely burn injured patients require repeated procedures and frequently have persistent issues of chronic pain, pruritus, post-traumatic stress and other psychological consequences.

☑ Pruritus is a common symptom following burns injury and alpha-2-delta ligands are useful in its management (**N**).

8.6 | Acute medical pain

Acute pain in medical wards is common (Vallano 2006 **Level IV**, n=1,675) with a prevalence of 37.7% to 84% (Gregory 2016 **Level IV SR** [PRISMA], 11 studies, n=17,705). Comparative rates with surgical inpatients are variably reported as higher (and less well treated) (Korczak 2013 **Level IV SR**, 16 studies, n unspecified) or lower (30-56% vs 55-78%) (5 studies, n=5,134), with severe pain prevalence ranging from 7 to 36% (5 studies, n=7,479) (Gregory 2016 **Level IV SR** [PRISMA], 11 studies, n=17,705).

8.6.1 | Acute abdominal pain

Acute abdominal pain may originate from visceral or somatic structures or may be referred; neuropathic pain states should also be considered. Recurrent acute abdominal pain may be a manifestation of a chronic visceral pain disorder such as chronic pancreatitis, pelvic pain or irritable bowel syndrome and will require a multidisciplinary pain management approach.

8.6.1.1 | Analgesia and the diagnosis of acute abdominal pain

A common misconception is that analgesia masks the signs and symptoms of abdominal pathology and should be withheld until a diagnosis is established. Pain relief (usually in the form of opioids) does not interfere with the diagnostic process in acute abdominal pain in adults (Manterola 2011 **Level I**, 8 RCTs, n=922) or in children (Green 2005 **Level II**, n=108, JS 5; Kim 2002 **Level II**, n=60, JS 5) and does not lead to increased errors in clinical management (Ranji 2006 **Level I**, 12 RCTs, n=1,389).

8.6.1.2 | Renal and ureteral colic/stones

Nonselective NSAIDs, opioids (Holdgate 2005b **Level I** [Cochrane], 20 RCTs, n=1,613) and metamizole (dipyrone) (Edwards 2002b **Level I** [Cochrane], 11 RCTs, n=1,053) provide effective analgesia for renal colic. Nonselective NSAIDs reduce requirements for rescue analgesia and cause less vomiting than opioids (particularly pethidine [meperidine]) (Holdgate 2005b **Level I** [Cochrane], 20 RCTs, n=1,613).

Specifically NSAIDs are superior to placebo and to antispasmodics in reducing pain of renal colic and requirements for rescue analgesia; indomethacin was less effective than other NSAIDs (Afshar 2015 **Level I** [Cochrane], 50 RCTs, n=5,734) (7 RCTs overlap with Holdgate 2005b). The combination of NSAIDs with antispasmodics results in better analgesia than NSAIDs alone, but does not show higher responder rates for 50% pain reduction and does not reduce requirements for rescue analgesia further. NSAIDs show a clinically marginal advantage in early pain reduction over opioids (MD –5.58/100; 95%CI –10.22 to –0.95) (11 RCTs, n = 1,985) with reduced rescue requirements and reduced vomiting rates (Pathan 2018 **Level I** [PRISMA], 36 RCTs, n=4,887) (9 RCTs overlap). NSAIDs do not differ for early pain relief vs paracetamol, but reduce rescue requirements.

Onset of analgesia was fastest when nsNSAIDs were administered IV (Tramer 1998 **Level I**, 26 RCTs, n=2,225), although suppositories were also effective (Lee 2005a **Level II**, n=200, JS 3). IV ibuprofen 800 mg was faster and more effective than IV ketorolac 30 mg in controlling pain caused by renal colic (Forouzanfar 2019 **Level II**, n=240, JS 3). Combination IV ketorolac/morphine provided a greater reduction in pain scores, earlier onset of complete pain relief and reduced need for rescue analgesia, vs using either analgesic alone (Safdar 2006 **Level II**, n=130, JS 5).

An overarching network meta-analysis on early pain management in renal colic concludes that NSAIDs are superior to opioids, paracetamol, and combination therapy and NSAIDs with IV or IM route ranked first from efficacy and safety perspectives (Gu 2019 **Level I** [PRISMA] [NMA], 65 RCTs, n=8,633) (many RCTs overlap with previous meta-analyses).

IV paracetamol 1 g provides analgesia for renal colic which is superior to IV morphine (MD -7.5/100; 95%CI -1.99 to -13.00) and comparable to NSAIDs (MD 0.01/100; 95%CI, -0.10 to 0.13) (Sin 2017 **Level I**, 5 RCTs, n=2,020). In contradistinction to their meta-analysed results, the authors advise against paracetamol as an alternative to opioids or NSAIDs in view of the poor quality of the RCTs included (ambiguous description of study protocol, incomplete presentation of data, small sample sizes, and/or methodological flaws).

If opioids are used for renal colic in the ED, there is no difference in clinical efficacy between morphine and pethidine (O'Connor 2000 **Level II**, n=103, JS 5). SL buprenorphine had similar analgesic and adverse effects to IV morphine (Payandemehr 2014 **Level II**, n=69, JS 5). Addition of IV ketamine (0.15 mg/kg or 0.2 mg/kg) to IV morphine (0.1 mg/kg) increased the effectiveness of pain relief and also decreased the rate of nausea, vomiting and use of rescue medication (Hosseininejad 2019a **Level II**, n=22, JS 5; Abbasi 2018 **Level II**, n=106, JS 4). IN ketamine (1 mg/kg) had a slower onset of action vs IV morphine (0.1 mg/kg), but analgesia was comparable after 15 min (Farnia 2017 **Level II**, n=53, JS 4). Addition of low dose naloxone to IV morphine made no difference to analgesia (Hosseininejad 2019b **Level II**, n=150, JS 5).

The smooth muscle relaxant buscopan failed to improve analgesia when combined with nsNSAIDs (Song 2012 **Level II**, n=89, JS 5; Jones 2001 **Level II**, n=59, JS 3), opioids (Holdgate 2005a **Level II**, n=192, JS 4) or metamizole (2 RCTs) (Edwards 2002b **Level I** [Cochrane], 11 RCTs, n=1,053).

IV ketamine 0.6 mg/kg is as effective as IV ketorolac 30 mg in the management of renal colic, but with an increased rate of adverse effects (Sotoodehnia 2019 **Level II**, n=126, JS 3). IV ketamine 0.15 mg/kg combined with IV NSAID lornoxicam 8 mg achieved better pain control with less adverse effects and better functional scores than IV pethidine 50 mg (Metry 2019 **Level II,** n=120, JS 3). Combination IV morphine 0.1 mg/kg with ketamine 0.15 mg/kg vs IV morphine alone improved control of renal colic pain and reduced further opioid requirements in the first 30 min (Abbasi 2018 **Level II**, n=106, JS 4). IN ketamine 1 mg/kg vs IV morphine 0.1 mg/kg resulted in better pain relief in the first 15 min (Farnia 2017 **Level II**, n=40, JS 5).

Papaverine was as effective as IV diclofenac in the initial treatment of renal colic but required increased use of rescue analgesia (Snir 2008 **Level II**, n=90, JS 2). However, as a rescue analgesic, papaverine was of similar efficacy to pethidine and superior to hyoscine in patients who failed to respond to initial treatment with a diclofenac-hyoscine combination (Yencilek 2008 **Level II**, n=110, JS 2).

IV ondansetron produced analgesia in 42% of patients with renal colic but was less effective than IM diclofenac (Ergene 2001 **Level II**, n=64, JS 3).

Ureteral calculus expulsive therapy using alpha-blockers (mainly PO tamsulosin) vs standard therapy reduces the number of pain episodes, the need for analgesic medication and even hospitalisation (Campschroer 2014 **Level I** [Cochrane], 32 RCTs, n=5,864; Hollingsworth 2016 **Level I** [PRISMA] 55 RCTs, n=5,990; Raison 2017 **Level I**, 67 RCTs, n=6,654) (overlap by a majority of RCTs). Tamsulosin was more effective in reducing analgesic requirements than nifedipine in this setting (Ye 2011 **Level II**, n=3,189, JS 2). However, PO tadalafil, a phosphodiesterase-5 (PDE5) inhibitor, resulted in a higher stone expulsion rate than tamsulosin (Kc 2016 **Level II**, n=99, JS 3).

IV lidocaine bolus provided superior analgesia to IV morphine in renal colic (2 RCTs and 1 study) (E. Silva 2018 **Level IV SR** [PRISMA], 6 RCTs & 2 studies, n=536; Masic 2018 **Level IV SR** [PRISMA], 4 RCTs & 9 studies, n=512) (1 RCT overlap). IV lidocaine/ketorolac bolus achieved better analgesia for renal colic patients vs IV lidocaine alone, but not vs IV ketorolac alone (Motov 2019, **Level II,** n=100, JS 3).

The addition of IV magnesium to morphine/ketorolac improved pain control and reduced the need for rescue analgesics (Jokar 2017 **Level II**, n=100, JS 5). However, addition of IV magnesium to ketorolac alone did not improve renal colic pain relief (Maleki Verki 2019 **Level II,** n=87, JS 3).

IV fluid therapy has no effect on pain outcomes or stone transition in renal colic (Worster 2012 **Level I** [Cochrane], 2 RCTs, n=118).

Desmopressin is inferior to NSAIDs in reducing pain of renal colic, but may be a useful adjuvant therapy to opioids based on weak evidence (Jalili 2016 **Level III-1 SR**, 9 RCTs & 1 study, n=1,000).

Intercostal nerve block at T 12 level improved pain vs IM diclofenac from 1 to 45 min (Maldonado-Avila 2017 **Level II**, n=60, JS 2)

TENS applied over the painful flank during prehospital transport reduced pain scores, anxiety and nausea in patients with renal colic (Mora 2006 **Level II**, n=73, JS 4).

The addition of aroma therapy (lavender) to standard treatment of renal colic with parenteral diclofenac improved pain scores at 30 min, but only in female patients (Irmak Sapmaz 2015 **Level II**, n=100, JS 0).

Sexual intercourse (3-4 times/wk) added to standard NSAID therapy prn reduced stone expulsion time, number of colic episodes and need for rescue analgesia in married male patients (Abdel-Kader 2017 **Level II**, n=66, JS 3). Similarly, sexual intercourse (3 to 4 times/wk) vs tamsusoline vs standard medical therapy (control group) increased rate of and reduced time to stone expulsion (Doluoglu 2015 **Level II**, n=90, JS 3).

8.6.1.3 | Biliary colic and acute pancreatitis

In the absence of any patient-specific contraindications, a multimodal analgesic regimen is recommended for the treatment of pain due to biliary colic and acute pancreatitis, including paracetamol, NSAIDs and opioids (Greenberg 2016 **GL**).

All opioids increase sphincter of Oddi tone and bile duct pressures in animal and human experimental models (Thompson 2001 **NR**). Morphine increased sphincter of Oddi contractions more than pethidine during cholecystectomy (Thune 1990 **Level IV EH**, n=36). However, there is no difference in the risk of pancreatitis complications or clinically serious adverse effects between the use of opioids or other analgesic options when treating acute pancreatitis (Basurto Ona 2013a **Level I** [Cochrane], 5 RCTs, n=227). Similarly, a systematic review of parenteral analgesia in acute pancreatitis found mainly RCTs of low (2 RCTs overlap).

NSAIDs for treatment of biliary colic pain result in better pain relief than placebo (5 RCTs) or spasmolytics (4 RCTs) with no difference to opioids (4 RCTs) (Fraquelli 2016 **Level I** [Cochrane], 12 RCTs, n=828). NSAIDs reduce cholelithiasis-related complications (eg acute cholecystitis, acute pancreatitis, jaundice, cholangitis) vs spasmolytic drugs (2 RCTs) but not vs placebo (3 RCT), with inadequate power to confirm no difference vs opioids (1 RCT).

The perioperative use of rectal indomethacin for ERCP reduces the risk of post ERCP pancreatitis (OR 0.49; 95%CI 0.34 to 0.71) vs placebo (NNT 17) (Ahmad 2014 **Level I**, 4 RCTs, n=1,422). This was subsequently confirmed for NSAID use in general via any route of administration with a similar reduction of risk of post ERCP pancreatitis (RR 0.54; 95%CI 0.45 to 0.64) vs controls (Liu 2019a **Level I** [PRISMA], 19 RCTs, n=5,031).

IM atropine was no more effective than saline in the treatment of acute biliary colic (Rothrock 1993 **Level II**, n= 55, JS 4). There is no difference in outcomes including exacerbation of pain between nasogastric and nasojejunal feeding in patients with acute pancreatitis (Chang 2013b **Level I**, 3 RCTs, n=151).

Epidural analgesia improved pain control in severe acute pancreatitis vs IV opioid PCA (Sadowski 2015 **Level II**, n=38, JS 2)

Rhubarb combined with trypsin inhibitor vs trypsin inhibitor alone improves outcome of acute pancreatitis including abdominal pain (Hu 2018 **Level I**, 16 RCTs, n=912).

8.6.1.4 | Irritable bowel syndrome and colic

Bulking agents are not more effective than placebo for treating pain in irritable bowel syndrome (4 RCTs, n=186), while antispasmodics (cimetropium/dicyclomine), peppermint oil, pinaverium and trimebutine (13 RCTs, n=1,392) and antidepressants (TCAs, but not SSRIs) are effective here (8 RCTs, n=517) (Ruepert 2011 **Level I** [Cochrane], 56 RCTs, n=3,725) as well as psychological interventions such as CBT, hypnotherapy, multicomponent psychological therapy, and dynamic psychotherapy (Ford 2014 **Level I,** 32 RCTs, n=2,189) (0 RCT overlap for psychological interventions).

$5HT_3$ antagonists (alosetron and cilansetron) significantly improve global IBS symptoms including abdominal pain and discomfort versus placebo or mebeverine (spasmolytic) (Andresen 2008 **Level I** [QUOROM], 14 RCTS, n=3,024). There is an increased risk of constipation and possibly ischaemic colitis.

Probiotics reduce the pain and symptom severity in IBS vs placebo (Didari 2015 **Level I**, 15 RCTs, n=1,793).

8.6.1.5 | Primary dysmenorrhoea

The management of primary dysmenorrhoea embraces both biological and psychosocial aspects and frequently uses multimodal pharmacological approaches (eg paracetamol, NSAIDs and the oral contraceptive pill). However, there is no evidence base for multimodal intervention with clinical trials restricted to single agents. Women with primary dysmenorrhoea have features of elevated pain sensitivity and reduced pain tolerance vs controls (Payne 2017 **Level III-2 SR EH**, 19 studies, n=1,975 [including 110 men]).

The oral contraceptive pill has limited evidence for better pain relief vs placebo (OR 2.01; 95%CI 1.32 to 3.08) (7 RCTs, n=497), with no differences between different preparations (Wong 2009 **Level I** [Cochrane], 10 RCTs, n unspecified).

Nonselective NSAIDs are more effective analgesics in dysmenorrhoea vs placebo, however withincreased rate of adverse effects (Marjoribanks 2015 **Level I** [Cochrane], 80 RCTs, n=5,820). Nonselective NSAIDs are more effective than paracetamol, with no difference between the different nsNSAIDs with regard to efficacy and safety. Nonselective NSAIDs also reduce bleeding and pain associated with the use of an intrauterine device (Grimes 2006 **Level I** [Cochrane], 15 RCTs, n=2,702).

There is no high-quality evidence to support the effectiveness of any complementary medicine in the treatment of dysmenorrhoea, but there is low quality evidence for effectiveness of some (Pattanittum 2016 **Level I** [Cochrane], 27 RCTs, n=3,101). See also Section 4.14.3.

High-frequency TENS is effective in primary dysmenorrhoea (Proctor 2002 **Level I** [Cochrane], 7 RCTs, n=164). See also Section 7.2.

Acupuncture, acupressure (Smith 2016a **Level I** [Cochrane], 42 RCTs, n=4,640) and acupoint stimulation (Chung 2012 **Level I**, 25 RCTs, n=3,109) reduce pain in primary dysmenorrhoea (vs no treatment or NSAIDs), but the quality of studies is low to very low. See also Section 7.3.

8.6.1.6 | Acute abdominal pain in children

Children and adolescents experience all of the above listed medical causes of abdominal pain.

For discussion of the management of recurrent abdominal pain which is mainly a paediatric disorder (Brusaferro 2018 **NR**), see Section 10.9.4. For the principles of management of abdominal

pain asscociated with vaso-occlusive crises in sickle cell disorder see Section 8.6.4.1 below and for paediatric issues Section 10.9.5. For CAMT interventions for infantile colic see Section 10.11.3.

KEY MESSAGES

1. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain and does not increase the risk of errors in clinical management (**U**) (**Level I** [Cochrane Review]).
2. NSAIDs, opioids and intravenous metamizole (dipyrone) provide effective analgesia for renal colic (**S**) (**Level I** [Cochrane Review]).
3. NSAIDs given for renal colic reduce pain (**N**) (**Level I** [PRISMA]) and rescue analgesia requirements with less vomiting compared with opioids, particularly pethidine (meperidine) (**S**) (**Level I** [Cochrane Review]).
4. Alpha blockers as expulsive therapy for ureteral stones reduce the number of pain episodes and analgesic requirements (**S**) (**Level I** [Cochrane Review]).
5. Antispasmodics and tricyclic antidepressants, but not bulking agents, are effective for the treatment of acute pain in irritable bowel syndrome (**S**) (**Level I** [Cochrane Review]) as well as psychological interventions (**N**) (**Level I**).
6. NSAIDs are effective in primary dysmenorrhoea and superior to paracetamol (**S**) (**Level I** [Cochrane Review]).
7. The smooth muscle relaxant buscopan does not add further analgesic benefit when combined with metamizole (dipyrone) (**U**) (**Level I** [Cochrane Review]), opioids or NSAIDS to treat pain of renal colic (**U**) (**Level II**).
9. High-frequency TENS, possibly some dietary supplements and acupuncture/acupressure are effective in the treatment of primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]).
9. NSAIDS are superior to placebo and spasmolytics and as effective as opioids in the treatment of biliary colic (**S**) (**Level I** [Cochrane Review])
10. The perioperative use of NSAIDs for endoscopic retrograde cholangiopancreatography (ERCP) reduces the risk of post ERCP pancreatitis (**S**) (**Level I** [PRISMA]).
11. $5HT_3$ antagonists reduce some of the symptoms of irritable bowel syndrome (**S**) (**Level I** [QUOROM).
12. The onset of analgesia is faster when NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
13. Intravenous paracetamol is as effective as intravenous morphine and superior to intramuscular piroxicam for analgesia in renal colic (**U**) (**Level II**).
14. There is no difference between pethidine and morphine for analgesia in renal colic (**U**) (**Level II**).
15. Low-dose ketamine is an effective analgesic for renal colic pain (**N**) (**Level II**).
16. IV lidocaine is an effective analgesic for renal colic pain (**N**) (**Level IV SR**).

8.6.2 | Herpes zoster-associated pain

Herpes zoster (shingles) is caused by reactivation of the varicella-zoster virus (VZV), which lies dormant in dorsal root and cranial nerve ganglia following primary infection with chickenpox (varicella), usually in childhood (Le 2019 **NR**). There is a marked increase in the lifetime risk of herpes zoster with increasing age and with diseases and drugs that impair immunity estimated at 30%, with 68% of cases occurring in those aged ≥50 y.

Herpes zoster-associated pain occurs in up to 90% of those affected and may occur before onset of the characteristic rash (during the prodrome), with onset of the rash or following its resolution (Le 2019 **NR**). The pain varies in intensity and may be described as "burning", "throbbing" or "shooting"; itching, dysaesthesias, and allodynia may also be present (Dworkin 2008). In the majority of cases, herpes zoster is an acute self-limiting disease, although it may progress to postherpetic neuralgia (pain that persists for >3 mth after the onset of herpes zoster). The incidence of postherpetic neuralgia increases with age (>50 y), occurring in up to 75% of patients aged ≥70 y who had herpes zoster (Johnson 2004 **NR**). Identified risk factors for the development of postherpetic neuralgia are prodromal pain (RR 2.29; 95%CI 1.42 to 3.69), severe acute pain (RR 2.23; 95%CI 1.71 to 2.92), severe rash (RR 2.63; 95%CI 1.89 to 3.66), and ophthalmic involvement (RR2.51; 95%CI 1.29 to 4.86) (Forbes 2016 **Level III-2 SR**, 19 studies, n=40,238). As previously reported there was an increase with older age; for individual studies, relative risk estimates per 10-year increase ranged from 1.22 to 3.11.

Early, aggressive treatment of herpes zoster infection and pain may reduce the incidence of postherpetic neuralgia, although data on preventive strategies are limited.

Detailed consensus-based guidelines on the treatment of herpes zoster have been published (Werner 2017 **GL**).

8.6.2.1 | Prevention of herpes zoster

Two vaccines are licensed for the prevention of herpes zoster and post-herpetic neuralgia in older adults: Zostavax®, a live attenuated vaccine, and Shingrix®, a recombinant subunit vaccine (Le 2019 **NR**). Zostavax® is still recommended in Australia for adults aged ≥60 y (Australian Vaccines Handbook **GL**) in NZ for adults aged ≥65 y (IMAC 2019 **GL**) and in the UK for adults aged 70-79 y. In the US, the US Advisory Committee on Immunization Practices (ACIP) updated its guidance and now recommends Shingrix® for adults aged ≥50 y (Dooling 2018 **GL**).

Zostavax® is effective in the prevention of herpes zoster (and thereby postherpetic neuralgia) in individuals aged >60 y (Gagliardi 2012 **Level I**, 8 RCTs, n=52,269). A large, multicentre, randomised placebo-controlled trial (The Shingles Prevention Study) demonstrated the vaccine's efficacy, with the incidence of herpes zoster reduced by 51.3%, that of postherpetic neuralgia by 66.5 % and herpes zoster-associated "burden of illness" by 61.1% (Oxman 2005 **Level II**, n=38,546, JS 4). The estimated number needed to vaccinate to prevent a case was 11 (95%CI 10 to 13) for herpes zoster and 43 (95%CI 33 to 53) for postherpetic neuralgia (Brisson 2008 **Level III-3**). Zostavax is less effective with increasing age and its efficacy wanes 10 y after vaccination (Morrison 2015 **Level IV**, n=6,867).

Shingrix® is a newer vaccine with substantially higher efficacy than Zostavax® (Syed 2018 **NR**) reducing the risk of herpes zoster infection by 97% vs placebo, with mean follow-up duration of 3.2 y (Lal 2015 **Level II**, n=15,411, JS 5). Unlike Zostavax®, the efficacy of Shingrix® was higher for patients over 70 y of age and reduced the incidence of postherpetic neuralgia by 88.8% (Cunningham 2016 **Level II**, n=13,900, JS 5). Protection, however, declines slightly four y after vaccination with long term efficacy unknown (Morrison 2015 **Level IV**, n=6,867). As it is not a live vaccine, Shringrix® should be theoretically safe to administer to immunocompromised

patients, unlike Zostavax®, though no recommendations have been made for vaccinating this group (Le 2019 **NR**; Syed 2018 **NR**).

8.6.2.2 | Treatment of acute herpes zoster-associated pain

Around 95% of patients will present with acute pain; processes of neuroinflammation are in part responsible for the acute pain state (Werner 2017 **GL**).

Antiviral agents

Antiviral agents should be considered in all patients with acute herpes zoster, in particular those who have severe disease, are over 50 y of age, immunocompromised, or have evidence of trigeminal nerve involvement (Werner 2017 **GL**; Le 2019 **NR**). Acyclovir (Wood 1996 **Level I**, 4 RCTs, n=691), valaciclovir (Beutner 1995 **Level II**, n=1,141, JS 5) or famciclovir (Tyring 2000 **Level II**, n=597, JS 5), given within 72 h of rash onset, accelerated the resolution of acute herpes zoster pain. Famciclovir, in various doses and frequencies, was as effective as acyclovir for herpes zoster-related outcomes including acute pain, with fewer adverse effects (Gopal 2013 **Level II**, n=100, JS 2; Shafran 2004 **Level II**, n=559, JS 5; Shen 2004 **Level II**, n=55, JS 5). Famciclovir or valaciclovir have replaced acyclovir as the drugs of choice in the treatment of herpes zoster because of more favourable pharmacokinetics and simpler dosing profiles (Cunningham 2008 **NR**). FV-100, a prodrug for the bicyclic nucleoside analogue CF-1743 with high specificity for the VZV showed faster resolution of clinically significant pain vs valaciclovir (Tyring 2017 **Level II**, n=450, JS 5).

Systemic analgesics

For mild herpes zoster-associated pain, simple analgesics such as paracetamol and NSAIDs such as ibuprofen are regarded as sufficient (Le 2019 **NR**). Multimodal analgesia with regular non-opioids, in addition to an opioid such as oxycodone or tramadol as required, has been recommended for more severe pain (Werner 2017 **GL**; Cunningham 2008 **NR**; Dworkin 2007 **NR**; Dwyer 2002 **NR**).

Oxycodone CR, but not gabapentin, effectively reduced the average worst pain during the first 14 d of herpes zoster vs placebo, although oxycodone-treated patients had higher withdrawal rates from the trial, primarily because of constipation (Dworkin 2009 **Level II**, n=87, JS 5).

Corticosteroids

Prednisolone added to acyclovir for acute herpes zoster minimally reduced pain intensity but improved the rate of skin lesion healing for up to 14 d, with no effect on the overall recovery rate at 3 wk (Wood 1994 **Level II**, n=400, JS 4). A later trial showed prednisolone, either as monotherapy or in combination with acyclovir, increased the likelihood of being “pain-free” at 1 mth by a factor of 2.3 (95%CI 1.4 to 3.5), with no difference in the rate of skin healing vs placebo (Whitley 1996 **Level II**, n=208, JS 4).

Anticonvulsants

A single dose of gabapentin 900 mg during herpes zoster reduced acute pain intensity by 66% (33% for placebo) and also reduced the area and severity of allodynia, for up to 6 h (Berry 2005 **Level II**, n=26, JS 5). When given in divided doses between 300 to 900 mg/day within 72 h of onset of rash, gabapentin reduced pain by 26 to 38% after 4 wk (Kanodia 2012, **Level II,** n=52, JS 3). This was also found with pregabalin 150 mg (Jensen-Dahm 2011 **Level II**, n=8, JS 5). However, one study showed no analgesic benefit was found when gabapentin up to 1,800 mg daily was administered for 28 d (Dworkin 2009 **Level II**, n=87, JS 5) or with pregabalin 150 to 300 mg daily for 3 wk (Krcevski Skvarc 2010 **Level II**, n=29, JS 3).

Topical lignocaine

Topical lignocaine patches (5%) applied for 12 h twice daily (on intact skin) during acute herpes zoster reduced pain intensity and improved patients' global impression of pain relief, vs a vehicle patch: the incidence and severity of adverse effects was low (Lin 2008 **Level II**, n=46, JS 5).

Aspirin

Topical aspirin, in either moisturiser or diethyl ether, was an effective analgesic in acute herpes zoster, vs similar preparations containing indomethacin, diclofenac or placebo (De Benedittis 1996 **Level II**, n=37, JS 3) or oral aspirin (Balakrishnan 2001 **Level II**, n=45, JS 3).

Neuraxial or sympathetic block

Nerve blocks in general for acute herpes zoster vs standard treatment without nerve blocks reduce duration of acute pain (MD −13.68 d; 95%CI −18.70 to −8.66) (1 RCT [2 stellate ganglion blocks LA/dexamethasone 1 wk apart]; 1 RCT [continuous PVB]; 1 study [continuous epidural analgesia]) (Kim 2017a **Level I**, 8 RCTs & 1 study, n=1,645).

Acupuncture and moxibustion

Based on data from one RCT for each outcome, acupuncture and moxibustion reduces acute pain of herpes zoster and its duration with questionable clinical significance (Coyle 2017 **Level I**, 9 RCTs, n=945).

8.6.2.3 | Prevention of postherpetic neuralgia

Immunisation of persons aged ≥60 y with live attenuated VZV vaccine reduces the incidence of herpes zoster and thereby the incidence of postherpetic neuralgia; however there is no evidence that the immunisation prevents postherpetic neuralgia beyond this effect (Chen 2011 **Level I** [Cochrane], 1 RCT, n=38,546).

The use of acyclovir does not significantly reduce the incidence of postherpetic neuralgia at 6 mth (Chen 2014 **Level I** [Cochrane], 6 RCTs, n=1,211). There is insufficient evidence to determine the preventive effects of other antiviral agents.

Similarly, systemic corticosteroids (Han 2013 **Level I** [Cochrane], 5 RCTs, n=787) are ineffective preventive strategies in postherpetic neuralgia.

Nerve blocks in general for acute herpes zoster vs standard treatment without nerve blocks reduce the incidence of PHN at 3 mth (RR 0.43; 95%CI 0.25 to 0.7) (7 RCTs and 1 study), at 6 mth (RR 0.41; 95%CI 0.2 to 0.83) (6 RCTs) and at 12 mth (RR 0.17; 95%CI 0.1 to 0.28) (2 RCTs) (Kim 2017 **Level I,** 8 RCTs & 1 study, n=1,645). With regard to specific blocks, stellate ganglion blocks (3 RCTs) and single epidural block had no preventive effect (1 RCT), while repeated or continuous epidural (2 RCTs, 1 study) and paravertebral analgesia (2 RCTs) have a preventive effect.

During acute herpes zoster, the early administration of amitriptyline (25 mg for 90 d) significantly reduced the incidence of postherpetic neuralgia at 6 mth (Bowsher 1997 **Level II**, n=80, JS 4).

KEY MESSAGES

1. Antiviral agents started within 72 hours of onset of the herpes zoster rash accelerate the resolution of acute pain (**U**) (**Level I**) but do not reduce the incidence, severity and duration of postherpetic neuralgia (**U**) (**Level I** [Cochrane Review]).
2. Immunisation of persons aged 60 years or older reduces the incidence of herpes zoster and thereby postherpetic neuralgia with Zostavax® (**U**) (**Level I** [Cochrane Review]) and Shingrix® (**N**) (**Level II**).
3. Continuous or repeated paravertebral blocks in the acute phase of herpes zoster reduce the incidence of postherpetic neuralgia at 3, 6 and 12 months (**N**) (**Level I**).
4. Amitriptyline (used in low doses for 90 days from onset of the herpes zoster rash) reduces the incidence of postherpetic neuralgia (**U**) (**Level II**).
5. Topical aspirin, topical lignocaine patch or controlled-release oxycodone provide analgesia in acute pain due to herpes zoster (**U**) (**Level II**).
6. Nerve blocks in the acute phase of herpes zoster reduce the duration of herpes zoster-associated pain (**N**) (**Level III-I SR**).
6. Continuous epidural analgesia in the acute phase of herpes zoster reduces the incidence of postherpetic neuralgia at 3 months (**N**) (**Level III-I SR**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Provision of early and appropriate analgesia is an important component of the management of herpes zoster and may have benefits in reducing the incidence of postherpetic neuralgia (**U**).

8.6.3 | Acute cardiac pain

Acute coronary syndrome refers to a range of acute myocardial ischaemic states including unstable angina and myocardial infarction. Typically, myocardial ischaemia causes central chest pain, which may radiate into the arm, neck or jaw; nontypical presentations can occur, particularly in the elderly patient (see also Section 9.2). Reducing ischaemia by optimising myocardial delivery, reducing myocardial oxygen consumption and restoring coronary blood flow will reduce ischaemic pain and limit myocardial tissue damage. The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation as outlined above.

Inhaled oxygen does not reduce all-cause mortality in acute myocardial infarction and also does not reduce chest pain measured directly or by surrogate outcome of opioid requirements (Cabello 2016 **Level I** [Cochrane], 5 RCTs, n=1,172). The meta-analysis could not rule out a potentially harmful effect. These findings are confirmed by a subsequent meta-analysis, which showed that oxygen therapy does not reduce the risk of in-hospital or 30-day mortality, infarct size or chest pain in patients with suspected AMI (Sepehrvand 2018 **Level I** [PRISMA], 8 RCTs, n=7,998) (5 RCTs overlap). Current guidelines by the Australian and New Zealand Cardiology Society (Chew 2016 **GL**) and by NICE (NICE 2016b **GL**) state that the use of supplemental oxygen is not recommended unless hypoxia (oxygen saturation [SaO_2] <94%) is present. In acute coronary syndrome, hyperbaric oxygen therapy reduced time to relief of ischaemic pain, although insufficient evidence exists to recommend its routine use (Bennett 2011a **Level I**, 6 studies, n=665).

Nitroglycerine (glyceryl trinitrate) was effective in relieving acute ischaemic chest pain; however, the analgesic response did not predict the diagnosis of coronary artery disease (Henrikson 2003 **Level IV**, n=459). During exercise testing, nitroglycerine caused changes in the systemic and coronary circulation that combine to reduce myocardial oxygen demand and to increase supply, thereby attenuating exercise induced ischaemia (Asrress 2017 **Level IV EH**, n=40). The Australian and New Zealand Cardiology Society (Chew 2016 **GL**) and NICE (NICE 2016b **GL**) provide recommendations to use nitrates to alleviate symptoms including pain in acute coronary syndrome.

In patients with suspected acute coronary syndrome, IV morphine significantly reduced pain within 20 min of administration (Everts 1998 **Level IV**, n=2,988); morphine doses were low (average of 7 mg over 3 d) and 52% of patients required no morphine at all. Independent predictors of increased morphine requirements included suspicion or confirmation of infarction, ST-segment changes on the admission electrocardiogram, male sex and a history of angina or cardiac failure. After an initial dose of IV metoprolol, IV morphine provided better analgesia than further IV metoprolol (Everts 1999 **Level II**, n=265, JS 4). It was associated with better cardiovascular outcomes during acute hospital admission and later follow-up, vs a fentanyl/droperidol mixture administered early in the treatment of patients with acute ischaemic chest pain (Burduk 2000 **Level II**, n=112, JS 2). IV bolus doses of morphine and alfentanil were equally effective in relieving acute ischaemic chest pain but the onset of analgesia was faster with alfentanil (Silfvast 2001 **Level II**, n=40, JS 2). Morphine was similar to buprenorphine (Weiss 1988 **Level II**, n=76, JS 3) and pethidine (Nielsen 1984 **Level II**, n=275, JS 4) in terms of analgesia and adverse effects. IN fentanyl and IV morphine were equally effective in reducing acute cardiac chest pain during prehospital transfer (Rickard 2007 **Level II**, n=258, JS 3).

However regarding impact on antiplatelet therapies, IV fentanyl lowered plasma concentrations of ticagrelor and delayed its antiplatelet function in patients undergoing PCI (McEvoy 2018 **Level II**, n=70, JS 3). Similarly, morphine decreased clopidogrel plasma concentrations and its effect (Hobl 2014 **Level II EH**, n=24, JS 5) and decreased ticagrelor (Hobl 2016a **Level II EH**, n=24, JS 5) and prasugrel plasma concentrations without affecting their antiplatelet effects (Hobl 2016b **Level II EH**, n=12, JS 5). On the other hand, morphine co-administered with metoclopramide in

patients with unstable angina resulted in significantly higher ticagrelor mean plasma concentrations within the first one and two h following loading dose (Sikora 2018 **Level II**, n=32, JS 3). Overall, morphine administration before loading with P2Y12 inhibitors (prasugrel or ticagrelor) possibly decreases their efficacy with regard to platelet inhibition and reduces ticagrelor plasma concentrations without a negative effect on a composite endpoint of in-hospital mortality, stroke and reinfarction (Vaidya 2019 **Level III-2 SR**, 8 studies, n=752).

The Australian and New Zealand Cardiology Society (Chew 2016 **GL**) and NICE (NICE 2016b **GL**) recommend IV morphine (or other IV opioids eg fentanyl) for treatment of chest pain in acute coronary syndrome. However, a subsequent meta-analysis with high risk of bias identified concerns with the use of morphine in acute coronary syndrome (Duarte 2019 **Level III-2 SR** [PRISMA], 5 RCTs, n=2,237 & 12 studies, n=63,112). The pooled results show associations between morphine administration and an increased in-hospital mortality (RR 1.45; 95%CI 1.10 to 1.91), major adverse cardiovascular events (RR 1.21; 95%CI 1.02 to 1.45) and increased platelet reactivity. However, in two cohort studies, prehospital use of morphine vs non-use was not associated with worse in-hospital complications or 1 y survival (HR 0.69; 95%CI 0.35 to 1.37) (Puymirat 2016 **Level III-3**, n=2,438+1,726).

In patients with chest pain due to cocaine-induced acute coronary syndrome, the addition of IV diazepam or lorazepam to treatment with SL nitroglycerine wasbeneficial (Honderick 2003 **Level II**, n=36, JS 3) or made no difference to chest pain resolution or cardiac performance (Baumann 2000 **Level II**, n=43, JS 5).

N_2O in oxygen was effective in relieving acute ischaemic chest pain, with a significant reduction in betaendorphin levels (O'Leary 1987 **Level II**, n=12, JS 2).

NSAIDs may be useful in the treatment of acute pain in pericarditis (Schifferdecker 2003 **NR**).

KEY MESSAGES

1. The routine use of oxygen in normoxic patients with acute myocardial infarction does not reduce pain or mortality (**S**) (**Level I** [Cochrane].
2. Morphine is an effective and appropriate analgesic for acute cardiac pain, but may interfere with pharmacokinetics and pharmacodynamics of some platelet inhibitors (**Q**) (**Level II**).
3. Nitroglycerine is an effective and appropriate agent in the treatment of acute ischaemic chest pain (**S**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation, nitroglycerine, beta blockers and strategies to improve coronary vascular perfusion (**U**).

8.6.4 | Acute pain associated with haematological disorders

8.6.4.1 | Sickle cell disease

Sickle cell disease (SCD) includes a group of inherited disorders of haemoglobin production. Haemoglobin S polymerises when deoxygenated, causing rigidity of the erythrocytes, blood hyperviscosity and occlusion of the microcirculation with resultant tissue ischaemia and infarction (Niscola 2009 **NR**).

Sickle cell disease is a systemic multiorgan disease that most commonly presents with painful vaso-occlusive crises (VOC), occurring either spontaneously or due to factors such as dehydration, infection, hypothermia and low oxygen tension. There is considerable interindividual variability in the frequency and severity of crises. Pain during an acute VOC is typically severe, in multiple sites and most frequently reported in the arm, shoulder, upper back, sternum, clavicle, chest and pelvis (McClish 2009 **Level IV**, n=308). Pain may last from hours to weeks. VOCs involving abdominal organs can mimic an acute surgical abdomen. Acute chest syndrome secondary to SCD may present with chest pain, cough, dyspnoea and fever (Niscola 2009 **NR**). An evidence-based approach and detailed consensus guidelines to the management of VOC in SCD are published (NICE 2012b **GL**; Glassberg 2011 **GL**; Mousa 2010 **GL**).

Treatment of pain

Biopsychosocial assessment and multidisciplinary pain management may be required when treating patients with frequent, painful sickle cell crises. Attendance to a multidisciplinary clinic specialising in the management of patients with SCD reduced hospitalisations and improved quality of life (Terry 2018 **Level III-3**, n=30). A pain management plan in the form of a letter, card or portfolio carried by the patient is recommended (Rees 2003 **GL**). The implementation of clinical practice guidelines (Morrissey 2009 **Level III-3**, n=263 [children]) or a clinical pathway (Ender 2014 **Level III-3**, n=68) for acute pain treatment in VOC leads to more timely and effective analgesia. An individualised pain management plan results in improved pain control, a higher level of patient satisfaction and reduced hospitalisations in children (Krishnamurti 2014 **Level III-2**). Underdosing of pain medication leads to a higher rate of ED visits for pain (Morrison 2018 **Level III-3**, n=100). Early achievement of maximum analgesia improved hospitalisation outcomes (Payne 2018 **Level III-3**, n=236).

NSAIDs

Single-dose parenteral ketorolac did not reduce opioid requirements in painful VOC (Hardwick 1999 **Level II**, n=41, JS 5; Wright 1992 **Level II**, n=24, JS 5). Patients who receive ketorolac for pain may be at risk of acute kidney injury and subsequently require longer periods of hospitalisation (Baddam 2017 **Level III-3**, n=197).

Opioids

Opioids are an integral component of treatment regimens for patients suffering from debilitating acute pain from SCD (Rodday 2018 **Level III-3**, n=449). Pain from a VOC is often undertreated in the hospital setting due to perceived opioid addiction and drug seeking behaviour despite a similar incidence of opioid addiction in the general population (Pack-Mabien 2001 **Level III-3**, n=77 [nurses]). Higher initial doses of opioids in the Emergency Department (ED) along with earlier introduction of oral opioids in a VOC results in significantly shorter hospital LOS and improved outcomes (Brandow 2015 **Level II**, n=204, JS 4). However, it is important to consider opioid tolerance in these patients as a large cohort study reported 40% of patients with SCD were taking regular opioid analgesics (Han 2018 **Level III-2**, n=3,882).

In the hospital setting, IV opioids are recommended for severe pain (NICE 2012b **GL**). When treating acute pain during a sickle cell crisis, IV opioid loading improved the analgesic efficacy of subsequent oral and PCA opioid therapy (Rees 2003 **GL**). PCA only was superior to background infusions only and PCA with background infusion as it reduced total opioid dose, total time on PCA , opioid-related adverse effects and hospital LOS (van Beers 2007 **Level II**, n=19, JS 2). Although IV opioid PCA is widely accepted in the management of acute pain in sickle cell disease, oral opioids are also effective. In one paediatric RCT, oral sustained-release morphine for acute pain was just as effective as a continuous IV morphine infusion (Jacobson 1997 **Level II**, n=56, JS 5). However, in children, the incidence of acute sickle chest syndrome (a severe complication in sickle cell crisis) and plasma levels of morphine and M6G, were significantly higher with oral morphine vs IV infusion (Kopecky 2004 **Level II**, n=50, JS 4). IN fentanyl was a suitable alternative in the ED to reduce time to initiation of opioid analgesic therapy, however did not reduce the need for IV opioid analgesia (Kelly 2018a **Level III-2**).

Care must be taken when prescribing opioids for the treatment of pain in SCD. In a review of 35 patients who died in hospital following an exacerbation of SCD, 9 received excessive opioids and "overdose" directly contributed to death in 5 patients (NCEPOD 2008 **Level IV**). Inadequate observations of sedation and respiratory rates after opioid administration was noted as a contributing factor and IM pethidine administration was prevalent.

Corticosteroids

Parenteral corticosteroids reduce the duration of severe pain and analgesia requirements and hospital LOS during VOC without major adverse effects (Dunlop 2006 **Level I** [Cochrane], 9 RCTs, n unspecified). In children, a short course of high dose IV methylprednisolone decreased the duration of severe pain associated with acute sickle cell crises, but patients who received methylprednisolone had more rebound attacks after therapy was discontinued (Griffin 1994 **Level II**, n=36, JS 5).

Ketamine

Low-dose ketamine improved analgesia and reduced opioid requirements (Puri 2019 **Level III-3**, n=4; Tawfic 2014 **Level IV**, n=9; Uprety 2014 **CR**). This approach is also suggested for paediatric patients (Neri 2013a **NR**); here a single sub-dissociative dose of ketamine given IV over 10 min was a suitable alternative to morphine for acute exacerbations of pain during a VOC (Lubega 2018 **Level II**, n=240, JS 5).

Dexmedetomidine

Dexmedetomidine may have a role in the management of recalcitrant pain due to VOC as infusions for up to 6 d duration reduced opioid requirements and pain scores without adverse haemodynamic effects (Sheehy 2015 **Level IV**, n=3).

Inhaled nitric oxide

Nitric oxide deficiency or defective nitric oxide-dependent mechanisms may underlie many of the processes leading to VOC. An early paediatric study suggested inhaled nitric oxide may be of benefit in painful acute VOC (Weiner 2003 **Level II**, n=25, JS 4); however in young adults admitted with VOC, there was no difference between inhaled nitric oxide vs nitrogen placebo in time to VOC resolution or LOS (Gladwin 2011 **Level II**, n=150**,** JS 5).

Inhaled nitrous oxide

Inhaled N_2O in 50% oxygen used for limited periods may provide analgesia for VOC pain in the primary-care setting (Rees 2003 **GL**).

Oxygen

Although oxygen supplementation is often prescribed during acute sickle cell crises, there was no difference in pain duration, number of pain sites or opioid consumption in patients treated with either air or oxygen (Robieux 1992 **Level II**, n=66, JS 2; Zipursky 1992 **Level II**, n=28, JS 3). However, nocturnal oxygen desaturation was associated with a significantly higher rate of painful VOC in children (Hargrave 2003 **Level IV**, n=95). Hyperbaric oxygen therapy was effective in reducing pain of VOC rapidly (Stirnemann 2012 **Level III-3**, n=9).

Rehydration

While commonly practiced, there is no evidence to support fluid replacement therapy to reduce pain associated with sickle cell crises (Okomo 2017 **Level I** [Cochrane], 0 RCTs, n=0).

Epidural analgesia

In severe crises, where pain is unresponsive to pharmacological measures, epidural analgesia has been used effectively in nine paediatric patients (Yaster 1994 **Level IV**, n=9). Epidural analgesia has also been described in a pregnant patient with poorly responsive pain from VOC (Winder 2011 **CR**).

Intravenous lidocaine

IV lidocaine Infusions (1 mg/kg/h to 1.3 mg/kg/h) for treating pain of SCD achieved more than 20% pain reduction in 53% of patients, while opioid requirements were reduced by 32% (Nguyen 2015 **Level IV**, n=11). These findings are confirmed in a subsequent study (Puri 2019 **Level III-3**, n=4).

Magnesium Sulphate

IV magnesium or oral magnesium therapy has been shown to have no effect on reducing pain during painful crises in SCD or hospital LOS (Than 2019 **Level I** [Cochrane], 5 RCTs, n=386).

