5

Administration of analgesic medicines

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5.0 | Administration of analgesic medicines

Analgesic medicines can be administered by a number of different routes, either relying on a systemic or local effect or a combination of both. The choice of route may be determined by various factors, including the aetiology, severity, location and type of pain, the patient's overall condition and the characteristics of the chosen administration technique. Additional factors to consider with any route of administration are ease of use, accessibility, speed of analgesic onset, reliability of effect, duration of action, patient acceptability and cost.

The principles of individualisation of dose and dosing intervals apply to the administration of all analgesic agents, particularly opioids, by any route. A lack of flexibility in dose schedules has often meant that intermittent and prn (as needed) methods of pain relief have been ineffective when the routes of administration discussed below have been used (Bandolier 2003 **NR**). Frequent assessment of the patient's pain and their response to treatment (including the occurrence of any adverse effects) rather than strict adherence to a given dosing regimen is required if adequate analgesia is to be obtained.

Sections 5.1 to 5.5 below relate to opioids, paracetamol, nsNSAIDs and coxibs. For information relating to oral, parenteral and regional routes of administration of adjuvant medicines, refer to Sections 4.6 to 4.12.

Sections 5.6 to 5.9 below relate to routes of administration involving techniques of regional and local analgesia.

5.1 | Oral and sublingual route

Oral administration of analgesic agents is simple, non-invasive, has good efficacy in most settings and has high patient acceptability. Other than in the treatment of severe acute pain and providing there are no contraindications to its use, it is the route of choice for the administration of most analgesic medicines (Chou 2016 **GL**).

Limitations to the oral route include vomiting or delayed gastric emptying, when absorption is likely to be impaired. If multiple doses of an oral analgesic medicine are given before return of normal gastric motility, accumulated doses may enter the small intestine at the same time once emptying resumes ("*dumping effect*"). This could result in an unexpectedly large systemic uptake of the medicine and an increased risk of adverse effects.

Rates of absorption will vary according to the formulation of the oral analgesic agent (eg tablet, suspension, slow release [SR] preparation). Bioavailability will also vary between medicines because of the effects of first-pass hepatic metabolism following uptake into the portal circulation. Titration of pain relief with oral analgesic medicines is slower compared with some of the other routes of administration discussed below.

Direct comparisons between oral opioid and nonopioid analgesics, or between oral and other routes of administration, are limited. Indirect comparisons, where the individual medicines have been compared with a placebo, have been used to generate a "*league table*" of analgesic efficacy (see Table 5.1). This table is based on randomised, double-blind, single-dose studies or meta-analyses of such studies in patients with moderate to severe pain and shows the number of patients that need to be given the active medicine to achieve at least 50% pain relief in one patient compared with a placebo ($NNT_{50\%}$) over a 4 to 6 h treatment period (Moore 2015 **Level I** [Cochrane], ≈460 RCTs, n≈50,000; Moore 2011 **Level I** [Cochrane], ≈350 RCTs, n≈45,000; Moore 2003 **Level I**, unspecified number of RCTs, n unspecified).

The validity of this approach as a true method of comparison of medicines may be questioned as there is no standardisation of the acute pain model or patient and only single doses of the analgesic agents are used. The effects of the analgesics may vary with different pain models (Gray 2005 reanalysing Barden 2004 **Level I**, 43 RCTs [paracetamol], n unspecified). However, it may be reasonable, in some circumstances, to extrapolate estimates of analgesic efficacy from one pain model to another (Barden 2004 **Level I**, 43 RCTs [paracetamol], n unspecified). Note for example that Ketoprofen 25 mg has a better $NNT_{50\%}$ of 2.0 (95% CI 1.8 to 2.3) than Ketoprofen 50mg $NNT_{50\%}$ 3.3 (95% CI 2.7 to 4.3) suggesting that significant caution should be undertaken comparing data in this way.

Table 5.1 | Table of analgesic efficacy (in all types of surgery)

Analgesic	Number of patients in comparison	$NNT_{50\%}$	Lower confidence interval	Higher confidence interval
Paracetamol + Ibuprofen 1000/400	543	1.5	1.4	1.7
Paracetamol + Ibuprofen 500/200	508	1.6	1.5	1.8
Dipyrone 1,000	113	1.6	1.3	2.2
Etoricoxib 120	798	1.8	1.7	2.0
Ketorolac 20	69	1.8	1.4	2.5
Ketorolac 60 (IM)	116	1.8	1.5	2.3
Oxycodone IR 10 + Paracetamol 1,000	289	1.8	1.6	2.2
Piroxicam 40	30	1.9	1.2	4.3
Ketoprofen 25	535	2.0	1.8	2.3
Diclofenac *potassium* 50	757	2.1	1.9	2.5
Diflunisal 1,000	357	2.1	1.8	2.6
Ibuprofen + caffeine 200/100	334	2.1	1.9	3.1
Ibuprofen *fast acting* 200	828	2.1	1.9	2.4
Ibuprofen *fast acting* 400	1364	2.1	1.9	2.3
Ketoprofen 100	321	2.1	1.7	2.6
Ibuprofen + codeine 400/26-60	443	2.2	1.8	2.6
Paracetamol 800/1,000 + Codeine 60	192	2.2	1.8	2.9

Analgesic	Number of patients in comparison	$NNT_{50\%}$	Lower confidence interval	Higher confidence interval
Oxycodone IR 5 + Paracetamol 500	150	2.2	1.7	3.2
Diclofenac *potassium* 100	787	2.3	2.0	2.5
Dipyrone 500	288	2.3	1.9	3.1
Ibuprofen + Oxycodone 400/5	603	2.3	2.0	2.8
Aspirin 1,200	249	2.4	1.9	3.2
Diclofenac *fast acting* 100	486	2.4	2.0	3.0
Ibuprofen + Caffeine 100/100	200	2.4	1.9	3.1
Ketoprofen 12.5	274	2.4	1.9	3.1
Flurbiprofen 100	416	2.5	2.0	3.1
Ibuprofen 400	6,475	2.5	2.4	2.6
Diclofenac *potassium* 25	502	2.6	2.2	3.3
Diflunisal 500	391	2.6	2.1	3.3
Celecoxib 400	722	2.6	2.3	3.0
Ketorolac 10	790	2.6	2.3	3.1
Tramadol 75 + Paracetamol 650	679	2.6	2.3	3.0
Flurbiprofen 50	692	2.7	2.3	3.3
Ibuprofen 600	203	2.7	2.0	4.2
Paracetamol 650 + Oxycodone IR 10	1,043	2.7	2.4	3.1
Naproxen 500/550	784	2.7	2.3	3.3
Naproxen 400/440	334	2.7	2.2	3.5
Piroxicam 20	280	2.7	2.1	3.8
Paracetamol 650 + Tramadol 112	201	2.8	2.1	4.4
Etodolac 400	222	2.9	2.3	4.0
Ibuprofen 200	2103	2.9	2.7	3.2
Lornoxicam 8	273	2.9	2.3	4.0

Analgesic	Number of patients in comparison	$NNT_{50\%}$	Lower confidence interval	Higher confidence interval
Morphine 10 (IM)	946	2.9	2.6	3.6
Pethidine 100 (IM)	364	2.9	2.3	3.9
Tramadol 150	561	2.9	2.4	3.6
Dexketoprophen 20/25	523	3.2	2.6	4.1
Diflunisal 250	195	3.3	2.3	5.5
Etodolac 200	670	3.3	2.7	4.2
Flurbiprofen 25	208	3.3	2.5	4.9
Ketoprofen 50	624	3.3	2.7	4.3
Ketorolac 30 (IM)	359	3.4	2.5	4.9
Naproxen 200/220	202	3.4	2.4	5.8
Paracetamol 500	561	3.5	2.2	13.3
Dexketoprofen 10/12.5	452	3.6	2.8	5.0
Paracetamol 975/1,000	3,232	3.6	3.2	4.1
Paracetamol 1,500	138	3.7	2.3	9.5
Paracetamol 1,000 + Oxycodone IR 5	78	3.8	2.1	20.0
Paracetamol 600/650 + Codeine 60	1,413	3.9	3.3	4.7
Mefenamic acid 500	256	4.0	2.7	7.1
Aspirin 600/650	4,965	4.2	3.8	4.6
Celecoxib 200	705	4.2	3.4	5.6
Ibuprofen 100	396	4.3	3.2	6.4
Lornoxicam 4	151	4.3	2.7	11.0
Oxycodone IR 15	228	4.6	2.9	11.0
Paracetamol 600/650	1,886	4.6	3.9	5.5
Ibuprofen 50	316	4.7	3.3	8.0
Etodolac 100	498	4.8	3.5	7.8
Tramadol 100	882	4.8	3.8	6.1
Aspirin 650 + Codeine 60	598	5.3	4.1	7.4

Analgesic	Number of patients in comparison	$NNT_{50\%}$	Lower confidence interval	Higher confidence interval
Tramadol 75	563	5.3	3.9	8.2
Paracetamol 325 + Oxycodone IR 5	388	5.4	3.9	8.8
Ketorolac 10 (IM)	142	5.7	3.0	53.0
Diclofenac *sodium* 50mg	284	6.6	4.2	17
Paracetamol 300 + Codeine 30	690	6.9	4.8	12.0
Dihydrocodeine 30	194	8.1	4.1	540
Etodolac 50 (dental only)	360	8.3	4.8	30
Tramadol 50	770	8.3	6.0	13.0
Gabapentin 250	327	11.0	6.4	35.0
Codeine 60	2,411	12.0	8.4	18.0

*Source: Compiled with data from Moore 2003 (**Level I**, unspecified number of RCTs, n unspecified), Moore 2011 (**Level I** [Cochrane], ≈350 RCTs, n≈45,000) and Moore 2015 (**Level I** [Cochrane], ≈460 RCTs, n≈50,000). Formulations and doses not approved for use in Australia, New Zealand, Europe, USA or Canada have been removed from the table.*

5.1.1 | Paracetamol

Single doses of paracetamol are effective in the treatment of postoperative pain. The NNTs for a variety of doses, as well as combinations of paracetamol with other analgesic medicines such as codeine, are listed in Table 5.1.

There is no good evidence for a dose-dependent analgesic effect of oral paracetamol; the effects of 500 mg ($NNT_{50\%}$ 3.5; 95%CI 2.7 to 4.8), 600/650 mg ($NNT_{50\%}$ 4.6; 95%CI 3.9 to 5.5) and 1,000 mg ($NNT_{50\%}$ 3.6; 95%CI 3.2 to 4.1) show no statistically significant difference (Moore 2015 **Level I** [Cochrane], 53 RCTs, n=5,679).

The oral bioavailability of paracetamol is good at between 63 and 89% (Oscier 2009 **NR**). However, rate of absorption and peak concentrations are reduced by factors such as recent food intake (Moore 2015 **SR**), pregnancy (Raffa 2014 **NR**), opioid administration (Raffa 2018 **BS**) and high altitude (Idkaidek 2019 **EH**). Early postoperative oral administration can result in plasma concentrations that can vary enormously after the same dose and may remain subtherapeutic in some patients (Holmer Pettersson 2004 **PK**), however there does not appear to be a clinical difference of oral vs IV paracetamol in total hip arthroplasty (THA) and total knee arthroplasty (TKA) (Sun 2018 **Level I** [PRISMA], 2 RCTs, n=236; Westrich 2019 **Level II**, n=154, JS 5), Caesarean section (Wilson 2019 **Level II,** n=141, JS 3) or laparoscopic cholecystectomy (Plunkett 2017 **Level II**, n=60, JS 4).

Paracetamol effervescent tablets are absorbed significantly faster than ordinary paracetamol (Rygnestad 2000 **PK**).

5.1.2 | Nonselective NSAIDs and coxibs

A number of nsNSAIDs and coxibs have been shown to be effective as sole therapy in a variety of acute surgical pain settings. The NNTs of each of these medicines is listed in Table 5.1.

In general, there is no good evidence that NSAIDs given parenterally or rectally are more effective, or result in fewer adverse effects, than the same NSAID given orally for the treatment of postoperative pain (Tramer 1998 **Level I**, 26 RCTs, n=2,225). Only in the treatment of renal colic do IV NSAIDs result in more rapid analgesia. Only rectal NSAIDs are effective for reducing post ERCP pancreatitis (Serrano 2019 **Level I** [PRISMA], 21 RCTs, n=6,854).

The formulation of oral NSAIDs such as diclofenac seems to significantly impact their efficacy (Derry 2015b **Level I** [Cochrane], 18 RCTs, n=3,714). For the same 50 mg dose, diclofenac sodium has an $NNT_{50\%}$ of 6.6 (95%CI 4.1 to 17) vs diclofenac potassium an $NNT_{50\%}$ of 2.1 (95%CI 1.9 to 2.5) and diclofenac fast acting (dispersible products, solutions, and softgel formulations) an $NNT_{50\%}$ of 2.4 (95%CI 2.0 to 3.0).

5.1.3 | Conventional and atypical opioids

Oral opioids can be as effective in the treatment of acute pain as opioids given by other more invasive routes, if equianalgesic doses are administered (Cheung 2017 **NR**; Chou 2016 **GL**; Macintyre 2015 **NR**). Both IR and SR formulations have been used. In a number of postoperative settings combinations of SR and IR opioids have been used successfully without any parenteral opioids to treat acute pain after ENT surgery (Pogatzki-Zahn 2013 **Level IV**, n=275), spine surgery (Rajpal 2010 **Level IV**, n=200), cardiac surgery (Ruetzler 2014 **Level II**, n=51, JS 2) and orthopaedic surgery (Lamplot 2014, **Level II**, n=36, JS 2}).

When opioids are prescribed for the treatment of acute pain, consideration should be given to duration of therapy. In most cases short-term use only of these medicines is warranted. Discharge planning must consider the duration of use of opioids prescribed for the short-term management of acute pain and the weaning of those medicines and, in a small minority of patients, the potential for prescribed opioids to be abused or misused (see Section 8.13).

5.1.3.1 | Immediate-release formulations

The NNTs for various IR opioids are listed in Table 5.1.

Oral doses of morphine and oxycodone have an onset of analgesic effect at around 30 min with a peak at 1 to 2 h (Hoeben 2012 **EH**).

The effectiveness of the different oral conventional and atypical opioids may change with the addition of paracetamol and NSAIDs.

- Oral codeine in a single dose of 60 mg is not an effective analgesic agent after a variety of operations ($NNT_{50\%}$ 12) (Moore 2015 **Level I** [Cochrane], 33 RCTs, n=2,411). The effect was even smaller in the subgroup after dental surgery ($NNT_{50\%}$ 21) (Derry 2010 **Level I** [Cochrane], 15 RCTs, n=1,146). Combined with oral paracetamol a significant dose response was seen with $NNT_{50\%}$ of 2.2 for 800 to 1,000 mg paracetamol/60 mg codeine, 3.9 for 600 to 650 mg paracetamol/60 mg codeine, and 6.9 for 300 mg paracetamol/30 mg codeine, and the combination extended the duration of analgesia by 1 h compared with paracetamol alone (Toms 2009 **Level I** [Cochrane] 26 RCTs, n=2,295). There are no data on combinations of oral paracetamol with codeine doses <30 mg. An oral combination of 5 mg hydrocodone/500 mg paracetamol did not provide superior analgesia to 30 mg codeine/300 mg paracetamol for extremity pain after ED discharge (Chang 2014 **Level II**, n=240, JS 5). However, 25.6 to 60 mg codeine barely improves the analgesic efficacy of

400 mg ibuprofen in a number of combinations (Derry 2015a **Level I** [Cochrane], 6 RCTs, n=1,342).

- Oral oxycodone IR in a single dose of 5 mg shows no benefit over placebo for the treatment of moderate to severe acute pain (Gaskell 2009 **Level I** [Cochrane], 3 RCTs [oxycodone 5 mg], n=317); doses of 15 mg ($NNT_{50\%}$ 4.6) (2 RCTs [oxycodone 15 mg], n=228), 5 mg oxycodone/325 mg paracetamol ($NNT_{50\%}$ 5.4) (3 RCTs [combination], n=388), 10 mg oxycodone/650 mg paracetamol ($NNT_{50\%}$ 2.7) (10 RCTs [combination], n=1,043) and 10 mg oxycodone/1,000 mg paracetamol ($NNT_{50\%}$ 1.8) (2 RCTs [combination], n=289) are more effective than placebo. Similar benefits are achieved by combining 5 mg oral oxycodone with 400 mg ibuprofen ($NNT_{50\%}$ 2.3) (Derry 2013 **Level I** [Cochrane], 3 RCTs, n=1,303).
- Oral tramadol IR is an effective analgesic agent for postoperative pain with $NNT_{50\%}$ of 7.1 for 50 mg, 4.8 for 100 mg and 2.4 for 150 mg (Moore 1997 **Level I**, 18 RCTs, n=3,453). The combination of tramadol 75 mg or 112.5 mg with paracetamol 560 mg or 975 mg is more effective than either of its two components administered alone (McQuay 2003 **Level I**, 7 RCTs, n>1,400).
- After 3rd molar surgery a meta-analysis of predominantly oral tramadol showed it is less effective and associated with more adverse events (MD 21.8%; 95%CI 13.8 to 29.9) than predominantly oral NSAIDs (Isiordia-Espinoza 2014 **Level I**, 4 RCTs, n=426 [oral] & n=51 [IM]).
- In women undergoing Caesarean section under single shot spinal anaesthesia with IT fentanyl, the regular administration of oral paracetamol, ibuprofen and tramadol resulted in lower pain scores (2.8 0.84 vs 4.1 0.48), higher satisfaction rate (9.1 1.2 vs 8.3 1.5), and more breastfeeds (23.7 6.5 vs 19.2 6.2) vs PRN administration (Yefet 2017 **Level II**, n=200, JS=3).
- Oral morphine IR is effective in the treatment of acute pain. Following preloading with IV morphine, oral morphine liquid 20 mg (initial dose 20 mg; subsequent doses increased by 5 mg if breakthrough doses needed) every 4 h with additional 10 mg doses prn has been shown to provide better pain relief after hip surgery than IM morphine 5 to 10 mg prn (McCormack 1993 **Level II**, n=47, JS 5).
- In comparison with IV PCA morphine alone, administration every 4 h of 20 mg but not 10 mg of oral morphine reduced PCA morphine consumption; however, there were no differences in pain relief or adverse effects (Manoir 2006 **Level II**, n=63, JS 5).
- Oral tapentadol and oral oxycodone have been compared mostly postoperatively using total pain relief over 24 h. Tapentadol IR 50 mg (MD -2.83/100; 95% CI-11.8 to 6.14) and 75 mg (MD -0.92/100; 95% CI -9.15 to 7.32) show efficacy similar to oxycodone IR 10 mg while 100 mg shows superiority (MD 9.4/100; 95% CI 2.56 to 16.24) (Xiao 2017 **Level I** [PRISMA], 3 RCTs, n=1,003 [50 mg vs 10 mg], 2 RCTs, n=885 [75 mg vs 10 mg], 1 RCT n=175 [100 mg vs 10 mg]). In the same meta-analysis looking at adverse events there was less constipation with 50 mg (RR 0.44; 95%CI 0.21 to 0.93) and 75 mg (RR0.37; 95% CI 0.24 to 0.59), less nausea with 50 mg (RR 0.64; 95%CI 0.48 to 0.85) and 75 mg (0.61; 95%CI 0.41 to 0.93) but more somnolence with 100 mg (RR 1.67; 95%CI 1.08 to 2.58). Overall side effects were only lower in the 75 mg group (RR 0.88; 95%CI 0.83 to 0.94) although the 50 mg group had less discontinuations due to side effects (RR 0.52; 95%CI 0.35 to 0.77).
- SL and IV buprenorphine show efficacy and side effects (including respiratory depression) similar to morphine, but with less pruritus (9 RCTs [sublingual], n=931) (White 2018 **Level I**, 28 RCTs, n=2,210).