Non-pharmacological management

Yoga in children admitted with VOC has demonstrated significant reduction in pain scores (Moody 2017 **Level II,** n=73, JS 1).

Based on limited evidence, there may be an effect of CBT on pain in SCD (1 RCT, n=59) (Anie 2012 **Level I** [Cochrane], 5 RCTs, n=260). In young adults, CBT reduced the affective (not sensory) component of pain (MD -0.99; 95% CI -1.62 to -0.36) but with no benefit for coping strategies (1 RCT, n=59).

Prevention of painful sickle cell crises

Hydroxyurea acts to increase fetal haemoglobin levels. It has demonstrated efficacy in reducing the frequency of acute crises, the severity of pain during an acute crisis, the need for blood transfusions and the incidence of acute chest syndrome (Nevitt 2017 **Level I** [Cochrane], 8 RCTs, n=899). Zinc supplementation reduces the incidence of painful sickle cell crises (Nagalla 2012 **Level I** [Cochrane], 3 studies, n=524). Niprisan (an anti-sickling agent) reduces the frequency of crises with severe pain (Wambebe 2001 **Level II**, n=82, JS 4) while the evidence for piracetam is insufficient to support its use (Al Hajeri 2016 **Level I** [Cochrane], 3 RCTs, n=169).

8.6.4.2 | Haemophilia

Deficiency of Factor VIII (haemophilia A) and deficiency of Factor IX (haemophilia B) are inherited disorders of coagulation characterised by spontaneous and post-traumatic haemorrhages, the frequency and severity of which are proportional to the degree of clotting factor deficiency. Bleeding into joints and muscle is common, although other sites such as abdominal organs may also be involved. In haemophilic arthropathy, the most frequent sites of pain are the ankle joints (45%), knee joints (39%), spine (14%) and elbow joints (7%) (Wallny

2001 **Level IV**, n=71). Pain is significantly associated with age and severity of disease (Rambod 2016 **Level III-3**, n=154). Patients with haemophilia presenting with acute pain have a background of chronic pain in 29% of cases (Witkop 2017 **Level III-3**, n=764 [haemophilia]). Patients with haemophilia may also have pain syndromes associated with HIV/AIDS (see Section 8.6.8). Recurrent acute pain may have a significant adverse impact on mood, mobility and QoL in haemophilia patients; biopsychosocial assessment and treatment should be considered (Wallny 2001 **Level IV**, n=71).

The following five features should be considered in the treatment of acute pain resulting from haemarthrosis; haematologic treatment, short-term rest of the involved joint, cryotherapy, joint aspiration and analgesic medication (Rodriguez-Merchan 2018 **NR**). Many haemophilia patients use Factor VIII to decrease pain associated with a bleeding episode (Wallny 2001 **Level IV**, n=71). Higher-dose Factor VIII replacement reduced the number of patients with restricted joint movement after an acute haemarthrosis (Aronstam 1983 **Level II**, n=114, JS 4). Despite this, approximately 30% of patients experience ongoing pain after the infusion of Factors VIII or IX (Rodriguez-Merchan 2018 **NR**). Joint aspiration may reduce pain and improve joint function (Baker 1992 **NR**).

Although there is no good evidence available, simple analgesics, opioids, cryotherapy and bandaging have been used in treating acute pain associated with haemophilia. In a Europe-wide survey, the preferred first-line drug was paracetamol for children and paracetamol or NSAIDs for adults (Holstein 2012 **Level IV**, n=5,103 [adults] & n=1,678 [children]). There are no data on NSAID use in acute haemarthrosis; coxibs may be of benefit due to a lack of platelet inhibitory effects (see Section 4.2.2.2). Pregabalin and gabapentin are increasingly used as part of a multimodal analgesia approach despite lack of evidence to support their use in this clinical setting (Powell 2014 **Level IV**). IM analgesics should be avoided due to the risk of bleeding.

8.6.4.3 | The porphyrias

The acute porphyrias are a group of inherited disorders of haem biosynthesis. The most common autosomal dominant forms are acute intermittent porphyria, variegate porphyria and hereditary coproporphyria. The disorder of haem biosynthesis leads to accumulation of neurotoxic aminolaevulinic acid and porphyrin metabolites, which can result in peripheral, visceral and autonomic neuropathies (eg clinical features might include motor weakness, abdominal pain and tachycardia) as well as CNS toxicity (neuropsychiatric symptoms, seizures, brainstem and pituitary dysfunction); some patients may have a cutaneous photosensitivity (Visser 2008 **NR**).

Pain management in acute porphyria is based on treatment of the disease, including resuscitation and supportive care, ceasing "triggers", the early administration of haematin (Herrick 1989 **Level II**, n=12, JS 4) and possibly high-dose IV dextrose or cimetidine administration ("*disease modifying agents*") (Rogers 1997 **NR**).

Specific evidence for pain management in acute porphyria is limited. Analgesia is based largely on the use of IV and (later) oral opioids (Anderson 2005 **NR**; Herrick 2005 **NR**). Analgesics that lower seizure threshold such as pethidine (Deeg 1990 **CR**) or tramadol and others (such as TCAs) should be avoided in acute porphyria because of increased seizure risk.

The safety of NSAIDs or coxibs in acute porphyria has not been established; paracetamol, buscopan (for colic) or inhaled N_2O in oxygen are considered safe (Anderson 2005 **NR**; Stoelting 1993 **NR**).

There may be a place for low-dose IV ketamine or regional analgesia, although the safety of these approaches has not been established in acute porphyria. Ketamine does not induce aminolaevulinic acid synthetase in rats (Harrison 1985 **BS**) and has been used for anaesthesia in porphyria patients without apparent problems (Capouet 1987 **CR**). However, one case report

noted increased porphyrin levels in a patient after induction with ketamine (Kanbak 1997 **CR**). A combined spinal epidural technique has been described in patients with porphyria undergoing Caesarean section with epidural analgesia continued in the postoperative period minimising IV opioid requirements (Horvat 2015 **Level IV**, n=2). As metoclopramide is contraindicated and the safety of $5HT_3$ antagonists is as yet unclear, droperidol has been suggested as the antiemetic of choice in acute porphyria (Anderson 2005 **NR**).

KEY MESSAGES

1. Parenteral corticosteroids reduce the duration of severe pain, analgesia requirements and hospital length of stay, without major adverse effects, during vaso-occlusive crises in sickle cell disease (**U**) (**Level I** [Cochrane Review]).
2. There is no evidence that fluid replacement therapy (**S**) or intravenous or oral magnesium reduces pain associated with vaso-occlusive crises in sickle cell disease (**N**) (**Level I** [Cochrane Review]).
3. Hydroxyurea decreases the frequency of vaso-occlusive crises, life-threatening complications and transfusion requirements in sickle cell disease (**S**) (**Level I** [Cochrane Review]).
4. Zinc reduces the incidence of painful vaso-occlusive crises in sickle cell disease (**U**) (**Level I** [Cochrane Review]).
5. Intravenous opioid loading optimises analgesia in the early stages of a vaso-occlusive crisis in sickle cell disease; effective analgesia may be continued with intravenous opioid therapy, optimally as PCA, or as oral opioids (**S**) (**Level II**).
6. Single-dose ketorolac does not reduce opioid requirements in vaso-occlusive crisis in sickle cell disease (**N**) (**Level II**), but may increase the risk of acute kidney injury (**N**) (**Level III-3**).
7. Oxygen supplementation does not decrease pain during a vaso-occlusive crisis in sickle cell disease (**U**) (**Level II**), but hyperbaric oxygen may be effective (**U**) (**Level III-3**).
8. Intravenous ketamine and intravenous lidocaine reduced pain intensity and opioid requirements in vaso-occlusive crisis in sickle cell disease (**N**) (**Level IV**).

8.6.5 | Acute headache

Headaches are a common cause of acute pain. Headaches may be primary or secondary. There are many causes of acute headache, some of which involve structures other than the head (eg the neck). Before treating acute headache, it is vital to exclude serious cranial pathologies such as tumour, infection, cerebrovascular abnormalities, acute glaucoma and temporal arteritis (Silberstein 2000 **GL**; Steiner 2002 **NR**).

The most frequent causes of acute primary headache are episodic tension type headaches (TTH) and migraine (Headache Classification Committee 2018 **GL**). Less common primary headaches are trigeminal autonomic cephalalgias (episodic cluster headache, episodic paroxysmal hemicrania and Short lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing [SUNCT]) or "secondary headaches", such as acute post-traumatic headache, postdural puncture headache (PDPH), headache attributed to substance use or its withdrawal and cervicogenic headache.

Comprehensive guidelines for the evaluation and treatment of acute headaches including migraine have been promulgated (Diener 2019 **GL**; Pringsheim 2016 **GL**; Marmura 2015 **GL**; Beithon 2013 **GL**; Worthington 2013 **GL**) including for children and adolescents (see Section 10.9.3).

8.6.5.1 | Tension-type headache

TTH may be episodic (frequent or infrequent) or chronic in nature. The lifetime prevalence of TTH in the general population is between 30 and 78%. Episodic TTH is usually bilateral and is often described as mild to moderate "pressing" or "tight" pain (sometimes with pericranial tenderness), not worsened by movement and not associated with nausea or vomiting. Photophobia or phonophobia may occasionally be present but not both (Headache Classification Committee 2018 **GL**).

The symptoms and pathogenesis of TTH may overlap with migraine and particularly with chronic daily headache, medication overuse headache and cervicogenic headache (NICE 2012a **GL**). Psychological, physical and environmental factors are important in TTH and should be addressed during assessment and treatment (Bougea 2013 **Level II**, n=35, JS 3; NICE 2012a **GL**; Bendtsen 2010 **GL**).

TTHs are frequently self-limiting with total duration under 12 h in many cases. Therefore, the efficacy of various treatments should be assessed against the background of natural history. The acute adverse effects and the propensity for analgesic medications to transform intermittent headaches to a chronic daily pattern must be considered in relation to choice of agents (Barbanti 2014 **NR**). Evidence-based guidelines for TTH treatment are published (Bendtsen 2010 **GL**).

Treatment

The NNTs for patients with TTH being pain free at 2 h vs placebo are similar for all oral analgesics in the range of 8.7–9.8 for paracetamol 1,000 mg (5 RCTs, n=1,387), ibuprofen 400 mg (3 RCTs, n=826) and ketoprofen 25 mg (2 RCTs, n=285) (Moore 2014 **Level I** [PRISMA], 55 RCTs, n=12,143).

In a meta-analysis of RCTs including a paracetamol arm, the NNT for 1000 mg vs placebo for being pain free at 2 h is higher at 22 (95%CI 15 to 40) (8 RCTs, n=5,890) and the NNT for less frequent rescue medication was 7.8 (95%CI 6.0 to 11) (6 RCTs, n=1,856) (Stephens 2016 **Level I** [Cochrane], 23 RCTs, n=8,079) (possible 22 RCTs overlap). Based on limited data, the efficacy of paracetamol 500 mg to 650 mg was not superior to placebo, and paracetamol 1000 mg was not different from either ketoprofen 25 mg or ibuprofen 400 mg.

A single dose of aspirin between 500 mg and 1000 mg provides some benefit in terms of less frequent use of rescue medication (NNT 6.0; 95%CI 4.1 to 12) and more participants satisfied

with treatment vs placebo (NNT 5.7; 95%CI 3.7 to 12) (Derry 2017a **Level I** [Cochrane], 5 RCTs, n=1,812) (3 RCTs overlap with Stephens 2016). The quality of the evidence is low and was downgraded because of the small number of studies and events, and because the most important measures of efficacy were not reported.

A paracetamol/aspirin/caffeine combination is superior to paracetamol alone (Diener 2014 **Level I**, 4 RCTs, n=1,900) (3 RCTs overlap with Stephens 2016).

Parenteral medications are more effective in TTH than oral ones; IV metoclopramide has an NNT of 2 and IV metamizole and IV chlorpromazine have an NNT of 4 (Weinman 2014 **Level I** [PRISMA], 8 RCTs, n=486).

IV lidocaine in refractory chronic daily headache was associated with reduced pain intensity over an 8.5 d treatment period from 7.9/10 to 3.9/10, with low incidence of adverse effects (Rosen 2009 **Level IV**, n=68).

IV magnesium was ineffective in treating acute TTH in the ED (Frank 2004 **Level II**, n=42, JS 5).

Acupuncture for TTH (at least 6 sessions) over 3 mth provides clinically relevant improvement in pain vs standard care (2 RCTs, n=1,472), but only minimal clinical improvement vs sham treatment (5 RCTs, n=703) (Linde 2016, **Level I** [Cochrane], 12 RCTs, n=2,349). See also Section 7.3.

8.6.5.2 | Migraine

Migraine is common, with a prevalence of 6 to 8% in males and 12 to 14% in females (Evers 2009 **GL**). Migraine headache is usually unilateral and is often severe, disabling and often worsened by movement. Either nausea/vomiting or photophobia/phonophobia must be present and 20% of migraineurs experience an aura.

Most migraines are successfully managed by the patient and their family doctor, with up to 57% of patients not seeking medical attention for significant attacks (Mitchell 1998 **Level IV**). However, a small number of patients fail to respond and present for treatment at EDs; approximately 80% of patients have tried their usual medications, including simple analgesics or triptans, before presentation.

Evidence-based recommendations for the treatment of migraine in ED settings are published (Orr 2015 **GL**). For treatment of migraine in the ED, see Section 8.11.2.6 below.

Treatment

The management of migraine includes avoidance of triggers such as sleep deprivation, stress, sensory stimulation such as bright lights, exercise, alcohol, foods etc. Management of associated symptoms, particularly nausea and vomiting is important, as is the prevention of acute recurrence.

Environmental modification (quiet dark room) and particularly sleep is integral to successful migraine treatment (Steiner 2007 **NR**).

Analgesia outcomes in migraine trials are usually listed as the proportion of patients who either:

- are pain free at 2 h;
- report significant pain relief at 2 h (no headache or mild headache);
- report a sustained response over 24 h (migraine stays away for at least 1 d).

Many trials fail to document associated outcomes such as improvement in nausea, vomiting or disability (Moore 2003 **NR**).

Strategies for the use of migraine medications

There are three major strategies for the use of analgesics in the treatment of acute migraine (Lipton 2000 **Level II**, n=930, JS 5):

- *Stratified care* — where for each attack, the severity and disability caused by the migraine is assessed and the patient uses simple analgesia for a mild attack and a triptan for a severe attack;
- *Step-up during an attack* — for each attack a simple analgesic is always tried first but the patient "steps up" to a triptan if there is no relief in 2 h;
- *Step-up across attacks* — a patient tries simple analgesics exclusively for the first three attacks; if there has been no benefit from simple analgesia over the trial period then a triptan is used for all further attacks.

The US Headache Consortium (Silberstein 2000 **GL**) and European Federation of Neurological Societies (Evers 2009 **GL**) have recommended a "stratified care" approach; Canadian guidelines recommend this as the most effective and cost-effective approach but also describe the two other approaches as suitable in selected patients (Worthington 2013 **GL**).

Placebo

A significant placebo effect has been observed in migraine trials, particularly if the treatment is administered by injection (Macedo 2006 **Level I** [QUOROM], 98 RCTs, n=35,481) and this may be more relevant in children and adolescents (Evers 2009 **Level I**, 27 RCTs, n unspecified). Accordingly, the beneficial effect of specific analgesic mechanisms may be underestimated by prominent placebo responses (Lund 2014 **Level II**, n=48, JS 5).

Simple analgesics

Patients who experience mild migraine-related headache and disability may be effectively treated with simple analgesics, either alone or in combination with an antiemetic. European consensus guidelines recommend the routine, early use of metoclopramide in adults (or domperidone in children) (Evers 2009 **GL**).

Paracetamol 1,000 mg is superior to placebo in the treatment of migraine but has a lower efficacy than other analgesics (NNT 12 for pain free at 2 h) (Derry 2013a **Level I** [Cochrane], 11 RCTs, n=2,942). The efficacy of the combination with 10 mg metoclopramide was comparable to oral sumatriptan 100 mg. Serious adverse effects occurred only with sumatriptan (NNH 32).

Aspirin 1,000 mg is of similar efficacy to sumatriptan 50 or 100 mg orally (NNT 8.1 for pain free at 2 h) with slightly fewer adverse effects (Kirthi 2013 **Level I** [Cochrane], 13 RCTs, n=4,222); adding 10 mg metoclopramide improves nausea and vomiting.

Ibuprofen is also effective here (NNT 7.2 for pain free at 2 h [400 mg]; NNT 9.7 [200 mg]) and soluble preparations provide faster onset of effect (Rabbie 2013 **Level I** [Cochrane], 9 RCTs, n=4,473). Adverse effects are similar to placebo.

Diclofenac has similar efficacy (NNT 6.2 for pain free at 2 h) and low rates of adverse effects for this indication (Derry 2013b **Level I** [Cochrane], 5 RCTs, n-=1,356).

Dipyrone is also effective for the treatment of migraine and episodic TTHs (Ramacciotti 2007 **Level I** [Cochrane], 4 RCTs, n=636).

Parecoxib IV was similarly effective to oral rizatriptan and SC sumatriptan in an RCT with no placebo arm (Muller 2011 **Level II**, n=57, JS 2).

In a network meta-analysis of NSAIDs and triptans for the treatment of migraine, triptans (in particular eletriptan and rizatriptan) have superior efficacy to NSAIDs; ibuprofen is slightly less effective, but has the best tolerability of all medications analysed (Xu 2016 **Level I** [NMA], 88 RCTs, n=9,372). The combination naproxen/sumatriptan in particular has increased efficacy and better

tolerability than sumatriptan on its own; this is also confirmed by another by systematic review (Law 2016 **Level I** [Cochrane], 13 RCTs, n=9,334) (4 RCTs overlap).

For paediatric information, see Section 10.9.3.1.

Triptans

All triptans are more effective in the treatment of acute migraine than placebo (Thorlund 2014 **Level I**, 74 RCTs, n unspecified), particularly in the presence of severe pain and disability where simple analgesia has failed to provide adequate relief in the past. This must be placed in the context of a high placebo response rate and interindividual differences in response to the different triptans, with recommendations for patients to trial a variety of drugs and doses until the most suitable regimen is found (Worthington 2013 **GL**; Pringsheim 2014 **NR**).

In a review of trials with an eletriptan arm, 30–40% of migraine sufferers do not respond to triptan treatments (Diener 2008 **Level I**, 10 RCTs, n=8,473). The three clinical variables that predict poor therapeutic response are: severe pain, photophobia or phonophobia, and nausea; while time of dosing following onset of headache has no effect on 2-h pain-free response.

The route of administration of a triptan may affect its efficacy, speed of onset and tolerability. For sumatriptan, a comparison of different routes of administration showed that SC administration (in comparison to oral, IN and rectal administration) has the highest efficacy and speed of onset but also the highest rate of adverse effects (Derry 2014b **Level I** [Cochrane], 4 Cochrane Reviews, n=52,236). Most effective doses for each route of administration are PO 100 mg, SC 6 mg, IN 20 mg and rectal 25 mg.

Zolmitriptan is effective in acute migraine with oral doses of 2.5 and 5 mg being comparable in efficacy to oral sumatriptan 50 mg (Bird 2014 **Level I** [Cochrane], 25 RCTs, n=20,162).

As most RCTs have compared a single triptan with placebo, it is difficult to determine the relative efficacy of different triptans. A multiple treatment comparison meta-analysis combining available head-to-head and placebo-controlled trials has been published (Thorlund 2014 **Level I** [NMA], 74 RCTs, n unspecified). It shows eletriptan followed by rizatriptan, zolmitriptan and sumatriptan having the highest efficacy at 2 h and eletriptan followed by zolmitriptan and sumatriptan at 24 h.

The combination of sumatriptan/naproxen provides a greater headache reduction in the acute treatment of migraine headaches than the same dose of either agent alone, but the difference in efficacy is small in comparison to sumatriptan alone (Law 2016 **Level I** [Cochrane], 13 RCTs, n=9,334). The combination and sumatriptan alone causes more adverse effects than naproxen (3 RCTs) or placebo (10 RCTs).

The most frequent adverse effects associated with triptans are dizziness, fatigue, sleepiness, nausea, chest tightness and paraesthesiae (Johnston 2010 **NR**). Triptans may cause an increase in light touch-evoked allodynia and thermal sensitivity (Linde 2004 **Level III-2 EH**, n=24). Concerns about an increase in cardiovascular events with the use of triptans could not be confirmed (Roberto 2015 **Level III-2 SR**, 4 studies, n≈131,000); the pooled OR of serious ischaemic events was 0.86 (95%CI 0.52 to 1.43).

Frequent use of triptans may lead to triptan-induced rebound headaches (medication-overuse headache), often described as chronic migraine (Tepper 2012 **NR**). This risk increases with increasing days of triptan use, in particular with use on more than 10 d/mth (Lipton 2013 **Level IV**, n=11,249).

Calcitonin Gene Related Peptide inhibitors

Calcitonin gene-related peptide (CGRP) inhibitors (humanised monoclonal antibodies or small molecule CGRP receptor antagonists) are useful in migraine management (Edvinsson 2018 **NR**). Currently, only two such monoclonal antibodies are registered in Australia, fremanezumab

(Silberstein 2017 **Level II**, n=1,130, JS 5) and erenumab (Jain 2018 **NR**) as preventive treatment, the latter also in New Zealand. As well, the CGRP pathway may be engaged for emergency management of acute headache utilising small molecule CGRP receptor antagonists (gepants) and serotonin 5-HT1F receptor agonists (ditans) may have a major role, but are currently only in Phase III trials and still awaiting registration (Moreno-Ajona 2019 **NR**).

Ergot derivatives

Ergotamine and dihydroergotamine preparations have been used for many years to treat migraine, although they have been superseded by the triptans, as they are less effective and have more adverse effects (Tfelt-Hansen 2008 **NR**). In particular, oral triptans are superior to oral ergotamine, because the bioavailability of oral ergotamine is extremely low (<1%).

IN dihydroergotamine (2 mg) has a NNT of 2.5 for 2 h headache response in migraine (Oldman 2002 **Level I**, 1 RCT [ergotamine], n=203). As a single agent, parenteral dihydroergotamine may not be as effective as other migraine treatments (Colman 2005 **Level I**, 3 RCTs [ergotamine alone], n=423). However, when dihydroergotamine is combined with an antiemetic such as metoclopramide, the efficacy of this combination is similar to valproate, ketorolac and opioids (Colman 2005 **Level I**, 8 RCTs [ergotamine/antiemetic], n=384).

Importantly, in contrast to the data for triptans, ergot derivatives cause an increased rate of ischaemic events (OR 2.51; 95%CI 1.10 to 5.71) (Roberto 2015 **Level III-2 SR**, 4 studies, n≈131,000).

Antiemetics and major tranquillisers

Parenteral metoclopramide, as monotherapy or in combination, is effective for the treatment of headache and nausea in acute migraine (Orr 2015 **Level I** [PRISMA], 8 RCTs [metoclopramide], n unspecified; Colman 2004 **Level I**, 13 RCTs, n=728) (2 RCTs overlap).

Parenteral droperidol is also effective in this indication; the minimum effective dose is 2.5 mg IM or IV (Thomas 2015 **Level I**, 5 RCTS, n=685).

Phenothiazines such as chlorpromazine (2 RCTs) and prochlorperazine (3 RCTs) vs placebo provide better headache relief (OR 15.02; 95%CI 7.57 to 29.82) (4 RCTs, n=303) and achieve more clinical success (OR 8.92; 95%CI 4.08 to 19.51) (5 RCTs, n=349) (Kelly 2009 **Level I**, 13 RCTs, n=917). Phenothiazines achieve also more clinical success than metoclopramide (OR 2.25; 95%CI 1.29 to 3.92) (4 RCTs, n=271) and combinations of other active compounds (OR 2.04; 95%CI 1.25 to 3.31) (10 RCTs, n=569), but not better headache relief. The overall clinical success rate of phenothiazines is high (78%; 95%CI 74 to 82). Butyrophenones achieve similar benefits in an ED setting, however with significant adverse effects (Leong 2011 **Level I**, 6 RCTs, n=574). IV prochlorperazine was more effective than IV promethazine for initial ED treatment of migraine (Callan 2008 **Level II**, n=70, JS 4). Buccal prochlorperazine was superior to an oral ergotamine/caffeine combination or placebo (Sharma 2002 **Level II**, n=45, JS 5).

A combination of indomethacin/prochlorperazine/caffeine (Di Monda 2003 **Level II**, n=112, JS 3) and a combination of prochlorperazine/diphenhydramine were more effective than SC sumatriptan (Thomas 2015 **Level II**, n=68, JS 5).

Conventional and atypical opioids

Opioids are of limited benefit in the treatment of migraine and should not be used (Casucci 2013 **NR**; Tepper 2012 **NR**). IV hydromorphone vs IV prochlorperazine/diphenhydramine was less effective for the treatment of acute migraine; the RCT was halted when the primary outcome was achieved by 60% of the prochlorperazine/diphenhydramine arm vs 31 % of the hydromorphone arm (Friedman 2017b **Level II**, n=127, JS 5).

Opioid use for migraine was associated with more severe headache-related disability, symptomology, comorbidities (depression, anxiety and cardiovascular disease and events), and

greater healthcare utilisation than no use (Buse 2012 **Level III-2**, n=5,796). Among current opioid users for migraine, 16.6% met criteria for probable dependence. Opioids induce migraine progression with a dose-dependent effect beyond approximately 8 d exposure/mth (Tepper 2012 **NR**; Bigal 2009 **NR**).

Despite these disadvantages and recommendations, opioids continue to be used in more than half of all patients attending EDs in the USA for migraine (Friedman 2014a **Level IV**). However, when other migraine treatments are contraindicated, use of opioids may have to be considered as a last resort (Dodson 2018 **NR**; Finocchi 2013 **NR**). Among patients requiring readmission for primary headache, those given opioids initially (22.8%) had significantly longer ED LOS (median 5.0 h vs. 3.9 h) and higher rates of return ED visits within 7 d (7.6% vs. 3.0%) vs those receiving non-opioids in a univariate analysis (McCarthy 2015 **Level III-3**, n=574); the association with longer length of stay remained significant in multivariable regression.

Overall, the most commonly trialled opioids in migraine (pethidine, tramadol and nalbuphine) are more effective in reducing migraine pain than placebo (Kelley 2012 **Level I**, 23 RCTs, n unspecified). Morphine without an antiemetic was no more effective than placebo (Nicolodi 1996 **Level III-1**). Butorphanol was effective when given by the IN or IM route (Hoffert 1995 **Level II**, n=157, JS 3; Elenbaas 1991 **Level III-1**). There is inadequate evidence to recommend parenteral tramadol in the treatment of acute migraine (Marmura 2015 **GL**).

Pethidine in particular is not recommended for the treatment of migraine, due to lack of evidence of efficacy, neurotoxicity of its metabolite norpethidine (epileptogenic) and the high risk of developing dependency. Pethidine is less effective than dihydroergotamine or antiemetics for the treatment of migraine; however, its efficacy is similar to ketorolac (Friedman 2008 **Level I**, 11 RCTs, n=625).

Ketamine

SC ketamine 0.08 mg/kg vs placebo was more effective in treating acute migraine pain (Nicolodi 1995 **Level II**, n=17, JS 3). In contrast, IV ketamine 0.2 mg/kg was not superior to placebo in acute migraine (Etchison 2018 **Level II**, n=34, JS 5). IV ketamine 0.3 mg/kg/IV ondansetron 4 mg vs IV prochlorperazine 10 mg/IV diphenhydramine 25 mg achieved inferior pain relief at 45 and 60 min (MD 20/100; 95%CI 2.8 to 37.2) and lower patient satisfaction at 24 h in primary headache (Zitek 2018 **Level II**, n=54, JS 5). Similarly, IN ketamine was not superior to standard treatment (metoclopramide/diphenhydramine) in the treatment of primary headache (Benish 2019 **Level II**, n=53, JS 4).

Other drug treatments

Parenteral dexamethasone reduces the rate of moderate or severe headache recurrence after 24 to 72 h (RR 0.71; 95%CI 0.59 to 0.86) (Orr 2016 **Level I**, 68 RCTs, n unspecified; Huang 2013 **Level I**, 8 RCTs, n=905) (1 RCT overlap). There are no differences in efficacy between oral and parenteral steroids. IM methylprednisolone acetate, a long-acting steroid, was not superior to IM dexamethasone in this setting (Latev 2019 **Level II**, n=220, JS 4).

The efficacy of lidocaine in the treatment of migraine is unclear. Analgesia provided by IV lidocaine was similar to dihydroergotamine but not as effective as chlorpromazine (Bell 1990 **Level II**, n=76, JS 2) and, in another trial, no better than placebo (Reutens 1991 **Level II**, n=25, JS 3). IN lidocaine was more effective than placebo (Maizels 1996 **Level II**, n=91, JS 4). IN lidocaine 10 to 20 mg repeated at variable intervals (4 RCTs using Barre method) vs placebo in primary headache (mainly acute migraine) shows some benefit only in poor quality RCTs (4 RCTs), but not in fair quality RCTs (2 RCTs); overall there is no effect on recurrence or repeat ED visits, but more adverse events and lower patient satisfaction (Dagenais 2018 **Level I** [PRISMA], 6 RCTs, n=685).

No firm conclusions can be drawn on the effect of IV magnesium in acute migraine due to the heterogeneity of the studies included in a systematic review; however, there may be some

effects on pain after >1 h, aura duration and need for rescue analgesia (Miller 2019 **Level I** [PRISMA], 7 RCTs, n=545).

IV sodium valproate is ineffective in treating acute migraine (Frazee 2008 **Level IV SR**, 3 RCTs & 4 studies, n=243). This was contradicted by a subsequent case series (Shahien 2011 **Level IV**, n=36), but confirmed in an RCT, which found sodium valproate inferior to ketorolac and metoclopramide (Friedman 2014b **Level II**, n=330, JS 5).

Propofol in 30–40 mg IV bolus doses was more effective than sumatriptan 6 mg SC at 30 min with less need for antiemetics and lower rate of recurrence (Moshtaghion 2015 **Level II**, n=91, JS 5). Propofol in 10 mg IV bolus doses (max 80 mg) was also superior to dexamethasone IV 0.15 mg/kg (max 16 mg) (Soleimanpour 2012a **Level II**, n=90, JS 5). The efficacy was also confirmed in a number of case series (Ward 2013 **Level IV**, n=15; Mosier 2013 **Level IV**, n=4; Soleimanpour 2012b **Level IV**, n=8), including one in paediatric patients (Sheridan 2012 **Level IV**). A susbequent paediatric RCT demonstrated similar pain reduction (51% vs 59) with low dose bolus IV propofol 0.25 mg/kg (1–5 doses) with IV fluid bolus vs standard IV combination therapy with less rebound headache at 24 h (7% vs 25) (Sheridan 2018 **Level II**, n=74, JS 2). Notably, guidelines give a weak recommendation against the use of propofol (Orr 2015 **GL**).

There is no evidence for use of caffeine alone in treatment of tension type headache or migraine. However, combinations of caffeine with simple analgesics improve their analgesic efficacy and tolerability in a number of painful conditions including primary headache and migraine (Derry 2014a **Level I** [Cochrane], 20 RCTs, n=7,238) (2 RCTs overlap with Stephens 2016). However, discontinuation of regular caffeine intake improves subsequent acute migraine management over the next 35 d (Lee 2016b **Level III-2**, n=108).

Pramipexole has been linked with a significant reduction in migraine, particularly the morning headaches in patients with concomitant restless legs syndrome (Suzuki 2013 **Level IV**).

SC Octreotide 100 mcg vs placebo had no analgesic effect in acute migraine (Levy 2005 **Level II**, n=51, JS 5).

Sublingual ginger (*Zingiber officinale*)/feverfew (*Tanacetum parthenium*) extract was more effective than placebo in aborting acute migraine when used in early mild headache (Cady 2011 **Level II**, n=60, JS 5).

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy was effective in relieving migraine headaches vs sham therapy (RR 6.2; 95%CI 2.4 to 16) (3 RCTs, n=58), but there was no effect on nausea and vomiting, rescue analgesic requirements or migraine prevention (Bennett 2015 **Level I** [Cochrane], 11 RCTs, n=209).

Intravenous fluids

IV fluid hydration is a common component of emergency department migraine therapy (Jones 2017 **Level IV**, n=1,251). However, in a post hoc analysis of data collected from 4 ED-based migraine RCTs, IV fluids/metoclopramide vs IV metoclopramide alone did not improve acute migraine outcomes (Balbin 2016 **Level III-2**, n=570) similar to the findings of a subsequent RCT (Jones 2019a **Level II**, n=49, JS 5).

TENS

TENS use in migraine reduces monthly affected days (SMD: -0.48; 95%CI -0.73 to - 0.23) and pharmacological treatment intake (SMD -0.78; 95%CI -1.14 to - 0.42) (Tao 2018 **Level I** [PRISMA], 4 RCTs, n=161). Similarly, TENS applied to the supraorbital nerve over 12 wk reduced days with migraine and days using rescue medications among patients with refractory migraine and not responding to topiramate (Vikelis 2017 **Level IV**, n=35).

One 60-min session of TENS treatment reduced pain intensity of acute migraine attacks at one and 24 h after treatment by 50%, and two thirds of the patients did not require rescue pain medication at 24 h (Chou 2017 **Level IV**, n=30).

See also Section 7.2.

Acupuncture

Similarly, acupuncture reduces migraine frequency at 3 mth vs no treatment or routine care (4 RCTs, n=2,199), but only minor improvements were seen vs sham treatments (14 RCTs, n=1,825) (Linde 2016 **Level I** [Cochrane], 22 RCTs, n=4,985). Acupuncture reported fewer adverse (5 RCTs, n=931) vs pharmacological prophylaxis and acupuncture was slightly superior at 3 mth but not 6 mth (3 RCTs, n=739). A subsequent RCT also found a prophylactic effect of electroacupuncture (5 sessions per wk for 12 wk) on migraine (Li 2017a **Level II**, n=61, JS 3).

See also Section 7.3.

8.6.5.3 | Menstruation-related migraine

Management of acute migraine during menstruation does not differ from treatment at other phases of the menstrual cycle. Prophylaxis is based on modifying hormone fluctuations, usually by intake of oestrodiol-containing oral contraceptive preparations (MacGregor 2010 **NR**).

Sumatriptan, zolmitriptan, rizatriptan and mefenamic acid are more effective than placebo for acute treatment (Pringsheim 2008 **Level I**, 10 RCTs [acute abortive treatment], n=3,255). Eletriptan is as effective to achieve 2 h pain relief in females in and outside of the menstrual phase but with higher rate of recurrence and less sustained suppression of nausea during menstruation (Bhambri 2014 **Level I**, 5 RCTs, n=3,217).

8.8.5.4 | Migraine in pregnancy and breastfeeding

Migraine can occur for the first time during pregnancy and pre-existing migraine may worsen, particularly during the first trimester or may improve in later pregnancy with the patient becoming headache-free (MacGregor 2014 **NR**). Approximately 60–70% of migraineurs improve during pregnancy (frequency, duration) with a sharp rise in the incidence after delivery (Kvisvik 2011 **Level IV**, n=2,126). Breastfeeding is protective (David 2014 **NR**).

Migraine in pregnancy is a risk factor for gestational hypertension and preeclampsia (OR 2.3; 95%CI 2.1 to 2.5) and is also associated with ischaemic stroke (OR 30.7; 95%CI 11.1 to 22.5), myocardial infarction (OR 4.9; 95%CI 1.7 to 14.2), deep vein thrombosis (OR 2.4; 95%CI 1.3 to 4.2) and thrombophilia (OR 3.6; 95%CI 2.1 to 6.1) (Bushnell 2009 **Level III-2**, n=33,956).

The major concerns in the management of migraine in pregnancy are the effects of medication and the disease itself on the fetus. Medication use should ideally be limited. Paracetamol, metoclopramide, caffeine, codeine (or perhaps other opioids) can be used during pregnancy, while aspirin, NSAIDs or coxibs should not be used during the third trimester (David 2014 **NR**).

There is contradictory information on the safety of triptan therapy during pregnancy. While there are human data suggesting potential teratogenicity (David 2014 **NR**), a large Scandinavian population study has shown no significant risk of congenital malformation but a small risk of uterine atony and haemorrhage with use during the second and third trimesters (Nezvalová-Henriksen 2013 **Level III-2**, n=181,124).

Ergot alkaloids during pregnancy may disrupt fetoplacental blood supply and cause uterine contractions, which can result in low birth weight and preterm birth (Banhidy 2007 **Level IV**, n=33,851). Birth defects and stillbirths due to vascular spasm have been reported and it is recommended that ergotamines be avoided in pregnancy (Acs 2006 **NR**). However,

dihydroergotamine has significantly fewer vasoconstrictor and uterotonic effects vs other ergotamines: dihydroergotamine use in pregnancy did not increase risk for major malformations but increased the risk of prematurity and resulted in a risk of spontaneous abortion similar to that of triptan and NSAID use (Berard 2012 **Level III-2**, n=59,707).

Low-dose acetylsalicylic acid, ibuprofen, sumatriptan, paracetamol, caffeine and metoclopramide are considered safe for the treatment of acute migraine in breastfeeding mothers (Davanzo 2014 **Level IV SR**; David 2014 **NR**; Hutchinson 2013 **NR**). Acute migraine medications that should be avoided include high-dose acetylicsalicylic acid, dihydroergotamine, ergotamine and opioids.

See also Section 9.1 and Tables 9.1 and 9.2.

8.6.5.5 | Cluster headache and other trigeminal autonomic cephalalgias

Cluster headache is a rare primary headache disorder, presenting almost exclusively in males with recurrent, acute episodes of brief, severe, unilateral, periorbital pain associated with autonomic phenomena such as conjunctival injection and tearing.

Guidelines for the treatment of cluster headache attacks propose as first-line treatments SC sumatriptan 6 mg, IN zolmitriptan 5 mg and 10 mg, and 100% oxygen 6–12 L/min (Francis 2010 **GL**).

Oxygen

High-flow oxygen is recommended as a first-line treatment (Francis 2010 **GL**); this is supported by a meta-analysis with limited quality of evidence, which suggests that more than 75% of cluster headaches were likely to respond to non-hyperbaric oxygen therapy (3 RCTs), but possibly not superior to ergotamine (Bennett 2015 **Level I** [Cochrane], 11 RCTs, n=209). One RCT not included in this meta-analysis found high-flow oxygen (12 L/min) superior vs high-flow air in cluster headache with regard to the outcome pain free at 15 min (78%; 95%CI 71 to 85 [150 attacks] vs 20%; 95%CI 14 to 26 [148 attacks]) (Cohen 2009 **Level II**, n=109, JS 5). High-flow oxygen treatment had a superior effect to high-flow room air in all types of headaches in an ED setting (Ozkurt 2012 **Level II**, n=204, JS 5). In a survey of patients with cluster headache, oxygen was rated highly effective with few complications (Pearson 2019 **Level IV**, n=2,193). The presence of nausea/vomiting and "*restlessness*" was predictive of a poor response to oxygen (Schurks 2007 **Level IV**, n=256).

Hyperbaric oxygen is no more effective than sham hyperbaric treatment in reducing the frequency or duration of cluster headaches (1 RCT) (Bennett 2015 **Level I** [Cochrane], 11 RCTs, n=209).

Triptans

Triptans are effective to treat cluster headaches; SC sumatriptan 6 mg is superior to IN zolmitriptan 5 mg or 10 mg for rapid response at 15 min, while oral routes of administration are not appropriate for this condition (Law 2013 **Level I** [Cochrane], 6 RCTs, n=1,180).

Calcitonin Gene-Related Peptide Inhibitors

Humanised monoclonal antibodies that selectively bind to calcitonin gene-related peptide (CGRP) are effective in rapidly reducing the frequency and intensity of acute headaches in individuals with episodic cluster headache and are awaiting registration (Ashina 2017 **NR**).

Local anaesthetic blocks

Sphenopalatine ganglion local anaesthetic block has moderate evidence support for the treatment of acute cluster headaches (1 RCT, 6 studies, 2 CR) (Ho 2017 **Level IV SR**, 88 studies, n unspecified).

Occipital nerve blocks have been shown to be effective in multiple case series and two RCTs but the mechanism is uncertain and the role of additional steroids unclear (Leroux 2013a **Level IV SR**, 12 studies, n≈334).

Neuromodulation

Sphenopalatine ganglion stimulation (1 RCT, 2 studies) and radiofrequency ablation (9 studies) as well as bilateral occipital nerve stimulation has been used successfully as a prophylaxis (Ho 2017 **Level IV SR**, 88 studies, n unspecified; Blumenfeld 2013 **GL**; Pedersen 2013 **NR**).

Non-invasive vagus nerve stimulation is a well-tolerated and effective acute treatment for episodic cluster headache (1 RCT, n=112), but less effective for chronic cluster headache (1 RCT, n=113) (de Coo 2019 **Level I**, 2 RCTs, n=225).

Other treatments

The efficacy of cannabis in cluster headaches is limited and should not be recommended (Leroux 2013b **Level IV**, n=139).

In attacks of high frequency, short courses of high-dose oral corticosteroids, dihydroergotamine and occipital nerve blocks with local anaesthetic and steroids are recommended with limited evidence (Becker 2013 **NR**).

8.6.5.6 | Paroxysmal hemicrania and SUNCT

Paroxysmal hemicrania and SUNCT are rarer forms of trigeminal autonomic cephalalgia. Paroxysmal hemicrania is similar to cluster headache except that it is more common in females, episodes are shorter, but more frequent, and diagnosis requires the complete abolition of symptoms with indomethacin, which is the suggested treatment of choice (Headache Classification Committee 2018 **GL**; May 2006 **GL**).

There is no high-level evidence to guide the treatment of SUNCT (Arca 2018 **NR**). However consensus guidelines and limited data suggest that IV lidocaine for acute treatment and lamotrigine, topiramate and gabapentin may be useful prophylactics (May 2006 **GL**; Weng 2018 **NR**). Occipital nerve stimulation (Lambru 2014 **Level IV**, n=9; Young 2012 **Level IV**) and non-invasive vagal stimulation may be a potential effective treatment for SUNCT and hemicrania continua (Tso 2017 **Level IV**, n=15).

8.6.5.7 | Postdural puncture headache

Postdural puncture headache (PDPH), usually following spinal anaesthesia, inadvertent dural puncture with an epidural needle, diagnostic or therapeutic lumbar puncture or neurosurgery, occurs with an incidence of approximately 0.7 to 50% (Bezov 2010a **NR**; Bezov 2010b **NR**). Up to 85% of cases improve spontaneously within 6 wk.

Risk factors are younger age, female gender, low BMI, history of prior PDPH and history of chronic headache. Children who undergo lumbar puncture may present a special group (Janssens 2003 **NR**) (see Section 10.6.3.5).

Spinal needle size, type and lumbar puncture technique

Data in the anaesthesiology and neurology literature indicate that needle calibre, bevel type and lumbar puncture technique affects the incidence of PDPH. The incidence of DPH following spinal anaesthesia is reduced by using a smaller gauge (-g) needle (26-g or less: NNT 3) or a needle with a noncutting bevel (eg pencil point: NNT 27) (Halpern 1994 **Level I**, 16 RCTs, n=3,593).

Subsequent studies support these findings for noncutting bevel needles (Schmittner 2011 **Level II**, n=363, JS 3) but could not find a difference between 23- and 25-g needles in patients >60 y (Kim 2011b **Level II**, n=53, JS 5) or between cutting 22- and 25-g needles in children aged 4 to 15 y (Crock 2014 **Level II**, n=93 [341 punctures], JS 5).

The incidence of PDPH is also reduced by orientating the cutting bevel parallel to the spinal sagittal plane (dural fibres) (Richman 2006 **Level I**, 5 RCTs, n=521) or by replacing the stylette prior to withdrawing a noncutting needle (Strupp 1998 **Level II**, n=600, JS 3); these techniques presumably reduce CSF loss. However, a subsequent study could not confirm the benefit of replacing the stylette in a 25-g Quincke needle (Sinikoglu 2013 **Level II**, n=630, JS 4).

Similarly for diagnostic lumbar punctures, noncutting (pencil point) needles significantly reduced the incidence of PDPH vs cutting (Quincke) needles (Lavi 2006 **Level II**, n=58, JS 4; Strupp 2001 **Level II**, n=306, JS 5), leading to a recommendation to use noncutting needles routinely in neurology practice (Arendt 2009 **NR**).

During epidural catheter insertion in labour, the incidence of accidental dural puncture was not reduced when using an 18-g epidural Sprotte (pencil point) needle vs a 17-g epidural Tuohy needle (Morley-Forster 2006 **Level II**, n=1,077, JS 5). However, the incidence of PDPH was significantly lower with the epidural Sprotte needle.

Epidural blood patch

The use of an epidural blood patch (EBP) for the treatment of PDPH has been recommended as first-line therapy (Bezov 2010a **NR**), especially in obstetric patients (Thew 2008 **NR**) and following inadvertent dural puncture with an epidural needle (Gaiser 2006 **NR**). However, the risks of the intervention must be carefully weighed with the benefits (Suescun 2016 **NR**).

EBP is more effective than conservative treatment (OR 0.18; 95%CI 0.04 to 0.76) (1 RCT) and a sham procedure (OR 0.04; 95%CI 0.00 to 0.39) (1 RCT) (Boonmak 2010 **Level I** [Cochrane], 9 RCTs, n=379).