IR oral opioids such as oxycodone, morphine and tramadol have also been used as 'step-down' analgesia after PCA, with doses based on prior PCA requirements (Macintyre 2015 **NR**) and after epidural analgesia (Lim 2001 **Level II**, n=101, JS 5).

5.1.3.2 | Slow-release formulations

The role of slow release (SR) formulations (also referred to as controlled-release, extemded-release or prolonged-release) in acute pain is controversial. ANZCA has published a position statement indicating their use should be avoided except on a temporary basis for post-operative and post-traumatic states where pain is prolonged (ANZCA 2018 **GL**); this is also in line with international guidelines (Chou 2016 **GL**).

Concerns regarding the use of SR formulations include:

- SR formulations are not registered for acute pain.
- SR formulations vary widely in time to peak plasma levels with many being in the 3 to 6 h range. In contrast and in most cases, the analgesic effect of the IR opioid preparations will be seen within about 40 to 60 min. Rapid titration to effect is therefore easier with IR formulations.
- Concerns about increased risk of OIVI with use of SR formulations in an acute setting as shown for SR oxycodone after TKA (Weingarten 2015 **Level IV**, n=11,970). This is in analogy to such increased events seen with continuous infusions of opioids (Schug 1993 **Level IV**, n=3,016) and with PCA use with a continuous background infusion (George 2010 **Level I**, 12 RCTs [adults], n=674) (see also Section 6.4.3). It is of note here that regularly (instead of prn) administered IR opioids would raise similar concerns.
- Where patients are taking SR formulations at home for acute pain there is concern about the ability of the patient to down titrate medications if their pain resolves faster than expected by the prescriber, which given the variability of pain is not an unlikely event (ANZCA 2018 **GL**; Macintyre 2015 **NR**). A retrospective analysis of US healthcare data found high rates of continued use at 1 y (27.3%) and 3 y (20.5%) in opioid naïve patients when the initial opioid prescribed was a SR opioid. However, it is unclear how many of these prescriptions were intentional initiations of medication for chronic pain (Shah 2017 **Level IV**, n=1,294,247).

However, SR formulations and regular analgesia may also provide some benefits:

- Regular analgesia may be more effective than prn only analgesia in some circumstances. Post LSCS under spinal anaesthesia, patients randomised to receive regular paracetamol, diclofenac and IR tramadol (note: an atypical opioid with reduced risk of OIVI [see Section 4.3.1.2]) had lower pain, better satisfaction, more breast feeding and less infant formula use than patients prescribed the same medications as prn (Yefet 2017 **Level II**, n=214, JS3).
- Some SR formulations may have a better tolerability profile. For example, SR tramadol formulations have lower adverse events vs IR tramadol in the treatment of chronic pain due to osteoarthritis (Langley 2010 **Level III-II SR**, 15 studies, n unspecified).
- Shorter duration medications dispensed to inpatients more frequently will take more time than dispensing a smaller number of longer lasting medications increasing dispensing cost and nursing and patient burden.

When SR formulations are used, consideration should then be given to opioids with the least sedative (and therefore respiratory depressant) effect such as the atypical opioids tramadol, tapentadol and transdermal buprenorphine (ANZCA 2018 **GL**). SR opioid preparations should only be used at set time intervals and IR opioids should be used prn for acute and breakthrough pain, and for titration of SR opioids.

SR oxycodone is an effective component in the immediate management of acute pain (Kampe 2004 **Level II**, n=40, JS 5; Sunshine 1996 **Level II**, n=182, JS 5). However, IR oxycodone and paracetamol 325 mg given every 6 h led to better pain relief than 10 mg SR oxycodone given every 12 h (Kogan 2007 **Level II**, n=120, JS 5). In comparison with IV morphine PCA alone, SR oxycodone in addition to morphine PCA resulted in improved pain relief and patient satisfaction after lumbar discectomy and a lower incidence of nausea and vomiting, as well as earlier return of bowel function (Blumenthal 2007 **Level II**, n=40, JS 5). SR oxycodone was found to be effective as 'step-down' analgesia after 12–24 h of PCA morphine (Ginsberg 2003 **Level IV**, n=189). However, after total knee and hip replacement, the addition of SR morphine 30 mg twice daily to usual care resulted in only minimally improved analgesia but increased adverse effects (Musclow 2012 **Level II**, n=200, JS 5).

The addition of oral naloxone to oral opioids results in less constipation in the setting of chronic pain (Nee 2018 **Level I** [PRISMA], 5 RCTs, n=838). While it was suggested that these benefits were transferable to acute pain settings (Kuusniemi 2012 **NR**), a difference was not found after laparoscopic hysterectomy (Comelon 2013 **Level II**, n=85, JS 5) or TKA (Oppermann 2016 **Level III-2**, n=80) but time to first bowel motion was improved after colorectal surgery (Creamer 2017 **Level II**, n=82, JS3).

Comparing oral SR tapentadol 50 mg with SR oxycodone/naloxone 10/5mg after orthopaedic trauma surgery found similar quality of analgesia (3.8 ± 1.9 vs 3.8 ± 2.1) and minor adverse effects (51% vs 49%; 95%CI for difference −8 to 14%) (Haeseler 2017 **Level II,** n=266, JS 2). In non-breastfeeding women undergoing Caesarean section with intrathecal morphine, SR tapentadol 50 mg was inferior to SR oxycodone in terms of summed pain intensity difference (SPID) at 36 h (MD -13.77; 95%CI -26.1 to -1.42), but not at 48 h nor was there a difference in pain scores or patient satisfaction at 36 or 48 h (Ffrench-O'Carroll 2019 **Level II**, n=68, JS3). There was an increased time to rescue medication with SR oxycodone/naloxone. Side effects were common and similar in quantity between SR tapentadol (70%) and SR oxycodone/naloxone (71%), although more patients received intraoperative antiemetic prophylaxis in the oxycodone group (71%) vs the tapentadol group (42%) including dexamethasone (43% vs 24%).

KEY MESSAGES

1. Oral combinations of paracetamol/ibuprofen provide superior analgesia to paracetamol/codeine; both combinations are more effective than the individual medicines and have a dose-response effect (**S**) (**Level I** [Cochrane Review]).
2. Oral combinations of paracetamol/tramadol are more effective than the individual medicines and have a dose-response effect (**U**) (**Level I**).
3. NSAIDs given parenterally or rectally are not more effective and do not result in fewer adverse effects than the same medicines given orally (**U**) (**Level I**).
4. The formulation of oral NSAIDs (eg fast acting, sodium vs potassium salt) can greatly affect their efficacy (**N**) (**Level I**).
5. Early postoperative oral administration of paracetamol results in highly variable plasma concentrations that may remain subtherapeutic in some patients (**U**) (**Level II**). However, no difference in clinical efficacy to IV administration is seen in hip and knee arthroplasty (**N**) (**Level I**), Caesarean section (**N**) (**Level II**) or laparoscopic cholecystectomy (**N**) (**Level II**).

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

☑ Other than in the treatment of severe acute pain, and providing there are no contraindications to its use, the oral route is the route of choice for the administration of most analgesic medicines (**U**).

☑ Immediate-release oral opioids should be used for breakthrough pain and for titration of slow-release opioids (**U**).

☑ Slow-release opioid preparations (particularly conventional opioids including methadone and transdermal fentanyl)) are not recommended for the management of opioid-naive patients with acute pain because of difficulties in short-term dose adjustments needed for titration and increased risk of OIVI. In some patients with prolonged post-operative and post-traumatic states, their use may be appropriate on a temporary basis with preference for use of atypical opioids (**S**).

☑ Slow-release oral opioid preparations should only be given at set time intervals (**U**).

5.2 | Intravenous route

Analgesic medicines given by the IV route have a more rapid onset of action compared with most other routes of administration.

5.2.1 | Paracetamol

IV paracetamol 1,000 mg is an effective analgesic after surgery with an $NNT_{50\%}$ of 4.0 (95%CI 3.5 to 4.8) over 4 h and an $NNT_{50\%}$ of 5.3 (95%CI 4.2 to 6.7) over 6 h (Tzortzopoulou 2011 **Level I** [Cochrane], 36 RCTs, n=3,896). As an adjunct to opioid analgesia, opioid requirements are reduced by 30% over 4 h after a single IV dose. For orthopaedic surgery specifically, IV paracetamol has similar benefits (Jebaraj 2013 **Level I** [PRISMA], 8 RCTs, n unspecified). After Caesarean section, IV paracetamol reduces opioid consumption (SMD -0.46; 95%CI -0.83 to -0.09) and pain (SMD -0.72; 95%CI -1.31 to -0.13) (Ng 2019 **Level I** [PRISMA], 7 RCTs, n=467).

IV paracetamol perioperatively reduces PONV when administered before incision and to a lesser extent before recovery from anaesthesia (Apfel 2013 **Level I** [PRISMA], 30 RCTs, n=2,364). This effect is correlated to pain relief achieved but not to reduced opioid consumption. IV paracetamol given within 1 h prior to incision is more effective than post incision in reducing pain at 1 h (MD -0.50; 95%CI -0.98 to -0.02) and 2 h (MD -0.34; 95%CI - 0.67 to -0.01), 24 h opioid consumption (SMD of -0.52; 95% CI -0.98 to -0.06) and PONV (RR 0.50; 95%CI 0.31 to 0.83) (Doleman 2015 **Level I** [PRISMA], 7 RCTs, n=544).

Dosing of IV paracetamol in bariatric patients remains undefined; in a study of adolescents and young adults undergoing bariatric surgery (mean BMI 46) plasma concentrations of paracetamol were undetectable 2 h after 1,000 mg dosing (Hakim 2019 **Level IV PK**).

The use of IV propacetamol and IV paracetamol and hypotension has been reported (with variable definitions: systolic vs MAP change: absolute value or 15-20% decrease) in mostly critically ill (often cardiac) patients (14/19 studies) (Maxwell 2019 **Level IV SR**, 5 RCTs & 14 studies, n=3,470). Hypotension may be more prevalent with IV vs NG paracetamol in critically ill patients (Kelly 2016 **Level II**, n=50, JS 3). Clinically significant hypotension appears to be an issue when patients have cardiovascular compromise prior to administration; importantly regular qid dosing with IV paracetamol exposes the patient to 0.23 mg/kg/d mannitol (with its diuretic and secondary hypotensive effect) (Chiam 2015 **NR**). Within the above SR, IV paracetamol (with mannitol excipient) vs mannitol vs placebo reduced MAP by only 1.8 mmHg in healthy adult volunteers (Chiam 2016 **Level II**, n=24, JS 5).

Due to the good bioavailability and tolerability of oral paracetamol, the use of the IV form should be limited to clinical circumstances where use of the enteral route is not appropriate.

There does not appear to be a clinically significant difference in efficacy between IV and oral paracetamol (see Section 5.1.1 above).

5.2.2 | Nonselective NSAIDs and coxibs

Compared with oral NSAIDs there are only a relatively limited number of nsNSAIDs or coxibs available for IV injection at present, although this number is growing.

IV/IM Ketorolac is an effective adjunct of multimodal analgesia with more beneficial effect of 60 mg than 30 mg and a greater opioid-sparing effect with IM than IV administration (MD -2.13 mg; 95%CI -4.1 to -0.21 mg) (De Oliveira 2012 **Level I** [PRISMA] 13 RCTs, n=782).

IV Ibuprofen in doses of 400 and 800 mg every 6 h postoperatively as an adjunct to IV PCA morphine resulted in improved analgesia, but only the 800 mg dose showed an opioid-sparing

effect (Southworth 2009 **Level II**, n=406, JS 3). IV Ibuprofen 800 mg has also shown efficacy after orthopaedic surgery (Singla 2010a **Level II**, n=185, JS 3), abdominal hysterectomy (Kroll 2011 **Level II**, n=319, JS 3) and laparoscopic cholecystectomy (Ekinci 2019, **Level II**, n=90, JS 4). IV ibuprofen at 800 mg was more effective at relieving renal colic pain at 15, 30 and 60 min than IV ketorolac 30 mg (Forouzanfar 2019 **Level II**, n=240, JS=4).

In single doses as the sole analgesic agent, the COX-2 selective medicine IV/IM parecoxib has been shown to be effective in a dose-dependent way (Lloyd 2009 **Level I** [Cochrane] 7 RCTs, n=1,446); $NNT_{50\%}$ compared with placebo are for 10 mg 3.1 (95%CI 2.4 to 4.5), 20 mg 2.4 (95%CI 2.1 to 2.8) and 40 mg 1.8 (95%CI 1.5 to 2.3).

A single dose of IV diclofenac is effective for postoperative pain after a variety of surgeries (McNicol 2018 **Level I** [Cochrane], 8 studies, n=1,756).

IV dexketoprofen 50 mg resulted in less IV PCA morphine usage after laparoscopic cholecystectomy over 24 h than 75 mg of IV diclofenac (18 vs 46mg) (Anil 2016, **Level II**, n=60, JS 2).

IV meloxicam used as a rescue for moderate-severe pain after bunionectomy reduced pain intensity and need for further rescue opioids vs placebo (Pollak 2018, **Level II**, n=201, JS=5). IV meloxicam (15, 30 and 60 mg) had a faster onset of and then longer-lasting analgesia than a single dose of PO ibuprofen (400 mg) after dental impaction surgery but IV meloxicam 15mg did not provide superior analgesia to PO ibuprofen 400 mg from 2 to 8 h post administration (Christensen 2018 **Level II**, n=230, JS 5).

IV (or IM) lornoxicam was effective for the treatment of acute renal cholic pain with no significant difference in efficacy between routes (Soylu 2019, **Level II**, n=51, JS 2).

IV flurbiprofen given 15 min before mastectomy and 6 h post reduced pain at 2 h but not at later points of time nor did it reduce overall opioid consumption. The number of patients with chronic postsurgical pain at 6 mth was reduced vs placebo (3.3% vs 26.7%) (Sun 2013, **Level II**, n=60, JS 5).

IV indomethacin is only approved for use in closure of a patent ductus arteriosus in neonates and there are no recent trials in humans for acute pain.

In most cases the route of administration does not seem to alter efficacy. IV NSAIDs or COX-2 selective inhibitors are more expensive than oral or rectal NSAIDs, although their efficacy and likelihood of adverse effects is similar (Tramer 1998 **Level I**, 26 RCTs, n=2,225). For renal colic, the onset of action of NSAIDs is faster when given IV vs IM, PO or PR administration. A comparison of rectal diclofenac and IV parecoxib showed no difference in pain relief, adverse effects or rescue analgesic requirements after laparoscopic sterilisation (Ng 2008 **Level II**, n=55, JS 5). Efficacy and times to onset of analgesia are similar with IV and IM parecoxib after oral surgery (Daniels 2001 **Level II**, n=304, JS 5).

5.2.3 | Conventional and atypical opioids

5.2.3.1 | Intermittent intravenous bolus doses

Titration of opioids for severe acute pain is best achieved using intermittent IV bolus doses as it allows more rapid titration of effect and avoids the uncertainty of medicine absorption by other routes. The optimal doses and dose intervals for this technique have not yet been established.

In a postoperative care unit, 2 mg or 3 mg bolus doses of morphine, given at 5 min intervals prn and with no limitation on the number of bolus doses administered, was more effective and resulted in no greater incidence of adverse effects than the same doses given at 10 min intervals or when a maximum of five doses only was allowed (Aubrun 2001 **Level III-3**, n=1,600; Aubrun 2012 **NR**).

In prehospital care, an initial dose of 0.1 mg/kg IV morphine was more effective than 0.05 mg/kg followed by half the initial dose at 5 min prn (VAS ≤30/100: 40% vs 17% at 10 min) (Bounes 2008 **Level II**, n=106, JS 5). In a comparison of IV fentanyl and morphine bolus doses every 5 min as needed for prehospital analgesia over a period of just 30 min, no difference was found in pain relief or incidence of adverse effects (Galinski 2005 **Level II**, n=54, JS 5).

A single dose of IV morphine 10 mg vs IV paracetamol 1 g in moderate to severe traumatic limb pain had a similar analgesic effect with significantly more adverse effects in the morphine arm; approximately one-third of patients in each group required rescue analgesia of titrated IV morphine (Craig 2012 **Level II**, n=55, JS 4).

Titration of IV bolus doses of an opioid is frequently accomplished using a treatment algorithm to guide management, which includes age-based bolus doses of opioid given at 3- or 5-min intervals prn (Macintyre 2015 **NR**).

Approximately one-third of patients given a 1 mg single bolus dose of hydromorphone (followed by another dose at 15 min if needed) desaturated below 95% (Chang 2009 **Level IV**, n=269). As a standardised therapy, a single 2 mg dose of IV hydromorphone in adults <65 y old resulted in more patients (11.6%; 95%CI 1.8% to 21.1%) not requiring further pain relief after 30 min vs standard care (any IV opioid in any dose) (Chang 2013 **Level II**, n=350, JS 4). Adverse effects of pruritus and nausea were significantly more common in the hydromorphone group, who received double the morphine equivalent dose; however, all patients received oxygen via nasal prongs to prevent desaturation. Comparing the 2 mg hydromorphone bolus to a "*1+1*" titration protocol, both showed similar efficacy and safety with an opioid-sparing effect noted in the titration group, where 42.3% required only the first bolus (Chang 2013 **Level II**, n=350, JS 4).

For acute traumatic pain in an ED setting, sufentanil given as an IV bolus of 0.15 mcg/kg followed by 0.075 mcg/kg every 3 min was not more effective than IV morphine 0.15 mg/kg followed by 0.075 mg/kg and less effective at 6 h (Bounes 2010 **Level II**, n=108, JS 5).

IV tramadol was found to be more effective than the same dose given orally after dental surgery, however it was recognised that the difference in bioavailability of a single dose of tramadol may be up to 30% (Ong 2005 **Level II**, n=72, JS 5). Large IV bolus doses of tramadol can result in a high incidence of emetic symptoms. This effect can be reduced by slowing delivery of the medicine or, in the surgical setting, by giving it before the patient emerges from general anaesthesia (Pang 2000 **Level II**, n=60, JS 5).

Comparing intermittent oxycodone with other opioids reveals oxycodone is more effective than fentanyl (5 of 6 RCTs) and sufentanil (1 of 3 RCTs) and equivalent to morphine (Raff 2019 **Level I**, 6 RCTs, n=466 [vs fentanyl]; 3 RCTs, n=287 [vs sufentanil]; 2 RCTs, n=135 [vs morphine]). There was more nausea (3 of 6 RCTs) and vomiting (1 of 6 RCTs) reported in individual RCTs with oxycodone vs fentanyl.

5.2.3.2 | Continuous infusions

A continuous infusion of opioids results in constant blood levels after approximately four to five half-lives of the opioid used. The aim of an infusion is to avoid the problems associated with the peaks and troughs of intermittent administration techniques. However, the variation in patient response, the changing intensity of acute pain with time and the delay between any alteration of the infusion rate and its subsequent effect, may result in inadequate treatment of incident pain or delayed onset of adverse effects, such as respiratory depression. Very close monitoring is therefore essential with continuous infusions of opioids.