The most effective blood volume for EBP administration is not known. Data vary significantly from 7.5 to 30 mL. There was no difference in the severity of PDPH at 3 d in patients who received either a 7.5 or 15 mL EBP, except for a lower incidence of nerve-root irritation during injection with the lower volume (Chen 2007 **Level II**, n=33, JS 3). EBP volumes in the range of 10 to 20 mL were effective in relieving PDPH in 98% of patients following spinal or epidural anaesthesia (Wu 1994 **Level IV**, n=159). There was no difference in the frequency of PDPH resolution (approximately 91%) with either 10 or 15 mL blood volumes randomised according to patient height (Taivainen 1993 **Level III-1**, n=81). Significant relief of PDPH was obtained in 93% of patients, who received a mean EBP volume of 23 (5) mL (Safa-Tisseront 2001 **Level IV**, n=504). With use of volumes of 15, 20 and 30 mL, permanent or partial relief of headache was achieved in 61%, 73%, and 67% respectively and complete relief in 10%, 32%, and 26% without a difference in backache (Paech 2011 **Level II**, n=121, JS 5); the authors recommended 20 mL as the "optimal" target volume.

EBP is sometimes performed prophylactically to prevent PDPH after an inadvertent dural puncture (eg by an epidural needle) (Bezov 2010a **NR**). However, there is conflicting evidence of benefit with prophylactic EBP administration; there is improvement vs no treatment (OR 0.11; 95%CI 0.02 to 0.64) (1 RCT), conservative treatment (OR 0.06; 95%CI 0.03 to 0.14) (2 RCTs) and epidural saline patch (OR 0.16; 95%CI 0.04 to 0.55) (1 RCT), but not vs a sham procedure (1 RCT) (Boonmak 2010 **Level I** [Cochrane], 9 RCTs, n=379). The authors of this Cochrane Review do not recommend prophylactic EBP due to concerns about inconclusive findings in small studies. However, a subsequent RCT showed benefit with reduction of incidence of PDPH from 79.6 to 18.3% by a prophylactic blood patch (Stein 2014 **Level II**, n=60, JS 3).

The use of autologous blood patch may be contraindicated in patients with cancer, leukaemia, coagulopathy or infection, including HIV, although there is debate for some of these in the literature (Tom 1992 **Level IV**, n=252).

Bed rest and hydration

There is no evidence of benefit with bed rest or fluid supplementation in the treatment or prevention of PDPH (Arevalo-Rodriguez 2013 **Level I** [Cochrane], 23 RCTs, n=2,477). However, patients with PDPH may have difficulty in mobilising and the headache subsides with bed rest.

Other treatments

PDPH is successfully prevented with morphine, cosyntropin and aminophylline, especially in patients with high risk of PDPH, while dexamethasone increased PDPH and there were inconclusive data for fentanyl, caffeine and indomethacin (Basurto Ona 2013b **Level I** [Cochrane], 10 RCTs, n=1,611). These findings are based on studies of limited quality with small sample size.

PDPH responds to caffeine (reducing persistence and further treatment requirements) and gabapentin, hydrocortisone and theophylline (reducing pain severity), while there is insufficient evidence for sumatriptan, adrenocorticotropic hormone, pregabalin and cosyntropin (Basurto Ona 2015 **Level I** [Cochrane], 13 RCTs, n=479). These findings are based on studies of limited quality with small sample size and limited generalisability.

A number of other studies and treatments were not considered in the above Cochrane reviews:

- Gabapentin (Vahabi 2014 **Level II**, n=120, JS 3) reduced the intensity and duration of PDPH; preoperative administration before spinal anaesthesia for elective Caesarean section did not reduce PDPH incidence, but did reduce severity (Nofal 2014 **Level II**, n=88, JS 5);
- IT administration of 5 mL normal saline reduced the overall incidence of PDPH from 24 to 2% (Faridi Tazeh-Kand 2014 **Level II**, n=100, JS 4);
- Topical sphenopalatine ganglion block has been used successfully in PDPH (Kent 2016 **Level IV**, n=3) and was superior to EBP with no complications (Cohen 2018 **Level III-3**, n=81; Dubey 2018 **Level IV**, n=11).

Low CSF pressure headache may result from disruption of the dural integrity, often in cervical or thoracic levels with persisting headaches of identical character to PDPH. Management requires careful evaluation of the potential site of CSF leak. Extradural spinal fluid may be apparent on careful MRI and a clue to the site of leak may come from the clinical history. Management is similar to that of PDPH (Mokri 2013 **NR**; Mokri 2003 **NR**).

8.6.5.8 | Other headaches

There is little evidence to guide the treatment of acute cervicogenic headache, post-traumatic headache (Minen 2019 Level I, 7 RCTs, n=1,108; Larsen 2019 Level IV SR, 7 studies, n=121 [adults] & 618 [children]) or acute headache attributed to substance use or its withdrawal, although general principles of evaluation of headache and management of acute pain must apply (Silberstein 2000 GL).

Giant cell arteritis

The treatment of giant cell arteritis is with high-dose steroids but there are no evidence-based guidelines and the steroid dose and route of administration are empirical. Because of the potential devastating effect on vision in this common vasculitic disorder, high-dose steroid is recommended: IV methylprednisolone 15 mg/kg/d showed more rapid and sustained remission vs oral prednisone 40 mg/d (Mazlumzadeh 2006 **Level II**, n=27, JS 5).

Tocilizumab, a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody has shown efficacy in the induction and maintenance of remission of giant cell arteritis (Schirmer 2018 **Level I**, 2 RCTs, n=281).

Headache attributed to substance withdrawal (severe analgesic "rebound" headache)

Patients may present with severe acute-on-chronic headache due to the overuse and/or withdrawal of antimigrainal (triptans or ergot alkaloids) or other analgesics. Inpatient treatment is often required to manage this chronic pain condition and may include cessation of analgesics, IV hydration, steroids, NSAIDs, antiemetics and benzodiazepines (Kristoffersen 2014 **NR**). Medication withdrawal is usually recommended as a first step in treatment with use of preventive medications, but current evidence does not provide definite guidance (Chiang 2016 **Level VI SR**, 68 studies, n unspecified). Limiting acute headache treatment to no more than 10 or 15 d/mth (depending on medication type) is commonly recommended to prevent headache frequency progression; analgesics including opioids may carry a higher risk of medication overuse headache than triptans and ergotamines (Thorlund 2016 **Level IV SR**, 29 studies, n=3,092).

KEY MESSAGES

Tension-type headache

1. Acupuncture may be effective in the treatment of tension-type headache (**S**) (**Level I** [Cochrane Review]).
2. Simple analgesics such as paracetamol or NSAIDs, either alone or combined, are effective in the treatment of episodic tension-type headache (**S**) (**Level I** [PRISMA]).
3. Metoclopramide, metamizole and chlorpromazine as parenteral treatments of tension-type headache have high efficacy (**U**) (**Level I** [PRISMA]).
4. The combination of caffeine/aspirin/paracetamol is superior to paracetamol in the treatment of episodic tension-type headache (**U**) (**Level I**).

Migraine

5. Paracetamol is effective in the treatment of migraine, however less than other analgesics; the efficacy is increased when combined with metoclopramide (**U**) (**Level I** [Cochrane Review]).
6. Aspirin, ibuprofen, diclofenac and dipyrone are effective in the treatment of migraine; soluble preparations of ibuprofen provide a faster onset (**U**) (**Level I** [Cochrane Review]).
7. For sumatriptan, subcutaneous administration achieves the fastest onset of effect and highest efficacy (**U**) (**Level I** [Cochrane Review]).
8. The combination naproxen/sumatriptan has increased efficacy and better tolerability than sumatriptan on its own (**N**) (**Level I** [Cochrane Review]).
9. The addition of caffeine to simple analgesics improves their analgesic efficacy and tolerability in acute migraine (**N**) (**Level I** [Cochrane Review]).
10. Hyperbaric oxygen therapy is effective in controlling pain in migraine, but no other symptoms and outcomes (**U**) (**Level I** [Cochrane Review]).

11. A significant placebo effect occurs in migraine treatment (**N**) (**Level I** [QUOROM]), leading to an underestimation of treatment effects of analgesic medications (**N**) (**Level II**).
12. Parenteral antiemetics, metoclopramide (**S**) (**Level I** [PRISMA]) and droperidol (**U**) (**Level I**) are effective in the treatment of migraine.
13. Phenothiazines and butyrophenones (at the expense of more adverse effects) are effective in the treatment of migraine, in particular in the emergency department (**S**) (**Level I**).
14. All triptans are more effective than placebo in the treatment of severe migraine (**S**) (**Level I**), however 30 to 40% of patients may not respond (**N**) (**Level I**).
15. Triptans and mefenamic acid are effective in treatment of menstruation-related migraine (**U**) (**Level I**).
16. Some opioids are more effective than placebo in the treatment of acute migraine (**U**) (**Level I**), but their use in this setting is associated with significant adverse effects and poor outcomes (**S**) (**Level III-2**).
17. Pethidine is less effective than most other migraine treatments and should not be used (**U**) (**Level I**).
18. Intravenous magnesium may have some analgesic effect compared to placebo in migraine (**Q**) (**Level I** [PRISMA]).
19. A "*stratified care strategy*" is effective in treating migraine (**U**) (**Level II**).
20. Ergotamine derivatives, but not triptans, increase the rate of severe myocardial ischaemic events (**U**) (**Level III-2 SR**).
21. Migraine in pregnancy is a risk factor for gestational hypertension, preeclampsia and cardiovascular complications (**U**) (**Level III-2**).

Cluster headache

22. Parenteral triptans (sumatriptan or zolmitriptan) or high-flow oxygen therapy are effective treatments for cluster headache attacks (**S**) (**Level I** [Cochrane Review]).
23. Sphenopalatine ganglion local anaesthetic block has moderate evidence support for the treatment of acute cluster headaches (**N**) (**Level IV SR**).

Postdural puncture headache

24. There is no evidence that bed rest or fluid supplementation are beneficial in the treatment and prevention of postdural puncture headache (**S**) (**Level I** [Cochrane Review]).
25. Epidural blood patch administration is more effective than conservative treatment or a sham procedure in the treatment of postdural puncture headache (**S**) (**Level I** [Cochrane Review]).
26. Risk of postdural puncture headache is reduced with preventive use of morphine, cosyntropin or aminophylline, especially in patients at high risk; preventive dexamethasone use increases risk of postdural puncture headache (**N**) (**Level I** [Cochrane Review]).

27. Caffeine, gabapentin, hydrocortisone or theophylline are effective treatments for postdural puncture headache (**S**) (**Level I** [Cochrane Review]).

28. The incidence of postdural puncture headache is reduced by using smaller-gauge spinal or non-cutting bevel needles or by orientating the cutting bevel parallel to the spinal sagittal plane (**U**) (**Level I**).

Medication overuse headache

29. Frequent use (>8–10 days/month) of paracetamol, NSAIDs and opioids for recurrent acute headache (more so than triptans and ergot derivatives) may lead to medication overuse headache; weaning and use of preventive medication are recommended management approaches (**S**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Opioids should be used with extreme caution in the treatment of headache; pethidine should not be used at all (**S**).

8.6.6 | Acute pain associated with neurological disorders

Pain associated with neurological disorders is usually neuropathic in nature, although nociceptive pain due to problems such as muscle spasms may also occur. Neuropathic pain may be acute or chronic and is due to a lesion or disease of the somatosensory system, either in the periphery or centrally (Jensen 2011 **NR**).

Treatment of acute neuropathic pain is based largely on evidence from trials for the treatment of a variety of chronic neuropathic pain disorders (see also Section 8.1.4 above). Effective treatments for neuropathic pain include TCAs, anticonvulsants, membrane stabilisers, NMDA-receptor antagonists, opioids or tramadol (see Sections 4.3, 4.4 and 4.7 to 4.9).

Associated psychosocial problems and physical disabilities must also be managed within a multidisciplinary framework.

8.6.6.1 | Multiple sclerosis

Chronic pain is experienced by 26 to 86% of patients with multiple sclerosis (Truini 2013 **NR**). These data are confirmed by a systematic review, which finds a prevalence of 63% (95%CI 55 to 70) (Foley 2013 **Level IV SR**, 17 studies, n=5,319).

A mechanism-based classification distinguishes the following types of pain related to multiple sclerosis (Truini 2013 **NR**):

- trigeminal neuralgia and Lhermitte's phenomenon (paroxysmal neuropathic pain directly related to the MS disease processes due to ectopic impulse generation along primary afferents) (Solaro 2013 **NR**);
- ongoing extremity pain (deafferentation pain secondary to lesion in the spinothalamocortical pathways);
- spasticity is the most common cause of pain in MS patients with 90% of patients with hypotonia experiencing pain: painful tonic spasms and spasticity pain (mixed pains secondary to lesions in the central motor pathways but mediated by muscle nociceptors);
- pain associated with optic neuritis (nerve trunk pain originating from Nervi nervorum);
- musculoskeletal pains (nociceptive pain arising from postural abnormalities secondary to motor disorders);
- migraine (nociceptive pain favoured by predisposing factors or secondary to midbrain lesions);
- treatment-induced pains.

The prevalence of headache (43%; 95%CI 33 to 52%), neuropathic extremity pain (26%; 95%CI 7 to 53%), back pain (20%; 95%CI 13 to 28%), painful spasms (15%; 95%CI 8.5 to 23%), Lhermitte's sign (16%; 95%CI 10 to 25%) and trigeminal neuralgia (3.8%; 95%CI 2 to 6%) is reported (Foley 2013 **Level IV SR**, 17 studies, n=5,319). Treatment approaches need to be targeted to the wide variety of different pain types occurring in multiple sclerosis balanced with adverse-effect profiles.

A systematic review of pharmacological management of pain in multiple sclerosis identified only two treatment approaches amenable to meta-analysis (anticonvulsants and cannabinoids) (Jawahar 2013 **Level I** [PRISMA], 15 RCTS, n unspecified). Various anticonvulsants have a pooled effect size (Cohen's d) of -1.88 (95%CI -3.13 to -0.64) on reducing pain intensity (Jawahar 2013 **Level I** [PRISMA], 4 RCTs [anticonvulsants], n=78). The pooled effect size (Cohen's d) for cannabinoids demonstrates no effect on pain intensity (0.08; 95%CI -0.74 to 0.89) (3 RCTs [cannabinoids], n=565). In contrast, a subsequent systematic review found moderate- to high-grade evidence supporting use of nabiximols to achieve modest reductions in pain as adjunctive therapy in MS-

related pain (Stockings 2018 **Level IV SR** [PRISMA], 3 RCTs and 13 studies [multiple sclerosis], n=9,958) (all 3 RCTs overlap). Adverse events occurred in 81.2% of cannabinoid-treated patients vs 66.2% of placebo treated patients (OR 2.33; 95%CI 1.88 to 2.89) (NNH 6; 95%CI 5 to 8) (10 RCTs, n=1,959); severe adverse events resulting in study withdrawal occurred in 15.8% vs 4.6% (OR 3.47; 95%CI 2.64 to 4.56) (NNH 40; 95%CI 35 to 49) (19 RCTs, n=3,265).

In spasticity due to multiple sclerosis, the treatment difference vs placebo is -0.32/10 (95%CI -0.61 to -0.04) for nabiximols (Sativex®; containing THC:cannabidiol = 1:1), with high numbers of subjects experiencing at least one adverse effect (Wade 2010 **Level I**, 3 RCTs, n=666). Overall, cannabinoids may be effective for pain and spasticity control in MS, but the effects may be relatively modest with issues of statistical significance versus clinical relevance and the lack of reporting of negative results in sponsored trials (Nielsen 2018 **Level III-3 SR**, 11 SRs of 10 RCTs and 22 studies, unspecified) (see also Section 4.11).

In MS patients, duloxetine (30 to 120 mg/d) vs placebo improved pain at wk 6 (-1.83/10 vs. -1.07/10) (Vollmer 2014 **Level II**, n=239, JS 5). Similarly, duloxetine (30 mg, then 60 mg) reduced average daily pain at 6 wk by 39% (29) vs placebo 10% (18.8) (Brown 2015 **Level II**, n=38, JS 4).

Microvascular decompression in MS related trigeminal neuralgia has shown limited effectiveness in comparison to non-MS trigeminal neuralgia; the relapse rate is up to 51% at 2 years and is complicated by sensory dysaesthesia in 11% of patients (Ferraro 2020 **Level III-2**, n=298).

Gamma knife radiosurgery may be effective compared with other interventions (Helis 2019 **Level IV**, n=74). The duration of pain relief has not been fully evaluated, although a 12 y follow-up indicated a clinically useful pain modification lasting up to 5 y with benefit from repeat Gamma knife treatment.

Overall, there is insufficient evidence to support medical or surgical therapy for MS related trigeminal neuralgia (Zakrzewska 2018 **Level IV SR**, 10 studies [medical management], 26 studies [surgical management], n unspecified). No study included long-term follow-up and all studies evaluated were of low quality.

Transcutaneous spinal direct current stimulation (ts-DCS) reduced MS-related central neuropathic pain in a pilot trial (Berra 2019 **Level II**, n=33, JS 3). Other techniques of neuromodulation may have a role in the management of MS-related pain (Abboud 2017 **NR**).

Exercise vs passive controls improves pain in patients with MS, however, the evidence is based on poor quality RCTs with high risk of bias (Demaneuf 2019 **Level I**, 10 RCTs, n=389). There is low level evidence from studies with no large-scale trials of yoga and other postural treatments in reducing acute MS pain (Aboud 2019 **NR**).

Mindfulness reduces fatigue, but not pain in multiple sclerosis (Simpson 2019b **Level I**, 10 RCTs, n=678).

8.6.6.2 | Parkinson's disease

Pain is a common distressing symptom in Parkinson's disease; between 30 and 50% of patients with Parkinson's disease have pain (Beiske 2009 **Level IV**, n=176; Fil 2013 **NR**). Pain may occur independently of Parkinson's disease, related to underlying musculoskeletal disorders (89%), radicular and peripheral neuropathic pain (31.5%) and dystonic pain (15.1%); however, Parkinsonian central pain resulting from disordered nociceptive processing has the lowest prevalence (4.1%), but highest severity, is poorly characterized and is difficult to describe not only by patients but also by neurologists (Chaudhuri 2015 **Level III-2**, n=261; Ozturk 2016 **Level IV**, n=113).

Optimization of dopaminergic therapies should always be the first step in the management of Parkinson's disease pain (Jost 2019 **NR**; Skogar 2016 **NR**). Medications used to treat pain include

specific Parkinson-related agents, mainly dopaminergic, as well as opioid and non-opioid analgesics, anticonvulsants, antidepressants particularly duloxetine, cannabinoids and botulinum toxin injections for dystonia related pain (Rukavina 2019 **NR**; Sophie 2012 **NR**; Ford 2010 **NR**). Currently, therapy is prescribed without necessarily considering special requirements of Parkinson patients and drug interactions. In many cases, pain is resistant to standard therapies: physiotherapy is essential in the management of Parkinson's disease related pain.

Tapentadol improved pain related to Parkinson's disease, but also anxiety, depression and quality of life (Freo 2018 **Level IV**, n=21).

Subthalamic Nucleus deep brain stimulation (DBS) is often used to improve motor function in advanced Parkinson's disease, but improvement in pain with this treatment has been observed, too. Severity of pain (from mean pain score 6.2/10 (SD 2.5) to 3.5/10 (SD 2.2) and number of body parts affected by pain (from 21 to 8) decreased over an 8 y follow-up after surgery; however, new pain developed in 75% of patients (Jung 2015 **Level IV**, n=24). In a comparison of Subthalamic Nucleus vs Globus Pallidus Internus DBS, both techniques provided similar analgesia (from 4.4/10 [1.67] before surgery to 1.1/10 [1.39] 4 mth after surgery) (Gong 2020 **Level III-3**, n=64).

8.6.6.3 | Central post-stroke pain

Central pain develops in 8–35% of stroke patients (Kumar 2009 **NR**). It is not only a consequence of thalamic stroke but also lateral medullar and parietal cortical stroke or ischaemic events affecting the spinothalamic or trigeminothalamic pathways (Flaster 2013 **NR**; Akyuz 2016 **NR**). The majority of the cases are intractable and unresponsive to analgesic treatment. Electrical stimulation such as deep brain stimulation and repetitive transcranial magnetic stimulation seems to be effective in certain cases: anticonvulsants, antidepressant, an opioid antagonist, acupuncture and transcutaneous magnetic stimulation all have minimal effect on pain (Mulla 2015 **Level I** [PRISMA], 8 RCTs, n=459).

IV lidocaine (Attal 2000 **Level II**, n=6 [poststroke], JS 5) and IV propofol in subhypnotic doses (Canavero 2004 **Level II**, n=44, JS 5) may provide short-term relief in central poststroke pain. Amitriptyline was more effective than placebo and carbamazepine (which were equivalent) (Leijon 1989 **Level II**, n=15, JS 4). Lamotrigine was moderately effective and well tolerated in central poststroke pain (Vestergaard 2001 **Level II**, n=30, JS 5). Pregabalin in poststroke pain did not result in significant pain relief at the endpoint of the trial but there was a profound placebo response and pain relief at other time points and secondary outcomes were in favour of pregabalin (Kim 2011a **Level II**, n=219, JS 5). The SSRI fluvoxamine showed benefit in poststroke pain (Shimodozono 2002 **Level IV**, n=31).

Non-invasive brain stimulation by two approaches (direct current stimulation [DCS] and repetitive transcranial magnetic stimulation) reduces intensity of post-stroke pain and also experimental pain sensitivity, however, based on low-quality evidence (Ramger 2019 **Level III-3 SR**, 1 RCT & 5 studies, n=111). Motor cortex stimulation specifically reduces refractory post-stroke pain by 35.2% (Mo 2019 **Level IV SR**, 12 studies, n=198).

Acupuncture may reduce post-stroke pain (MD −1.59; 95%CI −1.86 to −1.32]) (25 RCTs), however with low certainty due to poor study quality (Liu 2019b **Level I**, 38 RCTs, n=3,184).

On the basis of the limited data available, a practical guideline recommends trials of amitriptyline, lamotrigine, gabapentin or pregabalin or a combination of these to treat central poststroke pain with consideration of non-invasive brain stimulation for refractory patients (Kim 2014b **GL**). However, the available evidence suggests limited beneficial effect of any of the therapies that have been evaluated in RCTs and clinical practice guidelines are mainly empirical.

8.6.6.4 | Trigeminal neuralgia

Exacerbations of trigeminal neuralgia can present as acute neuropathic pain.

For acute exacerbations of trigeminal neuralgia, local anaesthetic (mainly lidocaine [administered ophthalmic, nasal or oral mucosal, trigger point injection, IV infusion, nerve block), anticonvulsants (phenytoin or IV fosphenytoin) and SC or IN sumatriptan reduce pain by 50% within 24 h (Moore 2019 **Level IV SR**, 4 RCTs & 14 studies, n unspecified); there is very limited evidence supporting IV magnesium sulphate and botulinum toxin by trigger point injection.

Sumatriptan, IN and IV lidocaine and botulinum toxin provide better analgesia vs placebo and ophthalmic proparacaine based on pooled estimates in a Bayesian mixed treatment comparison network meta-analysis (Sridharan 2017 **Level I** [NMA], 11 RCTs, n unspecified); the evidence is very low quality except for botulinum toxin. Pulsed and combined continuous and pulsed radiofrequency thermocoagulation may be the most effective invasive therapies.

Topiramate is as effective as carbamazepine at 1 mth after treatment commencement and slightly more effective at the 2 mth endpoint in trigeminal neuralgia (RR 1.20; 95%CI 1.04 to 1.39) (Wang 2011 **Level I**, 6 RCTs, n=354). All included RCTs were of poor methodological quality; this is also an issue for carbamazepine trials, which show probable effectiveness over placebo (Wiffen 2014 **Level I** [Cochrane], 10 RCTs, n=480). There is insufficient evidence to support or refute the use of gabapentin for trigeminal neuropathic pain (Ta 2019 **Level I** [PRISMA}, 2 RCTs, n=95). There is insufficient evidence to support the use of any nonantiepileptic medications (tizanidine, pimozide, tocainide) in trigeminal neuralgia (Zhang 2013c **Level I** [Cochrane] 3 RCTs [systemic medications], n=92). However, IV infusion of magnesium/lignocaine once/wk for 3 wk resulted in reduction of pain in patients with trigeminal neuralgia not responding to previous treatments (Arai 2013a **Level IV**, n=9). Duloxetine has been shown to have an effect in trigeminal neuralgia (Anand 2011 **Level IV**, n=15).

Topical ophthalmic anaesthesia has been studied with varying results. Proparacaine hydrochloride 0.5% was not superior to placebo (Zhang 2013c **Level I** [Cochrane] 1 RCT [proparacaine hydrochloride], n=47). Amethocaine 1% eye drops reduced paroxysms of pain in trigeminal neuralgia (Brill 2010 **Level IV**, n=40). Intraoral lignocaine 8% was also effective (Niki 2014 **Level II**, n=24, JS 4).

Motor cortex stimulation (MCS) has a positive effect on refractory pain and the total percentage improvement was 46.5% in trigeminal neuropathic pain (Mo 2019 **Level IV SR**, 12 studies, n=198).

Published guidelines mainly focus on chronic pain medications but do not identify sufficient evidence for the effectiveness of any IV medication in the acute setting (Cruccu 2008 **GL**). The same guidelines rate carbamazepine as effective and oxcarbazepine as probably effective and suggest that baclofen, oxcarbazepine, gabapentin, lamotrigine, tizanidine and pimozide may be considered, if the first-line medications are ineffective. An updated review of the evidence supports carbamazepine and oxcarbazepine with insufficient data to support baclofen, lamotrigine and gabapentin (Zakrzewska 2014 **NR**).

KEY MESSAGES

1. Various anticonvulsants (**U**) (**Level I** [PRISMA]) and duloxetine (**N**) (**Level II**) have beneficial effects in the treatment of neuropathic pain associated with multiple sclerosis
2. Cannabinoids have a clinically small effect on spasticity caused by multiple sclerosis (**U**) (**Level I**); the effect on neuropathic pain associated with multiple sclerosis is unclear and may depend on the preparation used (**W**) (**Level I** [PRISMA]).
3. With cannabinoid use in multiple sclerosis, there is a high rate of minor adverse effects and serious adverse psychopathological effects occur in nearly 1% of patients (**U**) (**Level I**).
4. Acupuncture (**N**) (**Level I**), non-invasive brain stimulation (**N**) (**Level III-3 SR**) and motor cortex stimulation (**N**) (**Level IV SR**) may reduce post-stroke pain.
5. Local anaesthetics (mainly lidocaine) by local and systemic administration, anticonvulsants (phenytoin or IV fosphenytoin) and sumatriptan reduce pain in acute exacerbations of trigeminal neuralgia (**N**) (**Level IV SR**).
6. Motor cortex stimulation may reduce acute pain in trigeminal neuralgia (**N**) (**Level IV SR**)
7. Deep brain stimulation may improve pain relief in Parkinson's disease (**N**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Treatment of acute pain associated with neurological disorders is based largely on evidence from trials for the treatment of a variety of chronic neuropathic pain states (**S**).

8.6.7 | Acute orofacial pain

Acute orofacial pain may be caused by infective, traumatic, neuropathic, vascular, neoplastic and other pathologies (Khawaja 2015 **NR**; Zakrzewska 2013 **NR**; Hegarty 2011 **NR**). Most commonly, acute orofacial pain is due to either dental or sinus disease. It may also be associated with flare-ups of more chronic orofacial pain syndromes eg temporomandibular disorders (TMDs; see Section 8.6.7.4 below), trigeminal neuralgia (see Section 8.6.6.4 above), migraine and other primary headaches (see Section 8.6.5 above). Pain may also be referred from adjacent structures such as the cervical spine, ear and throat.

Post-traumatic neuropathic orofacial pain (including post-traumatic trigeminal neuropathy) may be caused by nerve injury secondary to common dental surgical procedures eg extraction of teeth, root canal therapy, local anaesthetic injections or placement of dental implants. Such orofacial pain conditions may be exacerbated by repeated procedures, incorrect treatment and comorbid psychological factors.

A thorough medical/dental history and clinical examination (particularly of the mouth, jaw and cranial nerves) are essential components of the assessment of acute orofacial pain (Zakrzewska 2013 **NR**; Hegarty 2011 **NR**).

Recurrent or persistent orofacial pain may require additional biopsychosocial assessment and appropriate multidisciplinary management (de Leeuw 2018 **NR**; Vickers 2000 **NR**).

8.6.7.1 | Acute dental pain

In general, patients suffering acute oral and dental pain should be referred to a dentist for appropriate diagnosis and management. NSAIDs and emergency pulpectomy reduces pain in patients with acute apical periodontitis (Sutherland 2003 **Level I**, 8 RCTs, n=531), but there is insufficient evidence to determine if the addition of antibiotics reduces pain due to irreversible pulpitis (Agnihotry 2019 **Level I** [Cochrane], 1 RCT, n=40) or apical periodontitis or abscess (Cope 2018 **Level I** [Cochrane], 2 RCTs, n=62). Unless it has been established that infection is the cause, it is inappropriate for antibiotics to be prescribed, even though they may provide some symptomatic relief (Abbott 2007 **NR**). Pulpitis due to extension of caries into the pulp or pulp exposure may lead to pulp necrosis and acute apical periodontitis.

The use of local anaesthetics to permit dental treatment is not presented here as it is deemed beyond the scope of this document.

8.6.7.2 | Acute postoperative dental pain

Common dental surgical procedures, particularly tooth extractions and endodontic treatments, are frequently associated with acute postoperative pain, requiring pharmacological management.

Paracetamol and NSAIDs

Acute pain after third molar extraction is the most extensively studied model for testing postoperative analgesics in single-dose investigations. Nonselective NSAIDs or coxibs are recommended as "first-line" analgesics following third molar extraction (Derry 2011 **Level I**, 155 RCTs, n=16,104), however paracetamol is also safe and effective with a dose of 1,000 mg providing better pain relief than lower doses (Weil 2007 **Level I** [Cochrane], 21 RCTs, n=1,968). The best available evidence suggests the use of NSAIDs either with or without paracetamol is effective and well-tolerated (Moore 2018 **Level I**, 5 SRs, n unspecified).

Nonselective NSAIDs are more effective than paracetamol or codeine (either alone or in combination) (Ahmad 1997 **Level I**, 33 RCTs, n=5,171). Ibuprofen (200–512 mg) specifically is

superior to paracetamol (600–1,000 mg) in this setting and combining these two drugs improves analgesia further (Bailey 2014 **Level I** [Cochrane], 7 RCTs, n=2,241).

Based on a meta-analysis of limited quality, pre-emptive use of NSAIDs does not appear to be effective in reducing postoperative pain in this setting (OR 2.30; 95%CI 0.60 to 8.73) (4 RCTs, n=298) (Costa 2015 **Level I**, 6 RCTs, n=420).

For acute pain of endodontic origin, NSAIDs are the analgesic of choice (Aminoshariae 2016 **Level I** [PRISMA], 27 RCTs, n=400). When NSAIDs are not effective on their own, there is support for combining these with paracetamol, tramadol or an opioid; moderate evidence supports the use of steroids in symptomatic irreversible pulpitis.

In patients with preoperative pain, ibuprofen 600 mg and ibuprofen 600 mg/paracetamol 1,000 mg are similarly effective and provide superior analgesia after endodontic treatment vs placebo (Smith 2017a **Level I** [PRISMA], 15 RCTs, n=1,107). Ketoprofen 50 mg and naproxen 500 mg may be effective alternatives.

A number of RCTs not included in the above meta-analyses support their overall conclusions. The combination of paracetamol 1,000 mg with ketoprofen 100 mg was more effective than either drug given alone (Akural 2009 **Level II**, n=76, JS 5). IM/IV ketorolac 30 mg provided better analgesia with fewer adverse effects than IM pethidine 100 mg (Fricke 1992 **Level II**, n=145, JS 5) or IV tramadol 50 mg (Ong 2004 **Level II**, n=64, JS 3). IV meloxicam 60 mg showed faster onset of then longer-lasting analgesic effect than PO ibuprofen 400 mg (Christensen 2018 **Level II**, n=230, JS 5). PO meloxicam 15 mg provided superior analgesia to PO diclofenac 100 mg in a small RCT (Orozco-Solis 2016 **Level II**, n=36, JS 4).

In a direct comparison, PO diclofenac 50 mg provided superior analgesia to PO ibuprofen 400 mg and PO paracetamol 1,000 mg (Gazal 2017 **Level II**, n=120, JS 5).

Coxibs are of similar efficacy to nsNSAIDs in acute postoperative dental pain. Single-dose celecoxib 200 mg is less effective than ibuprofen 400 mg (Chen 2004 **Level I**, 18 RCTs, n=2,783); while celecoxib 400 mg provided similar analgesia to ibuprofen 400 mg with increased time to rescue analgesia following dental surgery (Cheung 2007 **Level II**, n=171, JS 5). In a comparison of PO celecoxib (400 mg, then 200 mg every 12 h), ibuprofen (400 mg every 8 h) and tramadol (100 mg PO every 8 h), celecoxib was the most effective analgesic (Akinbade 2018 **Level II**, n=135, JS 4). Single daily doses of etoricoxib 90 mg and 120 mg were similar in analgesic efficacy to ibuprofen 600 mg every 6 h but longer lasting, as well as superior to a paracetamol 600mg/codeine 60 mg combination (Brown 2013 **Level II**, n=588, JS 5).

A combination of oxycodone/ibuprofen (5/400 mg) was more effective than other combinations of paracetamol, ibuprofen, oxycodone or hydrocodone or placebo for analgesia following dental surgery (Litkowski 2005 **Level II**, n=249, JS 5).

A systematic review to investigate the influence of pain models revealed that the placebo response for analgesia was significantly lower post third molar extraction pain than in other acute pain models (Barden 2004a **Level I**, 160 RCTs, n=14,410).

Tramadol

Tramadol 100 mg had a similar efficacy to aspirin/weak opioid or paracetamol/weak opioid combinations in treating acute dental pain (Moore 1997 **Level I**, 18 RCTs, n=3,453). A tramadol/paracetamol combination is superior to tramadol alone with fewer adverse effects due to a reduced tramadol dose (Edwards 2002a **Level I**, 7 RCTs, n=1,376; Fricke 2004 **Level II**, n=456, JS 5) and was comparable to a codeine/acetaminophen/ibuprofen combination preparation (Jung 2004 **Level II**, n=128, JS 5).

However, tramadol provides inferior analgesia with an increased rate of adverse events vs NSAIDs in the treatment of acute dental pain (Isiordia-Espinoza 2014 **Level I**, 5 RCTs, n=200). This is confirmed by RCTs not included in this meta-analysis. PO Tramadol 100 mg was significantly less

effective than PO naproxen 500 mg (Mehrvarzfar 2012 **Level II**, n=100, JS 5). In comparison of PO tramadol (100 mg every 8 h), PO celecoxib (400 mg, then 200 mg every 12 h) and PO ibuprofen (400 mg every 8 h), tramadol was the least effective analgesic (Akinbade 2018 **Level II**, n=135, JS 4).

Steroids

Perioperative steroid administration reduced swelling and trismus, but not pain following third molar extraction (Markiewicz 2008 **Level I**, 12 RCTs, n=287). However, two subsequent studies suggested there might be an analgesic benefit from dexamethasone (Klongnoi 2012 **Level II**, n=20, JS 2), with dexamethasone 4 mg being similarly effective to 120 mg etoricoxib (Sotto-Maior 2011 **Level II**, n=50, JS 3).

A submucosal injection of dexamethasone 4 and 8 mg immediately before surgery similarly reduced postoperative facial swelling, but not pain or trismus, vs placebo at 48 h (Grossi 2007 **Level II**, n=72, JS 5). A single 40 mg injection of methylprednisolone into the masseter muscle following third molar extraction reduced pain, swelling and trismus (Vegas-Bustamante 2008 **Level II**, n=35, JS 5).

Following root canal treatment, there is an analgesic effect from steroid use, however, with marked heterogeneity of the included RCTs (Iranmanesh 2017 **Level I**, 18 RCTs, n unspecified)

Painful irreversible pulpitis may be alleviated for up to 24 h by administering dexamethasone (4 mg PO or by intraligamentary or root canal injection) (Nogueira 2018 **Level I** [PRISMA], 5 RCTs, n=292).

Ketamine (topical or infiltrated)

After mandibular molar extraction, topical administration (to the extraction sockets on resorbable gelatine sponges) of ketamine 0.5 mg/kg vs tramadol 1 mg/kg vs saline achieved the lowest pain scores and rescue analgesic use for the first 24 h after surgery (Gonul 2015 **Level II**, n=90, JS 2). In a similar setting, the addition of 0.3 mg/kg ketamine to lidocaine 2% for the local anaesthesia (inferior alveolar, lingual and buccal nerve blocks) reduced pain at 1 and 4 h and facial swelling at 1 d, while improving mouth opening up to 7 d (Kumar 2015 **Level II**, n=60, JS 1).

Pregabalin

Postoperative administration of PO pregabalin 75 mg provided better analgesic effects than administration before third molar extraction surgery (Cheung 2012 **Level II**, n=34, JS 5).

Nonpharmacological treatment

After 3rd molar extraction, cryotherapy is effective at reducing oedema (Fernandes 2019 **Level IV SR**, 11 studies, n=721). Results were mixed for an effect on pain where 5 of 11 studies found beneficial effect, but no meta-analysis was performed due to non-standardised evaluation methods. Facial compression reduced pain for up to 3 d, with no additional benefit from ice packs (Forouzanfar 2008 **Level II**, n=95, JS 5).

Acupuncture may have a beneficial effect on acute dental pain but the quality of evidence is limited (Ernst 1998 **Level III-1 SR**, 16 studies, n=941).

Low-level laser energy irradiation fails to reduce either pain or swelling after removal of third molar teeth, but reduces trismus slightly (Brignardello-Petersen 2012 **Level I**, 10 RCTs, n=581). This is contradicted by a subsequent meta-analysis which reports low-level laser therapy as effective for the treatment of pain, swelling and trismus (He 2015b **Level I** [PRISMA], 6 RCTs, n=193) (2 RCTs overlap). A subsequent RCT supports the effects on pain and swelling described in the latter meta-analysis (Eshghpour 2016 **Level II**, n=44, JS 3).

For paediatric patients, see Section 10.4 and 10.6.6

Systemic analgesics

In adults, paracetamol (2 of 2 RCTs), NSAIDs (2 of 9 RCTs: ibuprofen, ketoprofen, rofecoxib, lornoicam, celecoxib, parecoxib vs placebo or active comparator aspirin, diclofenac or ketorolac), dexamethasone (5 of 10 RCTs), gabapentinoids (3 of 3 RCTs), and dextromethorphan (2 RCTs) provide some limited analgesia on POD 1 after tonsillectomy (Tolska 2019 **Level I** [PRISMA], 29 RCTs, n=1,816). The limited efficacy of single medications suggests that multimodal analgesic strategies are required.

The risks of bleeding with the use of NSAIDs are discussed in detail in Section 4.2.1.2 in adult and in Section 10.4.2.3 in paediatric patients.

Alpha-delta-2 ligands

Preoperative gabapentin (6 RCTs) and pregabalin (3 RCTs) similarly reduce pain in the first 8 h, analgesic requirements in the first 24 h and PONV without increasing adverse effects after tonsillectomy (Hwang 2016a **Level I** [PRISMA], 8 RCTs [3 adult, 2 mixed, 3 paediatric], n=608; Tolska 2019 **Level I** [PRISMA], 4 RCTs [alpha-2-delta ligands], n=255) (2 RCTs overlap).

Steroids

Dexamethasone in doses >10 mg over 24 h given to adults undergoing tonsillectomy reduces pain by 23% at 4 h (MD -1.4/10; 95% CI -1.6 to -1.2) (Tolska 2019 **Level I [**PRISMA], 10 RCTs [dexamethasone], n=590). In tonsillectomy in adults and children, all steroids reduce pain severity at all time points up to POD 7 with a peak benefit on POD 1 (SMD -0.99/10; 95%CI -1.32 to -0.67) (41 RCTs, n=3,477) (Titirungruang 2019 **Level I** [PRISMA], 64 RCTs [22 adult], n=6,327) (8 RCTs overlap). These effects are similar for systemic vs local steroid administration. Furthermore, steroids reduce PONV (OR 0.31; 95%CI 0.24 to 0.40) (46 RCTs, n=4,784), while not increasing the risk of primary (OR 0.96; 95%CI 0.55 to 1.67) (15 RCTs, n=1,736) or secondary haemorrhage (OR 1.05; 95%CI 0.74 to 1.51) (23 RCTs, n=2,440).

Antibiotics

Perioperative antibiotics show no benefit in decreasing post-tonsillectomy pain (3 RCTs positive, 4 RCTs no difference, 1 RCT negative) and secondary haemorrhage rates (12 RCTs, n=1,397); adverse effects were more common with their use (Abdelhamid 2019 **Level I**, 12 RCTs, n=1,397). The conclusions reflected those of an earlier Cochrane review which found no difference in pain (6 RCTs), need for analgesia (6 RCTs) or secondary haemorrhage (7 RCTs) (Dhiwakar 2012 **Level I** [Cochrane], 10 RCTs, n=1,035) (5 RCT overlap).

Peritonsillar infiltration with local anaesthesia and analgesics

Peritonsillar injection or topical application of local anaesthetics produce equally modest reductions in post-tonsillectomy pain for up to 24 h (Grainger 2008 **Level I**, 13 RCTs, n=777). Ropivacaine 1.0% with adrenaline resulted in better pain relief up to 4 d after tonsillectomy than either bupivacaine 0.25% with adrenaline or placebo (Arikan 2008 **Level II**, n=58, JS 5). Peritonsillar infiltration with bupivacaine provided pain relief comparable to rectal paracetamol (Dahi-Taleghani 2011 **Level II**, n=110, JS 2).

Dexamethasone added to local anaesthetics reduces pain intensity, analgesic requirements and PONV (3 RCTs, n=361) (Vlok 2017 **Level I**, 11 RCTs, n=854). Magnesium added to local anaesthetics reduces pain intensity, analgesic requirements and incidence of laryngospasm, but not PONV (4 RCTs, n=240). There is only limited support for the addition of pethidine (1 RCT, n=80) or tramadol (1 RCT, n=60), and addition of clonidine shows no effect (2 RCTs, n=123).

Infiltration of the tonsillar bed with tramadol (Atef 2008 **Level II**, n=40, JS 5) as well as an equivalent IM tramadol dose reduced pain and analgesic requirements in the first few hours after tonsillectomy vs placebo (Ugur 2008 **Level II**, n=45, JS 5). Peritonsillar infiltration with tramadol resulted in better early pain control with preoperative infiltration (up to 2 h postop), but better late (beyond 8 h) pain control with postoperative infiltration (Maryam 2017 **Level II**, n=80, JS 3). See also Section 10.4.4.12.

Topical administration

There is poor and inconsistent evidence on the analgesic effects of oral rinses, mouthwashes and sprays after tonsillectomy, although lidocaine spray is more effective than saline spray (1 RCT) (Fedorowicz 2011 **Level I** [Cochrane], 6 RCTs, n=528 [131 adults]). While in a subsequent RCT, topical ropivacaine (swabs soaked in 1% ropivacaine packed into the tonsillar beds for 5 min) vs placebo had no effect on pain after tonsillectomy (Tolska 2017 **Level II**, n=160, JS 5).

Non-pharmacological treatment

Intraoperative cryotherapy (with a cryotherapy probe [-56°C]) (1 RCT) and ice-water cooling (4°C to 10°C) (2 RCTS) reduces post-tonsillectomy pain scores consistently by 21 to 32% (0.9/10 to 1.8/10) (Raggio 2018 **Level I** [PRISMA], 3 RCTs, n=153).

Acupuncture vs control or sham may reduce pain intensity, analgesic requirements and PONV for up to 48 h after tonsillectomy with high levels of heterogeneity (Cho 2016 **Level I**, 12 RCTs, n=1,025).

Honey in children vs placebo reduces pain and analgesic use for up to 5 to 10 d post-tonsillectomy; regimens of honey administered varied substantially in volume (4 to 15 mL), frequency (daily to hourly) and duration (1 to 10 d) (Hwang 2016b **Level I** [PRISMA], 4 RCTs n=264; Lal 2017 **Level I** [QUOROM], 8 RCTs n=545) (4 RCTs overlap). The analgesic medication regimens used in the included studies were not clear.

8.6.7.4 | Acute pain associated with temporomandibular disorders

Temporomandibular disorders (TMDs) are a group of musculoskeletal pains affecting the masticatory muscles and/or temporomandibular joints (TMJs) and are the most common cause of orofacial pain apart from the teeth (Zakrzewska 2013 **NR**; Hegarty 2011 **NR**). The common TMDs include masticatory myalgia, myofascial pain, TMJ disc interference disorders and TMJ degenerative joint disease. The primary TMD symptoms include painful limitation of mouth opening and/or deviation of the mandible on opening, TMJ tenderness, TMJ crepitus and/or clicking noise and masticatory muscle pain or tenderness. Headaches are often an associated feature. Management approaches to TMD pain include medication, physiotherapy, occlusal splints, self-management strategies, and interventions based on cognitive behavioural approaches.

There is limited evidence for the successful pharmacological management of TMD pain (Mujakperuo 2010 **Level I** [Cochrane], 11 RCTs, n=496). A subsequent systematic review and network meta-analysis identified NSAIDs as well as corticosteroid and hyaluronate injections as successful treatments for TMD joint pain (15 RCTs, n=790), while the muscle relaxant cyclobenzaprine is effective in TMD muscle pain (9 RCTs, n=375) (Haggman-Henrikson 2017 **Level I** [NMA], 41 RCTs, n=2,033). Based on transferable evidence from similar conditions, topical NSAIDs are a treatment option also as in adult patients with acute pain resulting from strains, sprains or sports injuries, topical diclofenac, ibuprofen, ketoprofen, piroxicam and indomethacin are effective vs placebo, whereas benzydamine is not (Derry 2015 **Level I** [Cochrane] 61 RCTs, n=8,386).

The evidence for IA morphine, tramadol, buprenorphine, fentanyl and NSAIDs was inconclusive due to a small number of low-quality studies for temporomandibular joint arthrocentesis (Gopalakrishnan 2018 **Level I** [PRISMA], 3 RCTs, n=91 [& 3 other studies]).

Low-level laser therapy in the treatment of TMD has no analgesic benefit vs placebo (WMD -19.4; 95%CI -40.8 to 2.0), but improves functional outcomes (Chen 2015 **Level I**, 14 RCTs, n=454).

8.6.7.5 | Acute pain associated with pharyngitis

Systemic analgesics

Paracetamol, nsNSAIDs, coxibs and opioids, administered as monotherapy or in combination, were effective in the treatment of pain associated with acute pharyngitis (Thomas 2000 **Level I**, 17 RCTs, n=3,259).

Corticosteroids

Corticosteroids provide relief of pain, in particular in patients with severe or exudative sore throat (Hayward 2012b **Level I** [Cochrane], 8 RCTs, n=743). Here, corticosteroids in combination with analgesics and antibiotics increase the likelihood of complete resolution of pain at 24 h (RR 3.2; 95%CI 2.0 to 5.1) and the time to onset of pain relief by 6.3 h (6 RCTs, n=609). In acute pharyngitis potentially caused by group A beta-haemolytic Streptococcus, corticosteroids reduce the time to clinically meaningful pain relief; however provide only a small reduction in pain scores at 24 h (Wing 2010 **Level I**, 10 RCTs, n=1,096) (8 RCTs overlap). Corticosteroids administered in a single dose (most commonly 10 mg dexamethasone orally) provide pain relief for sore throat including pharyngitis more effectively and faster than placebo (Sadeghirad 2017 **Level I**, 10 RCTs [7 RCTs in adults], n=1,426) (9 RCTs overlap). On the basis of these findings, clinical practice guidelines make a weak recommendation to treat acute sore throat with a single dose of oral corticosteroid (Aertgeerts 2017 **GL**).

Dexamethasone decreases incidence and severity of sore throat after extubation when administered IV at induction (Kuriyama 2019 **Level I** [PRISMA], 15 RCTs, n=1,849).

Following drainage and antibiotics for peritonsillar abscess, a single dose of IV corticosteroid reduces fever and with less certainty pain, trismus and hospital LOS (Hur 2018 **Level I** [PRISMA], 3 RCTs, n=153).

Antibiotics

Antibiotics for sore throat reduce pain, headache and fever by 50% on d 3; this effect was more pronounced if throat swabs were positive for Streptococcus (Spinks 2013 **Level I** [Cochrane], 27 RCTs, n=12,835). Antibiotics reduce throat soreness at 3 d vs controls (RR 0.68; 95%CI 0.59 to 0.72). Antibiotics also shortened the duration of symptoms by 16 h, although the absolute benefits are modest.

Topical analgesics

Topical analgesics such as lozenges containing amylmetacresol/2,4-dichlorobenzylalcohol (AMC/DCBA) (Weckmann 2017 **Level I** [PRISMA], 3 RCTs, n=661), flurbiprofen (Watson 2000 **Level II**, n=301, JS 5), ibuprofen (Bouroubi 2017 **Level II**, n=385, JS 5) and benzocaine (Chrubasik 2012 **Level II**, n=50, JS 3) as well as benzydamine spray (Thomas 2000 **Level I**, 17 RCTs, n=3,259) or benzydamine/chlorhexidine spray (Cingi 2010 **Level II**, n=164, JS 5) provide analgesia superior to placebo in acute sore throat with minimal adverse effects.

Ketamine gargle vs placebo or no treatment reduces the incidence of postoperative sore throat for up to 24 h (RR 0.42 to 0.52 over time points 0 to 24 h) based on high-quality evidence (Mayhood 2015 **Level I** [PRISMA] 5 RCTs, n=291); systemic absorption is an unknown factor.

Ambroxol, a mucolytic substance with local anaesthetic properties, reduces pain of pharyngitis slightly (with questionable clinical relevance) vs placebo (mint lozenges) (Chenot 2014 **Level I**, 3 RCTs, n=1,772).

Nonpharmacological treatment

A single-point acupuncture treatment at large intestine meridian for pain of acute pharyngitis and tonsillitis was not more effective than sham laser acupuncture (Fleckenstein 2009 **Level II**, n=60, JS 5).

8.6.7.6 | Acute pain associated with sinusitis and otitis media

Treatment of sinusitis and otitis media is primarily symptomatic using analgesics and antipyretics; it may be appropriate to use nsNSAIDs, coxibs, paracetamol, weak opioids or tramadol, based on evidence for treatment of dental pain. Evidence based clinical practice guidelines for the diagnosis and treatment of acute sinusitis (Chandran 2013 **GL**; Meltzer 2011 **GL**) and acute otitis media are published (Rosenfeld 2014 **GL**). Evidence for individual interventions are presented here.

Antihistamines and/or decongestants

Antihistamines and/or decongestants have no clinically relevant benefit in acute otitis media (Coleman 2008 **Level I** [Cochrane], 15 RCTs, n=2,695).

Antibiotics

Antibiotic treatment of acute otitis media vs placebo or control has no effect on acute pain after 24 h and leads to some pain reduction at 2–3 d, but with an $NNT_{50\%}$ of 20 (Venekamp 2015 **Level I** [Cochrane], 13 RCTs, n=3,401). Individual patient data meta-analysis from 959 children show no better analgesia at d 3 to 7 and from 247 children at d 7 to 14. As the effects on pain are questionable and adverse effects (such as vomiting, diarrhoea or rash) are increased (RR 1.38; 95%CI 1.19 to 1.59; NNH 14), for most children with mild disease antibiotic use might not be justified.

Steroids

Oral corticosteroids as a monotherapy are not effective and in combination with antibiotics may be modestly beneficial for symptoms of acute sinusitis (Venekamp 2014 **Level I** [Cochrane] 5 RCTs, n=1,193).

Topical treatment

For sinusitis, IN corticosteroids have consistently significant benefits for facial pain (Hayward 2012a **Level I**, 6 RCTs, n=2,495). Improvement or resolution of symptoms are more likely with IN corticosteroids than placebo or control, with higher doses being more effective (Zalmanovici Trestioreanu 2013 **Level I** [Cochrane], 4 RCTs, n=1,943) (4 RCTs overlap).

A phytotherapeutic nasal spray containing *Cyclamen europaeum* provided better facial pain relief than placebo in sinusitis (Pfaar 2012 **Level II**, n=99, JS 3).

Topical local anaesthetic drops (benzocaine/ antipyrine or lidocaine) used in acute otitis media in children, in addition to PO analgesia, are effective vs saline at 10 min (RR 2.13; 95%CI 1.19 to 3.80) and 30 min after instillation (RR 1.43; 95% CI 1.12 to 1.81) (2 RCTs, n=117) (Foxlee 2011 **Level I** [Cochrane], 5 RCTs, n=391). Superiority of local anaesthetic (amethocaine/ antipyrine) vs naturopathic drops (3–4 herbal extracts in olive oil) is not established in three RCTs (in addition to paracetamol in one RCT and amoxicillin in one RCT) (3 RCTs, n=274 [analysed]).

8.6.7.7 | Acute pain associated with oral ulceration/stomatitis

Acute oral ulceration/stomatitis due to trauma (physical, chemical, thermal), infection (eg herpes simplex), drugs, radiation or chemotherapy (mucositis) may be extremely painful and debilitating. Mucositis is a common adverse effect of high-dose chemo- and radiotherapy for

malignancies affecting the head and neck, for conditioning prior to bone marrow transplants and treatment of leukaemia. For details of chemotherapy-induced mucositis, see Section 8.9.8.2.

For recurrent aphthous stomatitis, laser treatment (Nd:YAG laser ablation, CO2 laser applied through a transparent gel [non-ablative] and diode laser in a low-level laser treatment [LLLT] mode) vs placebo, no therapy or topical corticosteroids leads to improved immediate and delayed pain control and reduced duration of healing (Suter 2017 **Level III-1 SR**, 10 RCTs & 1 study, n≈512).

In children with acute infectious mouth ulcers in the ED, viscous lidocaine solution applied did not enable increased oral intake (Hopper 2014 **Level II**, n=100, JS 5). However, 2% lignocaine gel was effective in children with mouth ulcers with a reduction of mucosal pain by 20/100 (+/- 18) (Coudert 2014 **Level II**, n=64, JS 5).

KEY MESSAGES

Acute dental pain

1. NSAIDs and emergency pulpectomy reduce pain in patients with acute apical periodontitis (**U**) (**Level I**) with insufficient evidence to support analgesic benefit from adding antibiotics (**S**) (**Level I** [Cochrane Review]).

Dental extraction

2. Paracetamol, nonselective NSAIDs and coxibs provide safe and effective analgesia with minimal adverse effects after dental extraction (**S**) (**Level I** [Cochrane Review]).
3. Combinations of paracetamol with ibuprofen (**U**) (**Level I** [Cochrane Review]) and other nonselective NSAIDs (**U**) (**Level I**) provide superior analgesia to either drug alone after dental extraction.
4. Tramadol provides equal analgesia to paracetamol/weak opioid and aspirin/weak opioid combinations (**U**) (**Level I** [Cochrane Review]) and tramadol/paracetamol combinations provide superior analgesia to tramadol alone after dental extraction (**U**) (**Level I**).
5. Nonselective NSAIDs and coxibs provide similar analgesia, which is superior to paracetamol, codeine, combinations of paracetamol/codeine (**U**) (**Level I**), tramadol (**S**) (**Level I**) and pethidine (**U**) (**Level II**) after dental extraction.
6. Perioperative corticosteroid administration reduces swelling, but not pain (**U**) (**Level I**), and reduces postoperative nausea (**U**) (**Level II**) after third molar extraction.

Tonsillectomy

7. Nonselective NSAIDs (**U**) (**Level I**), in particular aspirin and ketorolac (**U**) (**Level II**), increase the risk of reoperation for bleeding after tonsillectomy in adults, but not in children (**U**) (**Level I** [Cochrane Review]).
8. Intraoperative dexamethasone administration reduces postoperative pain, nausea and vomiting and time to resumption of oral intake after tonsillectomy (**S**) (**Level I** [Cochrane Review]), with no increase in adverse effects (**U**) (**Level I** [Cochrane Review]).
9. Paracetamol, NSAIDs (**S**) (**Level I** [PRISMA]), dexamethasone, preoperative alpha-2-delta ligands (**S**) and dextromethorphan are effective analgesics after tonsillectomy (**N**) (**Level I** [PRISMA]).
10. Intraoperative cryothgerapy may reduce post-tonsillectomy pain (**N**) (**Level I** [PRISMA]).
11. Oral administration of honey versus control reduces postoperative pain and analgesic use after tonsillectomy (**N**) (**Level I** [PRISMA]).
12. Peritonsillar infiltration or topical application of local anaesthetics are equally effective in producing a modest reduction in acute post-tonsillectomy pain (**U**) (**Level I**).
13. Dexamethasone, magnesium (and with limited support pethidine and tramadol) combined with local anaesthetics for peritonsillar infiltration improve analgesia and other outcomes after tonsillectomy (**N**) (**Level I**).
14. Perioperative antibiotics show no benefit in post-tonsillectomy pain, but increase adverse effects (**S**) (**Level I**).

15. Acupuncture may reduce post-tonsillectomy pain compared to control group or sham acupuncture (**N**) (**Level I**)

16. Peritonsillar infiltration with tramadol or ketamine may reduce post-tonsillectomy pain and analgesia requirements but was no more effective than equivalent doses administered parenterally (**U**) (**Level II**).

Pharyngitis

17. Corticosteroids (**S**) (**Level I** [Cochrane Review]) and antibiotics (**U**) (**Level I** [Cochrane Review]) improve analgesia and reduce duration of pain in pharyngitis.

18. Amylmetacresol/2,4-dichlorobenzylalcohol (AMC/DCBA) lozenges (**N**) (**Level I** [PRISMA]), ketamine gargle (**N**) (**Level I** [PRISMA]), benzydamine spray (**U**) (**Level I**) and other topical analgesics (**U**) (**Level II**) provide analgesia superior to placebo in acute sore throat with minimal adverse effects.

19. Corticosteroids reduce acute pain associated with peritonsillar abscess (following drainage and antibiotics) (**S**) (**Level I** [PRISMA]).

20. Paracetamol, NSAIDs (nonselective NSAIDs or coxibs) and opioids, administered as monotherapy or in combination, are effective analgesics in acute pharyngitis (**U**) (**Level I**).

Sinusitis and Otitis media

21. Oral corticosteroids have no analgesic effect in sinusitis (**U**) (**Level I** [Cochrane Review]), but intranasal corticosteroids reduce facial pain and improve recovery (**S**) (**Level I** [Cochrane Review]).

22. Antibiotic treatment of acute otitis media vs placebo or control has no effect on acute pain, only limited effect on later pain, but increases the risk of adverse effects (**N**) (**Level I** [Cochrane Review]).

23. In acute otitis media, topical local anaesthetic drops are effective in children compared to placebo and equivalent to naturopathic drops (**S**) (**Level I** [Cochrane Review]).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Codeine should not be used in children, especially after adenoidectomy or tonsillectomy, due to an increased risk of opioid-induced ventilatory impairment and death (**U**).

☑ Recurrent or persistent orofacial pain requires biopsychosocial assessment and appropriate multidisciplinary approaches (**U**).

☑ Neuropathic orofacial pain, which is often post-traumatic (iatrogenic), may be exacerbated by repeated dental procedures, incorrect drug therapy or psychosocial factors (**U**).

8.6.8 | Acute pain in patients with HIV infection

Pain is common in people infected with HIV (Ebirim 2013 **Level IV**, n=157; Namisango 2012 **Level IV**, n=302; Simmonds 2005 **Level IV**, n=100; Frich 2000 **Level IV**, n=95; Vogl 1999 **Level IV**, n=504; Larue 1997 **Level IV**; Breitbart 1996 **NR**) and may have diverse aetiologies, including HIV itself (which is a neurotropic virus), opportunistic infections and malignancies, and unrelated comorbidities (Hewitt 1997 **Level IV**, n=274; Glare 2001 **NR**; O'Neill 1993 **NR**). In untreated HIV infection, pain becomes more common as disease progresses and is almost universal among those with advanced acquired immunodeficiency syndrome (AIDS) (Kimball 1996 **Level IV**, n=157; O'Neill 1993 **NR**). Even among relatively well individuals, pain is prevalent and associated with depression and impaired function (Vogl 1999 **Level IV**, n=504; Singer 1993 **Level IV**).

Adults diagnosed with HIV today can have a near normal life expectancy with access to antiretroviral therapy, both in well-resourced and resource-limited settings (Gueler 2017 **Level III-2**, n=16,532 [HIV-positive patients]; Mills 2011 **Level IV**, n=22,315; van Sighem 2010 **Level IV**, n=4,612). This improvement in HIV prognosis has however been associated with an ageing HIV-infected population with increasing numbers of comorbidities and an ongoing high prevalence of pain (Balderson 2013 **Level IV**, n=452). The ongoing high prevalence of chronic pain among people living with HIV today has prompted the Infectious Diseases Society of America to publish specific management guidelines (Bruce 2017 **GL**).

Pain continues to be associated with poorer quality of life and impaired function among people living with HIV (Merlin 2013 **Level IV**, n=1,903; Ebirim 2013 **Level IV**, n=157; Namisango 2012 **Level IV**, n=302; Simmonds 2005 **Level IV**, n=100). Several studies have found that pain is undertreated in those with HIV infection, with both physician and patient barriers suggested (Ebirim 2013 **Level IV**, n-157; Frich 2000 **Level IV**, n=95; Breitbart 1998 **Level IV**, n=199; Larue 1997 **Level IV**, n=174; Breitbart 1999 **NR**; Breitbart 1996 **NR**). An unmet need for analgesia is one of the commonest reasons for people with HIV to use complementary therapies (Peltzer 2008 **Level IV**, n=618; Tsao 2005 **Level IV**, n=2,466). HIV/AIDS patients with diagnosed mood/anxiety or substance-use disorders report much higher levels of pain than HIV/AIDS patients without these comorbidities or the general population (Tsao 2009 **Level III-2**). Further, preliminary data support an association between perceived HIV stigma and pain in this population (Wadley 2019 **Level IV**, n=50).

8.6.8.1 | Treatment of pain in people infected with HIV

The optimal management of pain in an individual with HIV will depend on the cause of the pain. The general principles of treating the underlying cause where possible and providing adequate analgesia are the same as for any other individual with the same injury or illness. Some special considerations (particularly drug interactions) may be important and are set out below.

HIV and its treatment are frequently complicated by a distal, small-fibre, sensory neuropathy that is typically painful (painful HIV-associated sensory neuropathy) (Cherry 2012 **NR**). Prevalence rates >50% are described in cohorts exposed to stavudine (a potentially neurotoxic antiretroviral agent) (Wadley 2011 **Level IV**, n=395). Although stavudine use has been phased out, many patients living with HIV have previously been exposed to this drug. Further, a large, USA-based prospective survey found that 15% of adults with HIV who had never used stavudine are affected by painful sensory neuropathy, with older patients at higher risk (Ellis 2010 **Level IV**, n=1,539). Further follow-up of the same cohort has demonstrated new onset of distal neuropathic pain in 27% of patients after a median of 24 mth observation, associated with factors including older age, female gender, and failure to suppress HIV replication (Malvar 2015 **Level IV**, n=493).

Neuropathic pain is particularly difficult to treat in HIV. Despite anecdotal reports of individual patients responding well to each of the pain-modifying agents typically used in other small-fibre neuropathies, only smoking of cannabis, topical capsaicin and recombinant human nerve growth factor are more effective than placebo for HIV neuropathy pain (Phillips 2010 **Level I** [PRISMA], 14 RCTs, n=1,764). Smoking cannabis has only short term effects in studies with potential bias due to difficulties in patient blinding; in one trial 92% guessed treatment allocation correctly. Furthermore, no associations were found between marijuana use and either pain intensity or opioid use (Merlin 2019 **Level IV**, n=433). A meta-analysis of data on high-dose capsaicin 8% found limited efficacy with $NNT_{50\%}$ of 11 (Derry 2013c) **Level I** [Cochrane], 2 RCTs, n=801). Those with lower baseline pain scores and females may be most likely to respond (Katz 2015b **Level I**, 6 RCTs, n=1,014).

In a pilot study of hypnosis for managing HIV-neuropathy pain, 26 of 36 patients were responders with a mean 44% reduction in pain scores at 7 wk after the intervention (Dorfman 2013 **Level IV**, n=36). These data together with the larger placebo responses seen in HIV-neuropathy analgesia trials compared with studies of neuropathic pain from other causes suggest that nonpharmacological interventions may be useful in this difficult pain syndrome and warrant further study (Cepeda 2012 **Level I**, 94 RCTs, n=5,317).

The chronic nature of HIV disease as well as the many possible causes of pain in those infected mandate a holistic approach to managing HIV-associated pain. Ideally, disease-specific therapy, psychosocial interventions and physical modalities should accompany standard analgesic treatment (Glare 2001 **NR**)

8.6.8.2 | Special considerations in treating pain in patients with HIV infection

Drug interactions

Antiretroviral agents (notably non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and the "boosting" agents ritonavir and cobicistat) may cause important drug interactions by inducing and inhibiting various enzymes in the cytochrome P450 family. In addition, both cobicistat and ritonavir inhibit p-glycoprotein and can therefore increase absorption of susceptible drugs from the gastrointestinal tract. Several antiretroviral agents are also hepatically metabolised with potential for drug interactions. Predicting clinically relevant interactions is made extremely complex, both by the fact that antiretroviral drugs are used in combinations and because most interactions have not been formally studied. Updated information on likely interactions between individual antiretroviral agents (and cobicistat) and medications used to treat common comorbidities are provided by The University of Liverpool HIV Pharmacology Group at: https://www.hiv-druginteractions.org/checker (including a chart specific for interactions with a large number of analgesic medicines at https://liverpool-hiv-hep.s3.amazonaws.com/prescribing_resources/pdfs/000/000/002/original/TS_Analgesic_2019_Feb.pdf?1550073234.

The importance of routinely considering interactions with antiretroviral drugs when prescribing for individuals with HIV is highlighted by the variable interactions seen with opioids. For example, ritonavir (an HIV protease inhibitor) is a potent inhibitor of cytochrome P450 3A4. This results in clinically relevant inhibition of fentanyl metabolism (Olkkola 1999 **Level II**, n=12, JS 3), but no clinically meaningful interaction with methadone or buprenorphine (McCance-Katz 2003 **Level III-2**). Conversely, both lopinavir (another protease inhibitor) (McCance-Katz 2003 **Level III-2**) and nevirapine (a non-nucleoside reverse transcriptase inhibitor) (Arroyo 2007 **Level III-3**, n=10) significantly induce methadone metabolism and may lead to withdrawal in patients on maintenance doses. Reference to current resources such as the Liverpool site, together with involvement of a pharmacist

experienced in this area whenever possible, is strongly recommended when prescribing additional medications to patients on antiretroviral therapy.

Some medications used to treat opportunistic infections in HIV patients may also interact with analgesics. For example, both rifampicin and rifabutin may increase opioid metabolism (particularly methadone) (Finch 2002 **NR**) and fluconazole (and other azoles) may potentiate adverse effects of methadone (Tarumi 2002 **CR**). A useful online tool for checking interactions with antifungal agents and other medications, including analgesics, can be found at http://www.fungalpharmacology.org, which also offers a free app for smartphones.

HIV patients with a history of substance abuse

Pain may be more common in those with HIV and a history of injecting drugs (Martin 1999 **Level III-2**, n=211; Vogl 1999 **Level IV**, n=504) and is more likely to be inadequately treated in this group (Breitbart 1997 **Level IV**; Breitbart 1996 **Level IV**). Two cohort studies showed that that even though HIV-positive patients with a history of problematic illicit drug use/substance abuse report higher ongoing use of prescription analgesics specifically for pain, these patients continue to experience persistently higher levels of pain, relative to nonproblematic users (Tsao 2007 **Level III-2**, n=2,267; Passik 2006 **Level III-2**, n=73 [AIDS patients]). Importantly, opioid analgesia was similarly effective for treating severe pain in those with AIDS who had previously injected drugs as in those who were opioid naïve, although higher doses were required (Kaplan 2000 **Level III-2**, n=44). Similarly, patients in a methadone-maintenance program, who also suffered from HIV/AIDS-related pain, gained improved analgesia without adverse effects with use of additional methadone (Blinderman 2009 **Level IV**, n=53).

The principles of pain management in patients with a history of substance abuse are outlined in Sections 9.7 and 9.8.

KEY MESSAGES

1. High-concentration capsaicin patches have some efficacy in treating neuropathic pain in patients with HIV/AIDS (**S**) (**Level I** [Cochrane Review]).
2. Smoking cannabis has short-term efficacy in treating neuropathic pain in patients with HIV/AIDS, although potential study bias means that this is not recommended as routine treatment (**Q**) (**Level I** [PRISMA])**.**
3. HIV/AIDS patients with a history of problematic drug use report higher opioid analgesic use but also more intense pain (**U**) (**Level III-2**).
4. Pain, and notably neuropathic pain, is common in patients with HIV (**U**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ HIV/AIDS has become a chronic, manageable condition; in view of limited specific evidence, the treatment of pain in patients with HIV/AIDS should be based on similar principles to those for the management of acute, cancer and chronic pain in the general population (**S**).

☑ Interactions between antiretroviral medications, antibiotics and analgesics should be considered in this population and reference to a current guide of likely drug interactions is strongly recommended (**S**).

8.7 | Acute back pain

Acute back pain in the cervical, thoracic or, in particular, lumbar and sacral regions, is a common problem affecting most adults at some stage of their lives. The causes are rarely serious, most often nonspecific and the pain is usually self-limiting.

Appropriate investigations are indicated in patients who have signs or symptoms that might indicate the presence of a more serious condition ('red flags'). Such 'red flags' include symptoms and signs of infection (eg fever), risk factors for infection (eg underlying disease processes, immunosuppression, penetrating wounds), history of trauma or minor trauma, history of osteoporosis or taking corticosteroids, past history of malignancy, age >50 y, failure to improve with treatment, unexplained weight loss, pain at multiple sites or pain at rest, and the absence of aggravating features (Oliveira 2018 **GL SR**, 10 GL [acute low back pain]). In assessment of new acute back pain, 'red flags' to predict potential cancer as a cause have been proposed, yet the only evidence-based predictor of spinal malignancy is "*previous history of cancer*" (Henschke 2013 **SR** of diagnostic studies; Downie 2013 **SR** of diagnostic studies). A full neurological examination is warranted in the presence of lower limb pain and other neurological symptoms.

Psychosocial and occupational factors ('yellow flags') appear to be associated with an increased risk of progression from acute to chronic pain. Such factors should be assessed early in order to facilitate appropriate interventions (Oliveira 2018 **GL SR**, 10 GL [acute low back pain]).

NHMRC guidelines for the evidence-based management of acute musculoskeletal pain include chapters on acute neck, thoracic spinal and low-back pain (Australian Acute Musculoskeletal Pain Guidelines Group 2003 **GL**). In view of the high quality and extensiveness of these guidelines, and the subsequent publication of more recent international guidelines, no independent assessment of these topics has been undertaken for this document even though the Australian guidelines have been rescinded by the NHMRC because of their age. Subsequent international guidelines include those produced by:

- the American Pain Society and American College of Physicians — these cover diagnosis, treatment and medications for acute and chronic low-back pain (Chou 2007b **GL**; Chou 2007a **GL**);
- the Orthopedic Section of the American Physical Therapy Association (APTA) — these also cover acute and chronic back pain (Delitto 2012 **GL**);
- the Toward Optimized Practice (TOP) Program of Canada (Canada TOP 2015 **GL**);
- the NSW Agency for Clinical Innovation (NSW Agency for Clinical Innovation 2016 **GL**);
- the American College of Physicians (ACP) – presenting a clinical practice guideline on noninvasive treatments for acute, but also subacute (and chronic) low back pain (Qaseem 2017 **GL**);
- the Institute for Clinical Systems Improvement (ICSI 2018 **GL**);
- the National Institute for Clinical Excellence (NICE 2018 **GL**).

Overviews of these guidelines have been published (Koes 2010 **GL**; Verhagen 2016 **GL**) including a particularly useful overview of all recent guidelines (Oliveira 2018 **GL SR**, 10 GL [acute low back pain]). The reader is referred to these references for the diagnosis and management of acute back pain.

8.8 | Acute musculoskeletal pain

A summary of findings relating to acute musculoskeletal pain can be found in *Evidence-based Management of Acute Musculoskeletal Pain*, published by the Australian Acute Musculoskeletal Pain Guidelines Group and endorsed by the NHMRC (Australian Acute Musculoskeletal Pain Guidelines Group 2003 **GL**). In view of the high quality and extensiveness of these guidelines, no further assessment of these topics has been undertaken for this document, even though these guidelines have been rescinded by the NHMRC in view of a lack of an update.

An updated clinical practice guideline for acute musculoskeletal pain has been published by the Musculoskeletal Pain Task Force of the Orthopaedic Trauma Association in the USA (Hsu 2019 **GL**).

Guidelines for specific conditions such as acute shoulder pain by the American College of Radiology (Wise 2011 **GL**) or even more specific for acute and chronic subacromial pain by the Dutch Orthopaedic Association (Diercks 2014 **GL**) have been published.

A systematic review of clinical practice guidelines has been published, which condenses these to eleven key recommensations (Lin 2020 **SR of GLs**, 11 GLs).

Furthermore, the National Institute for Clinical Excellence (NICE) offers access to a multitude of guidelines via a website providing pathways for musculoskeletal conditions: https://pathways.nice.org.uk/pathways/musculoskeletal-conditions

8.9 | Acute cancer pain

Acute pain in the cancer patient may signify an acute oncological event including pathological fracture or microfracture, spinal cord or nerve compression, visceral obstruction or cutaneous ulceration due to tumour. Cancer pain may become acute in the presence of infection, and during diagnostic or therapeutic interventions. Anticancer therapies, including surgery, chemotherapy, hormonal therapy and radiotherapy, may be associated with both acute and chronic pain of a nociceptive or neuropathic nature. In progressive cancer, there is increasing potential for acute clinical change.

Pain is commonly associated with cancer and is one of the most feared symptoms (Swarm 2019 **GL**). The prevalence of cancer pain in an adult population is 39.3% after curative treatment, 55.0% during anticancer treatment and 66.4% in people with advanced, metastatic or terminal disease, with 38.0% of all patients reporting moderate to severe (NRS 5/10) pain (van den Beuken-van Everdingen 2016 **Level III-3 SR**, 117 studies, n=63,533 [pain prevalence], 52 studies, n=32,261 [pain severity]). It is recommended that all patients with cancer are screened for pain during the initial evaluation and at each subsequent contact, and whenever new therapy is initiated, using self-reported NRS (Swarm 2019 **GL**; AACPMGWP 2019 **GL**).

An overarching systematic review of interventions to treat acute cancer-related pain rates epidural analgesia and local anaesthetic infusions as recommended for clinical practice and gabapentin, intraspinal analgesia, music and music therapy, hypnosis and hypnotherapy as likely to be effective (Sundaramurthi 2017 **Level IV SR**, 114 studies, n unspecified).

8.9.1 | Assessment of acute cancer pain

Acute pain requires urgent assessment to exclude cancer recurrence or an oncological emergency requiring rapid treatment in addition to acute pain management (Swarm 2019 **GL**).

Where malignancy is advanced, there is urgency in differentiating an acute pain crisis, which is readily reversible, from an intractable painful condition (Moryl 2008 **NR**). Standardised assessment tools for the comprehensive assessment of cancer pain are advantageous, and required for quality research trials (Caraceni 2019 **NR**). There is no consensus on the ideal multidimensional pain-assessment tool for cancer pain, with electronic tools and a standard prognostic classification system for cancer pain being considered (Arthur 2017 **Level IV**, n=386; Burton 2014 **NR**). Palliative-care physicians identified the most important dimension to assess was pain intensity with unidimensional tools (eg NRS, VRS) followed by documentation of temporal pattern, treatments, exacerbating or relieving factors, location, pain interference, pain quality, pain affect, duration, pain beliefs and previous pain history (Holen 2006 **NR**). The revised Edmonton Staging System, the MPQ and the Brief Pain Inventory are well validated in many settings (Arthur 2017 **Level IV**, n=386; Gauthier 2014 **Level IV**; Nekolaichuk 2013 **Level IV**; Wu 2010 **Level IV**; Bennett 2009 **Level IV**; Fainsinger 2005 **Level IV**; Ngamkham 2012 **NR**).

8.9.2 | Principles of management of acute cancer pain

Comprehensive consensus best-practice guidelines relating to cancer pain management have been developed by several agencies worldwide (with online access provided to most) (AACPMGWP 2019 **GL**; Swarm 2019 **GL**; Fallon 2018 **GL**; Jara 2018 **GL**; WHO 2018 **GL**; Scarborough 2018 **NR**). A person-centred, multidisplinary team approach involving allied care health professionals and primary care health professionals is a recommended approach to pain management.

The WHO Analgesic Ladder (WHO 1996 **GL**) underpins these guidelines but was determined to provide inadequate pain relief in 12% of patients (Zech 1995 **Level IV**, n=2,118). Hence the WHO ladder has undergone considerable scrutiny over the last decade with proposals to abolish the second step of the WHO analgesic ladder in favour of the early use of morphine at low doses gaining more favour (Fallon 2018 **GL**). Where pain is moderate to severe, a jump from Step I (simple analgesics) directly to Step III (strong opioids) reduces the time to pain control relative to staged progression through Step II (weak opioids) (Maltoni 2005 **Level II**, n=54 [prematurely terminated], JS 2). In adult patients with moderate cancer pain, low-dose morphine had significantly higher response rate and early onset of response vs weak opioids (Step II), with a similarly good tolerability and comparable opioid-related adverse effects (Bandieri 2016, **Level II**, n=240, JS 3).

Simple analgesics, adjuvants and specific targeted therapies, such as anticonvulsant medicines for neuropathic pain and radiotherapy and bone-modifying agents for metastatic bone pain, should be considered at every step of the ladder. Despite availability of numerous consensus guidelines, a survey of Australian palliative care physicians identified barriers to best practice, notably access to nonpharmacological interventions, patient-educational resources, and optimal care coordination (Lovell 2013 **Level IV**).

Patient education about cancer pain is a key factor in optimising pain management (Marie 2013 **Level I**, 15 RCTs, n=1,710; Martinez 2014 **Level III-2 SR** 16 RCTs & 3 studies, n=2,192; Lee 2014 **Level III-3 SR**, 12 RCTs, n=2,380 & 5 studies, n=475; Lovell 2014 **NR**). Despite this, a patient-centred approach is often overlooked in guidelines (Luckett 2013 **Level IV SR**, 70 studies, n unspecified). For all patients with pain, education should be provided about cancer-related pain and its management with verbal and written information. It is also recommended to include the person's family, carers and significant others in education process (AACPMGWP 2019 **GL**).

There is similar urgency in managing an acute pain crisis in the patient with cancer as there is when managing any other medical crisis. Acute pain, particularly in patients with terminal cancer, causes immense distress in the patient, the family and the care team (Moryl 2008 **NR**). In such a crisis, hospital admission should be considered to evaluate the patient, assess and manage the aetiology of pain and achieve patient-specific pain goals (Swarm 2019 **GL**). Treatment of the underlying cause of pain may be urgent.

For data specific to pain management in children with cancer see Section 10.8.

8.9.3 | Medicines for acute cancer pain

8.9.3.1 | Paracetamol and NSAIDs

Any addition of NSAIDs or paracetamol to strong opioids should be justified on the basis of individual improved analgesia or reduction of opioid-related adverse effects, recognising the NSAID-associated risks of gastrointestinal bleeding and relative contraindications in patients with renal, hepatic and cardiac failure.

There is no convincing evidence that addition of paracetamol to established treatment with strong opioids provides any analgesic or quality of life benefit for cancer pain in adults (Wiffen 2017b, **Level I** [Cochrane], 3 RCTs, n=122).

The efficacy of oral NSAIDs for moderate or severe cancer pain alone or combined with opioids in adults is not supported by high-quality evidence (Derry 2017b **Level I** [Cochrane], 11 RCTs, n=949). There is very low-quality evidence that NSAIDs reduce pain after 1 to 2 wk of treatment (4 RCTs). Side-effects were inconsistently reported and discontinuation occurred commonly due to lack of efficacy (24%) or adverse events (5%). This is supported by a subsequent systematic review, which found no additional high-quality evidence and was unable to draw conclusions

due to heterogeneity in outcome measures and short duration of follow-ups (Magee 2019 **Level I**, 30 RCTs, n=2,329).

Use of parecoxib by continuous SC infusion for 7 days in cancer patients in a hospice setting resulted in a reduction in pain scores and the number of rescue opioid doses required without an opioid-sparing effect (Armstrong 2018, **Level III-3**, n=80).

Metamizole (dipyrone), another non-opioid analgesic, is effective in reducing cancer pain intensity vs placebo, even at low doses (1.5 to 2 g/d), with higher doses (3 x 2 g/d) being more effective than low doses (3 x 1 g/d) (Gaertner 2017 **Level III-2 SR**, 4 studies, n=252)

8.9.3.2 | Conventional and atypical opioids

Opioid analgesics play an important role in pain management for patients with cancer (NICE 2016a **GL**; Caraceni 2012 **GL**; Ripamonti 2011 **GL**; WHO 1996 **GL**). Nineteen out of 20 people with moderate or severe pain who were given and tolerated opioids have a reduction in pain intensity to mild or no pain within 14 d, although quantity and quality of evidence for this is low (Wiffen 2016 **Level I** [Cochrane], 9 SRs [152 RCTs], n= 13,524).

If the patient persistently requires doses of "as-needed" opioids, or if the "around-the-clock" opioid regimen fails to relieve pain at peak effect or at end of dose, it is recommended to consider increasing the dose of slow-release opioids (Swarm 2019 **GL**).

There is increased likelihood of patients using higher than 200 mg of oral morphine equivalent at home being undertreated with prn opioids in emergency departments (Patel 2017 **Level III-2**, n=216).

See also Section 4.3.1.

Routes of administration

Rapid analgesic control of acute pain or persistent pain exacerbations may be achieved with a regular dose schedule of a parenteral opioid with frequent reassessment and dose adjustment, or by use of PCA techniques. A single RCT demonstrated more rapid pain control with IV than oral morphine for severe cancer pain (Harris 2003 **Level II**, n=62, JS 2). IV and SC bolus dosing and infusions have similar tolerability and efficacy but IV route provides faster relief (Radbruch 2011 **Level III-2 SR**, 18 studies, n=674; Elsner 2005 **Level II**, n=39, JS 2; Anderson 2004 **NR**). The use of IV or SC PCA in patients with cancer pain is a safe and convenient method of delivering opioid analgesia (Nijland 2019 **Level IV SR,** 6 RCTs & 44 studies, n unspecified).

Consensus clinical practical guidelines and systematic reviews are available to guide the administration of short-acting opioids including IV, SC and rectal morphine in exacerbations of pain (Swarm 2019 **GL**; WHO 2018 **GL**; Caraceni 2012 **GL**; Klepstad 2011 **GL**).

Controlled release formulations

Once acute pain control is achieved, analgesia should be maintained with CR preparations of opioids. There is a lack of good evidence in the patient with cancer pain for differences in efficacy or safety between various CR opioids (Mesgarpour 2014 **Level III-2 SR**, 5 RCTs & 4 studies, n=2,626).

Combination opioid therapy

Combination opioid therapy for poorly controlled cancer pain has little evidence to support the practice despite encouraging preclinical scientific studies, and well-designed studies are needed (Fallon 2011 **Level III-2 SR**, 2 studies, n=36).

Opioid rotation/switching

Opioid rotation, due to preference, uncontrolled pain or intolerable adverse effects, may improve opioid response and reduce adverse effects (Mercadante 2011 **Level III-2 SR**, 31 studies, n=1,885). Opioid conversion should be carefully individualised, as conversion ratios may be

influenced by multiple factors including relative potency, prior doses, tolerance and reason for switch (Webster 2012 **NR**). Conversion ratios are less predictable at higher opioid doses and conversion tools of which there are many should be used with caution as opioid rotations undertaken based on such tables alone without consideration of clinical factors carry a significant risk of toxicity and even fatality.

When health care professionals (physicians, pharmacists, and nurse practitioners/physician assistants) were surveyed, there was a large variation in mean opioid conversions (Rennick 2016 **Level IV**, n=319). A detailed analysis of equianalgesic doses and suggestions for opioid rotations based on these calculations has been published (Treillet 2018 **Level IV SR**, 20 studies, n=949). FPMANZCA provides an opioid calculator including references and background material on a website (FPMANZCA 2019 **GL**), which is also available as an app ("Opioid Calculator") for smartphones.

Scientific evidence for opioid rotation remains poor because of a lack of controlled studies (Jara 2018 **NR**), although a parallel systemic review concluded that opioid rotation can improve analgesia and patient satisfaction (Schuster 2018 **Level IV SR** [PRISMA], 3 SRs, 4 RCTs & 5 studies, n=3,021).

Opioids in patients with renal dysfunction

Fentanyl, alfentanil and sufentanil are recommended in patients with renal impairment based on pharmacokinetics and clinical experience although there is very little clinical evidence for this (Sande 2017 **Level IV SR**, 18 studies, n=2,422). Morphine, hydrocodone and pethidine are not recommended in patients receiving dialysis treatment. Hydromorphone and fentanyl are advocated as safe opioids in patients receiving dialysis due to their favourable pharmacokinetic profile. Based on inconclusive evidence, morphine and oxycodone should be used with caution in patients with renal failure.

See also Section 9.6.

Side effects

As opioid-naïve patients are more vulnerable to opioid adverse effects, pre-emptive plans for aggressive management of adverse effects need to be clearly documented, including for prophylaxis against constipation from the onset of opioid therapy (for more details see also Section 4.3.1.4).

There is no evidence that opioids used for pain control in terminal cancer have any adverse impact on patient survival (Lopez-Saca 2013 **Level III-3 SR**, 10 studies, n=2,964). Optimising patient comfort, function and safety should be the goal of care. All management options should be fully discussed with the treating and palliative care teams, to meet the physical, psychosocial and existential needs of the patient and family, with consideration of an end-of-life care pathway when cancer is advanced.

Opioids have immunoregulatory actions that vary with mode and timing of administration. Concern regarding the potential impact of opioids on immune tumour surveillance is increasing. Overall, there is currently inadequate evidence to guide opioid selection in cancer patients, based on immune function, as no studies have measured any clinical endpoints or outcomes, including cancer progression or disease-free survival (Boland 2014 **Level III-3 SR**, 5 studies, n=106).

Conventional Opioids

Morphine

Oral morphine remains an effective analgesic for cancer pain (Wiffen 2016 **Level I** [Cochrane], 62 RCTs, n=4,241). Pain relief did not differ between CR and IR formulations. CR preparations of morphine were effective for 12- or 24-hrly dosing depending on the formulation. Adverse events were common and predictable; approximately 6% of participants discontinued treatment with

morphine because of intolerable adverse events. Morphine's efficacy and toxicity are related to morphine and morphine-metabolite concentrations (Gretton 2013 **Level III-2**, n=212). Higher morphine and metabolite concentrations are associated with severe central adverse effects, including drowsiness, confusion or hallucinations, particularly with higher metabolite:morphine ratios in plasma. Myoclonus occurs unpredictably at morphine doses >400 mg/d, with higher morphine and metabolite concentrations in adults with moderate to severe cancer pain.

Codeine

Despite shortcomings in the evidence available (small study size, other risk of bias, clinical and methodological heterogeneity), available evidence indicates that codeine is more effective in cancer pain treatment than placebo (Straube 2014 **Level I** [Cochrane], 15 RCTs, n=721).

Fentanyl

The TD route of administration is inappropriate for unstable acute pain due to its slow titratability. In cancer patients, TD fentanyl shows similar effectiveness for pain control as TD buprenorphine (Ahn 2019 **Level III-2 SR** [NMA], 15 studies & 2 SRs, n= 6,368) and oral morphine (RR 1.00; 95%CI 0.97 to 1.03) (29 RCTs, n=2,769), but lower rates of constipation (35 RCTs), nausea and vomiting (31 RCTs), drowsiness (28 RCTs), and urinary retention (24 RCTs) (Wang 2018a **Level I** [PRISMA], 35 RCTs, n=3,406). Studies of TD fentanyl for chemoradiation-induced mucositis indicated only gradual reduction in pain intensity over several days (Xing 2014 **Level III-3**, n=46).

Hydromorphone

Hydromorphone provides similar pain relief as oxycodone or morphine with a consistent analgesic effect, although overall quality of the evidence was very low (Bao 2016 **Level I** [Cochrane] 4 RCTs, n=604). Hydromorphone effectively reduced pain that was inadequately controlled by other analgesics, although pain relief was not associated with improved quality of life (Han 2014 **Level III-3**, n=432). Once-daily hydromorphone CR vs oxycodone CR BD (Yu 2014 **Level II**, n=137, JS 5) and hydromorphone IR QID vs oxycodone IR QID (Inoue 2018 **Level II**, n=183, JS 5) were non-inferior for relieving moderate to severe cancer pain.

Methadone

Appropriately titrated methadone, although more difficult to manage than morphine, has similar efficacy and tolerability and has a role in treating cancer pain (Nicholson 2017 **Level I** [Cochrane], 6 RCTs, n=388). Methadone requires considerable care in dose estimation, titration and monitoring, due to complex pharmacokinetics/pharmacodynamics and marked variability in response (Good 2014 **Level I**, 4 RCTs, n=272). Guidelines outline starting doses and recommended monitoring for drug accumulation and adverse effects, particularly over the first 4 to 7 days, with the caution that a steady state may not be reached for several days to 2 wk (McPherson 2019 **GL**; Swarm 2019 **GL**). Low-dose methadone may improve pain control when used as a co-analgesic in patients with cancer-related pain that were receiving another regularly scheduled opioid analgesic (Courtemanche 2016 **Level III-3**, n=146)

Oxycodone

Oxycodone provides similar analgesia and has a similar adverse effect profile to morphine; these agents can be interchangeable as first-line oral opioids for treatment of cancer-related pain (Schmidt-Hansen 2017 **Level I** [Cochrane], 23 RCTs, n=2,648); oxycodone CR provides similar analgesia to oxycodone IR with no significant differences in adverse events. Oxycodone/naloxone CR preparations are an effective treatment for moderate to severe cancer-related pain and provide relief from opioid-induced constipation (Morlion 2018 **Level III-3 SR**, 7 studies, n=981).

Atypical opioids in cancer pain

Buprenorphine

There is insufficient evidence to recommend buprenorphine as a first-line choice for cancer-related pain vs standard opioids like morphine, oxycodone and fentanyl (Schmidt-Hansen 2015 **Level I** [Cochrane], 19 RCTs, n=1,421). However, its various routes of administration, in particular TD (Ahn 2019 **Level III-2 SR** [NMA], 15 studies & 2 SRs [10 TD buprenorphine], n= 6,368) and SL, make it a practical option in some patients and in some clinical settings.

Tapentadol

There are limited data to support tapentadol use in cancer pain with insufficient numbers to pool RCTs; efficacy and safety were comparable to morphine and oxycodone (Wiffen 2015 **Level I** [Cochrane], 4 RCTs, n=1,029; Mercadante 2017 **Level IV SR**, 2 RCTs & 6 studies, n=791) (2 RCTs overlap). It may be a suitable alternative in patients who suffer considerable nausea, vomiting or constipation with use of conventional opioids (Mercadante 2017 **Level IV SR**, 2 RCTs & 6 studies, n=791; Kress 2019 **NR**). Opioid-tolerant cancer patients taking the equivalent of at least 60 mg oral morphine daily could be rotated to tapentadol (oral conversion ratio morphine:tapentadol 1:3.3) with significant improvement in pain control within the first week and few withdrawals due to uncontrolled pain (5/30), adverse effects (2/30) or other reasons (3/30) (Mercadante 2014 **Level III-3**, n=30). An analgesic benefit of controlled-release tapentadol for moderate to severe bone pain in opioid-naïve myeloma patients was found (Coluzzi 2015 **Level III-3**, n=25). Patients with haematological malignancies treated with slowly titrated doses of tapentadol (to a final dose of 244 mg ±106) for 1 mth showed reduction in neuropathic pain from 54% to 14%, and improvement in sleep quality to "good" or "refreshing" from 20% to 95% of patients (Brunetti 2016 **Level III-3**, n=36).