Compared with PCA, continuous IV opioid infusions alone in a general ward setting resulted in a five-fold increase in the incidence of respiratory depression (Schug 1993 **Level IV**, n=3,016).

Furthermore, morphine infusion 0.5 mg/h vs PCA alone after abdominal hysterectomy resulted in higher opioid requirements, pain intensity and adverse effects including emesis and dizziness (Chen 2011 **Level II**, n=60, JS 4).

PCA with a continuous background infusion increases the risk of respiratory events in comparison to PCA alone in adults only (OR 10.2; 95%CI 3 to 35) (George 2010 **Level I**, 12 RCTs [adults], n=674). Despite these safety concerns, a continuous infusion of low-dose oxycodone (0.01 mg/kg/h) in addition to PCA vs PCA alone reduced VAS at 1, 6 and 24 h after laparoscopic radical cervical surgery without altering satisfaction, PONV or FAS (Zhu 2019 **Level II,** n=90. JS 4).

KEY MESSAGES

1. Intravenous paracetamol is more effective in reducing pain, opioid consumption and PONV when given prior versus after surgical incision (**U**) (**Level I** [PRISMA]).
2. The onset of analgesia is faster when NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
3. Continuous intravenous infusion of opioids in the general-ward setting is associated with an increased risk of respiratory depression compared with other methods of parenteral opioid administration (**U**) (**Level IV**).

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

☑ Titration of opioids for severe acute pain is best achieved using intermittent intravenous bolus doses as it allows more rapid titration of effect and avoids the uncertainty of medicine absorption by other routes (**U**).

5.3 | Intramuscular and subcutaneous routes

IM and SC injections of analgesic agents (usually opioids) are still commonly employed for the treatment of moderate or severe pain. Absorption may be impaired in conditions of poor perfusion (eg in hypovolaemia, shock, hypothermia or immobility), leading to inadequate early analgesia and late absorption of the medicine depot when perfusion is restored.

5.3.1 | Nonselective NSAIDs and coxibs

Compared to oral NSAIDs there are only a relatively limited number of NSAIDs or COX-2 selective inhibitors available for IM injection at present and fewer still where Level I evidence for individual efficacy is available; IM ketorolac (Lloyd 2009 **Level I** [Cochrane], 7 RCTs, n=1,446) and IM parecoxib are effective analgesic agents (De Oliveira 2012 **Level I** [PRISMA], 13 RCTs, n=782).

IM diclofenac administration has been associated with rare soft tissue necrosis, particularly in obese patients where the needle may not be long enough to reach the muscle (Dadaci 2015 **Level IV**, n=17 [mean BMI 42]).

5.3.2 | Conventional and atypical opioids

5.3.2.1 | Intramuscular

IM injection of opioids has been the traditional mainstay of postoperative pain management despite the fact that surveys have repeatedly shown that pain relief with prn IM opioids is frequently inadequate. Although IM opioids are often perceived to be safer than opioids given by other parenteral routes, the incidence of respiratory depression reported in a review ranged from 0.8% (0.2 to 2.5) to 37.0% (22.6 to 45.9) using respiratory rate and oxygen saturation, respectively, as indicators (Cashman 2004 **Level IV SR**, 165 studies, n 20,000). For comparisons with PCA and epidural analgesia see Chapter 6; for comments on respiratory rate as an unreliable indicator of respiratory depression see Section 4.3.1.4.

Single doses of IM morphine 10 mg (McQuay 1999 **Level I**, 15 RCTs, n=1,046) and IM pethidine (meperidine) 100 mg (Smith 2000 **Level I**, 8 RCTs, n=364) have been shown to be effective in the initial treatment of moderate to severe postoperative pain.

The use of an algorithm allowing administration of IM morphine or pethidine hourly prn and requiring frequent assessments of pain and sedation, led to significant improvements in pain relief vs longer dose interval prn regimens (Gould 1992, **Level III-3**, n=235).

The quality of pain relief is lower with intermittent IM regimens vs IV PCA (McNicol 2015 **Level I** [Cochrane], 49 RCTs, n=3,412).

5.3.2.2 | Subcutaneous

The placement of SC plastic cannulae or 'butterfly' needles allows the use of intermittent injections without repeated skin punctures. In healthy volunteers, median time to reach maximum serum concentration (T_{max}) after SC injection of morphine was 15 min (Stuart-Harris 2000 **PK**). In elderly adults, mean T_{max} after a single SC injection of morphine was 15.9 min and the rate of absorption and the variability in the rate of absorption were similar to those reported after IM injection (Semple 1997 **Level IV PK**, n=22). In patients given a second and same dose of SC morphine 5 h after the first, it was shown that there can also be significant within-patient variations in absorption (Upton 2006 **PK**). The absorption rate of SC fentanyl was found to be similar to that of SC morphine with a significantly longer terminal half-life for fentanyl (10 h vs

2.1 h) (Capper 2010 **Level IV PK**). For SC oxycodone peak venous concentrations were seen after 22.10 min (±18.0) in healthy controls however, despite similar onset, peak plasma concentrations were markedly reduced in critically ill ICU patients vs these healthy volunteers (Krishnamurthy 2012 **Level IV EH PK**). Similarly, SC tramadol in healthy volunteers had a time to peak venous concentration of 20.6 min (±18.8), however, unlike oxycodone, plasma concentrations were not reduced in critically ill patients vs healthy controls (Dooney 2014 **Level IV EH PK**).

In children, there was no difference in rate of onset, analgesic effect and adverse effects with use of morphine SC vs morphine IM and there was a significantly higher patient preference for the SC route (Cooper 1996 **Level II**, n=55, JS 4; Lamacraft 1997 **Level IV**, n=220 [paediatric]). Also, IM and IV administration of morphine (along with IN fentanyl) were found to be equally effective with no significant differences in FLACC scores for postoperative pain in children (Hippard 2012 **Level II**, n=171, JS 5). A comparison of IM and SC morphine in patients after Caesarean section reported no significant differences in adverse effects, patient satisfaction or pain relief at rest, but lower pain scores after SC administration at 12, 16 and 20 h after surgery (Safavi 2007 **Level II**, n=60, JS 3).

A comparison of the same dose of morphine given as either a single SC or IV injection, showed that use of the IV route resulted in more rapid onset of analgesia (5 min IV vs 20 min SC) and better pain relief between 5 and 25 min after injection but also led to higher sedation scores up to 30 min after injection and higher $PaCO_2$ (Tveita 2008 **Level II**, n=40, JS 5). However, a comparison of intermittent IV and SC doses of hydromorphone (the doses adjusted in a similar manner according to the patients' pain scores and given at intervals of no less than 3 h) showed no differences in pain relief or adverse effects over a 48 h period after surgery; pain relief was the same but the incidence of pruritus lower vs PCA hydromorphone (Bell 2007 **Level II**, n=130, JS 3).

Continuous infusions of opioids via the SC route are as effective as continuous IV infusions (Semple 1996 **Level II**, n=30, JS 2).

Treatment algorithms for intermittent SC morphine, oxycodone and fentanyl using age-based dosing are published (Macintyre 2015 **GL**).

KEY MESSAGE

1. Intermittent subcutaneous morphine injections are as effective as intramuscular injections and have better patient acceptance (**U**) (**Level II**).

5.4 | Transdermal route

Not all medications applied topically have a local, peripheral action. The term 'transdermal' will be used to describe medicines that, while applied to the skin, have predominantly central effects that are the result of systemic absorption of the medicine. The term 'topical' will be used in the discussion of medicines – primarily NSAIDs – that are applied topically (including to skin) but have a predominantly peripheral effect. See Sections 5.4.2 and 5.5 below.

5.4.1 | Opioids

The stratum corneum of the epidermis forms a major barrier to the entry of medicines. However, medicines such fentanyl (Sathyan 2005 **PK**) and buprenorphine (Skaer 2006 **NR**) are available as TD preparations. The analgesic effects are a result of systemic effects rather than local peripheral opioid analgesia (Worrich 2007 **Level IV EH**, n=12).

5.4.1.1 | Transdermal fentanyl

TD fentanyl is commonly used in the management of cancer and chronic pain. Due to the formation of a significant intradermal reservoir, onset and offset times of this preparation are slow and this makes short-term titration impossible. The time to first analgesic effect is generally between 12 and 24 h after initial patch application and after the patch is removed, serum fentanyl concentrations decline with a mean terminal half-life of 17 h (Lotsch 2013 **NR**).

TD fentanyl patches are currently specifically contraindicated for the management of acute or postoperative pain in many countries and for use in opioid naïve patients (FDA 2019a **GL**; MIMS 2019 **GL**; emc 2014 **GL**).

Nevertheless, TD fentanyl patches have been trialled in the management of postoperative pain. For example after THA (Minville 2008 **Level II**, n=30, JS 2), TKA (Sathitkarnmanee 2014 **Level II**, n=40, JS 5; Abrisham 2014 **Level II**, n=40, JS 5), foot surgery (Merivirta 2015 **Level II**, n = 60, JS 5) and hysterectomy (Sandler 1994 **Level II**, n=120, JS 4), preoperative use reduced postoperative pain scores and supplementary opioid or other analgesic requirements. However, the wide variability of clinical effect (Peng 1999 **NR**) and the high incidence of respiratory depression that can occur in the postoperative setting (Bulow 1995 **Level II**, n=24 [then terminated for safety concerns], JS 4; Sandler 1994 **Level II**, n=120 [9 patients withdrawn due to severe respiratory compromise], JS 4) make TD fentanyl preparations unsuitable for acute pain management. In line with these concerns and reported fatal outcomes with perioperative use, guidelines advise against the use of transdermal fentanyl in acute pain management (ANZCA 2018 **GL**). There are concerns that studies in this indication are still undertaken and published (Nair 2017 **NR**).

Transdermal fentanyl for the management of acute pain as a PCA device is also available. See Section 6.5.5.

5.4.1.2 | Transdermal buprenorphine

TD buprenorphine patches are available for the management of chronic and cancer pain (Plosker 2011 **NR**). After application of the patch, steady state is achieved by 3 d; after removal of the patch, buprenorphine concentrations decrease with a terminal half-life of 12 h (range 10 to 24 h). High doses of buprenorphine patch (above 40 mcg/hr) may cause QT wave prolongation that is reversible with mu-opioid antagonists; clinical significance of this is unclear (Merivirta 2015 **Level III-1**, n=110). As with other chronic preoperative opioid use, patients on TD buprenorphine

preoperatively and continued through the perioperative period show higher opioid requirements and report worse pain than opioid-naïve controls (Martin 2019 **Level-III 2**, n=19).

TD buprenorphine showed a dose-dependent analgesic effect with no serious adverse effects in gynaecological postoperative patients Setti 2012 **Level II**, n=47, JS 4). Use of TD buprenorphine for acute pain management in spinal surgery was found to be noninferior to oral tramadol (Kim 2017 **Level II**, n=48, JS 3) and superior to placebo (Niyogi 2017 **Level II**, n=70, JS 5). TD buprenorphine in abdominal surgery was associated with superior analgesia but comparable adverse effect profile to placebo (Kumar 2016 **Level II**, n=90, JS 5). After surgical repair of hip fractures, TD buprenorphine 10 mcg/h vs PO tramadol 50 mg TDS provided better analgesia from 24 h to POD 7 with lower rescue requirements and less PONV and higher patient satisfaction (Desai 2017 **Level II**, n=5, JS 3). After hallux valgus repair, TD buprenorphine (10 mcg/h) provided superior analgesia vs celecoxib 400 mg/d and comparable analgesia to IV flurbiprofen 50 mg BD with highest patient satisfaction (Xu 2018 **Level II**, n=90, JS 3).

Inherent difficulty in titrating the dose according to changing analgesic requirement should be considered when using TD buprenorphine for acute pain management.

5.4.2 | Other medicines

There is no basis to recommend routine use of TD nicotine patches for acute pain management in view of no demonstrable effect on analgesia (Matthews 2016 **Level I** [Cochrane], 9 RCTs, n=666).

TD administration of ketamine as a patch delivering 25 mg over 24 h reduced rescue analgesic consumption after gynaecological surgery (Azevedo 2000 **Level II**, n=52, JS 4).

TD melatonin 7 mg patch was trialled for perioperative pain management in lumbar laminectomy and was found to be superior to placebo in analgesia and reduced supplementary analgesia consumption, but was associated with significant sedation (Esmat 2016 **Level II**, n = 75, JS 5).

TD diclofenac patches have been applied in nonsurgical settings for systemic (non-topical) analgesia. They have been trialled for acute pain management after dental surgery and were found to be comparable in effect to oral diclofenac (Krishnan 2015 **Level II**, n = 40, JS 2; Diwan 2019 **Level III-1**, n=20, JS 2). Another study found it to be noninferior to IM diclofenac but with a longer duration of action (Perepa 2017 **Level III-1**, n=60, JS 2).

KEY MESSAGES

1. Transdermal buprenorphine reduces postoperative pain with a low rate of adverse effects (**N**) (**Level II**)
2. Transdermal fentanyl (except for iontophoretic patient-controlled transdermal devices) should not be used in the management of acute pain because of safety concerns and difficulties in short-term dose adjustments needed for titration (**S**) (**Level IV**).

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

☑ Transdermal fentanyl preparations should not be used in opioid-naïve patients because of safety concerns and, in most countries, the lack of regulatory approval for use in other than opioid-tolerant patients (**U**).

5.5 | Transmucosal routes

Medicines administered by transmucosal routes (rectal, IN, SL, buccal and pulmonary) are rapidly absorbed directly into the systemic circulation, thus bypassing hepatic first-pass metabolism. The medicines most commonly administered by transmucosal routes in acute pain management are the more lipid-soluble opioids.

5.5.1 | Rectal route

Rectal administration (PR) of medicines is useful when other routes are unavailable. It results in uptake into the submucosal venous plexus of the rectum, which drains into the inferior, middle and superior rectal veins. Medicine absorbed from the lower half of the rectum will pass into the inferior and middle rectal veins and then the inferior vena cava, bypassing the portal system. Any portion of the medicine absorbed into the superior rectal vein enters the portal system, subjecting it to hepatic first-pass metabolism.

Potential problems with the administration of medicine by the rectal route relate to the variability of absorption, possible rectal irritation and cultural factors. Some suppositories should not be divided as the medicine may not be evenly distributed in the preparation. Contraindications to the use of this route include pre-existing rectal lesions, recent colorectal surgery, severe thrombocytopaenia and immune suppression. Whether the medicine is administered to a patient who is awake or under anaesthesia, it is important to obtain prior consent from the patient or guardian.

5.5.1.1 | Paracetamol

Paracetamol is effective when given by the rectal route (Romsing 2002 **Level I**, 8 RCTs, n=640), although absorption is slower and less predictable than after oral administration with bioavailability between 24 and 98% (Oscier 2009 **NR**). In children, it is also less effective than the same dose administered by the oral route (Anderson 1996 **Level II**, n=100, JS 4; Anderson 1999 **Level IV**, n=120). However, in children aged 3 to 36 mth, there were no differences in T_{max}, C_{max} and total medicine exposure between rectal and oral administration, possibly due to slower gastric emptying in this age group (Walson 2013 **Level II**, n=30, JS 2).

Doses of 1 g PR after cardiac surgery (Holmer Pettersson 2006 **Level II**, n=48, JS 2) and hysterectomy (Kvalsvik 2003 **Level II**, n=60, JS 4) as well as 2 g given PR to patients undergoing laparoscopic gynaecological surgery (Hahn 2000 **Level IV**, n=23) resulted in subtherapeutic blood levels, although levels may increase to within the therapeutic range after repeat administration (Holmer Pettersson 2006 **Level II**, n=48, JS 2). When available, the oral route is therefore preferable.

Higher doses may be more effective. Blood concentrations in the therapeutic range have been reported in adults after PR doses of 40 mg/kg but not 20 mg/kg (Beck 2000 **Level IV**, n=65) and sustained therapeutic levels followed the PR use of 35 mg/kg and 45 mg/kg, but not 15 mg/kg and 25 mg/kg (Stocker 2001 **Level IV PK**, n=10).

In children, initial PR doses of 40 mg/kg followed by 20 mg/kg also provided therapeutic blood levels without evidence of accumulation (Birmingham 2001 **Level IV PK**, n=16). In children after ophthalmic surgery, 20 and 40 mg/kg PR were equally effective and superior to placebo (Gandhi 2012 **Level II**, n=135, JS 4). PR paracetamol 30 mg/kg provided equivalent analgesia postoperatively vs peritonsillar infiltration of bupivacaine (Dahi-Taleghani 2011 **Level III-1**, n=110). For inguinal herniorrhaphy, administration of PR paracetamol in children appeared to be as effective as IV paracetamol, both in postoperative analgesia and reduction in nausea and

vomiting (Khalili 2016 **Level II**, n=120, JS 3). However, addition of PR paracetamol to caudal epidural block did not result in a meaningful improvement vs caudal block alone for the same procedure (Nnaji 2017 **Level II**, n=87, JS 4).

5.5.1.2 | NSAIDs

Rectal administration of nsNSAIDs provides effective analgesia after a variety of surgical procedures (Tramer 1998 **Level I**, 26 RCTs, n=2,225). This continues to be supported by a number of subsequent studies (Karaman 2016 **Level II**, n=82, JS 5; Nadeem 2016 **Level II**, n=60, JS 3; Pazouki 2015 **Level III-1**, n=130). A study comparing PR diclofenac vs PR indomethacin for postepisiotomy pain found both to be similarly effective but diclofenac appeared to have a shorter duration of action (Rezaei 2014 **Level II**, n=90, JS 3).

Local effects such as rectal irritation and diarrhoea have been reported following use of the rectal route but other commonly reported adverse effects such as nausea, vomiting, dizziness and indigestion are independent of the route of administration (Tramer 1998 **Level I**, 26 RCTs, n=2,225). Rectal NSAIDs may be particularly useful as a part of multimodal analgesia in cases where an enteral route cannot be established, such as immediately after upper GI surgery (Bameshki 2015 **Level II**, n=90, JS 2).

In comparison to PR paracetamol, PR NSAIDs were more efficacious (Nikooseresht 2016 **Level II**, n=102, JS 1; Ubale 2016 **Level II**, n=60, JS 2). The synergistic benefit of combining paracetamol with an NSAID was also confirmed for the rectal route. After an abdominal hysterectomy PR paracetamol/PR diclofenac vs PR diclofenac only or vs the placebo group resulted in superior analgesia and significantly reduced rescue opioid requirements (Samimi Sede 2014 **Level II**, n=90, JS 4). PR NSAIDs showed superior analgesic effect when combined with paracetamol in adults (Bakhsha 2016 **Level III-1**, n=90) and children (Yallapragada 2016 **Level II**, n=60, JS 2), and also with other analgesics such as pentazocine (Olateju 2016 **Level II**, n=116, JS 5).

To provide analgesia after gynaecological procedures, PR indomethacin was superior to placebo, but inferior to intrauterine lignocaine for hysteroscopy (Senturk 2016 **Level II**, n=206, JS 4), and conferred no advantage over placebo after endometrial biopsies (Kaya 2015 **Level II**, n=90, JS 2; Telli 2014 **Level II**, n=151, JS 4).

In paediatric setting, addition of PR diclofenac to caudal epidural block for inguinal herniorrhaphy did not result in improved analgesia vs caudal block alone (Nnaji 2017, **Level II**, n=87, JS 4).