Tramadol

Tramadol (with or without paracetamol) has only limited, very low-quality evidence supporting its use for treatment of cancer pain; tramadol is not as effective as morphine in this setting (1 RCT, n=227) (Wiffen 2017a **Level I** [Cochrane], 10 RCTs, n=958). As a non-controlled substance, it plays an important role in the treatment of cancer pain in countries where it may be the only opioid treatment option eg in parts of South-East Asia (Vijayan 2018 **NR**).

8.9.3.3 | NMDA receptor antagonists

Ketamine

Despite extensive evidence to support the use of ketamine for acute perioperative pain and procedural analgesia, very limited evidence guides its use in cancer-related pain (Bell 2017 **Level I** [Cochrane] 3 RCTs, n=215; Bredlau 2013 **Level IV SR**, 5 RCTs & 6 studies, n=483). The largest multicentre RCT included in these systematic reviews concluded that ketamine had no therapeutic benefit with an adverse safety profile in cancer patients (Hardy 2012 **Level II**, n=187, JS 5). Despite relating to chronic moderate to severe pain in a palliative setting and a broad patient population, this trial has negatively influenced the use of ketamine for all cancer-related pain, including acute exacerbations, with resultant debate and calls for further controlled studies targeting more specific cancer pain populations (Hardy 2014 **Level IV**, n=123 [clinicians]; MacKintosh 2012 **Level IV**; Jackson 2013 **NR**; Leppert 2013 **NR**). Certain types of cancer pain, including mucositis, bone and neuropathic pain, may be "good responders" to ketamine and merit more focussed, higher quality, controlled studies (Jackson 2005 **NR**).

Larger case series and individual reports have highlighted the wide range of clinical situations, routes of administration and dose schedules for ketamine in the cancer setting. Ketamine has been used successfully for morphine-resistant pain (Mercadante 2000 **Level II**, n=10 [cross over], JS 3), acute incident pain (Mercadante 2009 **Level IV**, n=2) and for cancer patients in the perioperative

period, where ketamine can be morphine-sparing, lower pain scores and promote earlier return of function (Nesher 2009 **Level II**, n=44, JS 3; Kollender 2008 **Level II**, n=60, JS 5). Oral and topical use of ketamine resulting in effective analgesia has been described in case series (Okamoto 2013 **Level IV**, n=46; Uzaraga 2012 **Level IV**, n=16; Soto 2012 **NR & CR**; Amin 2014 **CR**). Analgesia was successfully maintained when continuous ketamine infusion was converted to oral ketamine (Benitez-Rosario 2011 **Level III-2**, n=29). Topical ketamine-amitriptyline did not reduce chemotherapy-induced peripheral neuropathic pain (Gewandter 2014 **Level II**, n=462, JS 5).

Magnesium

Elemental magnesium (65 mg BD) added to morphine in patients with cancer did not improve analgesia, functional performance or quality of life nor reduce side effects (Baaklini 2017 **Level II**, n=43, JS 4).

8.9.3.4 | Glucocorticoids

Common indications for glucocorticoids in cancer include spinal cord compression, superior vena cava compression, raised intracranial pressure, bowel obstruction, anorexia and pain related to inflammation, bone tumour or neuropathy. Despite good evidence for many of these clinical scenarios, only weak evidence supports glucocorticoids for cancer pain (Paulsen 2013 **Level I** [PRISMA], 4 RCTs, n=667; Leppert 2012 **NR**). Methylprednisolone provided no significant analgesic benefit but improved fatigue, appetite and patient satisfaction (Paulsen 2014 **Level II**, n=50, JS 5). A meta-analysis of studies comparing corticosteroids, notably dexamethasone, to standard therapy did suggest a statistically significant, but clinically limited, reduction in cancer pain at 1 wk (MD -0.84/10; 95%CI -1.38 to -0.30); however, data were flawed by attrition, potential bias, small sample size and infrequent indication of adverse effect rates (Haywood 2015 **Level III-2 SR** [Cochrane], 15 studies, n=1,926). Once-daily dexamethasone (average dose of 13 mg [SD 10]) recommended by a specialty palliative care team in patients with cancer pain receiving opioids resulted in an opioid-sparing (-23% MEDD) and analgesic effect (-19% pain scores); in 61% the pain was primarily acute cancer pain (Barghi 2018 **Level III-3**, n=59).

Consequently, no recommendation can be made regarding selection of glucocorticoid, dose, route or duration of administration, and adverse-effect profile. Dexamethasone is often preferred due to high potency, long duration of action and minimal mineralocorticoid effect. Immediate adverse effects include immunosuppression, hyperglycaemia and psychiatric disorders, whereas longer-term use increases risk of proximal myopathy, peptic ulceration, osteoporosis and Cushing's syndrome (Leppert 2012 **NR**). Steroid/nsNSAID combination therapy in a large population of general hospitalised patients resulted in a 15-fold increase in gastrointestinal bleeding, reinforcing the need for gastroprotective therapy (Piper 1991 **Level III-2**, n=7,478). If glucocorticoids are used in the acute setting for >3 wk, a schedule of dose reduction must precede cessation.

8.9.3.5 | Anticonvulsants and antidepressants

Combining opioid analgesia with alpha-2-delta ligands does not improve pain relief in patients with cancer pain vs opioid monotherapy, although benefit in patients with neuropathic cancer pain could not be excluded due to heterogeneity of patient samples (Kane 2018 **Level I SR** [PRISMA], 7 RCTs, n=605); data on amitriptyline, fluvoxamine, and phenytoin were inconclusive. However, RCTs not included in the systemic review above support use of gabapentin with opioids in severe cancer pain (VAS 7) (Chen 2016 **Level II**, n=60, JS 5) and pregabalin with opioids in cancer patients with severe neuropathic pain (Dou 2017 **Level II**, n=40, JS 4). Pregabalin was more effective in relieving neuropathic cancer-related pain vs TD fentanyl (Raptis 2014 **Level II**, n=120, JS 3).

8.9.3.6 | Cannabinoids

In cancer pain, very low-quality evidence shows no benefit of nabiximols or THC (the only cannabinoids in the included RCTs) on any outcome including pain, sleep problems and opioid consumption, with increased adverse events (GI and nervous system) (Hauser 2019 **Level I** [PRISMA], 5 RCTs, n=1,534). There is no convincing, unbiased, high quality evidence for an effect of cannabinoids on anorexia or cachexia in a palliative care setting (Mucke 2018 **Level I** [PRISMA], 9 RCTs, n=1,561).

8.9.4 | Breakthrough pain

The term "breakthrough pain" typically refers to a transitory acute flare-up of pain in the setting of chronic cancer pain managed with a fixed opioid drug schedule. On the basis of two Delphi surveys, breakthrough pain has been defined as *"a transient pain exacerbation that can occur in patients with stable and adequately controlled background pain not necessarily treated with opioids"* (Lohre 2016 **GL**). There are specific tools that have been recommended to assess the prevalence and severity of breakthrough pain in patients with cancer (Webber 2014 **GL**). Despite stable therapy, breakthrough pain is common, heterogeneous, frequently severe or excruciating, often paroxysmal, and may occur several times daily for seconds to hours in duration (Deandrea 2014 **Level IV SR**, 33 studies, n unspecified; Portenoy 1990 **Level IV**, n=63). Some episodes of breakthrough pain may be an end-of-dose failure of maintenance opioids. In contrast, incident pain is predictably precipitated by some movement or action. Assessment should elucidate the severity, duration, pattern and cause of breakthrough pain.

Conventional management guidelines dictated that the opioid breakthrough dose should be a proportion (one-sixth to one-tenth) of the daily dose; for example, an oral breakthrough dose of morphine would be equivalent to a 4-hourly dose, or one-sixth the oral morphine equivalent daily dose. However, there is little evidence to support the standard practice of utilising the same opioid for breakthrough pain as for maintenance analgesia, and most recent studies indicate a poor relationship between rescue and maintenance doses (Zeppetella 2011). Rescue medication used for breakthrough pain should ideally have a pharmacokinetic profile that mirrors the time-course of that pain and ideally have high potency, rapid onset and fast offset. Meta-analyses of emerging evidence support the rapid efficacy and safety of several transmucosal immediate-release fentanyl (TIRF) preparations for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1,699; Rogriguez 2015 **Level I**, 11 RCTs, n unspecified; Jandhyala 2013 **Level I**, 5 RCTs, n=415; Brant 2017 **NR**) (significant overlap between all 3 SRs) (see also Section 5.5.3.1). These TIRF are superior to placebo at 15 min and require individual titration to effect. The titrated rescue dose is largely independent of background opioid dosing (Portenoy 1999 **Level IV**). The slower onset of oral morphine (45 min) limits its suitability to more gradual-onset pain or for pre-emptive anticipation of incident pain (1 RCT, n=89) (Zeppetella 2014 **Level I** [NMA], 10 RCTs [various transbuccal fentanyl formulations], n=892). Notably, not all breakthrough pain may be opioid responsive. A large observational study identified 23% of patients who found nothing to relieve their breakthrough pain, indicating further investigations are required in this area (Davies 2013 **Level IV**, n=1,000).

8.9.5 | Acute neuropathic cancer pain

8.9.5.1 | Incidence and diagnosis of neuropathic cancer pain

Neuropathic pain or mixed nociceptive-neuropathic pain has an estimated frequency of 31 to 40% in patients with cancer (Roberto 2016 **Level IV SR**, 40 studies (29 general cancer & 17 palliative settings), n=18,136; Bennett 2012 **Level IV SR**, 22 studies, n=13,683). Diagnosis was largely based on

clinical judgement rather than objective criteria, and most studies predated the updated IASP definition of neuropathic pain as pain due to a disease or lesion in the somatosensory system. Peripheral or central neuropathic pain may result from disease progression, cancer treatment, a comorbid condition or be multifactorial. No clear standardised approach or taxonomy has been used to assess neuropathic pain in cancer or to guide treatment. Improvements in the classification, assessment and diagnosis of neuropathic cancer-pain conditions are required to address gaps in understanding of this diverse condition (Lema 2010 **NR**). The neuropathic grading scale of the Neuropathic Pain Special Interest Group of the IASP is recommended for use in cancer patients to facilitate recognition, management and study of neuropathic cancer pain (Mulvey 2014 **GL**). Screening tools recommended for neuropathic pain such as Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique en 4 (DN4) or painDETECT (PDQ) show concordance with clinicians' diagnosis of neuropathic pain in cancer patients (Mulvey 2017 **Level IV SR**, 6 studies, n=2,301).

8.9.5.2 | Treatment of neuropathic cancer pain

Adjuvant medications may be needed for acute or persistent neuropathic cancer pain that is poorly responsive to opioids, or where opioid intolerance limits further dose escalation. Acute neuropathic cancer pain may also be associated with inflammation and require specific targeted therapy. A systematic review of European clinical practice guidelines for management of cancer-associated neuropathic pain highlighted a lack of evidence (Piano 2014 **SR**, 9 GLs). Extrapolation of data from individuals without cancer to a population with neuropathic cancer pain may not provide optimal care. Only 11% of references supporting European clinical practice guidelines came from patients with cancer.

All of the guidelines include recommendations for TCAs as first-line treatment, despite the lack of high-level evidence. Imipramine (to 75 mg; 1 RCT) and amitriptyline (to 50 mg; 1 RCT) in small RCTs in patients with advanced cancer or chemotherapy-induced painful neuropathy has resulted in only a small analgesic benefit, with increased adverse effects including sedation, confusion and dry mouth (Bennett 2011b **Level I**, 2 RCTs [TCAs], n=85). A further systematic review included two additional amitriptyline RCTs (to 100 mg), one venlafaxine and one trazodone RCT and calculated the weighted mean absolute risk benefit for antidepressants overall as 0.55 (95%CI 0.40 to 0.69) (Jongen 2013 **Level III-2 SR**, 6 RCTs [antidepressants], n=189 [analysed]); this is comparable to the effect of anticonvulsants here.

Anticonvulsant medications added to opioids for control of neuropathic pain caused by cancer have also only a small effect (Bennett 2011b **Level III-2 SR**, 3 RCTs and 3 studies [anticonvulsants], n=380). Anticonvulsants (gabapentin 2 RCTs and 2 studies; sodium valproate 1 study; phenytoin 1 RCT) provide limited improved analgesia within 4 to 8 d, after which benefits do not further increase. The addition of an adjuvant to a stable opioid dose results in only modest pain reduction at the expense of increased adverse effects, whereas when opioid dose is lowered after the introduction of the adjuvant, pain intensity is maintained or reduced, and adverse effects decreased. A further systematic review calculated a mean absolute relative benefit of 0.57 (95%CI 0.43 to 0.70) for anticonvulsants (Jongen 2013 **Level III-2 SR**, 14 RCTs & 16 studies, n=2,267) (2 RCTs & 3 studies overlap); gabapentin was the most studied anticonvulsant. A systematic review of pregabalin for neuropathic pain in cancer was unable to make any clear recommendations due to limitations in the study methodology and data (Bennett 2013 **Level IV SR**, 1 RCT, 3 studies & 1 CR, n= 761). A single RCT (included in both systematic reviews) compared the efficacy of amitriptyline, pregabalin and gabapentin for severe neuropathic cancer pain and reported efficacy of all treatments but superiority of pregabalin (Mishra 2012 **Level II**, n=120, JS 4).

Beneficial effects of antidepressants and anticonvulsants are found overall to outweigh harms in neuropathic cancer pain (Jongen 2013 **Level III-2 SR**, 14 RCTs & 16 studies, n=2,267). Benefits did not differ for neuropathic and mixed nociceptive-neuropathic pain states. Use of anticonvulsants or antidepressants in combination pharmacotherapy vs controls reduces global pain (MD -0.41/10; 95%CI -0.70 to -0.12) (Guan 2016 **Level I**, 8 RCTs, n=1,359).

Lack of data precluded conclusions regarding opioids alone, however oral methadone vs TD fentanyl in treating neuropathic pain in patients with head-and-neck cancer resulted in better analgesia at 1 and 3 wk (Haumann 2016 **Level II**, n=52, JS 3). In cancer pain in general, combining opioids with gabapentin or pregabalin does not improve pain relief and data on amitriptyline, fluvoxamine and phenytoin are inconclusive (Kane 2018 **Level I** [PRISMA], 7 RCTS, n=605). See also Section 8.1.4.

8.9.5.3 | Painful chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is resistant to treatment and remains poorly understood although multiple risk factors have been identified including cumulative chemotherapy dose, genetics, age, history of diabetes, history of neuropathy and low levels of physical activity (Kim 2017b **NR**). Approximately 68% of patients developed CIPN within 30 d of any chemotherapy and by 6 mth 30% of patients are still affected by CIPN (Seretny 2014 **Level III-3 SR** [PRISMA], 31 studies, n=4,179).

Acute severe CIPN may adversely limit cancer treatment and hence survival, while chronic CIPN is a major cause of pain and poor QoL in survivors. Chemotherapies causing painful CIPN include vinca alkaloids (vincristine), platins (cisplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), the proteasome inhibitor bortezomib and immunomodulatory agent thalidomide. Each class of agent has a distinct neuropathology, site of toxicity in the peripheral nerves and risk profile (Park 2013 **NR**). CIPN is dependent on dose and duration of treatment. CIPN is a predominantly sensory neuropathy, with many agents at higher doses also causing myalgia and myopathy (taxanes), muscle cramps (oxaliplatin, vincristine, thalidomide) and autonomic neuropathy (vincristine, bortezomib). Paclitaxel and oxaliplatin have distinct acute and chronic CIPN syndromes. Significant acute neurotoxicity complicates oxaliplatin infusion in 90% of patients for up to 1 wk and is exacerbated by exposure to cold. Acute pain (1 wk) is caused by oxaliplatin in 55.6% and chronic peripheral neuropathic pain in 49.2% of patients (Brozou 2018 **Level IV SR** [PRISMA], 96 studies, n unspecified).

Paclitaxel-induced acute pain syndrome with painful paraesthesias and numbness, poor motor skills, myalgias and arthralgias may persist up for up to 4 d. Bortezomib-induced CIPN is a common small-fibre neuropathy characterised by severe, sharp, burning pain in the feet that resolves by 3 mth in most affected patients. The severity of acute neuropathy and pain (paclitaxel, oxaliplatin) and the use of combination chemotherapies promoting neurotoxicity may be predictors of chronic CIPN.

There is a lack of evidence to support any agent for prevention of CIPN. Current protective strategies include dose modification or cessation of the causative chemotherapy. Risk stratification should include identification of individuals with pre-existing conditions predisposing to peripheral neuropathy. Multiple natural products and complementary therapies have been evaluated as possible preventive measures with some evidence that vitamin E and glutamine may prevent development of CIPN (Brami 2016 **Level I**, 13 RCTs, n=1,341).

There is limited specific evidence to guide treatment of established CIPN. Duloxetine (30 mg titrated to 60 mg/d over 5 wk) resulted in a modest reduction in pain severity vs placebo (MD -1.06/10; 95%CI 0.72 to 1.40); additional benefits included improved QoL and reduced numbness

and tingling of the feet (Smith 2013 **Level II**, n=231, JS 5). The analgesic benefit of duloxetine was greater in patients with oxaliplatin-induced CIPN.

Venlafaxine may be effective in acute oxaliplatin-induced CIPN but additional supportive evidence is recommended prior to any routine use in clinical practice (Hershman 2014 **GL**). Trials of amitriptyline (to 50 mg/d) and nortriptyline (to 100 mg/d), and gabapentin (2,700 mg/d) were inconclusive, while lamotrigine (300 mg/d) provided no benefit for CIPN. Tapentadol use in patients with moderate-to-severe neuropathic pain from CIPN that was unresponsive to maximum doses of antidepressants and anticonvulsants resulted in a reduction of overall and neuropathic pain scores in 86% of patients (Galie 2017 **Level III-3**, n=31). Nerve conduction values were unchanged from baseline to 3 mth suggesting that tapentadol relieved neuropathic pain without affecting or reversing peripheral nerve damage. There is insufficient evidence to support acupuncture for the treatment of CIPN (Li 2019b **Level I** [PRISMA], 3 RCTs, n=203) (1 RCT overlap with Brami 2016).

Taxane acute pain syndrome (TAPS) is characterised by acute onset of muscle and joint pain within a couple of days of receiving taxane chemotherapy. The pain is self-limiting and resolves within one week. Much like CIPN, TAPS can greatly affect patients' quality of life and can lead to dose decreases and chemotherapy discontinuation (Chiu 2017 **NR**). Multiple pharmacologic agents have been evaluated in the treatment of TAPS, including corticosteroids, gabapentin, glutamine and glutathione, with no studies showing benefit (Fernandes 2016 **Level III-3 SR**, 5 studies, n=311).

Guidelines for the management of CIPN concede that "*there are no agents recommended for the prevention of CIPN*" and support only duloxetine with the recommendation to try tricyclic antidepressants, gabapentin, and a compounded topical gel containing baclofen, amitriptyline HCL and ketamine despite lack of evidence (Hershman 2014 **GL**). These statements are supported by an overarching systematic review, which could only support use of duloxetine in the setting of CIPN (Hou 2018 **Level III-3 SR** [PRISMA], 13 RCTs & 22 studies, n=2,401).

8.9.6 | Procedural pain in cancer patients

Both adults and children with cancer may undergo multiple painful diagnostic and therapeutic procedures. Few trials have evaluated procedural pain in adults with cancer. Attention to adequate analgesia and anxiolysis is imperative to reduce anticipatory stress with repeat interventions. Simple techniques include premedication, administration of prophylactic breakthrough analgesia, application of topical local anaesthetic, inhalational analgesia including methoxyflurane via the Penthrox® inhaler and N_2O-oxygen as Entonox® (see Section 4.5), and sedation (midazolam, ketamine, propofol) by appropriately trained personnel (see respective sections of Chapter 4).

For pleurodesis in patients with malignant pleural effusion, NSAIDs provided comparable analgesia to opioids except for higher rescue analgesia requirements (Rahman 2015b **Level II**, n=206, JS 5); rates of pleurodesis efficacy at 3 mth were not inferior. Placement of 12 Fr vs 24 Fr chest tubes resulted in a modest pain reduction (MD −6.0/100; 95%CI −11.7 to −0.2), but was associated with higher pleurodesis failure (30% vs 24%).

Few interventions decrease acute pain during mammography, including provision of prior information about the procedure, some degree of self-control over the extent of breast compression and the use of breast cushions; in contrast, pre-emptive paracetamol was of no benefit (Miller 2008 **Level I**, 7 RCTs, n=1,671).

For paediatric information, see Sections 10.7.2 and 10.8.2.

8.9.7 | Acute pain due to bone cancer

Refractory severe pain with acute incident pain is commonly caused by primary and metastatic bone cancers, notably prostate, breast, lung, bladder, renal and thyroid cancers, and multiple myeloma. Bone pain may also be precipitated during some cancer treatments eg granulocyte-colony stimulating factor (G-CSF) for febrile neutropenia prophylaxis. Malignant bone pain often has mixed nociceptive, inflammatory and neuropathic components. Preclinical studies have highlighted the pathophysiology of malignant bone pain (Mantyh 2014b **BS**; Mantyh 2014a **BS**; Falk 2014 **BS**; Currie 2013 **BS**).

8.9.7.1 | Diagnosis of bone cancer pain

In the setting of known or potential bone primary or metastatic cancer, any new onset constant aching, gnawing pain over bone, or acute incident pain precipitated by movement or weight-bearing, requires prompt evaluation to pre-empt or exclude critical bone-related events, with assessment for pathological fracture, neurological deficit or hypercalcaemia. Many studies and reviews have informed guidelines to predict, expedite diagnosis and appropriately treat bone metastases. A systematic approach to assessment of spinal metastases is imperative. For detection of bone metastases, MRI and fludeoxyglucose F 18 PET offer advantages of sensitivity and/or specificity over bone scintigraphy and computed tomography (CT), although tumour type may influence diagnostic performance (Yang 2011 **SR** of diagnostic studies; Liu 2011 **SR** of diagnostic studies; Cheng 2011 **SR** of diagnostic studies). In assessment of new, acute back pain, 'red flags' to predict potential cancer have been proposed, yet the only evidence-based predictor of spinal malignancy is "*previous history of cancer*" (Henschke 2013 **SR** of diagnostic studies; Downie 2013 **SR** of diagnostic studies). "*History of cancer*" increased the probability of malignancy to between 7% (95%CI 3 to 16) and 33% (95%CI 22 to 46); "*older age*", "*unexplained weight loss*", and "*failure to improve after 1 mth*" increased probability by <3% (Downie 2013 **SR** of diagnostic studies). Diagnostic imaging pathways that advocate larger lists of red flags and promote imaging for a single red flag may lead to "*substantial and arguably unwarranted*" referrals for imaging. However, there is no data on the diagnostic accuracy of combinations of proposed red flags.

8.9.7.2 | Spinal cord compression

Risk of spinal cord compression is between 5 and 20% of patients with spinal bone metastases, yet diagnosis and treatment are often delayed until neurological dysfunction is irreversible. Early suspicion and referral improve outcome. Spinal cord compression risk relates to many factors including the type and characteristics of malignancy, extent of vertebral invasion, thoracic metastases, the number and duration of spinal metastases (Sutcliffe 2013 **Level III-3 SR**, 33 studies, n=5,782). Localised back pain is the most common presenting feature and neurological deficit is a late presentation; MRI is the investigation of choice (Cheng 2011 **SR** of diagnostic studies; Samphao 2010 **SR** of diagnostic studies).

Early referral for surgical assessment is required within 24 h of MRI. In addition to analgesic medications and adjuvants for pain, treatment options include corticosteroids, radiotherapy and decompressive surgery (Loblaw 2012 **GL**; Ivanishvili 2014 **NR**; Samphao 2010 **NR**). The Neurologic, Oncologic, Mechanical and Systemic (NOMS) framework is a recognised decision tree to optimise local tumour control, pain relief, neurological preservation and functional restoration (Laufer 2013 **NR**). A Canadian scoring system (LMNOP) also incorporates a spinal instability neoplastic score into a similar decision framework (Ivanishvili 2014 **NR**).

8.9.7.3 | Treatment strategies for bone cancer pain including spinal cord compression

Treatment strategies for bone cancer pain, including pain of spinal cord compression, should focus on analgesia, preservation of function and prevention of complications (WHO 2018 **GL**; Kane 2015 **NR**). Rapid analgesia should be provided and advice given regarding nonpharmacological strategies such as rest, avoidance of strenuous activity of painful areas and use of general mobility aids. For acute bone pain, an accepted approach includes omission of Step II of the WHO ladder when simple analgesics are inadequate, with progression directly to strong opioids (Maltoni 2005 **Level II**, n=54 [prematurely terminated], JS 2). For predictable incident pain, pre-emptive treatment with rapid-onset opioids should be prescribed. Preclinical data indicates a role for NSAIDs for bone pain but there is a lack of clinical evidence to support this. In a systematic review of NSAIDs (7 studies) and paracetamol (5 studies) added to strong opioids for cancer pain, no subgroup analysis of the combination for bone cancer pain was undertaken (Nabal 2012 **Level III-2 SR**, 12 studies, n=396). Using two NSAIDs (diclofenac 100 mg BD and celecoxib 400 mg/d) along with an opioid resulted in reduced pain scores, lower incidence of breakthrough pain as well as decreased opioid requirements vs using each NSAID in the same dose alone (Liu 2017b **Level II**, n=342, JS 3). Guidelines recommend topical diclofenac, including as gel or patch, to provide relief for pain due to bone metastases with minimal systemic adverse effects (Swarm 2019 **GL**)

Management of bone pain, in addition to complications of bone cancers, also includes targeted strategies that may be local (external beam radiotherapy, surgery) or systemic (chemotherapy, bisphosphonates, denosumab, hormonal therapy) (Kane 2015 **NR**; Poon 2013 **NR**; Samphao 2010 **NR**).

Tanezumab is a monoclonal antibody against neurotrophin nerve growth factor (NGF). In an RCT of painful bone metastases assessing tanezumab vs placebo, the primary endpoint of a difference in change from baseline in daily average pain was not achieved (Sopata 2015 **Level II**, n=59, JS 5). However, the data suggest improved analgesia and a Phase-3 trial is currently ongoing (Jara 2018 **NR**).

Electrochemotherapy, the combination of chemotherapy and local delivery of electric pulses to the tumour nodule (through electrodes surgically drilled into healthy bones surrounding metastases), was shown to be safe and feasible with improved pain scores >50% in 84% of patients and reduced opioid consumption (Bianchi 2016 **Level III-3**, n=24)

Generalised bone pain secondary to G-CSF treatment (eg pegfilgrastim) can result from a number of proposed mechanisms including bone marrow expansion, neuromodulation and alterations in bone metabolism (Lambertini 2014 **NR**). The most commonly utilised pain relief method for refractory severe pegfilgrastim-induced bone pain was use of the antihistamine loratadine (Pawloski 2016 **Level IV**, n=69).

8.9.7.4 | Surgery

In the case of imminent or actual pathological fracture of long bones and pelvis, surgical intervention with stabilisation may be of considerable benefit to reduce acute pain but has attendant risks. The incidences following surgical management of metastases in the humerus, femur and pelvis/acetabulum are 89 to 94% for pain relief, 91 to 93% for maintained or improved function, 17% for morbidity and 4% mortality (Wood 2014 **Level IV SR**, 47 studies, n=807). Placement of catheters for regional nerve or plexus block may eliminate acute incident pain leading up to orthopaedic surgery and during the perioperative period. The high infection rates (10%) after limb salvage surgery for primary bone cancer should be considered when evaluating and managing acute pain in the postoperative period (Racano 2013 **Level IV SR**, 48 studies, n=4,838). A

systematic review of treatment for metastatic spinal cord compression (1970 to 2007) that compared surgical stabilisation with or without radiotherapy and radiotherapy alone, concluded that tumour excision and instrumented stabilisation may improve clinical outcomes, with regard to both pain and neurological function (Kim 2012 **Level IV SR**, 33 studies, n=2,495). Periacetabular metastatic lesions treated by curettage and cemented reconstruction resulted in improved pain relief and functional status postoperatively, despite high rates of major complications (23%) and large mean surgical blood loss (3,150 mL) (Charles 2017 **Level IV**, n=35).

Radical surgical treatments should be considered where spinal metastases have a favourable prognosis, such as thyroid metastases (Zhang 2013a **Level IV**, n=22). Surgery to correct craniocervical instability also may alleviate acute pain, improve QoL and reduce hospitalisations (Kirchner 2014 **Level IV SR**, 9 studies, n=48). Prognosis should be re-evaluated, to ascertain the primary goals of treatment and to undertake risk-benefit assessment of potential treatment (Sutcliffe 2013 **Level III-3 SR**, 33 studies, n=5,782).

Out of 24 patients with cervical spine metastases who underwent palliative surgical treatment, 21 patients experienced complete or almost complete pain relief, and 7 patients experienced complete neurological recovery (Vazifehdan 2017 **Level IV**, n=24).

Resection of intradural extramedullary spine tumours appears to significantly improve patient QoL by decreasing patient disability and pain with improvement in each of the EQ-5D domains (Viereck 2016 **Level IV**, n=44).

8.9.7.5 | Radiation therapy

Radiotherapy effectively reduces malignant bone pain and may reduce complications of bone cancer. It is recommended as the first-line treatment for the majority of patients with spinal metastases causing spinal cord compression as it provides back pain relief in 50% to 58% of cases (Fallon 2018 **GL**; WHO 2018 **GL**).

At 1 mth after radiation therapy, around 25% patients experience complete pain relief (NNT 4.2; 95%CI 3.7 to 4.9) and 41% experience 50% pain relief (McQuay 2000 **Level I** [Cochrane] 43 RCTs, n=1,933). A later meta-analysis of palliative radiotherapy treatment for uncomplicated bone metastases indicates similar response rates following single-fraction (60%) and multiple-fraction (61%) radiation, including 23% and 24% complete response rates respectively (Chow 2012 **Level I**, 25 RCTs, n=5,263). Single fraction conventional radiation therapy for painful uncomplicated bone metastases shows similar results - improvements in pain in 60% to 81% of patients with complete responses (no pain and no increase in analgesic requirements) in up to 37% (with use of 10 Gy) (Chow 2017 **Level III-3 SR**, 27 studies, n=4,071) (7 RCTs overlap).

Radiotherapy for painful bone metastases provides equivalent pain relief with different regimens, including 3 Gy in 10 fractions, 4 Gy in 6 fractions, 4 Gy in 5 fractions and 8 Gy single dose (Lutz 2017 **GL** based on 4 meta-analyses/pooled analyses, 20 RCTs & 32 studies, n=7,163; Rich 2018 **Level I** [PRISMA] 26 RCTs, n=3,059 [single fraction], n=3,040 [multiple fractions]; Chow 2014 **Level I**, 25 RCTs, n=5,617) (significant overlap of RCTs between all 3 SRs). However, after single-fraction treatment, retreatment rates are higher and there is a trend for higher rates of pathological fracture and spinal cord compression. Multiple-fraction radiotherapy is favoured for borderline complicated metastases, without any high-quality supportive evidence.

Shorter hypofractionated radiotherapy (HFRT) schedules of 4 Gy in 5 fractions were as effective as more prolonged schedules for metastatic epidural spinal cord compression (Rades 2016 **Level-II**, n=203, JS 3)

For bone metastases with a neuropathic pain component, there was little evidence for multiple fraction vs single treatment in providing longer term benefit (Roos 2005 **Level II**, n=272, JS 3).

Retreatment

Reirradiation of bone metastases improves pain in about 58% patients, with complete response in 16–28%, time to response from 3 to 5 wk, with duration of 5 to 22 wk (Huisman 2012 **Level IV SR**, 7 studies, n=2,694). Retreatment of recurrent bone pain with 8 Gy single dose confirmed its efficacy and showed no disadvantage vs 20 to 26 Gy in 5 fractions (Chow 2014 **Level II**, n=425, JS 3); therefore, European Society for Medical Oncology Clinical Practice Guidelines recommend 8 Gy single dose to be considered the schedule of choice for re-irradiation (Fallon 2018 **GL**)

Radiopharmaceuticals

For patients with pain due to widespread bone metastases, radiopharmaceuticals may provide complete reduction in pain over 1 to 6 mth with no increase in analgesic use, but with common severe adverse effects of leukopenia and thrombocytopenia (Roque 2011 **Level I** [Cochrane], 15 RCTs, n=1,146). There are limited data comparing the various isotopes used (Strontium-89 [89Sr], Samarium-153 [153Sm], Rhenium-186 [186Re] and Phosphorus-32 [32P]) showing no significant differences (Fallon 2018 **GL**). In selected patients with multiple osteoblastic bone metastases, radioisotope therapy can be highly effective in achieving pain relief in multiple sites.

Radium-223 (an alpha emitter releasing short-range radiation with little bone marrow toxicity) in patients with castrate-resistant prostate cancer demonstrated improvements in skeletal-related events (SREs), pain, QoL and survival vs placebo (Sartor 2014 **Level II**, n=921, JS 5).

8.9.7.6 | Percutaneous vertebroplasty

Where other measures fail, percutaneous vertebroplasty is a procedure that aims to stabilise vertebral compression fractures, restore function and achieve rapid pain relief by the injection of bone cement (polymethylmethacrylate). A systematic review of vertebroplasty for bone metastases and myeloma highlighted low-level evidence from heterogeneous studies and identifies pain reduction rates of 47 to 87%, with no correlation between cement volume and pain relief (Chew 2011 **Level IV SR**, 30 studies, n=987). Serious complications may result from the technique and from cement injection or extravasation, including to the epidural space. Complications were reported in 2 to 11.5% of patients and may correlate with cement volume. These included haematoma, neuropathic pain, haemothorax and pulmonary embolism of cement, with five related deaths. No good evidence currently supports superiority of kyphoplasty over vertebroplasty. In multiple myeloma, vertebroplasty or kyphoplasty are equally effective resulting in prompt and sustained reduction in pain and reduced analgesic use (Khan 2014 **Level IV SR**, 23 studies, n=923). Vertebroplasty and kyphoplasty have similar complication rates in these patients, with the most frequent complication being new vertebral fracture at untreated levels. Technical difficulties of percutaneous vertebroplasty for a patient receiving denosumab, believed related to a sclerotic bone response, highlights the need for further investigation of this issue (Mattei 2014 **CR**).

Cementoplasty, with percutaneous fluoroscopic-guided injection of bone cement into pelvic bone malignancies involving acetabulum, superior and inferior pubic rami, ischium and sacrum, is also a therapeutic option for acute intractable pain from primary or metastatic bone disease (Kim 2013b **Level IV**, n=18 [32 sites]; Kelekis 2005 **Level IV**, n=14 [23 sites]; Marcy 2000 **Level IV**, n=18; Jakanani 2010 **CR**; Harris 2007 **CR**). A combined technique of embolisation, radiofrequency ablation and cementoplasty for painful pelvic bone metastasis of renal cell cancer resulted in profound and sustained pain relief and reduction of opioid requirements for up to 6 mth (Pellerin 2014 **Level III-2**, n=52).

8.9.7.7 | Bone-modifying agents

The evidence to support an analgesic role for bisphosphonates and denosumab is weak (Porta-Sales 2017 **Level I** [PRISMA], 28 RCTs, n=8,595 [bisphosphonates] & 15 RCTs, n=7,590 [denosumab]). Bisphosphonates and denosumab appear to be beneficial in preventing pain by delaying the onset of bone pain rather than by producing an analgesic effect per se. Therefore, these agents should not be used as a primary therapy for treatment of bone pain (Swarm 2019 **GL**).

Bisphosphonates

Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate with affinity for the hydroxyapatite matrix of bone, where they inhibit osteoclast-mediated bone resorption (see also Section 4.10.2). By this action, bisphosphonates reduce bone pain (see below), in addition to the primary role to decrease the risk of, and time to, skeletal-related events consequent to bone cancer, including fracture, spinal cord compression and hypercalcaemia. Hypercalcaemia is less frequent since bone-modifying agent use has increased but can still complicate widespread bone cancer and heighten the pain experience (Poon 2013 **Level I**, 11 RCTs [6 zoledronate & 4 pamidronate], n=7,834). Later generation bisphosphonates are now most widely used, have considerably greater inhibition of bone resorption, maximal effect by 3 mth, and prolong residence and duration of action in bone, for up to years for zoledronate (Kennel 2009 **NR**). Potential serious but uncommon problems include renal impairment and osteonecrosis of the jaw (ONJ); other effects include gastrointestinal symptoms, acute phase reaction with pyrexia, myalgia and arthralgia, hypocalcaemia, and idiosyncratic musculoskeletal pain or ocular inflammation. ONJ in cancer patients after bisphosphonates occurred in 6.7% of patients; the incidence is increased with time of exposure, a history of dental procedures, and zoledronate (Bamias 2005 **Level IV**, n=252). Clodronate or pamidronate use instead of zoledronate may reduce risk of ONJ but dental extractions remain the main risk factor for ONJ (RR 14.04; 99%CI 10.36 to 19.03) (Kyrgidis 2013 **Level III-2 SR**, 12 studies, n unspecified). Dental preventive measures decrease ONJ incidence (77.3%; 95%CI 47.4–90.2%) (Karna 2018 **Level III-2 SR,** 6 studies, n=2,332).

The efficacy of various bisphosphonates has been shown in a number of meta-analyses. In multiple myeloma, bisphosphonates ameliorate pain (RR 0.75; 95%CI 0.60 to 0.95) (Mhaskar 2012 **Level I** [Cochrane], 20 RCTs, n=6,692). Bisphosphonates improve pain control in patients with metastatic bone disease from lung cancer (Lopez-Olivo 2012 **Level I**, 12 RCTs, n=1,767). Zoledronate specifically reduces the likelihood of experiencing a bone-pain event in metastatic bone disease vs placebo (RR 0.83; 95%CI 0.76 to 0.89) (Zhu 2013 **Level I**, 12 RCTs, n=4,450). Analgesic effect is not shown in advanced prostate cancer (OR 1.54; 95%CI 0.97 to 2.44) (Yuen 2006 **Level I** [Cochrane], 10 RCTs, n=1,955). An IV infusion of 4 mg ibandronate gave equivalent overall pain relief to single-dose radiation therapy in prostate cancer (Hoskin 2015 **Level-II**, n=470, JS 3).

Denosumab

Activation of osteoclasts is driven by the receptor activator of nuclear factor kappa-B ligand/ osteoprotegerin (RANKL/OPG) gradient. Denosumab is a human monoclonal antibody to RANKL that blocks osteoclast development and hence bone resorption. In patients with metastatic and primary bone cancer, denosumab reduces bone pain and slows time to worsening of pain (Prommer 2015 **NR**; Rolfo 2014 **NR**; Iranikhah 2014 **NR**).

In bone metastases from breast cancer (1 RCT, n=2,046), prostate cancer (1 RCT, n=1,901) or other solid tumours (1 RCT, n=1,597), denosumab vs zoledronate delays onset of moderate/severe pain by 1.8 mth (median 6.5 vs 4.7 mth) (HR 0.83; 95 %CI 0.76 to 0.92) and clinically meaningful increases in overall pain interference by 2.6 mth (median 10.3 vs 7.7 mth) (HR 0.83; 95%CI 0.75 to 0.92) (von Moos 2013 **Level I**, 3 RCTs, n=5,544). Denosumab also reduces strong opioid use and worsening of health-related QoL. Compared to zoledronate, denosumab delays time to

worsening of pain in patients with skeletal metastases (RR 0.84; 95%CI 0.77 to 0.91) (Peddi 2013 **Level I**, 6 RCTs, n=6,142).

Denosumab can also lead to ONJ (Diz 2012 **NR**). Use of denosumab instead of zoledronate does not reduce the risk of ONJ (RR 0.71; 99%CI 0.41 to 1.24) (Kyrgidis 2013 **Level III-2 SR**, 12 studies, n unspecified), occurring in 1.6% of patients overall (1.3% with zoledronate and 1.8% with denosumab) (Saad 2012 **Level I**, 3 RCTs, n=5,723).

Calcitonin

Although calcitonin has been used to reduce metastatic bone pain and skeletal events, the limited evidence available does not support the effectiveness of salmon calcitonin in the treatment of acute and persistent metastatic bone pain (Martinez-Zapata 2006 **Level I** [Cochrane], 2 RCTs, n=90). See also Section 4.10.1.

8.9.7.8 | Treatment of acute malignant extradural spinal cord compression

Comprehensive clinical practice guidelines exist to optimise care and pain control of patients with malignant spinal cord compression (Loblaw 2012 **GL**). Corticosteroids are indicated for neurological deficit, particularly if there is to be radiotherapy eg dexamethasone (bolus 8 to 10 mg; maintenance 16 mg/d; higher doses for dense paraparesis). Early surgical consultation is required, with due consideration of the associated morbidity. Patients unsuitable for surgery should receive radiotherapy. Selected groups suitable for stereotactic radiosurgery, with spinal cord sparing, remain to be clarified. Pain is acute and may be exacerbated during early radiotherapy, with incident pain associated with movement and positioning for treatments. See also Sections 8.9.7.3 and 8.9.7.5 above.

8.9.8 | Other acute cancer pain syndromes

8.9.8.1 | Malignant bowel obstruction

Malignant bowel obstruction frequently complicates advanced abdominal cancers, develops over days to months, and presents as generalised abdominal pain or visceral colicky pain. Very little, and heterogeneous, trial data exists to inform guidelines and choice of best medical care, surgery or endoscopic interventions, which may vary according to acuity, degree of obstruction, disease prognosis and objectives of care. Treatment should be individualised. Pharmacological management is based on glucocorticoid, analgesic, antiemetic and antisecretory agents, with attention to adequate hydration (Mittal 2014 **Level IV**, n=48 [physicians surveyed]; Ripamonti 2008 **NR**). Acute severe pain can be managed with parenteral opioids, which also reduces colicky pain by reducing bowel motility. Oral opioids should not be used due to unpredictable absorption. For exacerbations of colic, the antispasmodic hyoscine butylbromide is of benefit and less sedating than hyoscine hydrobromide. Decompression and reduction in secretions may also assist with pain in patients with inoperable bowel obstruction. Hyoscine butylbromide and the somatostatin analogues octreotide reduce gastrointestinal secretions, slow motility and decrease both continuous and colicky pain intensity (Ripamonti 2000 **Level III-1**, n=17). There is little evidence for dexamethasone (6 to 16 mg IV) to improve bowel obstruction (Feuer 2000 **Level I** [Cochrane], 3 RCTs, n=89).

For inoperable bowel obstruction with peritoneal carcinomatosis, a staged protocol with analgesic, antiemetic, anticholinergic and corticosteroid as initial therapy (Stage 1), followed by a somatostatin analogue for persistent vomiting (Stage 2) and then venting gastrostomy (Stage 3) was highly effective in relieving symptoms and avoiding permanent nasogastric tube (Laval 2006 **Level IV**, n=80). Fluoroscopic-guided, percutaneous venting gastrostomy tube placement can

be technically difficult, with 72 and 77% primary and secondary technical success, and 10% incidence of major complications; prior intraperitoneal catheter to manage ascites may reduce the technical difficulty (Shaw 2013 **Level IV**, n=89). Endoscopic stenting may offer effective and safe palliation or act as a bridging step before surgery (34 studies, n=14,356) (Frago 2014 **Level IV SR**, 59 studies, n=20,762). Complications include perforation (3.76%), stent migration (11.81%) and reobstruction (7.34%) (Sebastian 2004 **Level IV SR**, 54 studies, n=1,198). Reports of no or mild nausea increased from 10% at baseline to 100% after treatment with olanzapine in patients with inoperable and incomplete bowel obstruction (Kaneishi 2012 **Level IV**, n=20).

8.9.8.2 | Mucositis

Mucositis is a common adverse effect of high-dose chemo- and radiotherapy for malignancies affecting the head and neck, acute leukaemias and for conditioning prior to bone marrow transplants. It may be complicated by opportunistic infections including herpes simplex and candidiasis. Quality of life and nutrition can be greatly impaired by the pain of cancer-related acute mucositis. In this indication, there is no significant difference in analgesia between PCA and continuous opioid infusion, except that PCA is associated with reduced opioid requirements and pain duration (Clarkson 2010 **Level I** [Cochrane] 33 RCTs, n=1,505). IV ketamine "burst therapy" may be effective in mucositis pain that is refractory to opioid analgesia (Jackson 2005 **NR**). Retrospective studies suggest some benefit from PO gabapentin (Milazzo-Kiedaisch 2016 **NR**) with one small RCT suggesting lack of benefit (Kataoka 2016 **Level II**, n=22, JS 3).

Several topical measures have been postulated to treat the pain of oral mucositis. Topical doxepin, amitriptyline, diclofenac and benzydamine (another nsNSAID) vs placebo provide pain relief due to mucositis (Christoforou 2019 **Level I** [PRISMA], 6 RCTs, n=441). One RCT not included showed that benzydamine reduced mucositis scores, but not pain, when used as an oral rinse for the prevention and treatment of mucositis (Chitapanarux 2018 **Level II**, n=60, JS 4). Mucosal analgesia may be achieved by topical application of EMLA® cream and 5% lignocaine (Vickers 1992 **Level II**, n=60, JS 5).

Povidone-iodine mouthwash significantly reduces the severity of oral mucositis vs sterile water, however chlorhexidine was ineffective (Potting 2006 **Level I**, 7 RCTs, n=863). The lack of effect of chlorhexidine has been confirmed by a subsequent specific meta-analysis (Cardona 2017 **Level I** [PRISMA], 12 RCTs, n=876).

Two different formulations of 200 mcg dose transmucosal fentanyl citrate were equal in efficacy, tolerability and adverse-effect profile, but no better than placebo for analgesia in radiation-induced mucositis (Leenstra 2014 **Level II**, n=155, JS 5; Shaiova 2004 **Level II**, n=14, JS 5).

Topical morphine (Vayne-Bossert 2010 **Level II**, n=11, JS 5; Cerchietti 2002 **Level II**, n=26, JS 3; Cerchietti 2003 **Level III-1**), and ketamine (Slatkin 2003 **CR**) may also provide analgesia. Topical morphine mouthwash (2%) for patients with severe mucositis (associated with treatment for head and neck cancer) was more effective than mouthwash containing viscous lignocaine, magnesium aluminium hydroxide and diphenhydramine, both administered in 10 mL aliquots 3-hourly (Sarvizadeh 2015 **Level II**, n=30, JS 5). Morphine mouthwash recipients had lowered WHO grading scores for mucositis after 6 d of treatment and reported increased satisfaction with their treatment.

Preventive strategies for mucositis such as palifermin (Bensinger 2008 **GL**) or oral cryotherapy (Batlle 2014 **Level III-2**; Tayyem 2014 **NR**) may be effective in specific circumstances. Polymyxin E, tobramycin and amphotericin B (PTA), GM-CSF, oral cooling and amifostine have a preventive effect by significantly reducing the incidence and severity of oral mucositis (Stokman 2006 **Level I**, 45 RCTs, n=4,145). Oral cryotherapy by having the patient suck on ice chips or hold ice water in his/her mouth before, during, and/or after rapid infusions of systemic therapies that are

associated with mucositis has been shown to be an effective preventive treatment (NNT 4) (Riley 2015 **Level I** [Cochrane], 14 RCTs, n=1,280). Situations studied include patients receiving fluorouracil (5-FU) for solid cancers, and, to a lesser extent, patients receiving high-dose mephalan before haematopoietic stem cell transplantation, melphalan for multiple myeloma and 5-FU for solid tumours. A subsequent RCT showed similar findings (Idayu Mat Nawi 2018 **Level II**, n=88, JS 2). This approach is also recommended in guidelines (Swarm 2019 **GL**).

Low-level laser therapy (LLLT) may be effective in reducing pain intensity, severity and duration of mucositis based on moderate evidence (Anschau 2019 **Level I** [PRISMA], 5 RCTs, n=315). This is in line with findings of two small low-quality studies not included in the meta-analysis (Abramoff 2008 **Level II**, n=11, JS 2; Arora 2008 **Level II**, n=28, JS 2). LLLT used prophylactically reduces the risk of severe mucositis and pain in patients with cancer or undergoing hematopoietic stem cell transplantation (Oberoi 2014 **Level I** [PRISMA], 18 RCTs, n=1,144). This approach is recommended in a specific clinical practice guideline (Zadik 2019 **GL**).

Honey shows benefit over placebo and other treatments for moderate to severe chemotherapy induced mucositis in adults, but not in teenagers (Yang 2019 **Level I** [PRISMA] [NMA], 17 RCTs, n=1,265).

Evidence-based clinical practice guidelines for the prevention and treatment of mucositis in cancer patients have been published (Zadik 2019 **GL**; Alvarino-Martin 2014 **GL**; Lalla 2014 **GL**)

For paediatric information, see Section 10.8.3.1.

8.9.9 | Interventional therapies for acute cancer pain

Although pain is adequately controlled in the majority of patients with advanced cancer, patients with severe acute exacerbations of pain may benefit from interventions.

Where pain is prolonged, but opioid-resistant, intractable, and associated with frequent acute exacerbations of pain, including incident pain or paroxysmal neuropathic pain, and adverse effects limit other pharmacological strategies, patients with advanced disease may benefit from longer-term local anaesthetic infusions, including neuraxial infusions, or more destructive neurolytic and other ablative procedures to manage pain.

8.9.9.1 | Peripheral nerve blocks

Local anaesthetic nerve or plexus blocks including continuous peripheral nerve block (CPNBs) may be used to control pain prior to surgery eg acute or imminent fracture, during painful diagnostic or therapeutic procedures, or while awaiting a response from other therapy such as radiation therapy (Klepstad 2015 **Level IV SR**, 16 studies, n=79; Chambers 2008 **NR**) (see also Section 5.8). Unilateral continuous erector spinae plane block (ESPB) may provide sufficient analgesia in patients with end-stage pulmonary malignancy suffering from severe unilateral thoracic pain (Aydin 2018 **Level IV**, n=2).

8.9.9.2 | Neuraxial techniques

Currently, epidural or IT infusions of several classes of agents by a variety of medication delivery systems may provide effective analgesia to cancer patients with previously refractory pain, poor tolerance of oral or systemic analgesia and poor performance status (see also Sections 5.6 and 5.7). There is only limited evidence supporting neuraxial treatment of cancer pain summarised in 2 systematic reviews. There is low quality evidence supporting these techniques resulting in a weak recommendation for their use based on better pain control found for all interventions; described comparisons include neuraxial combinations of opioid and adjuvant analgesic vs opioid alone (4 RCTs), neuraxial bolus vs continuous infusion (2 RCTs), neuraxial drug vs neuraxial placebo

(1 RCT) and neuraxial opioid vs other comprehensive medical management (2 RCTs) (Kurita 2015 **Level I**, 9 RCTs, n=686). Specifically, for IT administration, the 2 RCTs show benefits of IT morphine and IT ziconotide administration (Bruel 2016 **Level IV SR**, 2 RCTs & 8 studies, n=807) (2 RCTs overlap). A retrospective chart review of neuraxial analgesia for cancer pain showed good analgesic effect in 50% of 16 epidural and in 70% of 44 IT treatments (Kiehela 2017 **Level IV**, n=60). High dose systemic opioids (in the range of 700 to 900 mg oral MED) could be discontinued or significantly reduced in 83% of patients who received neuraxial infusions of morphine, commonly combined with low-dose bupivacaine and adjuvants including clonidine and ketamine. However, catheter dislocations occurred in 27% of cases.

Consensus guidelines for the use of neuraxial analgesia in cancer pain are based largely on this weak evidence, despite broad experience in the use of IT opioids, local anaesthetics, clonidine, baclofen and other neuraxial medications (Kurita 2011 **Level IV SR**, 44 studies, n=2,116 [cancer; 7 RCT overlap with Kurita 2015]; Clarke 2017 **GL**; Deer 2011 **GL**). These consensus guidelines and other systematic or practical reviews provide a framework to optimise safety and effectiveness of these techniques that may be used in various and potentially remote palliative settings (Myers 2010 **SR** of 3 SRs, 3 consensus conferences & 12 RCTs; Gulati 2014 **NR**; Upadhyay 2012 **NR**; Mercadante 2012 **NR**).

Breakthrough analgesia with either SL ketamine or an IT local anaesthetic bolus was used successfully in palliative patients with ongoing IT analgesia (Mercadante 2005 **Level IV**). Although infrequently used, morphine by the intracerebroventricular (ICV) route may offer advantages for patients with head, neck or upper limb malignancy causing intractable pain (Ballantyne 2005 **Level IV SR** [Cochrane], 13 studies [ICV], n=337). This review noted few treatment failures and excellent analgesia reported in 73% after ICV opioids with more reports of respiratory depression, sedation and confusion, but lower incidence of nausea, urinary retention, pruritus and constipation with ICV therapy than with IT and epidural routes.

Patient-controlled IT analgesia with a number of agents (morphine, hydromorphone, fentanyl, bupivacaine, clonidine, baclofen, and ziconotide) in the management of refractory cancer-related pain resulted in improved pain control and faster onset of effect vs conventional treatment for breakthrough pain (Brogan 2015 **Level III-3**, n=58).

Patient-controlled epidural analgesia vs intravenous analgesia in patients diagnosed with advanced cancer showed that epidural analgesia is associated with improved respiratory parameters, lower pain scores, higher satisfaction scores, and less opioid related GIT side effects (He 2015a **Level II**, n=50, JS 1).

8.9.9.3 | Spinal cord stimulation

Evidence is insufficient to establish any role for spinal cord stimulation for cancer pain in adults; four case series provide the only evidence base in cancer pain and nil further in an updated Cochrane review (Peng 2015 **Level III-3 SR** [Cochrane], 4 studies, n=92).

8.9.9.4 | Destructive procedures

Coeliac plexus block

For pain due to pancreatic cancer, neurolytic coeliac plexus block has been widely used (Nagels 2013 **NR**) with improved pain scores at 4 wk (-0.42/10; 95%CI -0.70 to -0.13) and at 8 wk (-0.44/10; 95%CI -0.89 to -0.01) and reduced opioid requirements (Arcidiacono 2011 **Level I** [Cochrane], 6 RCTs, n=358). Similar findings were reported by a systematic review including additional case series (Nagels 2013 **Level IV SR**, 5 RCTs, n=295 & 61 studies, n≈4,719) (3 RCTs overlap), while a subsequent meta-analysis confirmed reduced analgesic requirements with improved pain control only at

4 and not 8 wk (Zhong 2014 **Level I**, 7 RCTs, n=403) (4 RCTs overlap with Nagels 2013; 6 RCTs overlap with Arcidiacono 2011).

Percutaneous coeliac plexus ablation for treating severe cancer pain in upper abdomen improved not only pain and performance status scores in the treatment group, but also had health economic benefits by reducing medicine-specific and total health care costs vs controls (Cao 2017 **Level III-2**, n=81). There were no differences seen between the two groups in hospitalisation, examinations, or treatment costs. Better performance status and low daily opioid use before neurolytic coeliac plexus block were independent predictors of good analgesia after the procedure in patients with unresectable pancreatic cancer (Yoon 2018 **Level III-2**, n=112).

Bilateral vs unilateral endoscopic ultrasound-guided celiac plexus neurolysis for abdominal pain management for pancreatic malignancy reduced analgesic requirements, although pain relief and response to treatment were the same (Lu 2018 **Level III-2 SR**, 6 studies, n=437).

Splanchnic nerves

There was no difference in pain outcomes or complications when comparing alcohol versus phenol based techniques in splanchnic nerve neurolysis for pain related to upper abdominal malignancies (Koyyalagunta 2016 **Level III-3**, n=93). The treatment reduced pain scores but not opioid consumption. Furthermore, the procedure resulted in improvements in anxiety, depression, thinking clearly and feeling of well-being.

Radiofrequency ablation vs chemical neurolysis of bilateral thoracic splanchnic nerves in the management of refractory cancer pain due to upper abdominal cancers provided quicker onset and longer duration of analgesia with a higher success rate, along with a better safety profile (Amr 2018 **Level II**, n=60, JS 2).

Bilateral thoracoscopic splanchnicectomy was effective for intractable pain secondary to pancreatic cancer with only 28% of patients continuing to experience abdominal pain (Bhutiani N 2017 **Level III-3**, n=48). Daily opioid dose decreased in 74% of the patients and 67% discontinued analgesics completely.

Cordotomies

Cordotomies have also been performed successfully to treat cancer pain in highly selected cases (Raslan 2011 **NR**). In pain due to mesothelioma, percutaneous cervical cordotomy may be safe and effective (France 2014 **Level IV SR**, 9 studies, n=160). In pain mainly due to malignancies, CT-guided percutaneous cervical cordotomy provided pain relief in 98.13% of cases (Kanpolat 2013 **Level IV**, n=210). In another case series, 32 of 45 patients experienced significant pain relief without relevant adverse effects (Bain 2013 **Level IV**, n=45).

Other destructive procedures

Early vs later neurolytic sympathectomy for pain from abdominal or pelvic cancer resulted in reduced oral analgesic use and improved pain control and QoL (Amr 2014 **Level II**, n=109, JS 4).

Pulsed radiofrequency was used to treat pain from infiltration of the brachial plexus by a tumour (Arai 2013b **Level IV**, n=4; Magistroni 2014 **CR**; Rana 2013 **CR**).

In selected cases, IT neurolytic blocks can be a pain-relieving intervention (Candido 2003 **NR**).

8.9.9.5 | Other Therapies

High Intensity Focused Ultrasound

A meta-analysis concluded high intensity focused ultrasound (HIFU: a non-invasive thermal ablation technique) appears to be effective for pain reduction in advanced pancreatic cancer, although the heterogeneity of the data and the lack of RCTs prevents a strong recommendation (Dababou 2017 **Level IV SR** [PRISMA], 23 studies, n=865).

Acupuncture

Acupuncture for palliative care of cancer shows conflicting evidence regarding treatment of cancer-related pain, but some evidence for its use in management of cancer-related fatigue, chemotherapy-induced nausea and vomiting and leukopenia in patients with cancer (Wu 2015 **Level IV SR**, 23 SRs of 248 primary studies, n=17,392).

Music Intervention

Music interventions may be effective in reducing pain scores (SMD -0.91; 95%CI −1.46 to −0.36) (7 studies, n=528) as well as having some beneficial effects on physiological variables (heart rate, respiratory rate and blood pressure), anxiety, pain, fatigue and QoL in people with cancer (Bradt 2016 **Level III-1 SR** [Cochrane, 52 studies, n=3,731). Most trials were at high risk of bias and, therefore, these results need to be interpreted with caution.

KEY MESSAGES

1. Intranasal, sublingual and buccal fentanyl preparations are effective treatments for breakthrough pain in cancer patients (**U**) (**Level I** [Cochrane Review]) with similar efficacy to intravenous administration (**U**) (**Level I** [PRISMA]) and superior to oral morphine (**U**) (**Level I**).
2. Radiotherapy is an effective treatment of acute cancer pain due to bone metastases (**U**) (**Level I** [Cochrane Review]), while bone-targeting agents (bisphosphonates, denosumab) are beneficial in delaying the onset of bone pain rather than providing analgesia (**W**) (**Level I** [PRISMA]).
3. Neurolytic coeliac plexus block in pancreatic cancer lowers pain intensity and opioid analgesic requirements for at least 8 weeks (**U**) (**Level I** [Cochrane Review]).
4. Opioids, via PCA or a continuous infusion, provide effective analgesia in mucositis; PCA is associated with reduced opioid requirements and pain duration (**U**) (**Level I** [Cochrane Review]).
5. Oral cryotherapy (sucking on ice chips or holding ice water in the mouth before, during, and/or after rapid infusions of systemic therapies that result in mucositis) effectively prevents mucositis (**N**) (**Level I** [Cochrane Review]).
6. Music interventions may be effective in reducing pain intensity in patients with cancer (**N**) (**Level I** [Cochrane Review]).
7. Topical treatment with doxepin (**S**), amitriptyline (**N**), diclofenac (**N**), benzydamine (**N**) (**Level I** [PRISMA]), povidone-iodine (**U**) (**Level I**) and morphine (**S**) (**Level II**) compared to placebo improve pain relief due to mucositis.
8. Low-level laser therapy reduces and when used prophylactically prevents pain and severity of mucositis (**S**) (**Level I** [PRISMA]).
9. Patient education about cancer pain is a key factor in optimising pain management (**U**) (**Level I**).
10. Opioid doses for individual patients with cancer pain should be titrated to achieve maximum analgesic benefit with minimal adverse effects (**U**) (**Level II**).

11. Analgesic medications prescribed for cancer pain should be adjusted to alterations of pain intensity (**U**) (**Level III-2**).
12. Neuropathic pain or mixed nociceptive-neuropathic pain has an estimated frequency of 30-40% in patients with cancer (**S**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

- ☑ Acute pain in patients with cancer often signals disease progression; sudden severe pain in patients with cancer should be recognised as a medical emergency and immediately assessed and treated (**U**).
- ☑ Prompt assessment and fast coordinated management of spinal metastases with suspected spinal cord compression is required to mitigate against neurological deficit (**U**).
- ☑ Cancer patients receiving controlled-release opioids need access to immediate-release opioids for titration of breakthrough pain; ~~s~~election of breakthrough medication should consider the time course and aetiology of the pain flare (**U**).
- ☑ If nausea and vomiting accompany acute cancer pain, parenteral opioids are needed (**U**).
- ☑ Transdermal opioids are inappropriate to control acute unstable pain (**U**).
- ☑ High interindividual variability in opioid conversion rates dictates that all opioid rotations should be individualised and monitored, particularly where higher opioid doses are in use (**U**).

8.10 | Acute pain management in intensive care

Acute pain is a common occurrence in critically ill patients. As many as 80% of intensive care unit (ICU) patients experience moderate to severe pain at some point in their ICU admission and attribute it to a source of long term psychological morbidity (Rotondi 2002 **Level III-2**, n=150; Puntillo 2001 **Level III-2**, n=6,201), while approximately 50% of both medical and surgical patients experience pain at rest (Chanques 2006 **Level III-1**, n=230). However, barriers to effective pain report exist including the presence of an endotracheal tube, sedative infusions, restraints and neurological sequelae of critical illness (eg delirium, traumatic brain injury). Despite the limitations on pain assessment and the altered physiology of critical illness, a balanced, multimodal analgesic approach targeted at the sociopsychobiomedical aetiology of acute pain is warranted.

8.10.1 | Aetiology of pain in the intensive care unit (ICU)

The aetiology of acute pain in critically ill patients is complex and synergistic (see Table 8.2). Whilst not all of these are modifiable, targeted treatment of each of the potential aetiologies may result in a profound decrease in patient suffering both in the ICU and thereafter.

Table 8.2 | Aetiology of acute pain in the ICU

Biological	Underlying Illness (eg surgery, sepsis, trauma, burns) Iatrogenic interventions (eg ETT, repositioning, drains, dressing changes, vascular access, invasive monitoring) Complications (eg nosocomial infections) Prolonged immobility Inappropriate pain management (lack of multimodal analgesia, OIH) Pharmacotherapy (Sedation type) Pre-existing chronic pain
Psychological	Fear Hallucinations Post-Traumatic Stress Disorder Sleep deprivation Delirium Anxiety Depression
Social	Isolation and Rejection Circumstances of the injury Facing own mortality

Sources: Adapted from Sigakis 2015

8.10.2 | Barriers to pain management in the ICU

There exist multiple barriers to the provision of effective, multimodal analgesia to critically ill patients (see Table 8.3). Both patient-related and provider-related barriers should be addressed in analgesic management strategies. Simple strategies such as communication boards, patient education about their likely analgesic requirements, and health provider education can result in a marked improvement to overcoming the barriers to effective analgesia. Healthcare system-related barriers require policy development (including quality improvement or QI), education, workflow analysis and change methodology when implementing unit-wide analgesic guidelines.

Table 8.3 | Barriers to effective pain management in the ICU

Patient	Inability to report pain Differential reporting to doctors and nurses Fear of the consequences of reporting pain Fear of the side effects of analgesic medications Feelings that pain should be tolerated as part of the disease process (fatalistic beliefs) Altered cognitive status giving the impression of having effective analgesia (eg hypoactive delirium)
Provider	Knowledge deficits of aetiology, assessment and management strategies (eg sedation as an analgesic, multimodal analgesia) Pain management assigned a low priority (seen as "ICU Housekeeping") Failure to assess for the existence of pain Failure to evaluate effect of analgesic treatment Inconsistent practices, particularly around periprocedural analgesia Inappropriate attitudes regarding the use of opioids Overconcern about the side-effects of analgesics (eg opioid tolerance, NSAIDs) Lack of knowledge of the types and appropriate doses of analgesics Communication difficulties between the patient and the healthcare team Personal and cultural biases
Healthcare system	Lack of accountability for unsatisfactory outcomes related to inadequate analgesic management Inadequate local guidelines to guide pain management Lack of alternative non-pharmacological therapies (eg hot or cold compresses, mobilisation therapy whilst intubated) Inadequate quality improvement processes for pain management Logistic barriers to timely analgesic administration (eg high nursing burden) Implementation of change to pre-existing methods of analgesia and sedation

Sources: Adapted from Sigakis 2015

8.10.3| Pain assessment in the ICU

Assessment of pain in the critically ill patient is difficult, owing to the barriers previously mentioned and outlined in Table 8.3. A patient's subjective index of pain is often not possible or reliable because of altered cognitive status or co-administered sedative agents. In addition, a health provider's own biases may prevent recognition of pain. In a study of patient recollections, the presence of the endotracheal tube was rated on average as being 6/10 (5/10 at best and 8/10 at worst) (Rotondi 2002 **Level III-2**, n=150). For this reason, a patient post-laparotomy may be more likely to be assessed for pain compared with a patient receiving mechanical ventilation due to severe pneumonia. Hence, it is important to have a structured, consistent approach to analgesic assessment, regardless of the admission diagnosis.

The Society of Critical Care Medicine's (SCCM) Pain, Agitation, Delirium, Immobility and Sleep (PADIS) Guidelines (Devlin 2018 **GL**) advocate for self-reporting scales to be used as first line for pain assessment, followed by behavioural pain scores in those unable to self-report.

In responsive patients, the numerical rating scale (NRS) is the reference standard for pain assessment. The presence of an endotracheal tube should not prevent self-reporting, and the use of communication adjuncts (communication board, pen and paper, visual aid) should be encouraged. In unresponsive patients, the NRS is not applicable. Instead, the observation of behavioural and physiological responses may be the only information available to modify pain management (Puntillo 2002 **Level IV**; Puntillo 1997 **Level IV**; Chong 2003 **NR**). The use of such behavioural scales is recommended but only validated, reliable and feasible scales should be used (Gelinas 2013b **NR**).

The critical care pain observation tool (CPOT) has been developed and validated in sedated, mechanically-ventilated critically ill patients (Gelinas 2011 **Level III-2**; Gelinas 2006 **Level III-2**), including the cohorts with a brain injury (Joffe 2016 **Level III-2**), post-operative elective neurosurgical patients (Echegaray-Benites 2014 **Level III-2**) and delirium (Kanji 2016 **Level III-2**). The behavioural pain score (BPS) has also been described and validated for the evaluation of pain in sedated, mechanically ventilated, unresponsive patients (Aissaoui 2005 **Level III-1**; Payen 2001 **Level III-1**; Gelinas 2013b **NR**). The use of BPS vs CPOT resulted in a higher specificity (91.7% vs 70.8%), but a lower sensitivity (62.7% vs 76.5%) (Severgnini 2016 **Level III-2**).

8.10.4 | Analgesic management strategies in the ICU

The management of acute pain in intensive care requires an individualised, multimodal analgesic approach targeted at the sociopsychobiomedical aetiology of acute pain. Although there is a paucity of evidence to guide specific analgesic practices, the SCCM PADIS guidelines provide a framework for this challenging group (Devlin 2018 **GL**).

The use of protocolised analgesia management consisting of regular assessment of pain, analgosedation protocols, sedation assessment and management, delirium screening and management, and targeted analgesia was associated with improved analgesia, decreased duration of mechanical ventilation, ICU LOS, duration and dose of opioid and sedative infusions and decreased mortality (Georgiou 2015 **Level IV SR** [PRISMA], 10 studies, n=3,547; Mansouri 2013 **Level II**, n=216, JS 3; Chanques 2006 **Level III-1**; Barnes-Daly 2017 **Level III-2**, n=6,064; Payen 2009 **Level III-2**; De Jonghe 2005 **Level III-3**).

A summary of the principal recommendations of evidence-based pain guidelines includes (Devlin 2018 **GL**):

- An analgosedation-based protocol for assessment and management should be used (ie assess and treat pain first, followed by agitation/sedation assessment and management,

followed by delirium screening and management and withdrawal assessment/ management during weaning);
- Pain should be routinely monitored in ICU, using the BPS and the CPOT for patients who are unable to self-report;
- Vital signs alone should not be used for pain assessment;
- Opioids are recommended as first-line analgesics for non-neuropathic pain, administered at the lowest possible dose to achieve adequate analgesia;
- Paracetamol should be used as an adjuvant to opioids in pain management;
- Conditional recommendations for NSAIDs as an adjunct to opioids in pain management;
- Ketamine should be used to reduce opioid consumption in postsurgical ICU patients;
- Neuropathic pain medications should be used with an opioid for neuropathic pain.

Current practice still falls well short of these recommendations. In an Australian and New Zealand point-prevalence study, fewer than half of patients in the participating ICUs had their pain assessed within the 4 h period audited and 22% of those assessed were considered to have moderate or severe pain (Elliott 2013 **Level IV**, n=41 [ICUs]).

8.10.5 | Nonpharmacological analgesic management

As there may be a large psychosocial influence in development of acute pain in the critically ill patient, non-pharmacological interventions have the potential to act as powerful analgesic adjuvants. Attention to detail with positioning, pressure care, comfortable fixation of invasive devices, care in the management of secretions and excretions, minimisation of noise from spurious alarms and unnecessary equipment (such as the uncritical application of high-flow mask oxygen) can substantially lessen the burden of discomfort for the patient (Puntillo 2004 **Level III-3**; Chong 2003 **Level IV**; Aaron 1996 **Level IV**). Maintenance of a day-night routine (lighting and activity) is thought to aid sleep quality, which may reduce pain perception (Horsburgh 1995 **NR**).

Specific to analgesic management, cognitive behavioural techniques such as distraction therapy and music therapy, simple massage and facilitation of family presence were agreed by patients and nursing staff as the most effective non-pharmacological analgesic adjuvants (Gelinas 2013a **Level IV**). Massage may have beneficial effects in reducing pain and anxiety in ICU patients (Jagan 2019 **Level I** [PRISMA], 12 RCTs, n=779).

8.10.6 | Pharmacological analgesic management

Management of acute pain may be difficult in the presence of co-administered sedation. It is important, however, to attempt to monitor both processes with sedation scoring (via the Richmond Agitation-Sedation Scale: RASS) and an observational pain assessment tool. This may allow titration of both sedative and analgesic medications separately and decrease the risk of inappropriate therapies (eg increased sedation for agitation due to acute pain).

The mainstay of treatment of acute pain in mechanically ventilated ICU patients is parenteral opioid analgesia (Devlin 2018 **GL**). Despite this, multimodal analgesia should be the goal; the use of non-opioids as adjuvants to opioids in the ICU setting has beneficial effects (Zhao 2019 **Level I** [PRISMA], 12 RCTs, n=910). In particular in ICU patients with Guillain-Barre-Syndrome and after surgery, non-opioids reduce pain intensity, opioid requirements and nausea and vomiting. In addition to multimodal analgesia, sedative type may play a role in analgesic management. In healthy volunteers, moderate sedation with midazolam increased the pain perception of temperature and electrical pain, whilst propofol reduced ischaemic pain and dexmedetomidine reduced both ischaemic and cold pain (Frolich 2013 **Level II EH**, n=86, JS 2). This raises the possibility that midazolam may lower pain thresholds.

8.10.6.1 | Paracetamol

Paracetamol is a safe non-opioid analgesic in the critically ill cohort. IV paracetamol 1 g every 6 h in ICU patients with fever or suspected infection did not increase the incidence of hepatic dysfunction vs placebo (Young 2015 **Level II**, n=700, JS 5). In elective, post-operative surgical ICU patients, the addition of paracetamol improved analgesia, reduced opioid consumption and time to extubation (Memis 2010 **Level II**, n=40, JS 5).

However, IV paracetamol can result in hypotension (Chiam 2015 **NR**). The use of IV propacetamol and IV paracetamol and associated hypotension has been reported (with variable definitions: systolic vs MAP change in absolute value or 15-20% decrease) in mostly critically ill (often cardiac) patients (14/19 studies) (Maxwell 2019 **Level IV SR**, 19 studies [5 RCTs, 6 open-label trials & 8 retrospective reviews], n=3,470). Hypotension appears to be more prevalent with IV vs nasogastric paracetamol in an RCT included in the systematic review (Kelly 2016 **Level II**, n=50, JS 3).

8.10.6.2 | NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective analgesics. Their use, however, is restricted in the critically ill cohort due to the perceived increased risk of acute kidney injury, gastrointestinal bleeding, platelet inhibition and acute myocardial infarction.

When ketoprofen was added for 24 h to an opioid infusion in post-operative major abdominal surgery patients, the result was a reduction in pain scores, opioid consumption (by approximately 20%) and nausea and vomiting (Oberhofer 2005 **Level II**, n=44, JS 4). There were no reported bleeding events or episodes of acute kidney injury. The use of ketorolac in patients with rib fractures decreased the incidence of pneumonia and ventilation times, with no apparent increase in the risk of bleeding or renal failure (Yang 2014 **Level III-2**, n=619).

In a study comparing ibuprofen 10 mg/kg (max. 800 mg) four times daily to placebo in septic ICU patients, there was no increase in the incidence of acute kidney injury, renal replacement therapy, bleeding, or gastrointestinal bleeding (Bernard 1997 **Level II**, n=455, JS 4). Interestingly, the exclusion criteria for renal dysfunction was a creatinine >354 micmol/L. Despite this, there was no increase in renal adverse events in the ibuprofen group vs placebo. Hence, the incidence of side effects in the critically ill may be overestimated.

8.10.6.3 | Opioids

Type of opioid

Currently, there are no head-to-head studies comparing the main opioids used in ICU. Morphine and fentanyl are the predominant parenteral opioids administered in the ICU. Analysis of the opioid infusions in the SPICE 3 trial revealed that 80.0% of patients received fentanyl compared to 30% receiving morphine (some patients received more than 1 opioid) (Shehabi 2019 **Level II**, n=4,000, JS 5). Morphine was traditionally the first-line agent in patients without renal impairment, whereby accumulation of the active metabolite, morphine-6-glucuronide could potentiate the opioid effects (Casamento 2019 **NR**). Fentanyl has a short duration of action after a single dose due to redistribution, but its long elimination half-life leads to accumulation when given in high doses for long periods (Mather 1983 **NR PK**). The replacement of a fentanyl infusion with enteral methadone in mechanically ventilated patients was associated with a shorter weaning time (Wanzuita 2012 **Level II**, n=68, JS 4). Hydromorphone also lacks an active metabolite, but the inactive metabolite, hydromorphone 3-glucuronide may accumulate in renal failure and result in neuroexcitation (manifesting as delirium, altered mental status) (Murray 2005 **NR**). Parenteral oxycodone is being used more in the critical care setting, but there is a lack of

evidence to guide its use, particularly in the setting of end-organ dysfunction. Remifentanil, due to its pharmacokinetics, has the potential to lead to improved outcomes in ICU. However, remifentanil vs either another opioid or hypnotic agent has no benefits in mortality, duration of mechanical ventilation, ICU LOS or risk of agitation (Tan 2009 **Level I**, 11 RCTs, n=1,067). The use of remifentanil is only associated with a reduction in the time to extubation after cessation of sedation (2.04 h; 95%CI 0.39 to 3.69). A subsequent study confirmed this by failing to identify superiority of remifentanil over fentanyl in terms of analgesia, duration of ventilation or morbidity (Spies 2011 **Level II**, n=60, JS 5). There are ongoing concerns about remifentanil with regard to the development of OIH and acute opioid tolerance in the perioperative setting, which may also have implications in the ICU (Kim 2014d **Level IV SR** & **EH**, number of studies unspecified, n unspecified).

Opioid delivery: intermittent bolus vs continuous infusion

The use of intermittent boluses of opioids has the potential benefit of decreasing the duration of mechanical ventilation, opioid-related side-effects such as gastric stasis and nausea and vomiting and development of opioid tolerance. Patients initiated on a continuous infusion of fentanyl experienced more delirium than intermittent boluses of fentanyl (Wolf 2017 **Level III-2**, n=60). The duration of mechanical ventilation, ICU and hospital LOS and self-extubation were similar between the two groups. Unfortunately, pain scores and opioid consumption were not recorded. In another study, intermittent boluses of fentanyl were compared to parenteral paracetamol, with no difference in pain scores for 48 h in mechanically ventilated ICU patients (Kouchek 2013 **Level II**, n=40, JS 2).

Prolonged infusion and tolerance

In ICU patients receiving mechanical ventilation for a prolonged period, there is potential for opioid tolerance to occur (Martyn 2019 **NR**). This may manifest upon cessation of the opioid with a withdrawal syndrome and delirium. In a study looking at ICU patients receiving >7 d of continuous opioid and sedative infusions, abrupt cessation resulted in an acute withdrawal syndrome in 32.1% of patients (Cammarano 1998 **Level III-2**, n=28). Acute withdrawal was associated with a higher daily opioid dose. In another study of general ICU patients, the incidence of withdrawal was 16.7%; higher median cumulative opioid dose and duration of opioid infusion >6 d were associated with withdrawal syndrome, although this study was underpowered (Wang 2017b **Level III-2**, n=54). Hence, cautious opioid weaning should be considered in patients that have received a high cumulative dose of opioid or have been exposed to prolonged duration of infusion (>6 d).

See also Section 9.7 and for paediatric opioid tolerance Section 10.4.6.

8.10.6.4 | Alpha-2 agonists

The alpha-2 agonists have analgesic effects and may aid in analgesia both through the management of psychological contributors for acute pain (eg delirium, agitation and anxiety) and through the avoidance of potentially antalgesic sedatives (Frolich 2013 **Level II EH**, n=86, JS 2). However with use of dexmedetomidine, there was no difference in 90-day mortality, delirium-free or ventilator-free days, with an increased risk of adverse events, namely hypotension, bradycardia and an increased mortality in patients <65 y old (Shehabi 2019 **Level II**, n=4,000, JS 5). However in one RCT, dexmedetomidine was associated with lower morphine requirements than propofol-based sedation after cardiac surgery (Herr 2003 **Level II**, n=295, JS 2). It is also of note here that dexmedetomidine facilitated patient interaction such as the ability to use a VAS for pain assessment vs midazolam and propofol (Ahmed 2013 **Level II**, n=500, JS 5).

8.10.6.5 | Ketamine

Unlike other analgesics and sedatives in ICU, ketamine acts as a potent analgesic, sedative agent and bronchodilator that has positive effects on haemodynamics (Patanwala 2017 **Level IV SR** [PRISMA], 6 RCTs, n=223 & 6 studies, n=39). Its use as an adjunct to opioid therapy reduced cumulative morphine consumption by 27.5% in awake postsurgical ICU patients (Guillou 2003 **Level II**, n=101, JS 2). In mechanically ventilated patients in a surgical ICU, administration of low-dose ketamine infusion resulted in a decrease in morphine consumption by 20%, with a decrease in sedative requirements and vasopressor use (Buchheit 2019a **Level III-3**, n=40). There was, however, an increase in the number of patients with a Richmond Agitation-Sedation Scale (RASS) >0 (10 point scale -5 to +4). This may be due to the psychomimetic effects of ketamine or the reduced dose of propofol sedation. Additionally, opioid infusions were ceased within 24 h in 50% of patients receiving a ketamine infusion.

8.10.6.6 | Regional analgesia

Regional analgesic modalities are covered elsewhere (see Sections 5.6 to 5.8). The ICU patients who may derive benefit are those that receive thoracic epidural analgesia for abdominal aortic aneurysm surgery (Nishimori 2006 **Level I** [Cochrane], 13 RCTs, n=1,224 patients), traumatic rib fractures (Carrier 2009 **Level I**, 8 RCTs, n=232; Stundner 2012 **NR**) or thoracoabdominal procedures (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044).

Furthermore, there is an increasing utilisation of peripheral nerve blocks as techniques of regional analgesia. See also Sections 5.8 and 8.2.2.

8.10.6.7 | Guillain-Barré Syndrome

Gabapentin and carbamazepine, but not methylprednisolone, have analgesic efficacy in Guillain-Barré syndrome but the evidence is limited and of low quality (Liu 2013 **Level I** [Cochrane], 3 RCTs, n=277). IV lidocaine may be useful in the treatment of acute neuropathic pain in Guillain-Barré syndrome based on evidence of benefit in other neuropathic pain disorders (Kalso 1998 **Level I**, 17 RCTs, n=450).

Plasma exchange in acute Guillain-Barré syndrome was associated with a shortened duration of disease and improved outcomes, including pain (Raphael 2012 **Level I** [Cochrane], 6 RCTs, n=649). However, corticosteroids do not offer any benefits in this indication and may even delay recovery, while causing adverse effects (Hughes 2012 **Level I** [Cochrane], 6 RCTS, n=587).

8.10.6.8 | Periprocedural analgesia

There is often an assumption that patients who are intubated and sedated in an ICU will not recall or perceive pain during procedures. Lines and catheters are sometimes inserted without supplementary anaesthesia. A survey suggests that specific treatment of procedure-related pain occurs less than 25% of the time (Payen 2007 **Level IV**, n=1,381). Of patients who have memories of ICU, 54% recall discomfort and 12% overt pain.

Endotracheal tube suctioning and other medical interventions are consistently reported as being uncomfortable or painful (Jeitziner 2012 **Level III-2**, n=21). Therefore, adequate local and/or parenteral anaesthesia should be provided during any noxious procedure (Casey 2010 **Level II**, n=60, JS 5; Puntillo 2004 **Level IV**). Use of dexmedetomidine as the sole agent for painful procedures does not reliably prevent recall or acute stress disorder (MacLaren 2015 **Level II**, n=23, JS 5).

Bolus remifentanil at a dose of 1 or 0.5 mcg/kg prior to removal of chest drains after cardiac surgery was superior to placebo with the higher dose causing more respiratory depression (Casey 2010 **Level II**, n=60, JS 5). In a dose-response study, the 90% effective dose (ED_{90}) of sufentanil was 0.15 mcg/kg for turning patients during the first 5 d of sedation (Chaveron 2012 **Level II**, n=25, JS 5).

KEY MESSAGES

1. Plasma exchange in acute Guillain-Barre syndrome improves outcome including analgesia (**U**) (**Level I** [Cochrane Review]).
2. Carbamazepine and gabapentin may reduce the pain associated with Guillain-Barre syndrome, based on limited and low-quality evidence (**U**) (**Level I** [Cochrane Review]).
3. Non-opioids including NSAIDs and paracetamol improve analgesia in selected intensive care unit patients (**S**) (**Level I** [PRISMA]).
4. Remifentanil provides no advantages over other opioids in ventilated intensive care unit patients (**U**) (**Level I**).
5. Ketamine decreases cumulative opioid doses in mechanically ventilated patients, with positive effects on haemodynamics and reduced requirements for sedation, but with an increased risk of psychomimetic adverse effects (**N**) (**Level II**).
6. The formal assessment and management of pain and agitation in ventilated intensive care unit patients decreases the incidence of pain, the duration of ventilation, the length of ICU stay and mortality (**U**) (**Level III-1**).
7. Prolonged opioid infusions for >6 days and higher cumulative opioid dose increase the risk of acute withdrawal if the opioid infusion is abruptly ceased (**N**) (**Level III-2**).
8. Procedures such as endotracheal tube suctioning are consistently reported as uncomfortable and painful (**U**) (**Level III-2**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ The aetiology of acute pain in critically ill patients is complex and encompasses all domains of the sociopsychobiomedical model of pain (**N**).
- ☑ Observation of behavioural and physiological responses permits assessment of pain in unconscious patients (**U**).
- ☑ Routine monitoring for pain in sedated intensive care patients should be performed, using the Behavioural Pain Scale or the Critical-Care Pain Observation Tool (**U**).
- ☑ Analgesia management should be targeted to the potential aetiologies of acute pain (**N**).
- ☑ Opioids are the recommended first-line analgesic agents in ventilated intensive care patients (**U**).
- ☑ The risk of NSAIDs in critically ill patients may be overestimated; NSAIDs may provide effective analgesia as a part of multimodal analgesia (**N**).
- ☑ Regional analgesia techniques should be considered in patients undergoing large intra-abdominal surgical procedures and trauma (**N**).
- ☑ Intensive care unit patients should be provided with appropriate analgesia prior to and during potentially painful procedures, in particular as recall of discomfort, pain and procedures can be a source of post-traumatic stress (**S**).

8.11 | Acute pain management in emergency departments

Pain is the most common reason for presentation to the emergency department (ED) and many patients will self-medicate for pain before attending (Kelly 2008 **NR**). Analgesia should be simple to administer, safe, patient- and condition-specific and, where appropriate, based on local-regional rather than systemic techniques. Systems should be adopted to ensure adequate pain assessment, timely, adequate and appropriate analgesia, frequent monitoring and reassessment of pain and additional analgesia as required.

As in many other areas of health care, patients in EDs around the world can receive suboptimal pain management (Gueant 2011 **Level IV**, n=11,670), although this has been challenged (Cinar 2012 **Level III-3**, n=15,387; Green 2012 **NR**). A substantial proportion of patients in pain refuse pain medications (Kant 2019 **Level IV**, n=651). Although 70% of patients presenting to an ED rated their analgesia as "good" or "very good", patient satisfaction with analgesia did not correlate with pain scores at presentation or discharge or change in pain scores (Kelly 2000 **Level IV**, n=54). This indicates that other factors are involved (Shill 2012 **Level III-2**, n=476) including a strong association with staff compassion (Brown 2018 **Level IV**, n=115).

Strategies to improve analgesic administration in the ED include nurse-initiated processes (Shaban 2012 **Level III-3**, n=52 [Australian hospital EDs]), however, nurse-initiated analgesia was not associated with high satisfaction (Shill 2012 **Level III-2**, n=476). Other strategies include the introduction of a protocol-based opioid titration regimen (Curtis 2007 **Level III-3**), whilst mandatory pain scoring at triage was also associated with a faster time to analgesia (Vazirani 2012 **Level III-1,** n=35,628). A review of ED interventions to encourage measurement of pain, remove barriers which delay analgesia, improve staff attitudes to pain relief, employ multi-faceted interventions, or investigate specific departmental diagnostic analysis of problems in pain management did not recommend wide-spread adoption of any interventions (Sampson 2014 **Level III-3 SR**, 42 studies, n≈76,856).

8.11.1 | Systemic analgesics

8.11.1.1 | Paracetamol and NSAIDs

Both paracetamol and NSAIDs are useful for treating mild to moderate trauma pain, musculoskeletal pain, renal and biliary colic and some acute headaches, as discussed elsewhere (see Sections 4.1 and 4.2). Paracetamol and NSAIDs have comparable analgesic efficacy in adult patients in ED with minor musculoskeletal injuries, with no significant benefit if given together (Ridderikhof 2019 **Level I** [PRISMA], 7 RCTs, n=2,100). However, the combination of oral paracetamol and NSAIDs is generally more effective than the use of either agent alone in postoperative pain (Ong 2010 **Level I**, 21 RCTS, n=1,909) or dental pain (Bailey 2013 **Level I** [Cochrane], 7 RCTs, n=2,241). In acute musculoskeletal injuries in ED, addition of ibuprofen and codeine did not improve the analgesic effect of paracetamol but significantly more adverse events were recorded in the combination group (Gong 2019 **Level II**, n=119, JS 5). Addition of codeine or oxycodone to paracetamol and ibuprofen did not result in improved analgesia in patients with extremity pain (Chang 2017 **Level II**, n=416, JS 5), and more adverse events occurred in the group receiving oxycodone (Graudins 2016 **Level II**, n=182, JS 4).

IV paracetamol (mostly 1 g) is supported by limited evidence as a primary analgesic for acute pain in the ED based on RCTs with various methodological issues; 3 of 14 RCTs showed superior pain relief over comparators (IV morphine 2 RCTs, IM piroxicam 1 RCT) and 8 of 14 RCTs showing no differences in pain scores between IV paracetamol and comparators (opioids, NSAIDs, buccal

paracetamol) (Sin 2016 **Level I** [PRISMA], 14 RCTs, n=1,472). Two subsequent RCTs showed IV morphine 0.1 mg/kg was superior to IV paracetamol for sciatica, with both superior to placebo (Serinken 2016 **Level II**, n=300, JS 2) and IV hydromorphone (1 mg) was superior to IV paracetamol in acute severe pain, again with both causing meaningful analgesia (Barnaby 2019 **Level II**, n=220, JS 5). The addition of IV paracetamol 1 g to IV hydromorphone 0.5 mg did not improve analgesia in acute severe pain (Chang 2019 **Level II**, n=162, JS 3). IV paracetamol was comparable to IV dexketoprofen in acute musculoskeletal pain (Demirozogul 2019 **Level II**, n=200, JS 5; Yilmaz 2019 **Level II**, n=200, JS 5). In a comparison of PO to IV paracetamol as analgesia following an initial dose of IV opioid, both groups had modest and comparable improvements in pain scores at 30 min, with high proportions of participants in each group requiring rescue medications (Furyk 2018 **Level II**, n=142, JS 5). Consideration should be given to IV paracetamol when other analgesics are contraindicated.

Dose comparison studies showed similar efficacy for IV ketorolac (10 mg vs 15 mg vs 30 mg) across doses for acute moderate to severe pain in the ED (Motov 2017b **Level II**, n=240, JS 4), and for PO ibuprofen 400 mg vs 600 mg vs 800 mg (Motov 2019 **Level II**, n=225, JS 4). This suggests an analgesic ceiling for NSAIDs in this setting.

For severe pain, IV parecoxib 40 mg reduced pain scores similarly vs IV morphine 0.1 mg/kg with less adverse effects (Baharuddin 2014 **Level II**, n=32, JS 4). Similar results were found comparing morphine to IV dexketoprofen (Eken 2014 **Level II**, n=137, JS 5), IV ibuprofen (Pan 2016 **Level II**, n=293, JS 2) or PO hydrocodone/paracetamol (Pan 2018 **Level II**, n=206, JS 2). For soft tissue injuries, PO naproxen 250 mg and PO oxycodone 5 mg had comparable analgesic effects, but oxycodone required more rescue analgesic medication with higher rates of adverse effects (Fathi 2015 **Level II**, n=150, JS 5).