The role of PR diclofenac appears well established for periprocedural analgesia in ultrasound-guided prostate biopsy, where it was noted to be superior to placebo but inferior to the gold standard of periprostatic nerve block (Lee 2014a **Level I**, 106 RCTs, n unspecified). Administration 45 to 60 min prior to procedure was recommended. While the same systematic review found some benefit in combining PR diclofenac with periprostatic block, a subsequent RCT failed to find additional benefit with this approach vs periprostatic block alone (Ooi 2014 **Level II**, n=96, JS 4).

In the Emergency Department (ED) setting, PR indomethacin for acute renal colic was found to provide analgesia slightly inferior to PR morphine 10mg at 20 min and equivalent afterwards (Zamanian 2016 **Level II**, n=158, JS 5). PR indomethacin was inferior to IM tramadol 50 mg in a similar setting, with significantly higher need for rescue analgesia (Shirazi 2015 **Level II**, n=120, JS 3).

5.5.1.3 | Opioids

In most instances, similar doses of rectal and oral opioids are administered, although there may be differences in bioavailability and the time to peak analgesic effect for the reasons outlined above; rectal opioids play primarily a role in cancer-pain management (Kestenbaum 2014 **NR**). Here, no differences in either pain relief or adverse effects were found in a comparison of oral

and rectally administered tramadol (Mercadante 2005 **Level II**, n=60, JS 5). Analgesic effects of rectal opioids in acute procedural pain settings have been demonstrated (Imani 2018 **Level II**, n=90, JS 2; Rahimi 2016 **Level II**, n=70, JS 4); advantages of this approach are unclear if oral or parenteral routes exist.

5.5.1.4 | Ketamine

Rectal ketamine is advantageous for paediatric population, when a parenteral access may not be feasible and a degree of sedation in addition to analgesia is desirable. PR ketamine 2 mg/kg provided comparable analgesia to IV ketamine 0.5 mg/kg when delivered intraoperatively during tonsillectomy in a paediatric population (Yenigun 2015 **Level II**, n=120, JS 1). Higher doses of PR ketamine (4 mg/kg, 6 mg/kg and 8 mg/kg) were trialled in addition to 0.5 mg/kg midazolam for analgo-sedation for outpatient burns dressing changes in children, and it was noted that the higher dose of 8 mg/kg was associated with prolonged recovery time and adverse events (Grossmann 2019 **Level II**, n=90, JS 5); a dose of ketamine 6 mg/kg with midazolam 0.5 mg/kg appeared to provide the best balance between the degree of analgo-sedation and adverse effects.

5.5.2 | Intranasal route

A variety of different medicines can be administered by the IN route, including analgesic medicines. The human nasal mucosa contains medicine-metabolising enzymes but the extent and clinical significance of human nasal first-pass metabolism is unknown (Dale 2002 **NR**). It is suggested that the volume of a dose of any medicine given IN should not exceed 150 microL in order to avoid run-off into the pharynx (Dale 2002 **NR**). Absorption through the nasal mucosa depends on both the lipid solubility and degree of ionisation of the medicine (Shelley 2008 **NR**).

5.5.2.1 | NSAIDs

IN ketorolac has also been shown to be effective; after major surgery 31.5 mg (Singla 2010b **Level II**, n=321, JS 5) but not 10 mg IN ketorolac resulted in significant opioid-sparing and better pain relief (Moodie 2008 **Level II**, n=127, JS 5). This was also found after oral surgery (Grant 2010 **Level II**, n=80, JS 5). IN ketorolac 31.5mg was also found to be superior to placebo and at least as effective as IN sumatriptan for treatment of acute migraine (Rao 2016 **Level II**, n=72, JS 5).

5.5.2.2 | Opioids

Single-dose pharmacokinetic data in healthy volunteers for a number of opioids administered by the IN route have been published (Dale 2002 **NR**; Grassin-Delyle 2012 **NR**). The mean bioavailabilities and T_{max} reported were fentanyl 71% and 5 min; sufentanil 78% and 10 min; alfentanil 65% and 9 min; butorphanol 71% and 49 min; oxycodone 46% and 25 min; and buprenorphine 48% and 30 min. An analysis of multiple trials for IN fentanyl showed a bioavailability of 89% with an onset of analgesia at 2–5 min (Lotsch 2013 **NR**). Hydromorphone, when given to volunteers in doses of 1 mg or 2 mg IN vs 2 mg IV, had median T_{max} after the 1 mg and 2 mg IN doses of 20 min and 25 min respectively and an overall bioavailability of only 55% (Coda 2003 **PK**).

Clinical data exist for the effectiveness of several opioids administered via the IN route. IN fentanyl must be provided in a sufficient concentration to deliver an analgesic dose in a volume that does not exceed the nasal capacity. It is an effective treatment for breakthrough pain in cancer patients (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1,699) and has similar analgesic efficacy to IV administration (Hansen 2012 **Level I** [PRISMA], 3 RCTs, n=301). IN fentanyl spray vs oral

transmucosal fentanyl, fentanyl buccal tablet and oral morphine for the treatment of breakthrough cancer pain provides the greatest and fastest improvement (Vissers 2010 **Level I**, 6 RCTs, n=594) (see also Section 8.9.3.2). It provides also similar or better analgesia than other opioids or routes of administration in children without compromising safety (Mudd 2011 **Level IV SR**, 12 studies, n=1,743). Effectiveness of IN fentanyl for paediatric acute pain management is confirmed by two systematic reviews (Murphy 2014 **Level I** [Cochrane], 3 RCTs, n=313; Setlur 2018 **Level I** [PRISMA], 10 RCTs, n=5,945) (2 RCTs overlap) (see also Section 10.9.1.2). When IN fentanyl was used in the prehospital setting, there was no difference in effectiveness vs IV morphine (Rickard 2007 **Level II**, n=258, JS 3) and it has also shown effectiveness for burns dressing changes (Nederveld 2017 **Level III-2**, n=64) (see Section 8.5.3.1). In paediatric sickle cell crisis, it was superior to placebo at 20 min, but not earlier or later (Fein 2017 **Level II**, n=49, JS 5). Adding IN fentanyl to nitrous oxide 70% for paediatric procedural sedation does not confer any advantage (Seiler 2019 **Level II**, n=399, JS 5).

Two studies have examined the role of IN fentanyl delivered via postoperative nasal packing foam soaked in fentanyl solution after nasal passage operation (Kim 2018b **Level II**, n=152, JS 5) and nasal fracture repair (Kim 2019c **Level II**, n=65, JS 5). In both cases superior analgesia vs placebo lasting for up to 24 h was achieved without an increase in adverse events. The authors postulate a significant local analgesic effect in addition to systemic absorption.

Analgesic efficacy has also been shown for IN butorphanol (Wermeling 2005 **Level II**, n=60, JS 4; Abboud 1991 **Level II**, n=186, JS 5), IN pethidine (Striebel 1995 **Level II**, n=44, JS 2; Striebel 1993 **Level II**, n=60, JS 5), IN morphine (Stoker 2008 **Level II**, n=187, JS 5), IN hydromorphone (Wermeling 2010 **Level IV**, n=99) and IN sufentanil ((Mathieu 2006 **Level II**, n=40, JS 4; Stephen 2012 **Level IV**, n=15; Steenblik 2012 **Level IV**, n=40).

Butorphanol (Abboud 1991 **Level II**, n=186, JS 5) and morphine (Christensen 2008 **Level II**, n=225, JS 5) had similar efficacy when given by IN or IV routes. IN butorphanol was confirmed to be similarly effective to IV butorphanol, and provided advantages of reduced postoperative cognitive decline vs IV fentanyl, when given to patients aged over 65 y for palate-pharyngoplasty (Yang 2015 **Level II**, n=260, JS 2). IN pethidine was more effective than SC injections of pethidine (Striebel 1995 **Level II**, n=44, JS 2). IN sufentanil has been trialled in ED setting and was found to be superior to placebo at 0.4 mcg/kg (Lemoel 2019 **Level II**, n=144, JS 5) and superior to IV morphine 0.1 mg/kg at 0.7 mcg/kg (Sin 2019 **Level II**, n=60, JS 5). In both studies adverse event profiles were minor and transient.

Patient-controlled IN analgesia (PCINA) using diamorphine (bolus doses of 0.5 mg) was less effective than PCA IV morphine (1 mg bolus doses) after joint replacement surgery (Ward 2002 **Level II**, n=52, JS 2) but provided better pain relief in doses of 0.1 mg/kg than 0.2 mg/kg IM morphine in children with fractures (Kendall 2001 **Level II**, n=404, JS 3). PCINA fentanyl (54 mcg 4 min lockout) provided better postoperative analgesia vs regular IM pethidine in women after Caesarean section (Fleet 2015 **Level II**, n=156, JS 3).

Adverse effects can be related to the medicine itself or to the route of administration. Systemic effects appear to be no higher for IN administration than for other routes with equivalent efficacy; nasal irritation, congestion and bad taste have been reported (Grassin-Delyle 2012 **NR**; Dale 2002 **NR**).

Technical problems with pumps have been reported in up to 10% of cases and dispensing issues for techniques such as PCINA, which could allow ready and unauthorised access to the medicines, have not been addressed (Dale 2002 **NR**).

5.5.2.3 | Ketamine

IN ketamine has been shown to provide relatively rapid onset of effective pain relief within 15 min (peak effect 30 min) with estimated bioavailability of 45% (Farnia 2017 **Level II**, n=53, JS 4); any adverse effects were mild and transient (Andolfatto 2019 **Level II**, n=120, JS 5; Christensen 2007 **Level II**, n=40, JS 4). Its use in the adult ED setting has been validated for orthopaedic trauma (Mohammadshahi 2018 **Level II**, n=91, JS 5), general trauma (Shimonovich 2016 **Level III-1**, n=90) and in the prehospital setting with demonstrated efficacy over placebo and analgesia comparable to IN/parenteral opioid (Andolfatto 2019 **Level II**, n=120, JS 5).

IN ketamine for acute headache was not found to be superior to metoclopramide/diphenhydramine (Benish 2019 **Level II**, n=53, JS 4). In adult renal colic, IV fentanyl was superior in both analgesic and adverse effect profiles to IN ketamine (Mozafari 2019 **Level II**, n=130, JS 5).

As well as a premedication in paediatric patients, IN ketamine has been studied for paediatric ED pain management and was found to be similarly effective to the usual treatment of IN fentanyl, although associated with higher rate of mild transient adverse events (Frey 2019 **Level II**, n=90, JS 5; Reynolds 2017 **Level II**, n=82, JS 5; Graudins 2015 **Level II**, n=73, JS 5). See also Section 10.4.7.1.

IN ketamine for postoperative analgesia in paediatric tonsillectomy was similarly effective to IN fentanyl (Yenigun 2018 **Level III-1**, n=63). IN S-ketamine combined with midazolam delivered on demand provided analgesia comparable to IV morphine PCA for patients who underwent spinal surgery (Riediger 2015 **Level II**, n=22, JS 4).

5.5.2.4 | Others

IN dexmedetomidine is used in paediatric setting for preoperative sedation, and may confer additional analgesic benefits. A study found that IN dexmedetomidine at 2 mcg/kg, but not 1 mcg/kg, was associated with clinically significant postoperative analgesia vs placebo (Li 2018b **Level II**, n=90, JS 5). IN dexmedetomidine had a similar analgesic effect to IN fentanyl after myringotomy when administered intraoperatively (Dewhirst 2014 **Level II**, n=100, JS 2). IN dexmedetomidine provided persistently better analgosedation for IV cannulation (as evidenced by FLACC score) when given through a mucosal atomization device (MAD) vs IN administration of drops of solution (Xie 2017 **Level II**, n=106, JS 3)

The analgesic effect of IN dexmedetomidine has also been shown in adult populations such as after hysterectomy (Wu 2016 **Level II**, n=120, JS 3) and endoscopic sinus surgery (Tang 2015 **Level II**, n=60, JS 5).

IN lignocaine has shown poor efficacy in the treatment of acute headaches with significant adverse effects vs placebo (Dagenais 2018 **Level I**, 6 RCTs, n unspecified).

While IN nicotine may have a small analgesic effect, this has been inconsistently demonstrated and is associated with significant increase in PONV (Matthews 2016 **Level I** [Cochrane], 9 RCTs, n=666).

IN desmopressin relieved subacute pain after orthopaedic surgery for up to 24 h (Yang 2019 **Level II**, n=653, JS 3).

5.5.3 | Sublingual and buccal routes

When analgesic medicines are administered by the SL or buccal routes, their efficacy will in part depend on the proportion of medicine swallowed.

5.5.3.1 | Opioids

A number of different SL fentanyl preparations are currently on the market world-wide; these include oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablets (FBT), SL fentanyl citrate orally disintegrating tablet (ODT) and fentanyl buccal soluble film (FBSF); in addition, buccal or SL sprays and a wafer are under development (Schug 2017 **NR**; Paech 2012 **NR**).

The only registered indication of these preparations (commonly called 'Transmucosal Immediate-Release Fentanyl (TIRF) Medicines') in all countries is the treatment of break-through pain in opioid-tolerant cancer patients. SL and buccal fentanyl are effective treatments for breakthrough pain in cancer patients (Zeppetella 2013 **Level I** [Cochrane], 15 RCTs, n=1,699). In this indication OTFC, FBT and ODT are providing more efficacious analgesia than oral morphine (Jandhyala 2013 **Level I**, 5 RCTs, n=415). However, as outlined above, IN fentanyl was superior to OTFC and FBT here (Vissers 2010 **Level I**, 6 RCTs, n=594). See also Section 8.9.4.

In many countries, regulatory authorities have specifically noted that SL preparations must not be used in opioid-naïve patients or in the management of acute and postoperative pain: OTFC has been the suspected primary cause of death in 226 USA fatalities between 2004 and 2011 (Paech 2012 **NR**). As a consequence, warnings regarding the use of TIRF have been issued for all of them (FDA 2019b **GL**) and specifically for OTFC (MIMS 2019 **GL**; emc 2014 **GL**).

Oral transmucosal fentanyl citrate

OTFC incorporates fentanyl into a flavoured solid lozenge on a stick and is available in a range of doses from 200–1,600 mcg. Overall, the bioavailability of OTFC is about 50% vs IV fentanyl, with C_{max} achieved in 23 min (Lotsch 2013 **NR**); the time to onset of analgesia is about 4.2 min. The relative potency vs IV morphine is 1:8 to 1:14 (200 mcg OTFC≈2 mg IV morphine) (Lichtor 1999 **Level II**, n=133, JS 5).

Only a few studies have investigated the postoperative use of OTFC. It was found to be an effective analgesic after orthopaedic surgery (Ashburn 1993 **Level II**, n=38, JS 5), abdominal surgery (Lichtor 1999 **Level II**, n=133, JS 5), retinal photocoagulation (Hillier 2009 **Level II**, n=35, JS 5) and during burns wound care in paediatric patients (Sharar 2002 **Level II**, n=22, JS 3; Sharar 1998 **Level II**, n=14, JS 3). Pain relief at 15 min in children with lower extremity injuries was the same with IV bolus doses of morphine and OTFC, but lower with OTFC after that until the end of the 75-min study period (Mahar 2007 **Level II**, n=87, JS 3). However, because of the risk of achieving high peak plasma levels with unsupervised administration, the limited data available, and the specific lack of approval for use in opioid-naïve patients, OTFC cannot be recommended for the management of acute pain.

Fentanyl buccal tablets

FBTs use an effervescent medicine delivery technology that enables more rapid absorption and delivery of a larger proportion of the fentanyl dose vs OTFC (Grape 2010 **NR**); bioavailability is 65% with time to onset of effect 10 min (Lotsch 2013 **NR**). FBTs are effective in opioid-tolerant cancer patients for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1699; Jandhyala 2013 **Level I**, 5 RCTs, n=415; Vissers 2010 **Level I**, 6 RCTs, n=594) (significant overlap between all three SRs). Although only indicated for this usage, FBTs have been studied in the ED. Here, a 100 mcg FBT had faster onset of analgesia (10 vs 35 min) than an oxycodone 5 mg/paracetamol 325 mg combination tablet, with no other advantages (Shear 2010 **Level II**, n=60, JS 4). FBT 200 mcg was noninferior to oxycodone 10 mg/paracetamol 650 mg in an ED setting, but again without obvious advantage in terms of onset, efficacy or adverse effect profile (Arthur 2015 **Level II**, n=50, JS 2). FBT was also trialled for treatment of sickle cell crisis (De Franceschi 2016 **Level III-2**). Use of FBT for non-cancer pain in opioid-naïve patients cannot be recommend given significant safety concerns.

Sublingual fentanyl citrate orally disintegrating tablets

SL fentanyl citrate ODTs consist of a mixture of carrier particles coated with fentanyl and a mucoadhesive agent and are left under the tongue to dissolve, leading to rapid fentanyl absorption (Paech 2012 **NR**). This leads to a bioavailability of around 70% and a time to onset of effect of 15 min (Lotsch 2013 **NR**). They are effective in opioid-tolerant cancer patients for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1,699) and one subsequent RCT (Shimoyama 2015 **Level II**, n=37, JS 3). They have also been used with effect in breakthrough noncancer pain (Guitart 2013 **Level IV**, n=182).

Fentanyl buccal soluble film

FBSF consists of a small soluble disc-shaped film containing fentanyl in doses of 200–1,200 mcg, proportional to the film surface area (Grape 2010 **NR**); bioavailability is 71% and time to onset of effect 15 min (Lotsch 2013 **NR**). FBSF is effective in opioid-tolerant cancer patients for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1,699).

Other transmucosal fentanyl preparations

Fentanyl buccal spray has a bioavailability of 76% and a time to onset of effect of 5 min (Lotsch 2013 **NR**). It is effective in opioid-tolerant cancer patients for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane], 15 RCTs, n=1,699). Fentanyl SL wafers showed a bioavailability of 79% (Lim 2012 **PK**).

Sublingual buprenorphine

SL buprenorphine, given as a tablet, has an overall bioavailability of 30–50% and a long duration of action (mean half-life 28 h) (Mendelson 1997 **NR**; Kuhlman 1996 **NR**). SL buprenorphine 0.4 mg was found to be as effective as 10 mg morphine IM after abdominal surgery (Cuschieri 1984 **Level II**, n=89, JS 2) and 75 mg pethidine IM after gynaecological surgery (Moa 1990 **Level II**, n=96, JS 4). For adults with acute fractures in the ED, buprenorphine 0.4mg SL is as effective and safe as morphine 5 mg IV (Jalili 2012 **Level II**, n=49, JS 4). A significantly higher dose of SL buprenorphine "2 mg for renal colic achieved comparable analgesia and adverse event to 0.1 mg/kg IV morphine (Payandemehr 2014 **Level II**, n=69, JS 5).

First pass metabolism of buprenorphine is dependent on cytochrome P450-3A4. Concurrent administration of enzyme inhibitors such as voriconazole more than posaconazole significantly elevated plasma concentrations after sublingual buprenorphine in healthy volunteers (Fihlman 2016 **Level II PK**, n=12, JS 3). Similarly, co-administration of rifampicin, an enzyme inducer, reduced plasma concentration of buprenorphine after SL administration by up to 25%, but had no effect when buprenorphine was given intravenously (Hagelberg 2016 **Level III-2 PK**, n=12).

SL buprenorphine is at least as effective as parenteral morphine for treatment of acute pain with a comparable safety profile (Vlok 2019 **Level I** [PRISMA], 9 RCTs, n=826).

Sublingual sufentanil

Sufentanil is a lipophilic drug which rapidly crosses the blood-brain barrier (t1/2 ke0 6 min), resulting in a faster onset of action than morphine (Melson 2014 **NR**). Bioavailability of SL sufentanil is estimated at 60%, and vs IV administration, SL sufentanil has a blunted peak and prolonged plasma half-life (Ringold 2015 **NR**). A sublingual sufentanil tablet system (SSTS) has been developed commercially and incorporates a hand-held computerized dispenser which is activated by a radiofrequency ID tag linked to an individual patient, and dispenses SL sufentanil 15 to 30 mcg tablets in a patient-controlled manner with a 20 min lockout (Frampton 2016 **NR**). See Section 6.5.3.

SSTS has been trialled in both postsurgical and other acute pain settings. When compared to IV morphine PCA for analgesia after major abdominal or arthroplasty surgeries, SSTS 15 mcg provided analgesia that was noninferior to IV PCA with similar rate of adverse effects and

superior satisfaction ratings from patients and nursing staff (Melson 2014 **Level II**, n=357, JS 2). Specifically for postarthroplasty pain management, SSTS 15 mcg was found to be superior to placebo but associated with a higher rate of nausea and vomiting (Jove 2015 **Level II**, n=419, JS 5), while for abdominal surgeries the analgesia from SSTS was superior to placebo while adverse events profiles were similar (Ringold 2015 **Level II**, n=172, JS 5).

A similar trial compared SSTS 30 mcg to placebo for abdominal surgery pain and again found it superior to placebo but without increased adverse events, and with rapid onset of reported analgesic effect within 15 min of administration (Minkowitz 2017 **Level II**, n=161, JS 5). SSTS 30 mcg was also trialled for acute pain management in the ED setting (Miner 2018 **Level III-3**, n=76).

5.5.3.2 | Ketamine

A pharmacokinetic study in healthy volunteers calculated the bioavailability of oral ketamine as 20%, SL 30% and IN 45%: the pharmacodynamic effects of the active metabolite norketamine were thought to be of potential significance (Yanagihara 2003 **PK**). The bioavailability of a 25 mg ketamine lozenge was 24% when given by both SL and oral routes; peak plasma levels were seen at 30 min and 120 min respectively and terminal half-lives were similar at around 5 h (Chong 2009 **PK**). For both routes, norketamine concentrations exceeded the concentrations of ketamine and, given its pharmacological activity profile, norketamine is therefore likely to be a major contributor to the overall analgesic effect. A wafer preparation of ketamine showed an oral bioavailability of 29% (Rolan 2014 **PK**).

5.5.3.3 | Others

Sublingual nsNSAIDs have been used in a variety of acute pain settings. One study found SL piroxicam to be noninferior to IM diclofenac for renal colic (KandaSwamy 2015 **Level II**, n=100, JS 5), and another found SL ketoprofen to have similar efficacy to oral naproxen for acute lower back pain (Plapler 2016 **Level II**, n=83, JS 3). A novel formulation of buccal paracetamol 125 mg was noted to provide analgesia similar to IV paracetamol 1 g for limb trauma in ED (Pickering 2015 **Level II**, n=40, JS 5). Advantages of above formulations over their oral equivalents are not clear.

Sublingual desmopressin vs IM ketorolac for renal colic was found to be similarly effective (Pricop 2016 **Level II**, n=249, JS 2).

5.5.4 | Pulmonary

5.5.4.1 | Opioids

Opioids are rapidly absorbed after nebulised inhalation, reflecting the high blood flow, surface area and permeability of the lungs.

Clinical data exist for the effectiveness of several opioids administered via the pulmonary route including morphine (Thipphawong 2003 **Level II**, n=89, JS 5; Dershwitz 2000 **Level IV PK**, n=15) and fentanyl (Miner 2007 **Level II**, n=41, JS 3; Worsley 1990 **Level II**, n=30, JS 3).

For post-traumatic thoracic pain, there was no difference in the pain relief obtained from nebulised morphine and PCA morphine (Fulda 2005 **Level II**, n=44, JS 4). Nebulised morphine 20 mg every 10 min vs nebulised morphine 10 mg or IV morphine 2 mg every 5 min for ED trauma pain provided superior analgesia while being associated with a lower rate of adverse events than the IV group (Grissa 2015 **Level II**, n=300, JS 5). C_{max} following administration of morphine via a standard nebuliser occurred within 10 min but bioavailability was low with a mean of only 5% (Masood 1996 **PK**). Bioavailability may be improved (up to 59–100%) with C_{max} occurring at 2 min using specific pulmonary-medicine delivery systems (Dershwitz 2000 **PK**; Ward 1997 **PK**).

Bioavailability of inhaled fentanyl is significantly higher and may approach 100% (Mather 1998 **PK**). The pharmacokinetic profiles of inhaled and IV fentanyl showed similar peak arterial concentrations and areas under the curve (Macleod 2012 **Level II**, n=10, JS 5). The time to maximum concentration was slightly shorter for the inhaled than IV fentanyl (20.5 vs 31.5 s). As is with other nebulized medications, mode of delivery and specifically achieving a particle size small enough to reach the pulmonary alveoli, but large enough to not be expired, is important for absorption (Thompson 2016 **Level I** [PRISMA], 7 RCTs, n=583). Use of breath actuated atomizers may reduce the leak of drug to the general environment while allowing the clinician to establish total dose delivered.

Nebulised fentanyl provides analgesia comparable to IV morphine for acute pain management in a variety of settings with the advantages of lower adverse effect profile, noninvasive delivery and rapid onset (Thompson 2016 **Level I** [PRISMA], 7 RCTs, n=583). Nebulised fentanyl in the ED setting for adults provided analgesia for acute limb trauma that was noninferior to IV morphine (Farahmand 2014 **Level II**, n=90, JS 5). Using a breath actuated inhaler delivering atomized fentanyl provided faster onset of and superior analgesia to IV morphine for acute abdominal pain (Deaton 2015 **Level II**, n=40, JS 5). For renal colic, IV fentanyl provided better analgesia than nebulised fentanyl (Imamoglu 2017 **Level II**, n=117, JS 5).

In children requiring pain relief in an ED, nebulised fentanyl was as effective as IV fentanyl (Miner 2007 **Level II**, n=41, JS 3). See also Section 10.4.4.4.

5.5.4.2 | Other analgesic medicines

Nebulized ketamine and dexmedetomidine have been trialled for paediatric pre-medication and may contribute to improved postoperative analgesia (Zanaty 2015 **Level II**, n=60, JS 5).

See Section 4.5 for inhaled N_2O and methoxyflurane.

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 IV administration (**U**) (**Level I** [PRISMA]) and superior to oral morphine (**U**) (**Level I**).
2. Intranasal fentanyl is an effective treatment for paediatric acute pain management, with an acceptable adverse effect profile and ease of delivery (**N**) (**Level I**).
3. Intranasal fentanyl provides faster and better analgesia for breakthrough pain in cancer patients than oral transmucosal fentanyl and fentanyl buccal tablets (**U**) (**Level I**).
4. Sublingual sufentanil delivered by a PCA device provided analgesia comparable to IV PCA opioids in a number of acute pain settings (**N**) (**Level II**).

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

☑ Neither transmucosal immediate-release nor transdermal fentanyl preparations should be used in the management of acute pain in opioid-naïve patients because of safety concerns and, in most countries, the lack of regulatory approval for use in other than opioid-tolerant patients (**U**).

5.6 | Epidural analgesia

Epidural analgesia (ie the provision of pain relief by continuous administration of pharmacological agents into the epidural space via an indwelling catheter) is an important technique for the management of acute pain in adults and children, particularly after surgery (Weiss 2018 **NR**) and in women in labour (see Section 9.1.3.3). For epidural and caudal analgesia in children see Sections 10.6.3.1 and 10.6.3.2.

5.6.1 | Efficacy

The difficulty with interpretation of available data is that epidural analgesia is not a single entity but can be provided by a number of pharmacological agents administered into different levels of the epidural space for a wide variety of operations.

5.6.1.1 | Efficacy and outcomes in general

The universal efficacy of epidural analgesia has been well demonstrated. Regardless of analgesic agent used, location of catheter, type of surgery and type or time of pain assessment, epidural analgesia provides better pain relief than parenteral opioid administration (the following meta-analyses have significant overlap of multiple RCTs) (Guay 2019 **Level I** [Cochrane], 69 RCTs, n=4,680; Salicath 2018 **Level I** [Cochrane], 32 RCTs, n=1,716; Guay 2016a **Level I** [Cochrane], 15 RCTs [8 TEA, 2 LEA, 4 mixed, 1 unspecified], n=1,498; Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044).

One meta-analysis of epidural analgesia vs systemic opioids via PCA concludes that epidural analgesia provides better pain relief at rest and with movement after all types of surgery; with the exception of epidural analgesia using hydrophilic opioids only (Wu 2005 **Level I**, 50 RCTs, n=3,208). The epidural group has a lower incidence of nausea/vomiting and sedation but a higher incidence of pruritus, urinary retention and motor block than IV PCA. A meta-analysis of epidural analgesia provided with local anaesthetics for at least 24 h vs systemic analgesia after surgery (performed under general anaesthesia) shows reduced mortality with epidural analgesia (3.1 vs 4.9%) (OR 0.60; 95%CI 0.39 to 0.93) (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044), as did a large matched-cohort retrospective audit of administrative data (30-d mortality 1.7 vs 2.0%) (RR 0.89; 95%CI 0.81 to 0.98) (Wijeysundera 2008 **Level III-2**, n=144,744). The meta-analysis also reports benefits of epidural analgesia on perioperative morbidity with decreased risk of atrial fibrillation, supraventricular tachycardia, deep vein thrombosis, respiratory depression, atelectasis, pneumonia, ileus, and PONV and improved recovery of bowel function. A preceding meta-analysis reported similar results (Guay 2006 **Level I**, 70 RCTs, n unspecified). However, adverse effects of epidural analgesia include hypotension, pruritus, urinary retention and motor block (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044).

With regard to pulmonary outcomes specifically, epidural analgesia vs systemic analgesia reduced rate of pneumonia (OR 0.54; 95%CI 0.43 to 0.68), but also the need for prolonged ventilation or reintubation, improved lung function and blood oxygenation (Popping 2008 **Level I**, 58 RCTs, n=5,904); however, notably a decrease of relative benefit has occurred over time where from 1971 to 2006 the baseline risk of pneumonia in the opioid group has decreased from 34 to 12%, but remained 8% in the epidural group.

5.6.1.2 | Cancer surgery outcomes

Current data do not support a benefit for cancer recurrence or survival through addition of epidural anaesthesia/analgesia to general anaesthesia/systemic analgesia following cancer

surgery; neither overall survival (HR 1.03; 95%CI 0.86 to 1.24) nor progression-free survival (HR 0.88; 95%CI 0.56 to 1.38) are improved (Cakmakkaya 2014 **Level I** [Cochrane], 4 RCTs, n=746). Evidence was graded low to very low and all four studies are secondary data analyses of previously conducted RCTs. In a much larger systematic review including not only RCTs, overall survival was improved by epidural anaesthesia (HR 0.84; 95%CI 0.74 to 0.96), in particular after surgery for colorectal cancer (HR 0.65; 95%CI 0.43 to 0.99) (Chen 2013 **Level III-3 SR**, 14 studies, n≈47,000). However, epidural anaesthesia did not improve recurrence-free survival (HR 0.88; 95%CI 0.64 to 1.22). For gastroesophageal cancer surgery there is no evidence in favour or against an effect of epidural anaesthesia or analgesia on cancer outcomes (Perez-Gonzalez 2018 **Level I**, 6 RCTs, n=263).

5.6.1.3 | Procedure-specific efficacy

Open abdominal surgery

For intra-abdominal surgery of any kind (including hysterectomies, radical prostatectomies, Caesarean section, colorectal and upper gastrointestinal procedures), epidural analgesia (by continuous infusion [16 RCTs, n=418] or PCEA [16 RCTs, n=451]) vs IV PCA opioids improves pain relief at rest to 6 h by 5.7/100 (95%CI 1.9 to 9.5) (7 RCTs, n=384), 7 to 24 h by 9.0/100 (95%CI 4.6 to 13.4) (11 RCTs, n=558) and beyond 24 h by 5.1/100 (95%CI 0.9 to 9.4) (7 RCTs, n=393) (Salicath 2018 **Level I** [Cochrane], 32 RCTs, n=1,716). There is limited evidence for improvement of pain on movement and coughing based on few RCTs, but no evidence for differences in other outcomes such as mortality, venous thromboembolism, sedation, nausea and vomiting and respiratory parameters. However, in the epidural group, risk of failure of the analgesic technique is increased (RR 2.48; 95%CI 1.13 to 5.45) (10 RCTs, n=678) as is hypotension requiring intervention (RR 7.13; 95%CI 2.87 to 17.75) (6 RCTs, n=479) and pruritus (RR 2.36; 95%CI 1.67 to 3.35) (8 RCTs, n=492).

Epidural local anaesthetics vs systemic or epidural opioids after abdominal surgery reduce pain on movement (SMD -0.89; 95%CI -1.08 to -0.70; equivalent to 2.5/10) (35 RCTs, n=2,731) (Guay 2016b **Level I** [Cochrane], 128 RCTs, n=8,754). Outcomes with regard to gastrointestinal transit time are improved: time to first flatus (SMD -1.28; 95%CI -1.71 to -0.86; equivalent to 17.5 h) (22 RCTs, n=1,138) and to first stool (SMD -0.67; 95%CI -0.86 to -0.47; equivalent to 22 h). There is no effect on vomiting within 24 h and gastrointestinal anastomotic leakage, but very low-quality evidence on reduced LOS (SMD -0.20; 95%CI -0.35 to -0.04; equivalent to 1 d).

For a wide range of open and laparoscopic abdominal surgery in adults and children, epidural analgesia vs TAPB provides similar analgesia (MD 0.3/10; 95%CI -0.1 to 0.6), but TAPB reduces the risk of hypotension (RR 0.13; 95%CI 0.04 to 0.38) and LOS (MD -0.6 d; 95%CI -0.9 to -0.3) (Baeriswyl 2018 **Level I** [PRISMA], 10 RCTs, n=505).

After open abdominal surgery in the setting of enhanced-recovery programs (ERAS), TEA vs other analgesic approaches results in no more complications (OR 1.14; 95%CI 0.49 to 2.64) but better analgesia and earlier recovery of bowel function without reducing LOS (Hughes 2014 **Level I** [PRISMA], 7 RCTs, n=378).

A large retrospective cohort study after elective colectomy reported that postoperative epidural analgesia significantly reduced 7 d (OR 0.35; 95%CI 0.21 to 0.59) and 30 d (OR 0.54; 95%CI 0.42 to 0.70) mortality (Wu 2006a **Level III-2**, n=12,817). In another cohort study of patients with COPD undergoing major abdominal surgery, TEA added to general anaesthesia vs general anaesthesia alone did not reduce the incidence of postoperative pneumonia significantly (11 vs 16%), but was associated with decreased 30 d mortality (5 vs 9%) and with improved outcome for postoperative pneumonia (OR 0.5; 95%CI 0.3 to 0.9) (van Lier 2011 **Level III-2**, n=541 [324 epidural]). The beneficial effect of TEA increased with increasing COPD severity.

After major upper abdominal surgery, TEA in combination with NSAIDs and IV nutritional support prevented protein loss vs epidural analgesia alone or PCA with and without nutritional support (Barratt 2002 **Level II**, n=57, JS 3). Similarly, after colonic surgery, epidural analgesia increased the anabolic effect of amino acid infusions in diabetic patients (Lugli 2008 **Level II**, n=12, JS 3) and reduced whole body protein breakdown (Lattermann 2007 **Level II**, n=20, JS 2). Epidural anaesthesia/analgesia reduced insulin-resistance in comparison to general anaesthesia/systemic analgesia only in patients who were insulin-resistant preoperatively (Donatelli 2007 **Level II**, n=60, JS 2).

After abdominal cancer surgery, continuous TEA vs continuous IT thoracic analgesia resulted in similar efficacy and adverse effects (Mercadante 2008 **Level II**, n=60, JS 3). After open gastrectomy, TEA (PCEA) was superior to IT morphine combined with IV PCA opioids for all relevant outcomes including analgesia, mobilisation, bowel recovery and pulmonary complications (Lee 2014b **Level II**, n=64, JS 3) and was superior to IV PCA morphine with regard to pain control, gastrointestinal recovery and hospital LOS (Zhu 2013 **Level II**, n=67, JS 2). Compared to continuous wound infiltration with local anaesthetics in fast-track open colectomy, epidural analgesia reduced pain scores on mobilisation until hospital discharge, reduced time to return of bowel function and tolerance of a complete diet, improved sleep quality and reduced hospital LOS (4 vs 5.5 d) (Jouve 2013 **Level II**, n=50, JS 5). These benefits were not demonstrated in another, similar RCT (Bertoglio 2012 **Level II**, n=106, JS 3).

Laparoscopic colectomy

After laparoscopic colectomy, TEA is rarely used in the USA (2.14%) (Halabi 2014 **Level III-2**, n=191,576). After laparoscopic colectomy, TEA vs IV PCA opioids improves pain at rest and on walking at POD 1 and 2 and time to first bowel opening, but increases LOS and total rate of complications (Perivoliotis 2019 **Level I** [PRISMA], 8 RCTs, n=492).

Similarly, in a large case-matched analysis, TEA increased LOS by 0.6 d, hospital charges by USA$ 3,732.71 and higher of urinary tract infection without any clinical benefits (Halabi 2014 **Level III-2**, n=191,576). Outcomes were inferior with epidural vs IT analgesia or IV PCA (Levy 2011 **Level II**, n=99, JS 3). TEA also did not improve long-term survival in this setting, but increased LOS (median length 5 d vs 3 d with IV PCA) (Day 2012 **Level III-2**, n=424).

Hepatic surgery

For hepatic surgery, there is ongoing debate on the value of epidural analgesia. A large USA survey showed the technique is infrequently used in 5.9% of cases (Rosero 2014 **Level IV**, n=68,028).

Epidural analgesia vs IV PCA after open hepatectomy improves pain control at rest at 24 h (MD 0.59/10; 95%CI 0.30 to 0.88) and with movement at 48 h (MD 0.95/10; 95%CI 0.31 to 1.60) with no difference in LOS, overall and analgesia related complications nor effect on blood loss (Li 2019 **Level I** [PRISMA], 4 RCTs, n=278).

However, wound catheters vs epidural analgesia for open hepatectomy result in similar pain intensity on POD 1 and only slightly worse on POD 2 (WMD 0.29; 95%CI 0.09 to 0.49) with less opioid requirements (WMD -6.29; 95%CI -7.92 to -4.65) and faster functional recovery (WMD −0.73; 95%CI −1.13 to −0.32) and no other differences in complications (Gavriilidis 2019 **Level I** [PRISMA], 3 RCTs, n=240).

Applying propensity-score matching techniques to a cohort of patients after hepatectomy, there was an association of epidural anaesthesia/analgesia with higher need for blood transfusion and longer hospital LOS (Rosero 2014 **Level III-2**, n=1,604).

Compared to IT morphine with subsequent IV PCA fentanyl, TEA was not superior with the exception of pain at 12 h postoperatively and reduced blood loss (Kasivisvanathan 2014 **Level III-2**, n=73). However, an RCT found significantly improved analgesia and a 50% opioid-sparing effect

(Mondor 2010 **Level II**, n=44, JS 5). Similarly, after live liver donation, TEA vs IV PCA opioids improved analgesia but no other outcomes (Clarke 2011 **Level III-2**, n=228).