8.11.1.2 | Conventional and atypical opioids

In the ED, opioids are frequently prescribed for the treatment of severe pain and should preferably be titrated via the IV route, given the wide interindividual variability in dose response and the delayed absorption via the IM or SC routes (Motov 2018 **GL**). There is no clear consensus on what constitutes the most effective IV opioid and dosing regimen for analgesia in the ED. A comparison of IV opioids to treat severe pain in the ED shows no clinically significant differences in efficacy or adverse effects between all opioids studied (Patanwala 2010 **Level I**, 10 RCTs, n=2,095). Single IV doses below 0.1 mg/kg of morphine, 0.015 mg/kg of hydromorphone or 1 mcg/kg of fentanyl may be inadequate for severe acute pain without subsequent titration. Nurse-initiated or patient-driven protocols can provide better and faster analgesia but opioid titration is often poorly done, leading to suboptimal dosing and analgesia (Bijur 2012 **Level IV**, n=281).

Higher initial opioid doses may be associated with more rapid onset of analgesia but studies comparing high- vs low-dose titration regimens for IV morphine (Bounes 2008 **Level II**, n=106, JS 3) and hydromorphone (Chang 2013a **Level II**, n=334, JS 3) show similar pain relief by 30 min and a trend towards fewer adverse effects in the lower dose range. Patients require close observation for sedation, respiratory depression and occasionally hypotension (Coman 1999 **Level IV**, n=401).

Although studies have heterogenous results, PCA in the ED is at least comparable in analgesic effect to usual care with titrated opioid analgesia, but consistently improves patient satisfaction (Bijur 2017 **Level II**, n=636, JS 3; Smith 2015 **Level II**, n=200, JS 3; Birnbaum 2012 **Level II**, n=211, JS 3; Rahman 2012 **Level II**, n=96, JS 3).

In patients with difficult IV access, intraosseous morphine (Von Hoff 2008 **Level II**, n=22, JS 3), IN fentanyl (Hansen 2013 **Level I** [PRISMA], 3 RCTs, n=301), IN hydromorphone (Wermeling 2010 **Level III-1**) and nebulised morphine (Grissa 2015 **Level II**, n=300, JS 5; Farahmand 2014 **Level II**, n=90, JS 5) have similar pharmacokinetic and clinical profiles. Buprenorphine SL demonstrates effective

analgesic effects for acute pain in the ED (Vlok 2019 **Level I**, 9 RCTs, n=826) as did IN sufentanil in several RCTs (Blancher 2019 **Level II**, n=157, JS 5; Sin 2019 **Level II**, n=60, JS 5; Lemoel 2019 **Level II**, n=144, JS 5). IN fentanyl 2 mcg/kg was more efficacious than IV morphine 0.1 mg/kg in adults with abdominal pain (Deaton 2015 **Level II**, n=40, JS 5). Oral opioids in situations with delayed or difficult IV access are another option (Miner 2008 **Level II**, n=320, JS 3); oral oxycodone 0.125 mg⁄kg in a suspension vs IV morphine 0.1 mg⁄kg resulted in delayed onset of analgesia and lower patient satisfaction but similar efficacy at 30 min. Fentanyl 200 mcg buccal tablets had similar analgesic efficacy to PO oxycodone 10 mg/paracetamol 650 mg (Arthur 2015 **Level II**, n=50, JS 3).

In children requiring analgesia in the ED, fentanyl IN (Borland 2007 **Level II**, n=67, JS 5), inhaled (nebulised) (Furyk 2009 **Level II**, n=73, JS 5) or oral transmucosal (Mahar 2007 **Level II**, n=87, JS 3) provided effective analgesia (see Sections 5.5 and 10.9.1 for details). The use of IN fentanyl improves the time to analgesia in younger children without adverse effects (Holdgate 2010a **Level III-2**, n=118).

With regard to atypical opioids, IV tramadol had similar analgesic efficacy to IV morphine in equianalgesic doses (100 to 200 mg tramadol vs 5 to 20 mg morphine) (Vergnion 2001 **Level II**, n=105, JS 5). In patients with right lower quadrant pain, presumed to be due to appendicitis, IV tramadol reduced pain and did not affect the clinical examination (Mahadevan 2000 **Level II**, n=68, JS 5). For renal colic, tramadol was less effective than pethidine (Eray 2002 **Level II**, n=47, JS 1). For acute musculoskeletal pain, IM tramadol was similar to ketorolac in efficacy and adverse effects, also when both were combined with oral paracetamol (Lee 2008 **Level II**, n=78, JS 3). They were also equally effective administered SL in children with suspected fractures or dislocations (Neri 2013b **Level II**, n=131, JS 5). However, for musculoskeletal pain in the ED, oral tramadol 100 mg provided inferior analgesia to hydrocodone 5mg/paracetamol 500 mg (Turturro 1998 **Level II**, n=68, JS 5).

Opioid-tolerant patients pose a special challenge in the ED and their management is discussed in Section 9.7.

8.11.1.3 | Inhalational analgesics

In patients with moderate to severe traumatic pain in the ED, self-administered nitrous oxide (N_2O) 65% in oxygen inhaled by face mask was effective in acute pain management vs 100% oxygen placebo, with a low frequency of minor adverse events (Gao 2019 **Level II**, n=60, JS 5). Inhaled N_2O in oxygen is more effective than oxygen as an analgesic adjunct to IV fentanyl 50 mcg for relieving pain in patients with renal colic in the ED (Ahmadi 2018 **Level II**, n=120, JS 5). The difference was evident particularly 10 min from the start of the intervention but the difference between groups disappeared after a further dose of fentanyl.

Inhaled N_2O in oxygen (see Section 4.5.1) provided effective analgesia and anxiolysis for minor procedures in both adults and children (Gerhardt 2001 **Level II**, n=11, JS 5; Burton 1998 **Level II**, n=30, JS 5; Gregory 1996 **Level II**, n=28, JS 3; Gamis 1989 **Level II**, n=30, JS 5) and may be useful as a temporising measure while definitive analgesia is instituted (eg insertion of a digital nerve block for finger injury) (see also Section 10.7.4).

Methoxyflurane (see Section 4.5.2) is used most commonly in prehospital emergency care. In ED patients aged ≥12 y, methoxyflurane was significantly more efficacious than placebo, with only mild transient adverse effects such as dizziness (Coffey 2014 **Level II**, n=300, JS 4). Onset of analgesia was rapid at 4 min; peak analgesia was at 18.5 min. Safety was assessed over 14 d following administration and no significant adverse effects, including renal toxicity, were found. Since no RCTs comparing methoxyflurane and N_2O directly have been performed, an indirect comparison showed no significant differences between the two agents (Porter 2018 **Level I** [NMA], 2 RCTs, n=263). As part of a multimodal analgesic protocol, methoxyflurane with

paracetamol and oxycodone decreased pain in the first 5 to 10 min of care, with further decrease in pain intensity over 1 h (Viglino 2019 **Level IV**, n=200).

8.11.1.4 | Ketamine

Low dose IV ketamine 0.1 to 0.3 mg/kg was considered a safe and efficacious analgesic in the ED either as single therapy or in combination with IV morphine 0.1 mg/kg (Karlow 2018 **Level I** [PRISMA], 3 RCTs, n=261; Ghate 2018 **Level IV SR** [PRISMA], 6 RCTs, n=544 & 2 studies, n=65) (2 RCTs overlap). There are comparable improvements in pain intensity and need for rescue analgesia when comparing IV morphine 0.1 mg/kg with low dose IV ketamine 0.1 to 0.3 mg/kg (Lee 2016a **Level I**, 6 studies, n=438) (2 & 4 RCTs overlap). There is a higher rate of neurological and psychological adverse events with ketamine, but more major cardiopulmonary adverse events in the opioid group. Administering ketamine as a 15 min infusion decreased the proportion of patients with adverse events (particularly feeling of unreality and sedation) vs an IV bolus dose, with no differences in analgesic efficacy (Clattenburg 2018 **Level II**, n=62, JS 5; Motov 2017a **Level II**, n=48, JS 5).

As an adjunct to IV morphine, IV ketamine improves pain relief in the first 15 to 30 min and may have a lower rate of additional analgesic requirement in the ED (Sin 2019 **Level II**, n=60, JS 5; Abbasi 2014 **Level II**, n=220, JS 4).

IN Ketamine (0.5 to 1 mg/kg) was an effective analgesic in the ED (Shrestha 2016 **Level IV**, n=34; Andolfatto 2013 **Level IV**, n=40; Yeaman 2013 **Level IV**, n=28) and had comparable effects to IV morphine 0.1 mg/kg, but faster onset of analgesia than IM morphine 0.15 mg/kg (Shimonovich 2016 **Level II**, n=90, JS 3) (see also Section 4.6.1.1).

Ketamine/midazolam was more effective and had fewer adverse effects than fentanyl/midazolam or fentanyl/propofol for fracture reduction in children in the ED (Migita 2006 **Level I**, 8 RCTs, n=1,086).

8.11.1.5 | Centrally acting muscle relaxants

Adding cyclobenzaprine (or oxycodone/paracetamol) to naproxen did not improve pain or functional outcome at 1 wk in patients with acute low back pain (Friedman 2015 **Level II**, n=323, JS 5). Similar results were found with with adding other centrally acting muscle relaxants to ibuprofen including orphenadrine, methocarbamol (Friedman 2018 **Level II**, n=240, JS 5), diazepam (Friedman 2017a **Level II**, n=114, JS 5), or baclofen, metaxolone or tizanidine (Friedman 2019 **Level II**, n=300, JS 5). IM benztropine for acute non-traumatic neck pain (wry-neck) was not effective for analgesia or to improve movement, and anti-cholinergic side effects were common (Asha 2015 **Level II**, n=30, JS 3)

8.11.1.6 | Lidocaine

IV lidocaine has mixed results in treatment of painful conditions presenting to ED (Silva 2018 **Level IV SR**, 6 RCTs and 2 studies, n=536; Masic 2018 **Level IV SR**, 4 RCTs & 9 studies, n= 512) (4 RCTs overlap). There is limited evidence for effectiveness in critical limb ischaemia and renal colic when vs IV morphine, but inferior to standard treatments for migraine and no better than NSAIDs for radicular low back pain. IV lidocaine 1.5 mg/kg was as effective as IV morphine 0.1 mg/kg for decreasing pain scores in patients with extremity fractures experiencing moderate or severe pain (Farahmand 2018 **Level II**, n=50, JS 5; Forouzan 2017 **Level II**, n=280, JS 2). IV lidocaine was as effective as IV morphine in patients with undifferentiated severe pain in the ED, and could provide an opioid-sparing effect (Clattenburg 2019 **Level II**, n=32, JS 3), but was less effective than IV hydromorphone (Chinn 2019 **Level II**, n=154, JS 5). Safety data is limited with 20 adverse events

(rate 8.9%; 95%CI 5.5% to 13.4%) (6 studies, n=225) reported with use of IV lidocaine in the ED (19 nonserious and 1 classified as serious) (Silva 2018 **Level IV SR**, 6 RCTs and 2 studies, n=536).

IN lidocaine did not improve analgesia when used as an adjunct to metoclopramide for the treatment of migraine (Avcu 2017 **Level II**, n=162, JS 5).

8.11.1.7 | Corticosteroids

In low back pain, corticosteroid administration for analgesia has mixed results. For patients with low back pain with radiculopathy, in addition to routine care, a single dose of IV dexamethasone 8 mg was better than placebo in reduction of 24 h pain scores and decreased ED LOS but had no effect on functional scores (Balakrishnamoorthy 2015 **Level II**, n=58, JS 5). However, a 5 d course of oral prednisone 50 mg for patients discharged from ED with acute low back pain showed no benefit (Eskin 2014 **Level II**, n=79, JS 5).

For the treatment of acute gout in ED, prednisolone (30 mg/d) was as efficacious as indomethacin (initially 50 mg three times per d) in the first 2 h after commencement of treatment in ED, and for the subsequent 2 wk (Rainer 2016 **Level II**, n=416, JS 5). Paracetamol was used in both groups. Prednisolone was associated with a lower incidence of adverse events, particularly gastrointestinal symptoms. These findings were confirmed in a systematic review, where only two of the RCTs recruited patients in the ED (Billy 2018 **Level I**, 6 RCTs, n=817). There is insufficient evidence for the use of IA corticosteroids for the treatment of gout (Wechalekar 2013 **Level I**, 0 RCTs, n=0). Low dose colchicine is also recommended as treatment for acute gout, but no studies have compared corticosteroids and colchicine (van Echteld 2014 **Level I** [Cochrane], 2 RCTs, n=124).

8.11.2 | Analgesia in specific conditions

8.11.2.1 | Abdominal pain

Patients and physicians differ in their assessment of the intensity of acute abdominal pain in the ED, with physician estimates of severity of abdominal pain being significantly lower than patient reports (Marinsek 2007 **Level IV**, n=185). Administration of analgesia correlated with the physician's assessment of a pain score greater than 60/100. A patient's satisfaction with analgesia correlated with a reduction in pain of at least 20/100 and titration of analgesia to the patient's pain reports. Nevertheless, 60% of patients presenting to the ED with abdominal pain were satisfied with their analgesia on discharge. It is therefore reassuring that in patients presenting with abdominal pain to an ED (over a 10 y period) analgesia administration increased and time to administration decreased (Cinar 2013 **Level IV**, n=2,646).

Early pain relief (usually in the form of opioids) does not interfere with the diagnostic process in acute abdominal pain in adults (Manterola 2011 **Level I**, 8 RCTs, n=922; Kang 2015 **Level II**, n=213, JS 5) or in children (Green 2005 **Level II**, n=108, JS 5; Kim 2002 **Level II**, n=60, JS 5) and does not lead to increased errors in clinical management (Ranji 2006 **Level I**, 12 RCTs, n=1,389).

See also Section 8.6.1.

8.11.2.2 | Renal colic

NSAIDs are effective in the treatment of renal colic vs placebo or antispasmodics (Afshar 2015 **Level I** [Cochrane], 50 studies, n=5,734). For renal colic in patients with adequate renal function, treatment with NSAIDs provides effective and the most sustained pain relief, with fewer side effects, vs IV opioids or IV paracetamol (Pathan 2018 **Level I**, 36 RCTs, n=4,887; Al 2018 **Level II**, n=300, JS 4; Cenker 2018 **Level II,** n=200, JS 4).

For renal colic, the onset of action of NSAIDs is faster when given IV vs IM, PO or PR administration (Tramer 1998 **Level I**, 26 RCTs, n=2,225).

See Section 8.6.1.2

8.11.2.3 | Biliary colic

NSAIDs significantly reduce biliary pain and complications (eg acute cholecystitis, acute pancreatitis, jaundice, cholangitis) vs placebo or spasmolytic drugs (Fraquelli 2016 **Level I** [Cochrane], 12 RCTs, n=828).

See Section 8.6.1.3.

8.11.2.4 | Acute cardiac chest pain

See Section 8.6.3.

8.11.2.5 | Acute pain and sickle cell disease

See Section 8.6.4.1 and in children see Section 10.9.5.1.

8.11.2.6 | Headache

While a number of different classes of medicines are effective in the treatment of acute migraine, other more serious causes of headache, particularly subarachnoid haemorrhage and CNS infection, should always be considered during clinical assessment (American College of Emergency Physicians Clinical Policies Subcommittee on Acute Headache 2019 **GL**). Clinical improvement with medication directed at migraine relief is not specific and does not rule out alternative causes of headache (Pfadenhauer 2006 **Level IV**).

Simple treatment with oral NSAIDs, especially aspirin, is effective in ED patients with migraine who are not vomiting (Kirthi 2010 **Level I** [Cochrane], 13 RCTs, n=4,222). In patients unable to tolerate oral therapy, phenothiazines such as chlorpromazine and prochlorperazine (Kelly 2009 **Level I**, 13 RCTs, n=917), selective serotonin agonists especially sumatriptan (Derry 2012 **Level I** [Cochrane], 35 RCTs, n=9,365) and butyrophenones (however with significant adverse effects) (Leong 2011 **Level I**, 6 RCTs, n=574) provide effective analgesia in up to 80% of patients in the ED. A systematic review of treatment of migraine pain in ED settings supports these results with strong evidence in favour of prochlorperazine and moderate evidence for chlorpromazine, metoclopramide, sumatriptan and IV lysine acetylic acid (Orr 2015 **Level I** [PRISMA], 44 RCTs, n unspecified). A subsequent systematic review confirmed these results with neuroleptics providing the greatest pain reduction in the first h, with metoclopramide and NSAIDs also providing significant relief, but combinations of medications were not superior to single agents (Westafer 2018 **Level I**, 40 studies, n=3,489) (significant overlap between all SRs).

Dexamethasone is recommended to prevent headache recurrence vs placebo (OR 0.60; 95%CI 0.38-0.93) (3 RCTs, n=358) (Orr 2016 **Level I**, 68 RCTs, n unspecified). Recurrence following discharge from ED was comparable between IM dexamethasone 10 mg or IM methylprednisolone acetate 160 mg given in ED with IV metoclopramide (Latev 2019 **Level II**, n=220, JS 5).

IV Paracetamol 1 g was comparable to IV dexketoprofen 50 mg for acute migraine (Turkcuer 2014 **Level II**, n=200, JS 5). The addition of IV paracetamol to prochlorperazine and diphenhydramine for the treatment of headache resulted in an improvement of pain score and less need for rescue analgesia (Meyering 2017 **Level II**, n=90, JS 5) although there has been no direct comparison of adjunctive PO versus IV paracetamol.

Opioids are not recommended in the treatment of migraine or acute primary headache as the recommended medicines provide superior analgesia in comparisons with fewer adverse effects (American College of Emergency Physicians Clinical Policies Subcommittee on Acute Headache 2019 **GL**; Orr 2015 **GL**; Worthington 2013 **GL**) The following medications demonstrated worse or no better analgesia than standard treatment: IV ketamine (Etchison 2018 **Level II**, n=34, JS 5; Zitek 2018 **Level II**, n=54, JS 5), IN ketamine (Benish 2019 **Level II**, n=53, JS 5), caffeine (Derry 2014a **Level I** [Cochrane], 20 RCTs, n=7,238; Baratloo 2016 **Level II**, n=110, JS 5), IV valproate (Friedman 2014b **Level II**, n=330, JS 5), magnesium (Miller 2019 **Level I** [PRISMA], 7 RCTs, n=545), and propofol (Moshtaghion 2015 **Level II**, n=91, JS 5). The addition of IV fluids to standard therapy had no effect on analgesia (Jones 2019a **Level II**, n=49, JS 5; Balbin 2016 **Level III-2**, n=570).

Evidence-based recommendations for the treatment of migraine in ED settings are published (Orr 2015 **GL**).

See Section 8.6.5 for a more detailed review of the treatment of migraine and other acute headache syndromes and Section 10.9.3 for migraine treatment in children.

8.11.2.7 | Hip fracture

Regional blockade reduces pain after hip fracture, and is associated with a decreased risk of pneumonia, reduced time to mobilisation, and reduced cost of analgesia (Guay 2017 **Level I** [Cochrane], 31 RCTs, n=1,760). Regional nerve blockade in the ED is at least as effective and possibly superior to standard analgesia (opioids or NSAIDs) after a hip or femoral neck fracture and decreases overall opioid consumption (Ritcey 2016 **Level I**, 9 RCTS, n=447). FICB (Steenberg 2018 **Level I**, 11 RCTs, n=1,062), FNB (Riddell 2016 **Level I**, 7 RCTs, n=224) or 3-in-1 blocks (4 RCTs, n=199) (Ritcey 2016 **Level I** [PRISMA], 9 RCTs, n=547) are superior to systemic opioids in reducing pain on movement, decrease preoperative opioid requirements and lengthen time to rescue analgesia. These findings are consistent even in patients with dementia (Unneby 2017 **Level II,** n=266, JS 2).

Although opioids alone are not particularly effective in providing analgesia and have the potential for significant adverse effects such as respiratory depression and delirium in the older patient cohort, regional nerve blocks are underutilised in EDs in Australia (Holdgate 2010b **Level IV**, n=646) and the United Kingdom (Rashid 2014 **Level IV**, n=147 [responding EDs]).

Guidelines to direct care of hip fracture patients are published (ANZFHR Steering Group 2014 **GL**); integrated orthogeriatric care, utilisation of care bundles and adherence to clinical care standards improves outcomes in hip fracture patients (ACSQHC 2016 **GL**).

For more details, see also section 8.4.

8.11.2.8 | Shoulder dislocation

The majority of shoulder dislocations requiring reduction in an ED occur with procedural sedation and analgesia. Entonox® (inhaled N_2O:Oxygen) as a single agent is not as effective as procedural sedation using fentanyl and midazolam with regard to analgesia and patient satisfaction (Mahshidfar 2011 **Level II**, n=120, JS 3).

IA lidocaine (injected via landmark technique) for anterior shoulder dislocations provides analgesia comparable to systemic analgesics with fewer adverse effects (Wakai 2011 **Level I** [Cochrane], 5 RCTs, n=211; Jiang 2014 **Level I**, 9 RCTs, n=438) (5 RCTs overlap). US guided suprascapular nerve block (Tezel 2014 **Level II**, n=41, JS 2) and ultrasound guided interscalene block (Blaivas 2011 **Level II**, n=42, JS 2) showed similar benefits.

8.11.2.9 | Wounds

Local anaesthesia is frequently required for the treatment of wounds in the ED. Agents most commonly used for local infiltration are lignocaine or the longer acting bupivacaine, ropivacaine or levobupivacaine, depending on the duration of anaesthesia required and whether analgesia following the procedure is desirable.

It is less painful to infiltrate local anaesthesia by injection through the wound rather than in the tissues surrounding it (Bartfield 1998 **Level II**, n=63, JS 4). Buffering of lignocaine with bicarbonate reduces the pain of infiltration, particularly when using lignocaine with adrenaline (Cepeda 2010 **Level I** [Cochrane], 23 RCTs, n=1,067).

Digital nerve block with 0.75% ropivacaine significantly prolonged analgesia and reduced rescue analgesia requirements to 24 h, without a clinically significant increase in time to block onset vs 2% lignocaine (Keramidas 2007 **Level II**, n=70, JS 2).

Topical application of local anaesthetics has advantages over local injection although there is little evidence to choose one preparation over another for use on simple lacerations (Tayeb 2017 **Level I** [Cochrane], 25 RCTs, n=3,278). Topical tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lignocaine are as effective as EMLA® cream for dermal instrumentation (eg cannulation) analgesia in the ED (Eidelman 2005 **Level I**, 25 RCTS, n=2,096). For simple lacerations in children, topical anaesthetic preparations such as ALA (adrenaline, lignocaine, amethocaine) are effective alternatives to infiltration with local anaesthesia without the pain of local injection (Ferguson 2005 **Level I**, 7 RCTs, n=1,260). Topical lignocaine and adrenaline applied to a wound in sequential layers significantly reduced reports of pain during initial application vs a 2% lignocaine injection, but with no difference in pain scores during suturing (Gaufberg 2007 **Level II**, n=100, JS 3). A topical gel dressing containing morphine was no more effective than other gel dressings in reducing burns injury pain in the ED (Welling 2007 **Level II**, n= 49, JS 3).

8.11.3 | Nonpharmacological management of pain

Although analgesic agents may be required to treat pain in the ED setting, the importance of nonpharmacological treatments should not be forgotten. These include ice, elevation and splinting for injuries and explanation of the cause of pain and its likely outcome to allay anxiety. Psychological techniques such as distraction, imagery or hypnosis may also be of value (see Sections 7.1 and 10.7.5).

In young children, interventions such as distraction, positioning, sucrose and cold application may be helpful to manage pain in the ED (Wente 2013 **Level IV SR**, 14 studies, n=1,459).

In general, acupuncture is comparable to standard analgesic care, and provides superior analgesia when used as an adjunct to standard care in the ED (Jan 2017 **Level I** [PRISMA], 14 RCTs, n=1,210). This included studies of renal colic and back pain. Ear acupuncture shows significant improvements in pain score vs sham acupuncture or standard analgesic care and when used as an adjunct to standard care (Jan 2017 **Level IV SR** [PRISMA], 4 RCTs, n=286 & 8 studies, n=458). Acupuncture had lower pain scores at 60 min vs morphine 0.1 mg/kg in the treatment of patients with renal colic in the ED (Beltaief 2018 **Level II**, n=115, JS 5). Acupuncture and/or standard pharmacotherapy provided comparable reductions in pain within 1 h of administration for back pain, ankle sprain or migraine (Cohen 2017 **Level II**, n=528, JS 3). For more details see Section 7.3.2.1.

Spinal manipulation or exercise therapy for patients presenting to ED with nonradicular low back pain of less than 12 wk duration is no more effective than analgesic pharmacotherapy alone (Rothberg 2017 **Level I**, 2 RCTs, n=344 [spinal manipulation]; 4 RCTs, n=930 [exercise therapy]).

Physical interventions (physical therapy, mobilisation, mechanical support, manipulation), direct interventions (acupuncture, TENS, ultrasound), and indirect interventions (music therapy, aromatherapy, hypnosis, guided imagery) initiated in the ED, all significantly reduce pain vs controls in the short term (immediately in ED) and up to 12 wk later (Sakamoto 2018 **Level I** [PRISMA], 7 RCTs, n=593 [physical interventions]; 9 RCTs, n=975 [direct interventions]; 4 RCTs, n=375 [indirect interventions]). However, most of the included studies had high risk of bias, variable outcome measures, and heterogeneity across interventions.

KEY MESSAGES

1. Paracetamol, in particular if administered IV, and NSAIDs are effective primary analgesics for use in the emergency department (**N**) (**Level I** [PRISMA]).
2. Sublingual buprenorphine (**N**) (**Level I** [PRISMA]) or intranasal fentanyl (**N**) (**Level I**) are effective alternatives to parenteral opioids in the emergency department.
3. Low dose ketamine is a safe and effective analgesic alone or when combined with opioids in the emergency department, but increases neuro-psychological adverse events (**N**) (**Level I** [PRISMA]).
4. Appropriate doses of intravenous opioids are effective in treating acute severe pain in the emergency department and ideally should be titrated according to nurse-initiated and patient-driven protocols; there is no preference for a specific opioid (**U**) (**Level I**).

Abdominal pain

5. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain and does not increase the risk of errors in clinical management (**U**) (**Level I** [Cochrane Review]).

Migraine

6. NSAIDs, triptans (**S**) (**Level I** [Cochrane]), phenothiazines (prochlorperazine, chlorpromazine), butyrophenones and metoclopramide are effective to treat migraine in the emergency department (**U**) (**Level I**).

Fractured neck of femur

7. Lower limb nerve blocks with local anaesthetics reduce pain, analgesia requirements and lengthen time to rescue analgesia in hip fracture patients compared to systemic analgesia; there is no advantage of a specific nerve block, insertion technique or continuous versus single injection administration (**S**) (**Level I** [Cochrane Review]).

Shoulder Dislocation

8. Intra-articular local anaesthetics provide comparable analgesia for reduction of gleno-humeral dislocation to procedural sedation and analgesia methods with fewer adverse events (**N**) (**Level I** [Cochrane Review]).

Wounds

9. Buffering of lignocaine with bicarbonate reduces the pain of infiltration, particularly when using lignocaine with adrenaline (**U**) (**Level I** [Cochrane Review]).
10. Topical local anaesthetic agents (including those in liposomal formulations) (**S**) (**Level I** [Cochrane Review]) or topical local anaesthetic-adrenaline agents (**U**) (**Level II**) provide effective analgesia for wound care in the emergency department.

Musculoskeletal Pain

11. Centrally acting muscle relaxants do not improve analgesia in the acute treatment of lower back pain (**N**) (**Level II**).

Non-pharmacological management of pain

12. Acupuncture may provide effective analgesia as a single agent or adjunct in the emergency department (**N**) (**Level I** [PRISMA]).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ To ensure optimal management of acute pain, emergency departments should adopt systems to ensure adequate assessment of pain, provision of timely, adequate and appropriate analgesia, frequent monitoring and reassessment of pain (**U**).

8.12 | Prehospital analgesia

The previous section considered management of acute pain in patients admitted to EDs. However, many of these patients will also have required prehospital pain relief while under the care of paramedic or medical retrieval teams. While the term "prehospital" is also used to cover a greater variety of prehospital locations, it is beyond the scope of this document to look at pain relief administered in more complex situations such as medical retrievals, interhospital transfers, wilderness medicine, medical coverage for large public gatherings and disaster or war settings.

Although there is a paucity of specific research (particularly RCTs), the literature consistently suggests that substantial improvement in the provision of prehospital analgesia is needed (Parker 2015 **NR**), and a possible link between poor quality prehospital analgesia and post-traumatic stress disorder has been raised (Parker 2015 **NR**; Ellerton 2014 **NR**).

Pain may require management prior to and during transport, and the nature of the prehospital environment presents many challenges in addition to most of the issues seen in the hospital. These issues are often related to the relative paucity of resources, fewer treatment options (including medications and equipment), and a working environment where light, sound and issues of hygiene will impact on how pain can and should be managed. Furthermore, the patient is often in the acute or evolving stage of their condition, which may change rapidly. Guidelines for prehospital analgesia have been published (Gausche-Hill 2014 **GL**) as well as those for treatment of pain in remote environments (Russell 2014 **GL**) and a systematic review of guidelines (Yousefifard 2019 **GL SR**).

Pain in the prehospital setting is common, with pain severity rated as moderate to severe in up to 64% of ambulance patients (Galinski 2010 **Level IV**, n=2,279). In these patients, the factors associated with severe pain were cardiac pain and trauma, yet the proportion of patients given analgesics (opioid or inhalational) prior to transfer to an ED varies significantly. Subsequent surveys of ambulance services report an incidence of 28% of moderate to severe pain during ambulance transport (Friesgaard 2018 **Level IV**, n=41,241) and an incidence of 17% of severe and intolerable pain in ambulance attendances for trauma (Hebsgaard 2016 **Level IV**, n=985).

Factors associated with under-treatment of pain in a setting of physician-managed prehospital care were severe pain at initiation of treatment (OR 8.8; 95%CI 5.1 to 15.2), treatment by a female physician (OR 2.0; 95%CI 1.0 to 4.0), and relative inexperience of the physician measured in years of postgraduate experience (4 to 5 y [OR 1.3]; 3 to 4 y [OR 1.6]; 2 to 3 y [OR 2.6]; < 2.0 y [OR 16.7]) (Albrecht 2013 **Level IV**, n=1,202 [patients] & n=77 [emergency physicians]). In a subsequent study, male patients were more likely to receive opioids than females (OR 1.5; 95%CI 1.29–1.79), while sex of the paramedic did not influence opioid use (Lord 2014 **Level III-3**, n=42,051). Other factors reported to be associated with under-treatment of pain include children <15 y and non-white ethnicity in the USA (Hewes 2018 **Level IV**, n= 276,925 [ambulance attendances]) Another single municipality study from the USA showed that analgesia after falls was provided to 8.2% of patients with factors influencing this rate being ethnicity (less often to black vs white patients (OR 0.19; 95%CI 0.08 to 0.44)), an initial higher pain score (9.1/10 [95%CI 8.7 to 9.5] vs 5.8/10 [95%CI 5.5 to 6.2]) and injury location (extremity and hip injury vs head and neck injury) (Infinger 2014 **Level IV**, n=1,200).

Pain in children is less often assessed and treated than in adults (Browne 2016 **Level IV**, n=1,368 [paediatric ambulance attendances]; Rahman 2015a **Level IV**, n=202 [paramedics]) In paediatric patients <15 y, 55% with severe pain (8/10) did not receive any analgesia (Lord 2016

Level IV, n=38,167 [ambulance records]). In paramedic led services, barriers to providing pain relief to paediatric patients were concerns about pain and fear caused by IV cannulation (59.5%), parental influences (51.6%), difficulty assessing pain in children (47.2%), and concerns about allergic reactions (45.6%) (Whitley 2017 **Level IV**, n=127 [paramedics]). Other factors were perceived negative attitudes from receiving EDs (30.4%) and negative scrutiny from supervisors (11.8%). Similarly to adults, non-white ethnicity was associated with less pain score documentation (OR 0.52; 95%CI 0.44 to 0.62) and provision of analgesics (OR 0.64; 95%CI 0.50 to 0.82) (Johnson 2014 **Level IV**, n=5,057). In children and adolescents (0 to 15 y) admitted to a burns centre within 24 h of injury, pre-burn-centre analgesic administration (paracetamol, NSAID and/or opioid) increased over time (68 to 79%: from 2002-2004 to 2007-2008); flame burns and more extensive burns were predictors of receiving pre-burn-centre analgesics, whilst transfer/referral by ambulance services or general practitioners were predictors of not receiving pre-burn-centre analgesics (Baartmans 2016 **Level III-3,** n=622). For paediatric information, see Section 10.9.1.1.

In a survey of a number of emergency services in the Netherlands, nonpharmacological pain control was used in less than 50% of trauma cases, pharmacological treatment deviated from guidelines in 73 to 99% and time of administration of medication was not documented in 73 to 100% of cases (Scholten 2015 **Level IV**, n=1,066). Similarly in Germany, patients with a hip fracture reported an average pain score of 6.8/10 (2.7) with 22% rating their pain as 10/10; however only 28% received analgesia despite its effectiveness (mean pain score reduced from 7/10 [2.6] to 2.8 [1.4] at hospital arrival) (Oberkircher 2016 **Level III-2**, n=156) (See also Section 8.4). In the setting of a Swiss helicopter rescue service, patients who received pain management had higher initial pain scores (7.4/10 2.0) vs those who did not (2.8/10 1.8) (Eidenbenz 2016 **Level IV**, n=1,156). Beside high pain scores, diagnosis of a fracture was associated with increased analgesic use. Fentanyl (84%) was preferred over ketamine (14%), but ketamine was preferred by more experienced doctors and those with an anaesthesia background.

The presence of cognitive impairment in patients managed by ambulance staff is associated with markedly less analgesic administration despite having significant injuries (McDermott 2014 **Level IV**, n=224). "*Unnecessary pain*" was the second most common type of injury in 56 of 272 claims against ambulance trusts in the UK between 1995 and 2005 (Dobbie 2008 **Level IV**).

A survey of adult patients with suspected extremity fractures showed that just 18 (1.7%) were given any analgesia and only 2 received morphine (White 2000 **Level IV**, n=1,073). A later survey showed that only 12.5% of patients with isolated extremity injuries received any prehospital parenteral pain relief (Abbuhl 2003 **Level IV**, n=706). This trend continues with older patients and those with hip fractures being less likely to be given analgesia prior to arrival in the ED (McEachin 2002 **Level IV**, n=124). In contrast, another group reported that 51% of elderly patients with a fractured neck of femur were given prehospital analgesia; methoxyflurane in 47% of cases, N_2O in 10% and morphine in 6% (Vassiliadis 2002 **Level IV**, n=176).

A large (NSW Ambulance service) audit of ambulance patients who received analgesia found that 87% of all patients received single analgesic therapy (Bendall 2011b **Level IV**, n=97,705). Overall, inhaled methoxyflurane was the most commonly used analgesic (given to 60% of patients), followed by morphine IV (26%) and fentanyl IN (19%).

Despite concerns about opioids in the community, prehospital use of these medications may be increasing. In a 2005 survey, 29% of patients with isolated extremity injuries were given morphine (Michael 2007 **Level IV**, n=953) and 13% of females and 17% of males in pain were given morphine (Lord 2009 **Level IV**, n=3,357). Adequate use of morphine during the early treatment of acute pain after military trauma may significantly reduce the risk of developing post-traumatic stress disorder (OR 0.47; 95%CI 0.34 to 0.66) (Holbrook 2010 **Level III-2**, n=696). With use of

systemic opioids, 60 to 70% of prehospital care patients have pain scores above 30/100 at 10 min, falling to 30% at 30 to 40 min (Park 2010 **Level I**, 21 RCTs, n=6,212). Only two patients required naloxone and none needed ventilatory support.

The trend towards increasing opioid use is not universal in adults, and certainly does not seem to flow through to the paediatric patients seen in the prehospital environment. One study of children with fractures or soft tissue injuries reported that 37% received prehospital analgesic medicines (Rogovik 2007 **Level IV**, n=310). Another, which included patients with a diagnosis of limb fracture or burns, reported that analgesia was given to 51% of children between the ages of 5 and 15 y, but not to any child aged <5 y; a greater proportion of this younger group (70 vs 54%) were given opioid analgesia once in the ED (Watkins 2006 **Level IV**, n=45). Undertreatment in children under 5 y of age is a repeated finding of many prehospital investigations. A large study of adult and paediatric ambulance patients found that when a single agent was used, females were less likely to receive opioid analgesia than males (RR 0.83; 95%CI 0.82 to 0.84) (Bendall 2011b **Level III-2**, n=97,705). In contrast to the earlier series above, opioid use increased with increasing age; those aged >60 y were the most likely to receive opioids. While, children were less likely to receive opioids vs methoxyflurane (RR 0.65; 95%CI 0.63 to 0.67) and when given, IN fentanyl was the most common opioid. Prehospital administration of opioids to children (and assessment of pain intensity) occurred infrequently despite implementation of several best practice recommendations in a USA ambulance service; factors associated with opioid use were presence of vascular access (OR 11.89; 95%CI 7.33 to 19.29), longer patient transport time (OR 1.07; 95%CI 1.04 to 1.11), age (OR 0.93; 95%CI 0.88 to 0.98) and pain score documentation (OR 2.23; 95%CI 1.40 to 3.55) (Browne 2016 **Level IV**, n= 1,368 [paediatric ambulance attendances]).

Although pain relief has been acknowledged as a key area for investigation, evidence regarding management of acute pain in patients in the prehospital setting remains limited. Many analgesic techniques that work in hospital environments have been transcribed to the prehospital environment, but these do not always comply with the ideal of simplicity, safety and effectiveness when used in the field. Attitudes toward analgesia by the prehospital caregivers may be another factor in the apparent underuse of prehospital analgesia. In a small survey of experienced paramedics, the following themes arose as reasons why analgesia was withheld: reluctance to administer opioid unless there were significant signs (for example an obvious fracture), concerns regarding malingering behaviour, uncertainty regarding the endpoint ("*pain free*" or "*take the edge off*"), concern regarding analgesia masking diagnostic symptoms and a reluctance to use larger initial opioid doses (>5 mg morphine) (Walsh 2013 **Level IV**, n=15 [paramedics]).

System wide interventions in an emergency medical service including education and implementation of a pain management protocol resulted in increased frequency of opioid administration, but only a limited and not sustained increase in pain score documentation (Haley 2016 **Level III-3**, n=15,228; Brown 2014 **Level III-3**, n=3,491). Telemedically delegated analgesic administration by paramedics in ambulances following an algorithm vs physician-administered analgesia was safe and similarly effective (Brokmann 2016 **Level III-3**, n=160).

Table 8.4:
Factors that influence the provision of prehospital analgesia and the direction of this influence

Factors	Negatively affected by:	Variably affected by:
Patient	Paediatric patients Female sex Physiological instability Comorbidities	Reported pain score Culture Severity of injury
Clinician	Perceived negative response from receiving hospital Concerns regarding IV cannulation in children Lack of training Lack of confidence Fear of adverse events	
Other	Guardian/parental refusal in paediatrics Presence/lack of IV access Resource limitations Limitation of therapeutic options Urgency of transport	

(compiled from Hewes 2018; Whitley 2017; Samuel 2015; Rahman 2015a; Albrecht 2013)

8.12.1 | Assessment of pain in the prehospital environment

As in other settings, pain intensity is best assessed using patient self-report measures such as VAS (Galinski 2005 **Level II**, n=54, JS 4; Kober 2002 **Level II**, n=60, JS 5), VNRS (Bounes 2008 **Level II**, n=106, JS 5; Rickard 2007 **Level II,** n=258, JS 3; McLean 2004 **Level IV**, n=1,227; Woollard 2004 **Level II**, n=175, JS 3), VDS (Vergnion 2001 **Level II**, n=105, JS 5; McLean 2004 **Level IV**, n=1,227) or faces pain scale (Rogovik 2007 **Level IV**, n=301). In a comparison between VAS and VNRS in the prehospital setting, both performed comparably (r 0.87 to 0.93) with a preference by patients and paramedics for VNRS (Ismail 2015 **Level III-2**, n=133). A ruler incorporating both visual analogue and faces pain scales has also been used to measure pain in patients prior to arrival at hospital (Lord 2003 **Level IV**). A cohort study of ambulance patients having had acute trauma showed that patients had poor recall of initial pain scores at 1–2 d after injury (Easton 2012 **Level III-3**, n=88). In some instances, it may not be possible to obtain reliable self-reports of pain (eg patients with impaired consciousness or cognitive impairment, young children [see Section 10.3], elderly patients [see Section 9.2.2], or where there are failures of communication due to language difficulties, inability to understand the measures, unwillingness to cooperate or severe anxiety). In these circumstances other methods of pain assessment based on observation of patient behaviours should be used. For further details on assessment tools, see Chapter 2.

In a survey of a number of emergency services in the Netherlands, standardised tools to assess pain in trauma patients were used in 0 to 52% (depending on the service); reassessment of pain following treatment was only performed in 50% of patients under the care of a helicopter-based service, and not performed by any other services (Scholten 2015 **Level IV**, n=1,066).

8.12.2 | Systemic analgesics

The ideal prehospital analgesic agent should be simple to use, safe (both in terms of side effects and adverse effects on the patient's condition), effective, not lead to delays in transport and have a rapid onset and short duration of action, so that it can be repeated as often as necessary and titrated to effect for each patient (Alonso-Serra 2003 **NR**). Consideration should be given to both choice of analgesic medicine and route of administration.

In a systematic review, PO and IV paracetamol and IV opioids (morphine and fentanyl) are identified as effective analgesics in the prehospital trauma setting, while results for NSAIDs are mixed (Dijkstra 2014 **Level IV** SR, 10 RCTs & 15 studies [12 prehospital], n=5,339).

8.12.2.1 | Paracetamol and NSAIDs

The use of parenterally administered paracetamol and NSAIDs has been suggested for prehospital analgesia (McManus 2005 **NR**; Alonso-Serra 2003 **NR**) and their use seems to be increasing. However, their slower onset of effect as well as the risk of adverse effects (eg bleeding, renal impairment; see Section 4.2), especially in patients who have lost blood and may be hypovolaemic, means they are often overlooked (Scholten 2015 **Level IV**, n=1,066). Similarly, injectable paracetamol is not commonly used. Oral paracetamol or other analgesics may have a limited role in the prehospital management of moderate to severe pain.

8.12.2.2 | Conventional and atypical opioids

The administration of systemic opioids as an effective prehospital analgesic is widespread in ambulance services staffed by paramedics. Their application is influenced by the knowledge and judgment required to use them and the differing legislation for the drugs of dependence between countries. In this setting, use of IV or IN routes will enable a more rapid and predictable onset of action than other routes of administration. Opioids should not be administered IM/SC in the prehospital environment, because of unpredictable pharmacokinetics in the poorly perfused patient. Following resuscitation, morphine may undergo reabsorption from earlier IM administration, which may lead to a potential risk of delayed adverse effects.

Both morphine and fentanyl are commonly used for prehospital analgesia. Morphine (Friesgaard 2016 **Level IV**, n=2,348; Fullerton-Gleason 2002 **Level IV**; Bruns 1992 **Level IV**, n=69), fentanyl (Kanowitz 2006 **Level IV**, n=2,129) and tramadol (Ward 1997 **Level IV**, n=142) have been shown to provide effective and safe pain relief in patients being transported by road. Fentanyl was also safe and effective when given to patients during helicopter transportation (Krauss 2011 **Level IV**, n=1,055; Thomas 2005 **Level IV**, n=213 [doses in 177 patients]). Morphine was the most used opioid by the NSW ambulance service, followed by fentanyl, then ketamine (with no difference in the rate of vomiting between all three) (Zhang 2018 **Level III-3**, n=196). IV fentanyl in a dose of 1 to 3 mcg/kg is an effective analgesic in the prehospital care of children (Samuel 2015 **Level IV SR**, 19 studies [13 paediatric, 6 mixed adult/paediatric], n>67,287).

IV morphine doses of 0.1 mg/kg followed by 0.05 mg/kg every 5 min as needed provided more rapid pain relief and patient satisfaction than doses that were 50% lower (Bounes 2008 **Level II**, n=106, JS 5). Similarly, a liberal treatment protocol (3 mcg/kg) vs a standard treatment protocol (2 mcg/kg) of fentanyl administration resulted in use of higher doses (117.7 mcg [95% CI 116.7 to 118.6] vs 111.5 mcg [95%CI 110.7 to 112.4]) with a higher proportion of patients achieving sufficient pain control (44.0% [95%CI 41.8 to 46.1] vs 37.4% [95%CI 35.2 to 39.6]; aOR 1.47 [95%CI 1.17 to 1.84]) (Friesgaard 2019 **Level II**, n=5,737, JS 3).

Comparisons of IV fentanyl and morphine bolus for prehospital analgesia demonstrated no difference in analgesic efficacy or incidence of adverse effects (Galinski 2005 **Level II**, n=54, JS 4).

This was also confirmed in ischaemic chest pain (Weldon 2016 **Level II**, n=207, JS 5). Similarly, there was no difference in pain relief or adverse effects reported in a comparison of IV tramadol and morphine (Vergnion 2001 **Level II**, n=105, JS 5).

A comparison of IV nalbuphine 5 mg and 10 mg given and repeated at 3 min intervals to a total of 20 mg showed that use of the larger dose led to better pain relief but higher patient-reported drowsiness; over half the patients in both groups still had significant pain on arrival at the hospital (Woollard 2004 **Level II**, n=175, JS 3).

In rural and suburban settings with ambulance services relying on basic life support emergency technicians instead of paramedics, SC fentanyl (maximum first dose 1.5 mcg/kg) has been used successfully to treat pain with only 1.6% of patients experiencing minor adverse effects not requiring intervention (Lebon 2016 **Level IV**, n=288).