Abdominal aortic surgery

After open abdominal aortic surgery in comparison with systemic opioid administration (Guay 2016a **Level I** [Cochrane], 15 RCTs [8 TEA, 2 LEA, 4 mixed, 1 unspecified], n=1,498), epidural analgesia reduces:

- Pain scores on movement in POD 1 to 3 postoperatively (MD -1.78/10; 95%CI -2.32 to -1.25);
- Time to tracheal extubation (SMD -0.42; 95%CI -0.70 to -0.15; equivalent to 36 h mean reduction);
- Time spent in the ICU (SMD -0.23 (95% CI -0.41 to -0.06); equivalent to 6 h mean reduction);
- Acute respiratory failure (RR 0.69; 95%CI 0.56 to 0.85); NNT 8 [95%CI 6 to 16]);
- Myocardial infarction (RR 0.54; 95%CI 0.30 to 0.97; NNT 28 [95%CI 19 to 1423]);
- Gastrointestinal bleeding (OR 0.20; 95% CI 0.06 to 0.65); NNT 32 [95%CI 27 to 74]).

However, the reduced morbidity does not translate to a difference in mortality between epidural vs systemic opioids use (RR 1.06; 95%CI 0.60 to 1.86).

Studies not included in this meta-analysis support these results: TEA vs systemic opioids improved pain, mobility and time to oral intake (Salman 2013 **Level III-1**, n=80) and pain and postoperative respiratory function in COPD patients (Panaretou 2012 **Level III-2**, n=30). After endoluminal aortic aneurysm repair, TEA provided better analgesia than IV opioids (Sen 2014 **Level III-2**, n=32). However, in a fast-track setting for abdominal aortic aneurysm repair, TEA was similarly effective vs continuous local anaesthetic wound infiltration with no effects on overall outcome (Renghi 2013 **Level II**, n=60, JS 3).

Gynaecological surgery

In gynaecological surgery, epidural ropivacaine infusion provided only slightly better analgesia in the first 8 h postoperatively vs wound infiltration/infusion of ropivacaine with no other clinically relevant improvements (Ammianickal 2018 **Level II**, n=102, JS 3; Fassoulaki 2014 **Level II**, n=80, JS 3). After open abdominal hysterectomy (midline incision), epidural analgesia increased duration of postoperative analgesic use, nonserious postoperative complications and LOS vs parenteral opioids (Belavy 2013 **Level III-2**, n=257). Similarly, after uterine artery embolisation for uterine fibroids, epidural analgesia increased complications but reduced pain scores at high costs (179 Euro for 1/10 pain score reduction) (van der Kooij 2013 **NR**). After open hysterectomy, TAPB vs epidural analgesia (both regional techniques maintained by bolus injections of 8 mL bupivacaine 0.125% every 6 h) vs parenteral analgesia provided the best pain relief and the lowest opioid rescue requirements (Mathew 2019 **Level II**, n=60, JS 4). In contrast, single bolus TAPB was inferior to single bolus epidural analgesia in the same setting with higher pain intensity 6 to 24 h and higher rescue tramadol requirements (68.8 mg [SD 25.5] vs. 5.3 mg [SD 11.6]) (Raghvendra 2016 **Level II**, n=60, JS 3).

After open hysterectomy, epidural analgesia and IT morphine (200 mcg) provided acceptable analgesia over 24 h, but IT morphine resulted initially (0 to 16 h) in better pain relief and lower opioid requirements (Hassan 2017 **Level II**, n=32, JS 3).

Urologic surgery

After radical retropubic prostatectomy, TEA vs patient-controlled local anaesthetic wound infusion reduced pain scores upon coughing and opioid requirements, with better preservation of expiratory muscle strength (Fant 2011 **Level II**, n=50, JS 5). However, a cohort study found an

increased median hospital LOS with use of epidural analgesia for this operation (6 vs 7 d), which remained significant after adjusting for complications (Mir 2013 **Level III-2**, n=239). Malignancy recurrence based upon prostate-specific antigen change was more common in the epidural group (14.8 vs 4.8%). TEA had no effect on blood loss or transfusion rates (Baumunk 2014 **Level II**, n=235, JS 2).

Thoracic surgery

Following thoracotomy, there is moderate-quality evidence that shows comparable analgesic efficacy at rest and after coughing, with TEA vs PVB (Yeung 2016 **Level I** [Cochrane], 14 RCTs, n=698). There is low to very low-quality evidence that shows no significant difference in mortality and major complications. There is moderate-quality evidence that PVB has a superior minor complication risk vs TEA including hypotension (RR 0.16; 95%CI 0.07 to 0.38) (8 RCTs, n=445), nausea and vomiting (RR 0.48; 95%CI 0.30 to 0.75) (6 RCTs, n=345), pruritus (RR 0.29; 95%CI 0.14 to 0.59) (5 RCTs, n=249) and urinary retention (RR 0.22; 95%CI 0.11 to 0.46) (5 RCTs, n=258). These results are consistent with a parallel meta-analysis showing that continuous PVB reduces the incidence of nausea, vomiting, hypotension and urinary retention vs thoracic epidural analgesia, wound infiltration or IV opioids with comparable post-cardiothoracic surgery analgesia (Scarfe 2016 **Level I** [PRISMA], 23 RCTs, n= 1,120) (overlap 10 RCTs with Yeung 2016).

For oesophagectomy, TEA vs systemic analgesia does not improve pain relief at 24 h (MD 0.89; 95%CI −0.47 to 2.24) (2 RCTs & 2 studies) or 48 h (MD 0.15; 95%CI −0.60 to 0.91) (2 RCTs & 2 studies) nor does it reduce the rate of pulmonary complications (RR 1.69; 95%CI 0.86 to 3.29) (2 RCTs & 2 studies) (Visser 2017 **Level III-2 SR**, 5 RCTs & 5 studies, n=891). Technical failure with TEA occurs in 17 to 22%. These findings are supported by a subsequent systematic review (Hughes 2018 **Level I** [PRISMA], 3 RCTs, n=93 [oesophagectomy]) (2 RCTs overlap).

After lung resection, postoperative TEA reduced mortality at 7 d (OR 0.39; 95%CI 0.19 to 0.80) and 30 d (OR 0.53; 95%CI 0.35 to 0.78) in a retrospective cohort study (Wu 2006b **Level III-2**, n=3,501). TEA in patients after lobectomy resulted in better pain relief and pulmonary function vs IV morphine (Bauer 2007 **Level II**, n=93, JS 5).

After video-assisted thoracic surgery, PCEA achieved similar pain control as IV fentanyl PCA/low-dose ketamine with no difference in analgesia-related adverse effects (Tseng 2019 **Level II**, n=74, JS 3).

Following open thoracotomy, 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) (7 RCTs, n=499) (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027).

Cardiac surgery

A meta-analysis of epidural analgesia vs multiple comparators for cardiac surgery with or without cardiopulmonary bypass finds insufficient evidence to show an effect of epidural analgesia vs peripheral nerve blocks (4 RCTs), interpleural analgesia (1 RCT) or wound infiltration (1 RCT) (Guay 2019 **Level I** [Cochrane], 69 RCTs, n=4,680). In comparison to systemic analgesia, there is a reduction of pain at rest and on movement for the first 72 h eg from 6 to 8 h (SMD -1.35/10; 95%CI -1.98 to -0.72) (10 RCTs, n=502) and an increase in hypotension (RD 0.21; 95%CI 0.09 to 0.33) (17 RCTs, n=870) not leading to increased need for inotropes or vasopressors (RD 0.00; 95%CI -0.06 to 0.07) (23 RCTs, n=1,821). With regard to other outcomes, there is no difference in mortality, cerebrovascular accidents or pneumonia, there may be a reduction in myocardial infarction at 0 to 30 d, respiratory depression (RD -0.03; 95%CI -0.05 to -0.01) (21 RCTs, n=1,736) and risk of atrial fibrillation or atrial flutter at 0 to 2 wk (RD -0.06; 95%CI -0.10 to -0.01) (18 RCTs, n=2,431). A difference in mortality is reported in a meta-analysis including RCTs and case-matched studies; here epidural anaesthesia/analgesia reduces mortality (59/3123 [1.9%] vs 108/3260 [3.3%]) (RR 0.65; 95%CI 0.48 to 0.86; NNT 70) and rate of myocardial infarction (67/2785 [2.4%] vs

108/2933 [3.7%]) (RR 0.68; 95% CI 0.51 to 0.90]; NNT 78) (Landoni 2015 **Level III-2 SR**, 57 studies, n=6,383).

In smaller studies, high TEA improved left ventricular function (Schmidt 2005 **Level III-3**, n=37) and increased stroke volume index and central venous oxygenation in elderly cardiac surgery patients, without an increase in heart rate or mean arterial pressure (Jakobsen 2012 **Level II**, n=60, JS 3). Prior to CABG surgery, high TEA improved myocardial oxygen availability in patients with ischaemic heart disease (Lagunilla 2006 **Level II**, n=52, JS 4) and partly normalised myocardial blood flow in response to sympathetic stimulation (Nygard 2005 **Level III-3**, n=20). After CABG surgery, high TEA postoperatively reduced insulin requirements and hyperglycaemia (Greisen 2013 **Level II**, n=42, JS 3) (included in Guay 2019). However, TEA did not reduce the ICU LOS or improve the quality of recovery in the ICU (Nielsen 2012 **Level II**, n=60, JS 3). The discussion on the overall value of epidural analgesia after cardiac surgery continues, with concerns regarding anticoagulation risk being a key factor (Ziyaeifard 2014 **NR**).

Rib fractures

Compared to thoracic epidural analgesia, systemic IV analgesia provides inferior analgesia for rib fractures (11 RCTs & studies, n=1,057) (Peek 2019 **Level III-2 SR** [PRISMA], 8 RCTs & 11 studies, n=2,081). There was no significant difference in secondary outcomes such as duration of mechanical ventilation, ICU LOS, hospital LOS and pulmonary complications. Thoracic epidural analgesia provides similar analgesia to continuous intercostal and paravertebral blocks with no significant difference in duration of mechanical ventilation, ICU LOS, hospital LOS and pulmonary complications (6 RCTs & studies, n=1,045).

In patients with multiple traumatic rib fractures, provision of TEA with local anaesthetic reduced the duration of ventilation vs other forms of analgesia (including LEA) (Carrier 2009 **Level I**, 8 RCTs, n=232) (2 RCTs overlap with Peek 2019); however, mortality and ICU LOS was not different in pooled analysis of all routes of epidural administration vs parenteral opioids and hypotension was more frequent in the epidural groups when TEA with local anaesthetic was used.

After blunt chest trauma with three or more rib fractures, the use of TEA was more common in USA trauma centres than in nontrauma centres; the use of TEA vs other methods of analgesia reduced adjusted mortality at 30 d (OR 0.08; 95%CI 0.01 to 0.43), 90 d (OR 0.09; 95%CI 0.02 to 0.42) and 365 d (OR 0.12; 95%CI 0.04 to 0.42) (n=100 [TEA]) (Gage 2014 **Level III-2**, n=836). See also Section 8.3.

Orthopaedic surgery

Spinal fusion

After spinal fusion, patient controlled epidural analgesia (PCEA) vs IV PCA opioids provides better analgesia on POD 1 (MD −0.47/10; 95%CI −0.74 to −0.20) and POD 2 (MD −0.66; 95%CI −1.14 to −0.19), but not on POD 3 (Tian 2015 **Level I**, 8 RCTs, n=482). There were no differences in PONV rates, but PCEA increased rates of pruritus (RR 1.53; 95%CI 1.08 to 2.6) and paraesthesia (RR 3.34; 95%CI 1.12 to 9.98). A parallel meta-analysis not differentiating results as detailed as the previous one finds similar results for analgesia overall and no differences in all pooled adverse effects (Lu 2015 **Level I**, 9 RCTs, n=436) (7 RCTs overlap).

In RCTs not included in these meta-analyses, epidural analgesia with levobupivacaine reduced pain scores, opioid consumption, nausea, blood loss and time to first stool vs IV opioid analgesia (Servicl-Kuchler 2014 **Level II**, n=81, JS 5). Similarly, after major spinal surgery, epidural analgesia (levobupivacaine/fentanyl/epinephrine) vs systemic opioids reduced pain and nausea, permitted earlier mobilisation and increased satisfaction (Ezhevskaya 2013 **Level II**, n=85, JS 2). In addition, it resulted in less intraoperative and postoperative blood loss and reduced stress response markers (glucose, cortisol, IL-1beta, IL-6, and IL-10). However, when added to systemic

multimodal analgesia, TEA did not provide a significant opioid-sparing effect (Choi 2014 **Level II**, n=39, JS 5).

Lower limb arthroplasty (TKA and THA)

After THA and TKA, LEA provides better pain relief than parenteral opioids, in particular with movement (Choi 2003 **Level I** [Cochrane], 13 RCTs, n unspecified). A subsequent study showed that epidural analgesia vs systemic opioids reduced inflammatory response measured by a number of parameters after total knee replacement (Chloropoulou 2013 **Level II**, n=56, JS 3).

However, in comparison to peripheral nerve blocks (FNB and ACB by single injection or catheter), LEA does not improve pain for 0 to 48 h, but is associated with increased PONV (RR 1.65; 95 %CI 1.20 to 2.28), hypotension (RR 1.76; 95 %CI 1.26 to 2.45) and urinary retention (RR 4.51; 95%CI 2.27 to 8.96) (Gerrard 2017 **Level I** [PRISMA], 12 RCTs, n=670). In comparison to local infiltration analgesia (LIA) by single injection or via catheter for TKA, LEA has similar analgesic effects at rest for <24 h, but LIA achieves better analgesia at 48 and 72 h (MD −1.08/10; 95%CI −1.86 to −0.29 and MD −0.82/10; 95%CI −1.24 to −0.4) (Yan 2016 **Level I**, 9 RCTs [TKA], n=537). Pain on movement was similar at <24 h, but better controlled by LIA at 48 h and LIA enabled a better range of movements at all time points.

For comparisons with other regional analgesic techniques see also Section 5.8. below.

Vascular surgery of the lower limbs

Used in vascular surgery of the lower limbs, LEA improved outcome by reducing incidence of graft occlusion (Christopherson 1993 **Level II**, n=100, JS 3; Tuman 1991 **Level II**, n=80, JS 1). However, these findings have not been confirmed by other investigators in retrospective reviews (Schunn 1998 **Level III-2**, n=294; Pierce 1997 **Level III-1**, n=423), although a subsequent data base analysis of the USA National Surgical Quality Improvement Program (NSQIP) showed a number of outcome advantages (re graft failure, cardiac events, postoperative pneumonia) with epidural (and spinal) over general anaesthesia (Singh 2006 **Level III-2**, n=14,788).

For effects of epidural analgesia on pain after amputation see Section 8.1.5.1.

5.6.1.4 | Level of administration

TEA is widely used for the treatment of pain after major abdominal and thoracic surgery. Administration of local anaesthetics into the thoracic epidural space resulted in improved bowel recovery after abdominal surgery, while these benefits are not consistent with lumbar administration (Jorgensen 2000 **Level I** [Cochrane], 22 RCTs, n=1,023). In a direct comparison between TEA and LEA for thoracotomy, TEA vs LEA reduced pain scores and opioid requirements as well as hypotension, bradycardia, atelectasis and need for ICU treatment (Sagiroglu 2014 **Level II**, n=134, JS 4). Benefits of epidural analgesia after abdominal aortic surgery were found with impact on nonanalgesic outcomes significant for TEA but not LEA (see above) (Nishimori 2012 **Level I** [Cochrane], 15 RCTs, n=1,297). In patients with multiple traumatic rib fractures, provision of TEA with local anaesthetic reduced the duration of ventilation vs other forms of analgesia including LEA (Carrier 2009 **Level I**, 8 RCTs, n=232). A comparison of TEA and LEA in patients undergoing gynaecological surgery showed that TEA provided better pain relief only when the incision extended above the umbilicus; TEA led to less motor block but more pruritus (Richman 2007 **Level II**, n=103, JS 5). Motor block with epidural analgesia (mainly by infusion of bupivacaine 0.1%/fentanyl 2 mcg/mL) occurred in 36.5% of patients with the highest incidence when the catheter was placed at levels L2/3 and L 3/L4 (Ahmed 2016 **Level IV**, n=123).

TEA permits early removal of urinary catheters in many patients vs LEA; rates of urinary retention are variably reported as 6.6% (Tripepi-Bova 2013 **Level IV**, n=61), 11.9% (vs 2.2% after TEA was discontinued) (Stubbs 2013 **Level III-2**, n=118) and 26.7% (vs 12.4% in historic controls) (Hu 2014

Level III-3, n=101). Post removal of the urinary catheter, effective bladder emptying took hours to normalise (defined as post-void volumes <200 mL) in patients who received TEA, however without need for recatheterisation; this effect was prolonged when the urinary catheter was removed early on the morning after surgery rather than remaining *in situ* for the duration of TEA therapy (345 min 169 vs 207 min 122) (Zaouter 2012 **Level II**, n=205, JS 2). TEA for thoracotomy did not change the post-void volume from the preoperative findings in men and women (Wuethrich 2011b **Level III-3**, n=26); only three men >50 y with prostrate hypertrophy had post-void volumes >100 mL. However, in women undergoing nephrectomy, early removal of the urinary catheter under TEA led to a significant increase in post-void residual volume (median 5 mL vs 220 mL) and negatively affected other parameters of bladder emptying (detrusor pressure, maximum flow rate, voided volume) (Wuethrich 2011a **Level III-3**, n=13); the authors suggest that this necessitates indwelling or intermittent catheterisation or monitoring.

5.6.1.5 | Patterns of administration

Routinely, epidural analgesia is maintained by continuous infusion. More recently, programmed intermittent epidural bolus (PIEB) has been suggested as a superior technique, based on data in labour analgesia (see Section 9.1.3.3). PIEB vs continuous infusion (both delivering 3 ml/h of 0.125% bupivacaine/0.005% morphine) reduced pain scores and rescue analgesia requirements after total knee joint replacement (Kang 2013 **Level II**, n=53, JS 2). In comparison to continuous infusion in patients after major abdominal or gynaecological surgery (TEA), PIEB with both techniques delivering 6 mL/h ropivacaine 0.2% resulted in reduced PCEA requirements in the first 48 h postoperatively (median 10 mL [IQR 2 to 28] vs 28 mL [12 to 64]) without any other clinically relevant benefits (Wiesmann 2018 **Level II**, n=110, JS 5). In a similar RCT in patients undergoing open gynaecological surgery (TEA), PIEB vs continuous infusion with both techniques delivering 4 mL ropivacaine 0.2%/fentanyl 2 mcg/mL every h resulted in slightly reduced PCEA requirements, but also improved pain control from 3 to 48 h (Satomi 2018 **Level II**, n=57, JS 5).

5.6.2 | Medicines used for epidural analgesia

Differences in analgesic effect, duration and adverse effects depend upon the various local anaesthetic, opioid and adjuvant medicines used in epidural analgesia.

5.6.2.1 | Local anaesthetics

For epidural infusions, dose-ranging studies established that 0.2% ropivacaine was a suitable concentration (Scott 1995 **Level II**, n=40, JS 3; Schug 1996 **Level II**, n=50, JS 4). Therefore, most investigators compare infusions of bupivacaine or levobupivacaine at 0.1 or 0.125% with ropivacaine 0.2%, which removes any imbalance in comparative potency. For more information on differences in efficacy and adverse effects between the local anaesthetics used for epidural analgesia see Section 4.4.

5.6.2.2 | Opioids

Opioids alone via the epidural route appear to be of limited benefit. In particular, when administered via TEA, opioids fail to demonstrate any advantage over parenteral opioids except for a slight reduction in the rate of atelectasis (Ballantyne 1998 **Level I**, 48 RCTs, n unspecified) with no benefit with regard to bowel recovery (Jorgensen 2000 **Level I** [Cochrane], 22 RCTs, n=1,023). On the basis of the available studies, the benefits of administering lipophilic opioids alone by the epidural route appear to be marginal, or unproven in the case of upper abdominal surgery, and

in many situations will not outweigh the risks of the more invasive route of administration. For a detailed discussion see (Wheatley 2001 **NR**) and Section 4.3.2.

For information on the epidural use of morphine, ER morphine, pethidine, fentanyl, alfentanil, sufentanil, diamorphine and hydromorphone see also Section 4.3.2.

5.6.2.3 | Local anaesthetic-opioid combinations

Combinations of low concentrations of local anaesthetic agents and opioids provide consistently superior pain relief vs either of the medicines alone (Curatolo 1998 **Level I**, 18 RCTs [fentanyl], n unspecified). Addition of fentanyl to a continuous epidural infusion of ropivacaine reduced the rate of regression of sensory block after orthopaedic (n=80) and abdominal gynaecological surgery (n=39) (Kanai 2007 **Level II**, n=119, JS 3) and decreased the discontinuation of postoperative epidural infusion due to lack of efficacy (Scott 1999 **Level II**, n=244, JS 4).

Addition of 4 mcg/mL of fentanyl to levobupivacaine 0.125% improved quality of analgesia and reduced the stress response (ACTH, cortisol and prolactin levels) after total knee joint replacement vs plain levobupivacaine (Bayazit 2013 **Level II**, n=40, JS 4). Addition of 0.5 mcg/mL sufentanil to 0.1% ropivacaine vs higher sufentanil concentrations and 4 mcg/mL fentanyl resulted in no difference in quality of analgesia after arthroplasty and had the lowest rate of pruritus (Jeon 2011 **Level II**, n=80, JS 3). The MLAC of epidural lidocaine of 0.785% (95%CI 0.738 to 0.864) was reduced by 2 mcg/mL fentanyl to 0.596% (95%CI 0.537 to 0.660) and by 3 mcg/mL to 0.387% (95%CI 0.329 to 0.446) (up-down sequential titration) (Zhang 2012 **Level III-1**, n=120).

5.6.2.4 | Adjuvant medicines

The efficacy of adding of adjuvant medicines such as adrenaline (epinephrine), clonidine, dexmedetomidine, ketamine, midazolam, neostigmine and magnesium to solutions used for epidural analgesia has also been investigated (see Chapter 4).

5.6.3 | Patient-controlled epidural analgesia

The use of PCEA is based on similar concepts as for other patient-controlled techniques. It has been shown to be safe and effective in standard ward settings (Golster 2014 **Level IV**, n=4,663; Kim 2013 **Level IV**, n=2,276; Tan 2011 **Level IV**, n=928; Liu 2010 **Level IV**, n=3,736).

5.6.3.1 | Comparison with continuous epidural infusions

A systematic review comparing PCEA, continuous epidural infusions and IV PCA opioids after surgery showed that both forms of epidural analgesia (with the exception of hydrophilic opioid-only epidural regimens) provide better pain relief with rest and with activity than PCA opioids (Wu 2005 **Level I**, 50 RCTs, n=3,208). However, analgesia with a continuous epidural infusion is superior to PCEA, countered by higher incidence of nausea, vomiting and motor block.

For specific procedures, results of PCEA vs continuous infusion are conflicting. After colonic resection, PCEA was superior to continuous epidural infusion with regard to pain control, requirements for top-ups and systemic analgesia as well as patient satisfaction (Nightingale 2007 **Level II**, n=205, JS 5). In contrast, comparisons of PCEA and continuous epidural infusions for pain relief after thoracotomy using both high (0.5%) and low (0.15%) concentrations of levobupivacaine showed no differences in quality of analgesia, morphine consumption or satisfaction; more patients in the high concentration continuous epidural infusion group had significant motor block (Dernedde 2008 **Level II**, n=82, JS 3).

5.6.3.2 | Concurrent background (continuous) infusions

The addition of a continuous background infusion to PCEA using bupivacaine and fentanyl following gastrectomy resulted in better dynamic pain scores, with higher total doses and a greater incidence of pruritus than PCEA-bolus dose only (Komatsu 1998 **Level II**, n=40, JS 2). The use of a night-time-only background infusion with PCEA bupivacaine-fentanyl, also post gastrectomy, resulted in better sleep, but total cumulative doses were similar and pain scores were only better in the morning of postoperative d 2 (Komatsu 2001 **Level II**, n=40, JS 2). A Swedish case series over 7 y (Golster 2014 **Level IV**, n=4,663) and a USA case series (Liu 2010 **Level IV**, n=3,736) describe successful and safe use of PCEA with a background infusion.

Other studies have found no improvement in pain relief with background infusions. After lower abdominal surgery there was no difference in pain scores but higher total cumulative doses and incidence of adverse effects when a background infusion was added to PCEA with ropivacaine and fentanyl (Wong 2000 **Level II**, n=42, JS 2). The addition of a background infusion to bupivacaine-fentanyl PCEA did not improve pain relief after pelvic reconstruction (Nolan 1992 **Level II**, n=23, JS 5).

5.6.3.3 | Medicines used in postoperative patient-controlled epidural analgesia

The medicines used for PCEA are typically the same as those used for continuous epidural infusions. Conclusions about the efficacy of different medicines and medicine combinations administered via PCEA are difficult to make because of the wide variety of analgesic agents and concentrations used in the various studies.

5.6.4 | Adverse effects

5.6.4.1 | Neurological injury

Permanent neurological damage is the most feared complication of epidural analgesia.

A systematic review identified 647 cases of epidural haematoma (n=387) and abscess (n=260) after neuraxial anaesthesia (Bos 2018 **Level IV SR**, n=409 [reports]). Epidural anaesthesia was related to 58% of haematomas and 83% of abscesses. After epidural haematoma 28% had partial and 25% no recovery. After epidural abscess 21% had partial and 11% no recovery. Persistent neurological deficits were correlated with the severity of the initially presenting neurology.

A retrospective survey from Sweden put the risk of a severe neurological complication after obstetric epidural analgesia at 1 per 25,000 and for all other patients at 1 per 3,600; 67% of events resulted in permanent neurological deficit (Moen 2004 **Level IV**, n=450,000). It also identified osteoporosis as a previously neglected risk factor. A review of data from publications reporting adverse effects after obstetric epidural analgesia reported a risk estimate of 1 per 240,000 for persistent neurological injury and 1 per 6,700 for transient (resolution within 12 mth) neurological symptoms (Ruppen 2006a **Level IV SR**, 27 studies, n≈1.37 million).

A review of data from published studies of the risk of neurological injury associated with epidural and other regional anaesthesia and analgesia techniques differentiated between the risk of permanent neurological injury (deficit lasting >12 mth) and transient neuropathy (Brull 2007 **Level IV SR**, 32 studies, n unspecified). This review focussed on adverse neurological sequelae associated with the various regional techniques and did not address the overall risk of epidural haematoma or abscess. The incidence of transient neuropathy (radiculopathy) after epidural anaesthesia was estimated to be 2.19 per 10,000 (95%CI 0.88 to 5.44) (Brull 2007 **Level IV SR**, 4 studies [epidural], n unspecified). The risk of permanent neurological injury was lower and the incidences reported in the studies included in this review ranged from 0 to 7.6 per 10,000. The

rates of paraplegia and cauda equina syndrome associated with epidural anaesthesia were estimated to be 0.09 per 10,000 (95%CI 0.04 to 0.22) and 0.23 per 10,000 (95%CI 0.14 to 0.39) respectively.

A project in the UK (NAP3) assessed the incidence of neurological complications in an estimated 97,925 adult patients with perioperative epidural catheters (Cook 2009 **Level IV**). Depending on the inclusion or exclusion of cases with unlikely causation, pessimistic and optimistic assessments were published. The incidence of permanent injury was pessimistically assessed as 17.4 per 100,000 (95%CI 7.2 to 27.8; 1 in 5,800) and optimistically as 8.2 per 100,000 (95%CI 3.5 to 16.1; 1 in 12,200). Laminectomy was performed with an incidence of 12.3 per 100,000 cases (95%CI 6.3 to 21.4; 1 in 8,100). Paraplegia was caused in 6.1 per 100,000 (95%CI 2.2 to 13.3; 1 in 16,400) in the pessimistic and in 1.0 per 100,000 (95%CI 1.0 to 5.7) in the optimistic model.

Audit data from a single (nonobstetric) tertiary institution of epidural catheters inserted over a 16 y period for postoperative pain relief found two spinal haematomas and six epidural abscesses; only one patient (with an epidural abscess) required surgical decompression and no patient suffered any long-term neurological deficit (Cameron 2007 **Level IV**, n=8,210 [epidural catheters]). The largest published audit of patients undergoing arthroplasty with epidural analgesia at one institution described no persistent neurologic deficit despite four patients developing epidural haematoma and two requiring surgical compression (Pumberger 2013 **Level IV**, n=62,856). Another audit at a single institution reported 1 epidural haematoma, but 57 postoperative neurologic deficits, which resolved within 3 mth except for one being permanent (unilateral lower limb paraesthesia) (Kang 2014 **Level IV**, n=5,083).

The incidence of transient neuropathy after epidural analgesia in large case series was in the range of 0.013–0.023% (Auroy 1997 **Level IV**, n=30,413; Tanaka 1993 **Level IV**, n=40,010; Xie 1991 **Level IV**, n=1,304,214).

5.6.4.2 | Epidural haematoma

A major concern is the development of an epidural haematoma with subsequent, potentially permanent, SCI. A review including case series involving over 1,335,000 patients with epidural analgesia reported seven cases of haematoma (1 per 191,000) (Wulf 1996 **Level IV**). On the basis of this case series, the possible incidence is in the order of 1 per 100,000 at the upper limit of the 95%CI. The Swedish case series quoted above puts the overall risk of epidural haematoma after epidural blockade at 1 per 10,300 (Moen 2004 **Level IV,** n=450,000). A Finnish closed-claims study calculated a risk of 1 per 26,400 (Pitkanen 2013) **Level IV**, n=216 [claims]). An even higher incidence of epidural haematoma (1 per 3,100) has been estimated for epidural analgesia in association with inappropriate low molecular weight heparin (LMWH) dose regimens (Horlocker 2003 **GL**) (see Section 5.9).

A systematic review of the risks of epidural haematoma and neurological injury associated with epidural anaesthesia/analgesia in cardiac, vascular and thoracic surgery patients concluded that the maximum risks of epidural haematoma were 1 per 1,700, 1 per 1,700 and 1 per 1,400 respectively (Ruppen 2006b **Level IV SR**, 12 studies, n=14,105). However, this was a calculated risk only; there were actually no cases of epidural haematoma reported in the studies used in this analysis and the maximal calculated expected rate of permanent neurological injury associated with epidural haematoma was 1 per 4,600.

In a large USA case series of patients having epidural analgesia perioperatively, seven patients developed haematoma requiring surgical evacuation (1 per 8,921; 95%CI 1/4,330 to 1/22,189) (Bateman 2013 **Level IV**, n=62,450)). In four of the seven patients, management of anticoagulation was not in line with the guidelines of American Society of Regional Anesthesia and Pain Medicine

(ASRA) discussed later (see Section 5.9). In a similarly large case series of patients having arthroplasty with an indwelling epidural catheter at one institution, four epidural haematomas occurred (1 per 15,714), of which two required emergency decompression and none resulted in persisting neurological deficits (complete recovery at 6 wk) (Pumberger 2013 **Level IV**, n=62,856). It is of note that all four patients had combined spinal and epidural anaesthesia, took at least one medication affecting coagulation (aspirin, TCA, NSAIDs, clopidogrel) and had preoperative hypertension. Additional risk factors were clopidogrel only discontinued for 4 d in one, thrombocytopenia (70,000/microL) at day of insertion and removal in one and excessive alcohol consumption in two.

In a case series after cardiac surgery, the risk of epidural haematoma was calculated at 1 per 12,000 (95%CI 1 per 2,100 to 1 per 68,000); comparable to an obstetric population (Bracco 2007 **Level IV**, n=1,293). It was described as being in the same risk range as receiving a wrong blood product (or the yearly risk of having a fatal traffic accident in a Western country). A subsequent study including a survey in cardiac surgery identified a risk of epidural haematoma of 1 per 3,552 (95%CI 1 per 2552 to 1 per 5841) (Landoni 2015 **Level IV**, n=88,820 [estimated epidural catheters]).

A review of data from publications reporting adverse effects after obstetric epidural analgesia reported a risk estimate of 1 per 168,000 for epidural haematoma (Ruppen 2006a **Level IV SR**, 27 studies, n≈1.37 million). In a large USA series of obstetric epidural analgesia, no epidural haematoma was found (Bateman 2013 **Level IV**, n=79,837); the haematoma rate in this setting was significantly lower than in the perioperative data from the same series.

Case reports of epidural haematoma after neuraxial blockade (spinal and epidural) have increased from 1994 to 2015, primarily due to increased rates in elderly women (Lagerkranser 2017a **Level IV SR**, n=166). Anticoagulants, in particular heparins, remain an important risk factor, but epidural haematomas occur also in patients with no risk factors and despite following guidelines. 80% present with paresis or paralysis, early MRI scan is the best diagnostic measure and over the period studied, outcomes have improved (Lagerkranser 2017b **Level IV SR**, n=166).

Early diagnosis and, if indicated, immediate decompression (<8 h after the onset of neurological signs) increases the likelihood of partial or good neurological recovery (Horlocker 2003 **GL**). This is confirmed by a case series of epidural haematomas (n=163), which showed worse outcome with decompression delayed > 12 h vs earlier decompression (OR 4.5; 95% CI 2.1 to 9.9) (Bos 2018 **Level IV SR**, n=409 [reports]). This is confirmed by a further case series, although some patients operated >24 h regained full motor function (Lagerkranser 2017b **Level IV SR**, n=166).

5.6.4.3 | Epidural abscess and septic meningitis

Serious neuraxial infections following epidural anaesthesia have previously been reported as rare. However, prospective studies have found rates in the range of 0.015 to 0.05% (Wang 1999 **Level IV**, n=9,232; Rygnestad 1997 **Level IV**, n=2,000; Kindler 1996 **Level IV**, n>13,000). It is of note that in the studies with these high incidences, patients had long durations of epidural catheterisation; the mean duration in patients with an epidural space infection was 11 d, no infection occurred in any patient whose catheter was *in situ* for <2 d and the majority of patients were immunocompromised (Wang 1999 **Level IV**, n=9,232).

Only 5.5% of 915 cases of epidural abscess published between 1954 and 1997 developed following epidural anaesthesia and analgesia; 71% of all patients had back pain as the initial presenting symptom and only 66% were febrile (Reihsaus 2000 **Level IV**, n=915). The classic triad of symptoms (back pain, fever and neurological changes) was present in only 13% of patients with an epidural abscess (in a study unrelated to epidural catheterisation); diagnostic delays occurred in 75% of these patients and such delays led to a significantly higher incidence of residual motor weakness (Davis 2004 **Level IV**, n=63 [epidural abscesses]).

Audit data showed that of 8,210 patients with epidural catheters over a period of 16 y, six developed epidural abscesses (Cameron 2007 **Level IV**). Only one of these required surgical decompression and they did not suffer any long-term neurological loss. The authors stress the importance of appropriate patient monitoring and early diagnosis using MRI. In five of the six patients diagnosed with an epidural abscess, both fever and epidural insertion site infection were present. They therefore suggested that MRI investigation may be warranted if this combination is present and that urgent investigation is especially indicated if there is a third sign that could indicate an abscess, such as back pain or neurological change (Cameron 2007 **Level IV**, n=8,210). If the diagnosis of epidural abscess can be made before the onset of any neurological deficit, conservative treatment (antibiotics only) may be effective. The presence of severe or increasing back pain, even in the absence of a fever, may indicate epidural space infection and should be investigated promptly.

Thoracic epidural abscesses have been analysed; most common presentations were neurological deficits (68%) (paraparesis 48% and paraplegia 20%), back pain (64%), fever (24%) and loss of bowel or bladder control (16%) (Howie 2018 **Level IV SR** [PRISMA], 25 studies, n=25 [thoracic epidural abscesses]). Recommended diagnostic measures are early MRI scans, laboratory tests (ESR, CRP, blood count and sedimentation rate/C-reactive protein, complete blood count), empiric antibiotics (until abscess culture) and immediate surgical decompression in neurological deficits as immediate surgical compression achieves better recovery than a failed antibiotic course before surgical decompression.

A review of data from publications reporting adverse effects after obstetric epidural analgesia reported a risk estimate of 1 per 145,000 for epidural space infection (Ruppen 2006a **Level IV SR**, 27 studies, n≈1.37 million).

Septic meningitis has also been associated with neuraxial anaesthesia and analgesia, although most cases were associated with spinal or combined techniques; only 25 of 234 cases identified were linked to epidural techniques (Zorrilla-Vaca 2018 **Level IV SR**, n=234). Not using surgical masks was the most common association and *staphylococcus aureus* the most common bacterium. Time to onset of meningitis was longer with epidural than spinal techniques (96 h; IQR 84 to 240 vs 24 h; IQR 8 to 72) and mortality rate 13.3%.

Bacterial colonisation of epidural catheter tips is reported to occur in 0 to 28% of patients (Yuan 2008 **Level IV**, n=205; Mishra 2006 **Level IV**, n=466; Steffen 2004 **Level IV**, n=502; Simpson 2000 **Level IV**, n=1,442). The most common organism cultured from the catheter tips was coagulase-negative staphylococcus.

Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo or povidone-iodine-impregnated dressings reduced the incidence of catheter colonisation (Ho 2006 **Level I**, 8 RCTs, n=2,588). Chlorhexidine was also the superior skin disinfectant prior to regional catheter insertion with a positive skin culture immediately after skin disinfection of 10% vs 35% of povidone-iodine treated (NNT 4) (Krobbuaban 2011 **Level II**, n=100, JS 4). Chlorhexidine is therefore the recommended skin disinfectant before insertion of regional catheters (Campbell 2014 **GL**). However, chlorhexidine is neurotoxic and skin preparation solutions must be allowed to dry before instrumentation of the epidural space. For this reason, chlorhexidine must also be kept clearly identified and separate from all solutions used for injection. As 2% chlorhexidine is not superior to 0.5% for skin disinfection, UK guidelines recommend the use of 0.5% to reduce neurotoxicity (Campbell 2014 **GL**).

Experimental data suggest that after accidental epidural catheter disconnection, cutting the catheter 2 cm distal to the level of contamination left all such treated catheters sterile, while spray-wipe disinfection or employing ropivacaine 0.75% as flushing solution or a combination of these measures were not as effective (Scholle 2014 **BS**). The authors suggest spray-wipe disinfection and cutting as the safest strategy.