IN fentanyl is often used in the prehospital setting for treating acute pain in both children and adults (19% of patients) (Bendall 2011a **Level III-2**, n=3,312; Murphy 2017a **Level IV**, n=94). This route requires a small volume (high-concentration preparation of fentanyl 300 mcg/mL and 50 mcg/mL have been used) and ideally atomisation eg with a metered aerosol device MAD® attached to a syringe. In Australia, this route is sanctioned under an exemption from the TGA. Fentanyl has a relatively high lipid-solubility that enables rapid absorption from the nasal mucosa. Compared with IV fentanyl, the IN route shows similar pharmacokinetics (Foster 2008 **PK**). Bioavailability is 89% with an interpatient variability of 30%. Absorption and onset of analgesia are slightly delayed vs IV fentanyl (T_{max} 13 vs 6 min) (see Section 5.5.2). The analgesic efficacy of IN fentanyl vs alternatives (IV morphine, methoxyflurane) for the treatment of pain in the prehospital setting is unclear but appears to be favourable (Murphy 2017a **Level IV**, n=940). There is only low-quality evidence to support the use of IN fentanyl prehospital (Hansen 2013 **Level III-3 SR**, 4 studies, n=47,407). The one included prehopsital RCT found no difference in pain score reduction between IN fentanyl and IV morphine (Hansen 2013 **Level III-3 SR**, 1 RCT: Rickard 2007 **Level II**, n=258, JS 3). The study was likely underpowered and the findings complicated by use of IV morphine as the rescue analgesic in the IN fentanyl group. Oral transmucosal fentanyl (Actiq®) in battlefield casualties showed suitable effectiveness and safety with ease of administration (Wedmore 2012 **Level IV**, n=286).

For paediatric information, see also Section 10.9.1.1.

8.12.2.3 | Inhalational agents

Nitrous Oxide

Inhalational analgesics can provide early pain relief in the prehospital environment. However, variations in the availability of different agents have a marked impact on regional practices. In one series, patients with extremity fractures were more likely to receive N_2O than morphine (White 2000 **Level IV**, n=1,073), whereas in another series N_2O was not used at all (Rogovik 2007 **Level IV**, n=310).

N_2O is included in prehospital management protocols for manipulation, splinting and transfer of patients with lower limb fracture (Lee 2005b **NR**) and as a second-line in burns patients if opioids are not available (Allison 2004b **GL**). Although N_2O has been reported to provide pain relief in >80% of patients requiring prehospital analgesia (Thomas 2008 **NR**), this practice was not based on RCTs (Faddy 2005 **NR**) and there are few studies comparing efficacy with other agents. In one paediatric series, a higher proportion of children receiving N_2O rather than opioids had pain on arrival in the ED but interruption of delivery during transfer from the ambulance may have contributed (Watkins 2006 **Level IV**, n=45). Based on data from hospital studies, N_2O has been suggested as a safe analgesic in prehospital settings, although specific contraindications (such as pneumothorax and decreased consciousness) may be particularly relevant in this patient group

(Faddy 2005 **NR**) (see Section 4.5.1 for further details). Administration of 50% N_2O vs medical air to trauma patients in the prehospital setting showed effective analgesia; 67% of the N_2O group had pain score ≤3/10 at 15 min compared with only 27% in the air group (Ducasse 2013 **Level II,** n=60, JS 4).

Provision of N_2O in ambulances is hampered by difficulties providing scavenger systems that minimise occupational exposure and the bulk/logistical issues associated with managing cylinders of oxygen and N_2O (Entonox® cylinders are a mixture of 50% N_2O and 50% oxygen) that separate at low temperatures. The demand valves are costly and require maintenance, and the inability to activate the valve and effectively use Entonox® equipment has been rated as a major factor limiting use in children <5 y (Watkins 2006 **NR**).

Methoxyflurane (Penthrane®)

Methoxyflurane is not available in most countries, but in Australia and New Zealand it has largely replaced N_2O in prehospital settings with reviews on its characteristics available in the literature (Blair 2016 **NR**). Methoxyflurane is delivered by a Penthrox® inhaler which contains 3 mL of methoxyflurane and lasts for 25–30 min (Medical Developments International 2001). It is now licensed in the UK, but not in the European Union nor the USA. It is more costly per dose than opioid analgesics (>$20/dose). Methoxyflurane is contraindicated in patients with renal impairment, which is difficult to reliably assess in the acute prehospital environment. Caution against its use has been expressed by one UK medical college until further studies have been undertaken (Fairhurst 2011 **GL**).

Methoxyflurane use reduced pain scores (mean 2.47/10 ± 0.24) in adults, the majority of whom had musculoskeletal pain (Buntine 2007 **Level IV**, n=83); the incidence of nausea was 8%, and 11% had increased drowsiness. Results on the efficacy of methoxyflurane when compared to Fentanyl (IV or IN) or IV morphine are mixed. Methoxyflurane produced greater initial reduction in pain scores than IN fentanyl (2.0 vs 1.6/10) but IN fentanyl produced greater pain reduction by the time of arrival at hospital (3.2 vs 2.5/10) (Johnston 2011 **Level III-3**, n=1,024). Methoxyflurane reduced NRS pain score by ≥30% for 78% of children (aged 5 to 15 y), while among those who received IV morphine and IN fentanyl this was achieved for 88 and 90% respectively (Bendall 2011a **Level III-2**, n=3,312). In a smaller series, methoxyflurane also reduced pain scores in children and adverse effects were reported (Babl 2006 **Level IV**, n=105); the overall incidence of drowsiness was 27% but the risk of deep sedation was significantly higher in younger children (see also Section 10.9.1.1). Yet a further review reported IN Fentanyl or IV morphine to be of superior analgesic efficacy with moderate to severe pain (Blair 2016 **NR**).

There have been no reports of toxicity with analgesic use of methoxyflurane if doses are limited to 3 mL repeated once per event with a maximum of 15 mL per wk or a maximum of 0.5% for 1 h (Grindlay 2009 **NR**) (see also Section 4.5.2). A large population database study found no long term (up to 14 y) adverse effects in patients who had been given methoxyflurane by an ambulance service (Jacobs 2010 **Level IV**, n=17,629).

8.12.2.4 | Ketamine

Ketamine has been administered for prehospital procedural analgesia and sedation in both adults (Bredmose 2009b **Level IV**, n=1,030; Porter 2004 **NR**) and children (Bredmose 2009a **Level IV**, n=164) for many years (Henderson 2016 **NR**). A preference for ketamine has been reported in adult cases with severe pain but less so in paediatric patients. A case-series of patients treated by paramedics trained in the use of ketamine/midazolam found it was highly efficacious (reduction of mean pain score from 8/10 to 3/10) and safe (adverse effects 2.8%, no change in vital signs) (Haske 2014 **Level IV**, n=528). IV ketamine provided similar analgesia to IM morphine for trauma patients in rural areas (Tran 2014 **Level II**, n=308, JS 2). The ketamine group had a higher rate of

agitation and hallucinations (11 vs 1.5%) but a lower rate of vomiting (5 vs 19%). After trauma, patients who responded poorly to a first dose of IV morphine 5 mg had better analgesia with subsequent IV ketamine than morphine bolus doses but with more minor adverse effects (Jennings 2012 **Level II**, n=135, JS 3). In a low-resource rural trauma service in Iraq, provision of prehospital analgesia with IV ketamine vs IV pentazocine resulted in better physiologic severity scores vs no analgesic recipients (respiration and blood pressure); IV ketamine achieved positive change for blood pressure in more severely injured patients (Losvik 2015 **Level III-2**, n=1,876).

8.12.3 | Anxiolytics

Anxiolytics, for example low doses of midazolam, are sometimes used to alleviate some of the acute anxiety or agitation that may complicate effective control of pain in stressful prehospital conditions (McManus 2005 **NR**). However, there are no studies looking at efficacy and safety, and midazolam does not enhance the analgesic effect of morphine in a prehospital setting (Auffret 2014 **Level II**, n=91, JS 5). It should be remembered that the combination with opioids will increase the risk of respiratory depression and that anxiety and agitation may be indicators of other more serious underlying conditions such as a head injury or hypoxia (McManus 2005 **NR**). Low-dose IV midazolam (1 mg typically) in combination with ketamine administered by ambulance officers did not produce any drug-related adverse effects (Haske 2014 **Level IV**, n=528).

8.12.4 | Regional analgesia

Use of regional analgesia in the prehospital setting (excluding war or disaster situations) is uncommon but increasing. Initiation of a fascia iliaca compartment block (FICB) for analgesia in patients with isolated femoral shaft fractures reduces pain intensity across all studies; success rate is 90% with only one adverse event (Hards 2018 **Level IV SR**, 1 RCT, 5 studies & 1 CR, n=254 [blocks]). In the included studies, these blocks were administered by physicians (3 studies), paramedics (1 RCT: McRae 2015 **Level II**, n=24, JS 3), anaesthetists (1 study & 1 CR) and emergency medical service nurses (1 study: Dochez 2014 **Level IV**, n=108 [blocks])

The approach was supported by paramedics in a survey (Evans 2019 **Level IV**, n=11 [paramedics]).

Prehospital treatment of dislocated extremity fractures with US-guided PNBs (FNB, sciatic nerve block, brachial plexus block) vs analgosedation (midazolam/ketamine or midazolam/fentanyl) by anaesthetists resulted in lower pain intensity during the reduction (median 0/10 [IQR 0 to 0] vs 6/10 [IQR 0 to 8]) and on the first POD (1/10 [IQR 0 to 5] vs 5/10 [IQR 5 to 7]), as well as higher rate of successful reduction and patient satisfaction (Buttner 2018 **Level II**, n=30, JS 2).

8.12.5 | Nonpharmacological management of pain

Although analgesic agents are often used to treat pain in the prehospital setting, the importance of nonpharmacological treatments should not be forgotten. The role of psychological intervention with reassurance and distraction in the management of acute pain in an anxious patient is often undervalued.

Physical interventions specific for traumatic injuries include ice, elevation and splinting and these can be effectively delivered in the prehospital environment. Local active warming resulted in analgesia for females in pelvic pain during prehospital transport (Bertalanffy 2006 **Level II**, n=100, JS 3).

TENS used in the prehospital setting reduced pain intensity vs pain before TENS use (MD 38/100; 95%CI 28 to 44) and vs sham TENS (MD 33/100; 95%CI 21 to 44), as well as acute anxiety

secondary to pain (Simpson 2014 **Level I** [PRISMA], 4 RCTs, n=261). The logistical and practical implications of implementing TENS into widespread prehospital practice is unclear.

Acupressure performed by paramedics using "*true points*" led to better pain relief and less anxiety than acupressure using "*sham points*" (Lang 2007 **Level II**, n=32, JS 5) or sham or no acupressure (Kober 2002 **Level II**, n=60, JS 5).

8.12.6 | Analgesia in specific conditions

8.12.6.1 | Acute cardiac pain

The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation, including the use of supplemental oxygen (Pollack 2008 **GL**; Cannon 2008 **GL**) and glyceryl trinitrate (Henrikson 2003 **Level IV**, n=459). Whether supplemental oxygen is beneficial or harmful (especially if used in a nontargeted way) when used in acute coronary syndrome remains unclear (Cabello 2013 **Level I** [Cochrane], 4 studies, n=430). Current guidelines by the Australian and New Zealand Cardiology Society (Chew 2016 **GL**) and NICE (NICE 2016b **GL**) state that the use of supplemental oxygen is not recommended unless hypoxia (oxygen saturation [SpO_2] <94%) is present because of these concerns.

When used to treat acute cardiac chest pain during prehospital transfer, IV alfentanil provided more rapid relief than IV morphine (Rickard 2007 **Level II**, n=258, JS 3; Silfvast 2001 **Level II**, n=40, JS 4). In two cohort studies, prehospital use of morphine vs non-use was not associated with worse in-hospital complications and 1 y survival (HR 0.69; 95%CI 0.35 to 1.37) (Puymirat 2016 **Level III-3**, n=2,438 [1,726 survival analysis]).

See also Section 8.6.3 above.

8.12.6.2 | Abdominal pain

As noted in Section 8.6.1 above, administration of opioids does not interfere with the diagnostic process in acute abdominal pain.

8.12.6.3 | Patients with head injury

Caution is often expressed about the use of opioids for pain relief in patients with a head injury (Thomas 2008 **NR**). This is largely because of the potential adverse effects of opioids and their ability to interfere with recovery and neurological assessment, as well as the concern that OIVI will lead to hypercarbia and increased intracranial pressure (Nemergut 2007 **NR**). While there is little specific information regarding the use of opioids in patients with a head injury in the prehospital setting, opioids have been safely used in patients after craniotomy (see Section 8.1.8 above).

The use of opioids in patients with a head injury in the prehospital environment will need to be based on an individual risk-benefit assessment for each patient.

KEY MESSAGES

1. Transcutaneous electrical nerve stimulation TENS provides pain relief in the prehospital setting (**N**) (**Level I** [PRISMA]).
2. Intravenous morphine, fentanyl and tramadol are equally effective in the prehospital setting (**S**) (**Level II**).
3. Nitrous oxide is an effective analgesic agent in prehospital situations (**U**) (**Level II**).
4. Methoxyflurane, in low concentrations, is an effective analgesic with rapid onset in the prehospital and hospital setting with good safety data (**U**) (**Level II**).
5. Ketamine is a safe and effective analgesic in the prehospital setting (**U**) (**Level II**).
6. Moderate to severe pain is common in both adult and paediatric patients in the prehospital setting (**S**) (**Level IV**) and is often poorly managed (**N**) (**Level III-2**).
7. Fascia iliaca compartment block is an effective analgesic technique for patients with isolated femoral shaft fractures in the prehospital setting (**N**) (**Level IV SR**).
8. The prehospital setting presents challenges beyond those encountered in hospital to the assessment, documentation, treatment and reassessment of pain in both adult and paediatric patients (**N**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion:

☑ Nonpharmacological measures are effective in providing pain relief and should always be considered and used if practical (**U**).

8.13 | Discharge opioid medication for acute pain management

The number of patients discharged from hospital with opioid medication is rising (Macintyre 2014 **NR**), partially because the range of patients and procedures considered suitable for short-stay or early discharge are increasing (see Section 8.1.7).

Ideally, multimodal analgesia approaches should be the cornerstone of the discharge analgesic regimen (Desai 2018 **Level III-2**, n=42,000). A multimodal bundle of standardised use of preoperative paracetamol, postoperative comfort education, simethicone, postoperative gum chewing and abdominal binders reduced opioid requirements in hospital and with more women receiving <20 tablets of oxycodone at discharge (96.7% vs 26.3%) (Burgess 2019 **Level III-1**, n=9,313).

In a multimodal regimen for discharge, oral immediate release opioid is prescribed if required, to be used on an 'as needed' (prn) basis, ideally for a defined period. Not all, but many patients will require opioid medications at discharge to manage moderate to severe postoperative pain and optimise recovery and rehabilitation (Association of Anaesthetists of Great 2011 **GL**; Steyaert 2013 **NR**).

Before prescribing discharge opioids, consideration needs to be given to possible opioid adverse effects including the potential risks of long term opioid use, drug diversion, misuse or abuse, and death from accidental overdose (Roughead 2019 **Level III-3**, n=24,854; Desai 2018 **Level III-2**, n=42,000; Macintyre 2014 **NR**). See further discussion below in 8.13.2.

Anaesthetists are ideally placed to enforce opioid stewardship (Macintyre 2014 **NR**); they and surgeons need to take responsibility for discharge opioid prescribing as they are in a good position to influence behaviour (Dunn 2017b **NR**). Furthermore, emergency departments play a central role in community opioid supply with need for better coordination between community and hospital specialities (Allen 2014 **NR**).

For discharge medication after ambulatory surgery, see also Section 8.1.7.4.

For discharge opioid prescribing in children, see also Section 10.4.5.

8.13.2 | Adverse effects of opioids

8.13.2.1 | Opioid-related deaths

Opioid overdose in 2016 resulted in death for 1,045 Australians aged 15-64 y (Roxburgh 2018 **Level IV**). The majority of these deaths (76%) were attributable to prescription opioids. There has been a significant increase over the last 10 y in opioid-related deaths, from 3.8 to 6.6 deaths per 100,000 Australians per year. Similarly, but on a lower scale, the rate of opioid-related deaths in New Zealand has increased by 33% from 2001 to 2012, with more than half (n=179) being unintentional opioid overdoses (Shipton 2017 **Level IV**, n=325). In the USA, over a similar period, over 183,000 deaths have been attributed to prescription opioids with numbers increasing each year (Morrison 2017 **NR**). There is evidence that illicit fentanyl is significantly contributing to the growth in opioid deaths in the USA and Canada, but not in Australia or New Zealand (Roxburgh 2018 **Level IV**, n=1,045).

Non-fatal overdose events are 7 to 11 times more common than fatal events and lead to significant morbidity. Most of the non-fatal overdose events occur in patients who have used opioids for <90 d (ie acute, not chronic opioid users) (Brat 2018 **Level III-2**, n=1,015,116).

As the average daily dose (in oral morphine equivalent doses [MED]) increased, so did the opioid overdose death rate (Zedler 2018 **Level III-2**, n=18,365,497; Mudumbai 2016 **Level III-3**, n=64,391; Garg 2017 **Level IV**, n=150,821). The daily opioid dose correlated with risk of fatal overdose in patients prescribed opioids (Garg 2017 **Level IV**, n=150,821). Compared to patients

taking between 1 and 19 mg/d, the adjusted HRs (aHR) were 2.3 (95%CI 1.4 to 4.1) for 50 to 89 mg/d, 4.0 (95%CI 2.2 to 7.3) for 90 to 119 mg/d, 3.8 (95%CI 2.1 to 6.9) for 120 to 199 mg/d and 4.9 (95%CI 2.9 to 8.1) for 200 mg/d

In the same study, compared to use of opioids only, using opioids in combination with sedatives and hypnotics increased the risk of overdose death (aHR 6.4; 95%CI 5.0 to 8.4), even with lower opioid doses between 1 and 19 mg/d (aHR 5.6; 95%CI; 1.6 to 19.3). The highest risk was recorded with opioids combined with oral benzodiazepines and centrally acting skeletal muscle relaxants (aHR 12.6; 95%CI 8.9 to 17.9).

Co-prescription of pregabalin and opioids is associated with increased mortality in a dose dependent fashion: higher doses of pregabalin were associated with a higher risk of opioid-related death and low doses associated with a lower, but still statistically significant, increased risk (Gomes 2018 **Level III-2**, n=6,514). The mechanism of the association is unclear, but alpha-2-delta-ligands can augment the ventilatory impairment associated with opioids (Morrison 2017 **NR**) and have reversed opioid tolerance in rodent studies (Nicolodi 1995 **BS**). Data from many countries (USA, UK, Germany, Finland, India, South Africa and France) show that over 75% of deaths attributable to alpha-2-delta-ligands also involve opioids (Smith 2016b **Level IV SR**, 34 studies [including 23 CR], n=49,570).

See also section 4.8.

Contribution of discharge opioids to overdose mortality

Although relatively rare, there is a small increased risk of opioid overdose in the month after discharge from hospital following surgery (Mudumbai 2019 **Level III-3**, n=64,391; Ladha 2018 **Level III-3**, n=1,305,715). Immediately after discharge (0-30 d) the risk of overdose is much higher than later (31 to 365 d) (RR 10.80; 95%CI 8.37 to 13.92) (n=476) and this risk may increase stepwise as intensity of discharge opioid increases: from no opioids; tramadol only; short-acting opioid only; long-acting only; to short- and long-acting combined (Mudumbai 2019 **Level III-3**, n=64,391). Patients on short- and long-acting opioids combined had the highest risk of overdose (HR 4.84; 95%CI 3.28 to 7.14). Preoperative use of high doses of opioids was another risk factor (Ladha 2018 **Level III-3**, n=1,305,715).

An analysis of deaths related to opioid toxicity in Canada found that the source of opioid in 6.6% of cases was an acute pain prescription (Madadi 2013 **Level III-3**, n=2,330 [drug-related deaths]). While in the USA in people who died of prescription drug overdose, 5% of prescriptions came from emergency or urgent care specialists and anaesthetists provided only 1.7% of the total prescriptions involved (Lev 2016 **Level III-3**, n=4,336 [prescriptions]).

8.13.2.2 | Opioid-induced Ventilatory Impairment (OIVI)

For inpatients, OIVI is estimated to occur in less than 0.5% of acute pain patients using opioids post-operatively (Dahan 2010 **NR**). The time periods of greatest risk of OIVI occurrence being the day of and the night following surgery has implication for discharge of short-stay surgery patients (Lee 2013a **Level IV**, n=341); in children following tonsillectomy with or without adenoidectomy most clinically significant OIVI cases occurred within 2 d of the procedure (FDA 2013 **GL**). Positive predictors identified for inpatient OIVI include: age over 70 y, male sex, major organ failure (including cardiac, respiratory and renal disease) and opioid naïvety (Khanna 2018 **Level IV**, n=1,650). Other risk factors have included: sleep disordered breathing (Lee 2013a **Level IV**, n=341; Macintyre 2011 **NR**); increasing daily opioid doses (Zedler 2018 **Level III-2**, n=18,365,497; Garg 2017 **Level IV**, n=150,821); and, for chronic opioid users, a history of alcohol dependence (Gomes 2011 **Level III-2**, n=1,463 opioid-associated deaths [498 age matched controls]). These have presumed but unproven significance in patients discharged home postoperatively with opioids.

For outpatients, risk factors for OIVI have included:

- The combination of long-acting plus short-acting opioids (Garg 2017 **Level IV**, n=150,821);
- Additional non-prescribed opioids; alcohol and other nonopioid sedating medications such as benzodiazepines (Garg 2017 **Level IV**, n=150,821), antidepressants (Gomes 2011 **Level III-2**, n=2,122 deaths [498 opioid-associated]; Rintoul 2011 **Level IV**, n=320; Webster 2011 **NR**) and pregabalin (Gomes 2011 **Level III-2**, n=2,122 deaths [498 opioid-associated]);
- Magnitude of prescribed daily opioid dose (a significant positive correlation starts at MED 20 mg/d, with the highest risk in those prescribed MED >100 mg/d) (Garg 2017 **Level IV**, n=150,821)
- Duration of opioid use (users with 31 to 89 d cumulative duration 4 times more likely to have an opioid related death than those using opioids for <30 d) (Garg 2017 **Level IV**, n=150,821);
- History of opioid dependence; hospitalisation during the 6 mth prior to the event; liver disease; co-prescription of sedatives including benzodiazepines, skeletal muscle relaxants and pregabalin; and the use of long-acting opioids (Zedler 2018 **Level III-2**, n=18,365,497).

For outpatients at perceived increased risk of OIVI due to opioid overdose, WHO is recommending the provision of take-home naloxone (WHO 2014 **GL**). In Australia, an IM and an IN naloxone preparation suitable for take home use are commercially available and guidelines for their use have been proposed (Lintzeris 2020 **GL**).

On the basis of these identified risk factors, risk prediction tools for OIVI have been proposed for both inpatients and outpatients prescribed opioids (Zedler 2018 **Level III-2**, n=18,365,497). Although these factors have been identified to increase the risk of significant OIVI, no patient can be said to be risk free. As total opioid dose increases, the risk of respiratory depression increases but some patients experience respiratory depression with very small opioid doses.

Older patients may be at greater risk of OIVI, but young patients with no identified comorbidities have died of OIVI post-operatively (Lee 2013a **Level IV**, n=341). Thus, it has been recommended that health care professionals involved in prescribing, administering or dispensing opioids should adopt a cautious and standardised approach, consider every patient at risk of adverse events and titrating dose to effect and side-effects (NPS Medicinewise 2019 **GL**; Macintyre 2014 **NR**).

8.13.2.3 | Patient falls

Patients treated with opioids for any reason may be at increased risk of falling.

Those using opioids chronically for noncancer pain may be at greater risk of falling and requiring hospital admission than those not on opioid medication; the overall risk is greatest in week 1 following initial prescription and decreases over time (Rolita 2013 **Level III-2**, n=13,354). Patients newly treated with opioids may similarly be at increased risk of falling. There is an increased risk of presentation to hospital with a falls related injury in the 2 to 4 weeks following the filling of an opioid prescription (Daoust 2018 **Level III-2**, n=67 929; Soderberg 2013 **Level III-2**, n=167,257). In an analysis of fall-injured patients 4.5% had a first opioid prescription less than 28 d prior to their fall (Soderberg 2013 **Level III-2**, n=167,257). Fall risk was greatest in younger patients (18 to 29 y) and decreased with increasing time from initial prescription. In a similar study, 4.9% of fall-injured patients had filled an opioid prescription in the 2 wk prior to the injury and were more likely to have a fall related injury than through another mechanism (aOR 2.42; 95%CI 1.94 to 3.02) (Daoust 2018 **Level III-2**, n=67,929).

Despite the correlation of opioid prescription and increased fall risk, there is no evidence of causation. The mechanism by which prescribed opioids may trigger injurious falls is unclear; it may be directly due to adverse opioid effects (sedation, dizziness or cognitive impairment),

underlying patient risk factors or comorbidities that make the prescription of opioids more likely, or increase of risky activities which the opioid analgesic effect allows (Soderberg 2013 **Level III-2**, n=167,257).

8.13.2.4 | Impaired driving

Prescription opioid use is associated with a significantly increased risk of fatal crash involvement; 5.0% of US drivers involved in fatal crashes tested positive for prescription opioids vs 3.7% of drivers overall (OR 1.72; 95%CI 1.37 to 2.17) (Li 2019a **Level III-2**, n=19,206). Of drivers involved in fatal crashes, 56% tested positive for alcohol only vs 7% of roadside tested drivers (aOR 17.9; 95%CI 16.19 to 19.84); 2.2% tested positive for both prescription opioids and alcohol vs 0.2% of roadside tested drivers (aOR 21.89; 95%CI 14.38 to 33.32). The interaction with alcohol is in line with previous data (EMCDDA 2012 **Level III-2**; Brady 2014 **Level IV**, n=23,591). Pooled data for prescription opioids only showed increased risk for accidents (OR 2.29; 95%CI 1.51 to 3.48) and for culpability (OR 1.47; 95%CI 1.01 to 2.13) (Chihuri 2017 **Level III-3 SR**, 15 studies, n=926 to 72,685). Self-reported driving under the influence of prescription opioids was also asscoiated with an increased risk of collision (aOR 1.97; 95%CI 1.08 to 3.60) (Wickens 2018 **Level IV**, n=7,857).

Opioids are known to cause sedation, to diminish reaction times, reflexes and coordination and to decrease the ability to concentrate (Wilhelmi 2012 **Level IV SR**, 58 studies, n>80,940); they reduce attention specifically in cognitive tests and this effect increases when used together with antidepressants or anticonvulsants (Allegri 2019 **Level III-2 SR** [PRISMA], 9 studies, n=683). They may thus interfere with the ability to perform a complicated task such as driving. These effects are both subjectively and objectively evident when opioid naïve patients take medicinal opioids in commonly prescribed amounts, although some studies have found less significant objective than subjective impairment (Wilhelmi 2012 **Level IV SR**, 58 studies, n unspecified). Attention and visual function are most sensitive in experimental studies, where doses up to 5 mg morphine IV (leading to plasma concentrations of 50 nmol/L [≈14.3 ng/mL]) had very few effects on traffic-relevant performance tasks (Strand 2017 **Level I EH**, 15 RCTs, n=324 [tests performed]). The overall degree of driving impairment by prescription opioids was similar to that of a blood alcohol reading of 0.05 to 0.08 g/dL (EMCDDA 2012 **Level III-2**); no attempt was made in this analysis to distinguish between acute and chronic opioid use.

In chronic pain patients, it has been traditionally considered that as tolerance develops the driving performance of patients on long term stable opioids may not be negatively affected by their medication and may not have an increased crash risk (Wilhelmi 2012 **Level IV SR**, 58 studies, n unspecified; Dassanayake 2011 **Level III-2 SR**, 21 studies [13 case control n>26,603 drivers in accidents vs n>60,508 controls]). In this setting, no significant impact of regular therapeutic opioid agonists on people's driving-related psychomotor skills has been found (Ferreira 2018 **Level III-3 SR** [PRISMA], 3 studies, n=426). However, driving risk may be increased in the first few weeks following the initiation of a prescription opioid (Dassanayake 2011 **Level III-2 SR**, 21 studies [5 opioid n unspecified]) and may be dose dependent (EMCDDA 2012 **Level III-2**). Similarly, when patients on long term opioids have their dose increased, their psychomotor impairment returns (Wilhelmi 2012 **Level VI SR**, 58 studies, n unspecified). These findings may have implications for the discharge management of acute postoperative pain.

8.13.2.5 | Risk of inducing long term opioid use

Between 2 and 10% of patients continue to use opioid medication for months or even years following its postoperative initiation (Roughead 2019 **Level III-2**, n=24,854; Brat 2018 **Level III-2**, n=1,015,116; Stark 2017 **Level III-2**, n=1,013). Any post-discharge prescription of opioids at all seems

to be a risk factor for ongoing use, but risk increases with every further repeat prescription or refill in all dose ranges (Brat 2018 **Level III-2**, n=1,015,116).

In Australia, 15.7% of patients admitted to mainly private hospitals under the veteran care system for a surgical admission were discharged on opioids, of which 3.9% became chronic users of opioids (Roughead 2019 **Level III-2**, n=24,854). Similarly, in Canada, 3.1% of opioid naïve patients having major elective surgery showed prolonged opioid use after being discharged on opioids (Clarke 2014 **Level III-2**, n=39,140).

Even after day-stay surgery, patients receiving an opioid prescription within the 7 d following surgery were more likely to use opioids within the next year in comparison to those without a prescription (OR 1.44; 95%CI 1.39 to 1.50) (Alam 2012 **Level III-2**, n=391,139). Discharge NSAID prescriptions were also more likely to be associated with persistent NSAID use (OR 3.74; 95%CI 3.27 to 4.28).

Risk factors for prolonged opioid use have included the type of surgical procedure with higher rates in orthopaedic and spinal surgery (Stark 2017 **Level III-2**, n=1,013); after surgical procedures odds ratios ranging from 1.28 (95%CI 1.12 to 1.46) for Caesarean section to 5.10 (95% CI 4.67 to 5.58) for TKA have been reported (Sun 2016 **Level IV**, n=641,941 [surgical patients]). Risk factors have also included medical comorbidities such as diabetes, heart failure and chronic lung disease, behavioural and social factors such as lower household income (Clarke 2014 **Level III-2**, n=39,140; Namba 2016 **Level III-3**, n=12,859), mental health comorbidities including depression, anxiety and psychosis (Brummett 2017 **Level III-2**, n=36,177; Lalic 2018 **Level III-3**, n=431,963; Namba 2016 **Level III-3**, n=12,895), preoperative pain disorders (Brummett 2017 **Level III-2**, n=36,177) and preoperative use of certain medications, specifically benzodiazepines, SSRIs and ACE inhibitors (Carroll 2012 **Level III-2**, n=109; Sun 2016 **Level IV**, n=641,941 [surgical patients]). Preoperative prescription opioid use, alcohol and substance use disorders and depressive or anxiety symptoms have, in some studies, more accurately predicted prolonged opioid use than the duration or severity of postoperative pain (Stark 2017 **Level III-2**, n=1,013; Carroll 2012 **Level III-2**, n=109).

Characteristics of the initial opioid prescribing pattern have been linked to long term opioid use. In a database analysis of the records of opioid naïve patients who received a new prescription for opioids in the US, with each additional day's supply of opioids in the initial prescription, the probability of chronic opioid use increased (Shah 2017 **Level IV**, n=1,294,247). The sharpest increases in chronic opioid use occurred after the fifth and thirty-first day of continual use, after the second prescription and after a cumulative opioid dose of 700 MME. In this study there was no distinction made between perioperative patients, acute non-operative patients and chronic pain patients.

However, the greatest risk for prolonged opioid use after surgery may be preoperative opioid use (Mohamadi 2018 **Level IV SR** [PRISMA], 37 studies, n=1,969,953; Dunn 2018b **Level III-3**, n=1,477 [patient records reviewed]; Bedard 2018 **Level III-3**, n= 35,894). Of over 6,000 USA veterans undergoing TKA that did not subsequently require revision, 60% had used an opioid in the year prior to surgery (Hadlandsmyth 2018 **Level IV**, n=6,653). In patients on long term opioids at the time of surgery, 69% received opioids for at least 6 mth and 57% for at least 12 mth after TKA. In patients not on long term opioids at the time of TKA, only 4% received opioids for at least 6 mth and 2% for at least 12 mth after TKA. Similarly, with patients having lower limb arthroplasty who used opioids at least 80% of the time for >4 mth preoperatively, over 70% became persistent users (Kim 2017c **Level IV**, n=57,545).

Australian pharmaceutical benefit (PBS) scheme data show persistent opioid use is more likely if initiated with transdermal preparations, higher doses, in older patients, with comorbid depression (Sullivan 2018 **NR**) or psychotic illness, and prior dispensing of pregabalin or benzodiazepines (Lalic 2019 **Level IV**, n=769,334).

For paediatric information, see Section 10.4.5.4.

8.13.2.6 | Risk of diversion, misuse and abuse

There is a growing awareness of prescription opioid abuse in the general population and among injecting drug users (Degenhardt 2013 **Level IV**; Fischer 2010 **NR**). This has been described by some as a major public health problem and is associated with prescription opioid-related overdoses and deaths (Cicero 2017 **Level IV SR** [PRISMA], 17 studies, n=816).

Overprescribed and subsequently unused opioids prescribed for postoperative pain are potentially a large reservoir for opioid abuse, misuse and diversion. Following urological surgery, 67% of those who filled their prescriptions for opioids had leftovers, which 91% planned to keep (Bates 2011 **Level IV**). After dermatological surgery, 35% of those prescribed an opioid did not use it at all and 55% of these planned to keep the leftover tablets (Harris 2013 **Level IV**). Following upper limb surgery, 31% of 245 patients used fewer than half of the opioid tablets prescribed with over 4,000 tablets in total unused (Rodgers 2012 **Level IV**). In opioid naïve patients discharged to home after major gastrointestinal or colorectal surgery, 85% of patients were prescribed an opioid and only 38% of prescribed tablets were taken (Hill 2018a **Level IV**, n=333). For paediatric information, see Section 10.4.5.6.

These opioids are not just a danger to the patient for whom they are prescribed. Patients who retain unused tablets are usually willing to share them. It has been estimated that 71% of chronic opioid users receive their medications through diversion (Hill 2018a **Level IV**, n=333). After receiving opioid prescriptions for an acute episode, 64% of patients kept unused opioids and 34% shared them with others (Lewis 2014 **Level IV**, n=191). In the USA, one third of college students prescribed an analgesic for acute pain report having diverted opioids to others (Arria 2011 **Level IV**, n=192).

Sharing opioid medication may expose the user to an increased risk of adverse reaction or drug interaction as there is often no assessment made of the underlying cause of the opioid requirement and no advice given by a doctor or pharmacist (Ward 2011 **Level IV**, n=641; Ellis 2009 **NR**).

Hoarded medication may also be a source of opioids for nonmedical use (Macintyre 2014 **NR**). The most common source of prescription opioids for nonmedical use in both the USA (Lipari 2013 **Level IV**, n 10,700,000) and Australia (Belcher 2014 **Level IV**, n=952) is a friend or relative, with no charge incurred.

The total duration of opioid use post-operatively may be the strongest predictor of subsequent opioid misuse (Brat 2018 **Level III-2**, n=1,015,116). Prescribing patterns and their association with subsequent misuse events were considered in a study of surgical claims from a linked medical and pharmacy administrative database in the USA. Each additional week of opioid use was associated with a 34% increase in the rate of misuse. For example, one refill in addition to the opioid prescription on discharge doubled the rate of misuse, and each additional prescription increased the rate by 70%. In this study, the dosage prescribed was a far weaker predictor of misuse. Even high doses (>MED 150mg/d) were associated with only small increases in misuse risk when the duration of prescription was short. For prescriptions <2 weeks, misuse rates for MED 40-50 mg/d were similar to rates for MED 100 to 150 mg/d.

Other risk factors associated with opioid misuse events have included benzodiazepine use, bariatric surgery, tobacco use disorder, other chronic pain and major depressive disorder (Brat 2018 **Level III-2**, n=1,015,116).

For paediatric information, see Section 10.4.5.5.

8.13.2.7 | Discharge opioid prescribing regimens

"*Over-prescription*" of opioids is common on discharge and may be explained by difficulties in estimating the postoperative opioid analgesic requirements of patients following day surgery or short inpatient stay. For post-operative patients, post-discharge opioid requirement may best be predicted by opioid use the day prior to discharge (Hill 2018a **Level IV**, n=333); the number of opioid tablets used at home was associated with the number of tablets taken the day before discharge and the patient age, but not the type of surgery. The following regimen satisfied home opioid requirements of 85% of the patients discharged: if a patient took no opioids the day prior to discharge, no prescription was required; if 1-3 tablets were taken the day prior to discharge, then a prescription for 15 pills was appropriate; and if 4 or more pills were used then 30 pills were given. Such an individualised approach to opioid prescribing is supported after Caesarean section (predicted based on each patient's inpatient opioid use), where individualised vs standard prescription (30 PO oxycodone 5 mg tablets) resulted in 50% reduced unused tablets and, most interestingly, 50% reduced opioid use (8 vs 15 tablets) with no difference in pain scores (Osmundson 2018 **Level II**, n=190, JS 3).

Although this approach may seem intuitive, it is not commonly done. Even when opioid requirements have been established, excessive prescription commonly occurs; 19% of postoperative patients prescribed oxycodone for discharge from a large Australian teaching hospital had not needed any opioid in the 24 h prior to discharge (Platis 2011 **Level IV**) and of the 36% of an American surgical cohort who received no opioids in the 24 h prior to discharge, 46% were prescribed opioids to take home (Chen 2018 **Level IV**, n=18,343).

Opioid prescribing limits for acute pain are a prominent component of the USA response to the opioid epidemic, often limiting prescription to "*7 days*" (Chua 2019 **NR**). Due to the heterogeneity of patient requirements, such prescribing limits may be either excessive for some patients, contributing needlessly to the community's "*opioid pool*", or inadequate for others, resulting in inadequate pain control and an increased risk of pseudoaddiction, chronic pain and potentially overdose (Brat 2018 **Level III-2**, n=1,015,116).

Many patients discharged from EDs with opioid medication do not safely store and dispose of these medicines (Hill 2018a **Level IV**, n=333). Other studies have shown that less than 10% of patients take unused opioid tablets back to the pharmacy or to a safe box drop (Bicket 2017 **Level III-3 SR** [PRISMA], 6 studies, n=810), some flush them down the toilet, some simply discard them and others keep them at home (Hill 2018a **Level IV**, n=333).

Patients should be advised of these risks and also of the safe way to dispose of unused opioid medicines; in Australia this is to return them to a pharmacy (Macintyre 2014 **NR**). In the USA when patients were provided with a written brochure describing how to dispose of unused opioids, disposal rates increased from 11% to 22% (Hasak 2018 **Level III-3**, n=334). A clear plan for analgesia reduction after discharge and robust systems for communication with usual treating practitioners in the community is essential and will assist in avoiding unintended dose escalation (Hanna 2019 **NR**; Katz 2015a **NR**). Pain specialists and clinics have a role in assisting with transition of these patients to the community postoperatively and future developments may include transitional pain services for those discharged home with high dose opioids (Katz 2015 **NR**, De Pinto 2012 **NR**). Pharmacist led "*opioid exit plans*" can also assist with care on discharge (Genord 2017 **NR**).

For paediatric information, see Section 10.4.5.7.

8.13.3 | Selection of opioid for discharge medication

A position paper by ANZCA and FPMANZCA advises that slow-release (SR) conventional opioids (including transdermal opioid patches and methadone) are not recommended for routine use in the management of opioid naïve patients with acute pain (ANZCA 2018 **GL**). This position is based on the following facts:

- The inappropriate use of slow-release opioids for acute pain has been associated with sedation and respiratory depression resulting in severe adverse reactions and deaths;
- There is significant variation in opioid responsiveness between individuals which makes accurate dose prediction of slow release opioids difficult;
- Initial opioid dose should be titrated to effect and side effects, with the initial dose of immediate release opioid age-based;
- Acute pain intensity normally reduces rapidly over a few days, and so should opioid doses and controlled-release preparations do not allow for this rapid tapering;
- The use of controlled-release opioids in the initial treatment of pain is associated with an increased risk of long term opioid use and subsequent prescribed opioid dependence (Shah 2017 **Level IV**, n=1,294,247).

These recommendations are equally applicable to inpatient and discharge opioid medication.

There is no strong evidence that any one immediate release oral opioid is best for the management of pain on discharge following surgery (Macintyre 2014 **NR**). Hydromorphone or oxycodone, when used as the initial discharge opioid, have both been associated with a higher rate of long term misuse than other opioids (hydrocodone, codeine and tramadol) in opioid naïve patients undergoing surgery in the USA (Brat 2018 **Level III-2**, n=1,015,116). In Australia, the most commonly abused prescription opioids are oxycodone, tramadol and morphine (AIHW 2018a **Level IV**).

8.13.4 | Identification of patients at risk of opioid misuse

Many screening tools have been proposed to predict the risk of opioid misuse before opioid prescription in chronic pain patients (Chou 2009 **Level IV SR**, 16 studies, n=2,570; Passik 2008 **NR**) and are often recommended and utilised in the chronic pain setting (Webster 2011a **NR**). Their validity has, however, been questioned (Clark 2018 **Level IV**, n=225; Dowell 2016 **GL**). No risk prediction tool has been validated for use in acute pain patients although many have been proposed (Calcaterra 2018 **Level IV**, n=12,933) and an informal 'risk assessment' is often advocated using the risk factors discussed above.

8.13.5 | Practical opioid prescribing on discharge

It has been recommended that prescribing physicians use a "universal precautions" approach to opioid prescribing. Universal precautions have been described as a "systematic set of procedures and tools that aid the physician in gathering relevant information, help the physician interpret the information collected and provide a pathway for responsible decisions" (Webster 2010 **NR**).

Strategies include:

- **Risk assessment** for chronic opioid use and misuse (the type of surgical procedure, behavioural and social factors, medical comorbidities and preoperative pain disorders, the use of benzodiazepines, alpha-2-delta ligands, antidepressants (SSRIs), antipsychotics and ACE inhibitors, prescription opioid use, alcohol and substance use disorders and depression or anxiety (Carroll 2012 **Level III-2**, n=109; Sun 2016 **Level IV**, n=641,941 [surgical patients]);

- **The use of a multi-modal analgesic** regimen including non-opioid pain medications if they are not contraindicated (Dowell 2016 **GL**);
- **Appropriate opioid dose** when applicable is best predicted by usage the day before discharge home (Chen 2018 **Level IV**, n=18,343; Hill 2018a **Level IV**, n=333);
- **Limited prescribing and duration of therapy** (which should be communicated clearly to the patient) (Dowell 2016 **GL**). Patients should be instructed (verbal and written) on the expected duration of needing opioids, and recommendations should be individualised based on patient factors and anticipated pain trajectory after discharge;
- **Appropriate patient education** about the risk of opioids, including OIVI and addiction, and the safe disposal of opioids (Dowell 2016 **GL**) eg by the provision of educational material such as (NPS Medicinewise 2019 **GL**);
- **Monitoring of effect and compliance** (close follow-up of at-risk patients after discharge) and having a plan should opioid abuse, misuse or diversion be suspected (Thorson D 2014 **GL**; Webster 2010 **NR**; Passik 2009 **NR**).

A consensus statement for the prescription of discharge medications after surgery has been published in Canada (Clarke 2020 **GL**).

Pre-operative opioid users may be included in this strategy. However, patients who are taking high doses of opioids, long-acting opioids, or have a pain management contracts preoperatively fall outside of these recommendations and a postoperative pain management plan should be developed before surgery in coordination with their primary prescriber (Dowell 2016 **GL**). In using a multimodal discharge analgesic regimen, oral immediate release opioid should be prescribed only if required (based on prior in hospital use), to be used on an 'as needed' basis, for a defined period. Discharge planning should include a discussion of the plan for reduction and discontinuation of opioids as the acute pain resolves (Chou 2016 **GL**). If further opioid analgesia is required, the patient should first be reviewed by a medical officer (AMWG 2017 **GL**).

KEY MESSAGES

1. Short-term opioid therapy may lead to long term opioid use and misuse (**S**) (**Level III-2**); risk factors for prolonged postoperative use include preoperative opioid use, type of surgery, slow-release opioids, psychological and social factors and pre-existing alcohol or substance use disorder (**N**) (**Level III-2**).
2. Recent introduction of opioid therapy may increase the risk of falls (**S**) (**Level III-2**).
3. Recent introduction of opioid therapy or recent dose escalation may impair driving (**S**) (**Level III-2**), thereby leading to increased driving accidents (**N**) (**Level III-3 SR**); this risk is further increased by combined use of opioids and alcohol (**N**) (**Level III-2**).
4. Many patients who retain unused opioid tablets are willing to share them with others (**S**) (**Level III-2**); this contributes to increased risks of abuse and adverse effects in the recipients (**N**) (**Level IV**).
5. The most common source of prescription opioids for nonmedical use is a friend or relative (**N**) (**Level III-3**).

The following tick boxes represent conclusions based on clinical experience and expert opinion:

☑ Unused opioids prescribed for postoperative pain are potentially a large reservoir for opioid abuse, misuse and diversion (**S**).

☑ A "universal precautions" approach for opioid prescribing should be used in the setting of prescribing discharge medications (**S**).

☑ Prescribing discharge medications should be done in consideration of opioid requirements on the day before discharge, avoiding slow-release opioids and for a limited duration (**N**).

☑ Patient education about risks of opioids and safe disposal of unused medication by return to a pharmacy and follow-up by GP or pain medicine services in case of ongoing issues improve safety of discharge medications (**N**).

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