An *in vitro* comparison of the antibacterial activity of medicines used in epidural solutions showed that the minimal inhibitory concentration of bupivacaine for *Staphylococcus aureus*, *Enterococcus faecalis* and *Escherichia coli* was between 0.125% and 0.25% (growth of *Pseudomonas aeruginosa* was not affected at any of the concentrations investigated) (Coghlan 2009 **Level III-2 BS**). Levobupivacaine and ropivacaine showed no activity against *S aureus*, *E faecalis* and *P aeruginosa*, even at the highest concentrations tested, and minimal activity against *E coli* (minimum inhibitory concentrations 0.5 and 1% respectively). The addition of fentanyl, clonidine and adrenaline did not improve antibacterial activity

Comprehensive reviews of infectious complications associated with central neuraxial and PNB, including epidemiology, factors affecting bacterial colonisation of the epidural catheter as well as use in febrile, infected and immunocompromised patients are published (Hebl 2011 **NR**; Horlocker 2008 **NR**).

Guidelines for skin antisepsis prior to neuraxial block (Association of Anaesthetists of Great Britain and Ireland, Obstetric Anaesthetists' Association, Regional Anaesthesia UK, Association of Paediatric Anaesthetists of Great Britain and Ireland) recommend thorough handwashing with surgical scrub solution, the use of barrier precautions, including the wearing of a cap, mask, sterile gown and gloves, and of a large sterile drape (Campbell 2014 **GL**). Chlorhexidine in alcohol (0.5%) should be used for skin preparation, but meticulous care must be taken to avoid this reaching epidural space or CSF.

5.6.4.4 | Respiratory depression

The incidence of respiratory depression with epidural opioid analgesia depends on the criteria used to define respiratory depression. In a review of published case series and audit data, the reported incidence of respiratory depression ranged from 1.1 (0.6 to 1.9%) using respiratory rate to 15.1% (5.6 to 34.8%) using oxygen saturation (see Section 4.3.1.5 for comments on respiratory rate as an unreliable indicator of respiratory depression); this was very similar to the incidence reported for PCA (Cashman 2004 **Level IV SR**, 165 studies, n 20,000).

5.6.4.5 | Hypotension

The incidence of hypotension depends on the dose of local anaesthetic and criteria used to define hypotension. In the same review as above, the reported incidence of hypotension was 5.6% (3.0–10.2%) (Cashman 2004 **Level IV SR**, 165 studies, n 20,000). In the large meta-analysis quoted above, incidence of hypotension is increased by epidural analgesia (OR 4.92; 95%CI 3.11 to 7.78) (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044). Hypotension requiring intervention is increased in another meta-analysis after abdominal surgery (RR 7.13, 95%CI 2.87 to 17.75) (6 RCTs, n=479) (Salicath 2018 **Level I** [Cochrane], 32 RCTs, n=1,716); a subsequent meta-analysis shows an increase in hypotension (RD 0.21; 95% CI 0.09 to 0.33) (17 RCTs, n=870) not leading to increased need for inotropes or vasopressors (RD 0.00; 95%CI -0.06 to 0.07) (23 RCTs, n=1,821). (Guay 2019 **Level I** [Cochrane], 69 RCTs, n=4,680) (significant overlap between all three SRs).

But while TEA was associated with arterial hypotension after thoracic or abdominal surgery, this did not predict inability to walk (Gramigni 2013 **Level IV**, n=161); early mobilisation may be carefully attempted despite hypotension or orthostatic changes.

5.6.4.6 | Treatment failure

Epidural analgesia may not always be successful due to a number of factors including catheter malposition or displacement, or technical and patient factors resulting in an inability to achieve effective analgesia (Hermanides 2012 **NR**). Intolerable adverse effects may also be an indication for premature discontinuation. In a large prospective audit, 22% of patients had premature termination of postoperative epidural infusions (Ballantyne 2003 **Level IV**, n=5,628): the most common causes were dislodgement (10%), inadequate analgesia (3.5%) and sensory or motor deficit (2.2%). Most of these failures occurred on or after POD 2. The rate of technical failures in a meta-analysis of epidural analgesia was 6.1% (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044) and risk of failure of the analgesic technique is increased in another meta-analysis (epidural vs IV PCA) (RR 2.48; 95%CI 1.13 to 5.45) (10 RCTs, n=678) (Salicath 2018 **Level I** [Cochrane], 32 RCTs, n=1,716). After oesophagectomy, technical failure with TEA occurred in 17 to 22% (Hughes 2018 **Level I** [PRISMA], 3 RCTs, n=93)

Tunnelling and then suturing the epidural catheter subcutaneously vs fixation with adhesive tape without tunnelling reduced incidence of clinically relevant dislocation of epidural catheters (>20 mm; 1/60 vs 9/61) (Sellmann 2014 **Level II**, n=121, JS 3). There was also a trend towards lower bacterial contamination (8/59 vs 14/54). Length of the catheter in the epidural space may also influence rate of dislocation; in an RCT of 3, 5 and 7 cm insertion one patient in the 7 cm group had unilateral sensory block and four patients in the 3 cm group had epidural catheter dislodgement (Afshan 2011 **Level II**, n=102, JS 5). The authors suggest that 5 cm is the ideal depth of insertion.

5.6.4.7 | Anastomotic leakage

There has been concern among surgeons about increased risk of anastomotic leakage after bowel surgery due to the stimulating effects of epidural administration of local anaesthetics; so far there is no evidence to support these claims in colorectal surgery. This is supported by a large meta-analysis which shows no difference in the incidence of gastrointestinal anastomotic leakage (RR 0.74, 95%CI 0.41 to 1.32) (17 RCTs, n=848) (Guay 2016b **Level I** [Cochrane], 128 RCTs, n=8,754). An audit of patients undergoing surgery for colorectal cancer in one centre showed that epidural analgesia had no influence on occurrence of anastomotic leakage (Lai 2013 **Level III-2**, n=1,312). After oesophagectomy, TEA reduced the risk of anastomotic leakage (OR 0.13; 95%CI 0.02 to 0.71) (Michelet 2005 **Level III-2**, n=207).

KEY MESSAGES

1. For all types of surgery, epidural analgesia provides better postoperative pain relief compared with parenteral (including PCA) opioid administration (**S**) (**Level I** [Cochrane Review]); except epidural analgesia using a hydrophilic opioid only (**U**) (**Level I**).
2. Thoracic epidural analgesia for open abdominal aortic surgery reduces pain intensity, time to tracheal extubation, time spent in the intensive care unit, rate of acute respiratory failure, myocardial infarction and gastrointestinal bleeding when compared with IV opioids (**S**) (**Level I** [Cochrane Review]).
3. High thoracic epidural analgesia used for coronary artery bypass graft surgery reduces postoperative pain, risk of dysrhythmias, pulmonary complications and time to extubation when compared with intravenous opioid analgesia (**Q**) (**Level I** [Cochrane Review]).
4. Thoracic epidural analgesia for thoracotomy reduces the risk of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
5. Thoracic epidural analgesia improves bowel recovery after abdominal surgery (including colorectal surgery) (**S**) (**Level I** [Cochrane Review]).
6. Epidural analgesia is not associated with increased risk of anastomotic leakage after bowel surgery (**S**) (**Level I** [Cochrane Review]).
7. Epidural analgesia provided with local anaesthetics for at least 24 hours compared to systemic opioid analgesia reduces perioperative mortality and multiple morbidities (including ileus, pneumonia, respiratory depression and arrhythmias) but increases hypotension (**U**) (**Level I** [PRISMA]).
8. After laparoscopic colectomy, thoracic epidural analgesia compared to intravenous PCA reduces initial pain scores and time to first bowel opening, but length of hospital stay, total rate of complications (**S**) (**Level I** [PRISMA]), urinary tract infection rates and hospital costs are increased (**U**) (**Level III-2**).
9. Combinations of low concentrations of local anaesthetic agents and opioids for epidural analgesia provide consistently superior pain relief compared with either of the medications alone; epidural opioids alone have no advantage over parenteral opioids (**U**) (**Level I**).
10. Epidural local anaesthetic administration improves oxygenation and reduces pulmonary infections and other pulmonary complications compared with parenteral opioids (**U**) (**Level I**).
11. Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo- or povidone-iodine-impregnated dressings reduce the incidence of catheter colonisation (**U**) (**Level I**).
12. In patients with multiple rib fractures, thoracic epidural analgesia improves pain relief versus parenteral opioids (**N**) (**Level III-2 SR**), but does not reduce incidence of pneumonia and mortality (**U**) (**Level I**) and may not reduce need for ventilation (**Q**) (**Level III-2 SR**).

13. The combination of thoracic epidural analgesia with local anaesthetics and nutritional support leads to preservation of total body protein after upper abdominal surgery (**U**) (**Level II**).
14. The incidence of permanent neurological damage in association with epidural analgesia is extremely low, especially in the obstetric population, but increases with various comorbidities and risk factors; the incidence is higher where there have been delays in diagnosing an epidural haematoma or abscess (**S**) (**Level IV SR**).
15. Immediate decompression of an epidural haematoma (within 8 hours of the onset of neurological signs) increases the likelihood of partial or good neurological recovery (**S**) (**Level IV SR**).
16. Epidural abscesses present mainly with neurological deficits and back pain; they are best diagnosed with early MRI and best treated with empiric antibiotics (until abscess culture) and immediate surgical decompression when neurological deficits are present (**S**) (**Level IV SR).**

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

☑ The provision of epidural analgesia by continuous infusion, programmed intermittent bolus or patient-controlled administration of local anaesthetic-opioid mixtures is safe on general hospital wards, as long as supervised by an anaesthesia-based pain service with 24-hour medical staff cover and monitored by well-trained nursing staff (**U**).

☑ Prior to insertion of an epidural catheter, thorough handwashing with surgical scrub solution, the use of barrier precautions including the wearing of a cap, mask, sterile gown and gloves and use of chlorhexidine in alcohol for skin preparation are recommended; but meticulous care must be taken to avoid the chlorhexidine solution from reaching epidural space or cerebrospinal fluid (**U**).

5.7 | Intrathecal analgesia

5.7.1 | Medicines used for intrathecal analgesia

5.7.1.1 | Local anaesthetics

IT local anaesthetics provide short-term postoperative analgesia. The use of spinal microcatheters (<24-gauge) for postoperative infusions of local anaesthetics became controversial when multiple cases of cauda equina syndrome were reported (Bevacqua 2003 **NR**). See also Section 5.7.1.1. above.

5.7.1.2 | Opioids

Morphine is the most frequently studied IT opioid followed by fentanyl (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338; Meylan 2009 **Level I**, 27 RCTs, n=1,205). Reported IT use of other opioids includes pethidine (meperidine), hydromorphone, diamorphine, pentazocine, sufentanil, tramadol and buprenorphine (Staikou 2014 **Level I**, 105 RCTs, n unspecified). Some clinical studies used very high IT morphine doses (ie 500 mcg or more) without additional benefit. Lower doses (<300 mcg) should be used as there is no clear dose-response relationship with IT morphine for duration of analgesia nor for adverse effects (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338; Meylan 2009 **Level I**, 27 RCTs, n=1,205).

For patients having procedures amenable to spinal anaesthesia alone (orthopaedic, urologic, gynaecologic), the addition of IT morphine (50 mcg to 2 mg) was found to consistently provide an increase in duration of analgesia (as time to first requirement of additional opioid analgesia) (WMD 503 min; 95%CI 315 to 641)) vs IT local anaesthetic alone (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). IT fentanyl (10 to 50 mcg) prolonged the duration of analgesia by a WMD of 114 min (95%CI 60 to 168). There was also a reduction in cumulative morphine consumption when IT morphine was used (WMD -12 mg; 95%CI -18 to -5). There was considerable heterogeneity in the study data and no dose-responsiveness could be identified.

For major abdominal or thoracic surgery, IT opioids are typically combined with a general anaesthetic technique. In patients having abdominal, cardiothoracic or spinal surgery, IT morphine (100 to 500 mcg, without local anaesthetic) reduced pain scores at rest and with movement at 12 h by 1/10 and 2/10 respectively, and also at 24 h by 1/10 and 2/10 (Meylan 2009 **Level I**, 27 RCTs, n=1,205). Morphine-sparing was evident for up to 48 h postoperatively, being more pronounced at 24 h after abdominal than cardiothoracic surgery

IT fentanyl is inferior to IT dexmedetomidine which prolongs the pain free period (SMD 2.98; 95%CI 1.69 to 4.27) without increasing the incidence of adverse events including hypotension and bradycardia (Sun 2017 **Level I**, 9 RCTs, n=639).

Lower limb arthroplasty (TKA and THA)

In comparison to IT morphine for THA and TKA, local infiltration analgesia (LIA) results in a small reduction of pain scores at rest and at mobilisation at 24 h, but not at 48 h (Jia 2017 **Level I**, 4 RCTs, n=242). There is no difference in the rescue opioid consumption. Nausea, vomiting and pruritus are increased in the IT morphine group.

IT morphine vs FNB for TKA shows similar pain scores at 6 h (SMD -0.09; 95%CI -1.62 to 1.43) as well as at 12 h and 24 h with no difference in morphine consumption for the same time points and PONV (Li 2016 **Level I**, 4 RCTs, n=185). The risk of postoperative pruritus is reduced with FNB (RD 0.41; 95%CI 0.29 to 0.54). Another meta-analysis of the same issues shows significant inconsistencies in representing trial results, which makes it difficult to be confident of the

conclusions drawn (Tang 2017 **Level I** [PRISMA], 5 RCTs, n=225) (overlapping by 4 RCTs). Therefore, and in view of the significant overlap between both meta-analyses, only the results of the previous meta-analysis are considered (Li 2016 **Level I**, 4 RCTs, n=185).

Several RCTs and studies have shown that the use of low-dose IT morphine has analgesic benefit. One RCT included in both meta-analyses had a third group combining continuous FNB with IT morphine, with no advantage of the combination over the continuous FNB, which was superior to IT morphine alone (Olive 2015 **Level II**, n=81, JS 4). In contrast, a small dose of IT morphine (35 mcg) improved pain scores significantly when added to a continuous FNB, although the authors noted a higher rate of severe pain in both groups than in comparable studies of FNB (Sundarathiti 2016 **Level II**, n=70, JS 4). For TKA under spinal anaesthesia, where all patients had LIA, addition of IT morphine 100 mcg to adductor canal block achieved the lowest pain scores and morphine requirements vs adductor canal block alone and sham adductor canal block (Biswas 2018 **Level II**, n=201, JS 5). However, there was no difference in the primary outcome 'Timed Up and Go (TUG)' test on POD 2 and any other short- or long-term functional outcomes. IT morphine in addition to systemic multimodal analgesia for THA and TKA (and a continuous FNB or Adductor Canal Block (ACB) for TKA until POD 1) achieved better analgesia, reduced opioid consumption, better mobilisation and less nausea (Cheah 2018 **Level III-2**, n=598). When compared to an US guided fascia iliaca block for THA under spinal anaesthesia, IT morphine reduced the cumulative morphine consumption at 48 h and time to mobilisation (by 2 h) without a significant difference in adverse side effects (Kearns 2016 **Level II**, n=108, JS 5). Compared to a continuous lumbar plexus catheter technique for THA, IT morphine (100 mcg) added to spinal anaesthesia resulted in similar pain scores and opioid supplementation rates, but higher rates of pruritus (Fredrickson 2015 **Level II**, n=50, JS 2).

Caesarean section

IT opioids have been used as a component of the spinal anaesthetic for Caesarean section for many years. The addition of IT morphine increases the median time to first analgesia from 2 h (range 1 to 4 h) to 27 h (range 11 to 29 h) (Dahl 1999 **Level I**, 15 RCTs, n=535). Higher doses of IT morphine (>100 to 250 mcg) vs lower doses (50 to 100 mcg) for analgesia after Caesarean section lead to a longer time to first analgesic request (MD 4.49 h; 95%CI 1.85 to 7.13), but with no significant difference in pain scores or morphine consumption (Sultan 2016 **Level I**, 11 RCTs, n=480). The high-dose IT morphine group has higher incidence of PONV and pruritus (NNH 5.9; 95%CI 3.4 to 20.0) with no effect on Apgar scores.

IT morphine in a dose of 50 mcg had similar analgesic effects to 100 and 150 mcg when used with a spinal block and ketorolac with a similar side effect profile (with the lowest dose having a slightly reduced incidence of pruritus) (Berger 2016 **Level II**, n=144, JS 5). IT morphine 50 mcg had similar analgesic effects to 100 mcg, but the higher dose resulted in a significantly higher rate of pruritus (64 vs 40%) (Mikuni 2010 **Level II**, n=75, JS 3). Using an up–down sequential allocation the ED_{90} was determined to be 75 mcg (95%CI 46 to 93) for IT hydromorphone and 150 mcg (95%CI 145 to 185) for IT morphine with no difference between both for analgesia, side effects and patient satisfaction (Sviggum 2016 **Level II**, n=80, JS 5).

IT fentanyl added to spinal anaesthesia leads to a longer time to first analgesic request (MD 91 min; 95%CI 69 to 113) and reduces the incidence of nausea/vomiting (RR 0.41; 95%CI 0.24 to 0.70) (NNT 6.5), but increases the incidence of intraoperative pruritus (RR 5.89; 95%CI 2.07 to 16.79) (NNH 13.5) (15 RCTs, n=759) (Uppal 2020 **Level I** [PRISMA], 17 RCTs, n=1,064).

IT fentanyl/morphine combination (25mcg/100mcg) vs morphine alone improved intraoperative analgesia and did not affect 24 h postop opioid requirements, but increased 12 h opioid requirements and PONV rates (Weigl 2017 **Level II**, n=60, JS 5).

Compared to a transversus abdominus plane (TAP) block, 100 mcg of IT morphine resulted in lower pain scores, but only at 10 h, while causing more PONV and pruritus (Loane 2012 **Level II**, n=66, JS 5). This study failed to achieve full recruitment. IT morphine (100 mcg) vs ropivacaine 0.2% via wound catheter had the same efficacy with no difference in median time to first morphine request (Lalmand 2017 **Level II**, n=192, JS 5). Both techniques were superior to the control group with spinal anaesthesia by bupivacaine/sufentanil only.

Labour

Adding IT morphine (50 to 250 mcg) to single-shot IT bupivacaine/fentanyl or bupivacaine/sufentanil prolongs pain relief during labour by 61 min (range 3 to 155 min) with no effect on SMD of pain intensity (Al-Kazwini 2016 **Level I** [PRISMA], 5 RCTs, n=286).

Spinal surgery

IT morphine vs systemic opioids after spinal surgery results in reduced pain scores and postoperative opioid consumption during the first 24 postoperative h in the IT morphine group with a higher rate of pruritus; respiratory depression only occurred in the IT morphine group (6/231) (Pendi 2017 **Level I**, 8 RCTs, n=393).

Administration of IT morphine (3.5 mcg/kg) after lumbar laminectomy reduced the morphine requirements at 24 h (32.7 mg versus 59.4 mg), but did not significantly reduce pain scores vs a placebo injection (Yen 2015 **Level II**, n=32, JS 4).

Cardiothoracic surgery

IT morphine (7mcg/kg) prior to surgical aortic valve surgery had a better analgesic effect postoperatively vs titrated systemic fentanyl, with reduced parenteral opioid requirements and increased time to first opioid rescue (Elgendy 2017 **Level II**, n=44, JS 5). In addition, the IT morphine group had a slightly earlier extubation and shorter ICU LOS. There were no reports of increased side effects. In minimally invasive cardiac surgery, IT morphine reduced PCA-opioid requirements and pain scores (Mukherjee 2012 **Level II**, n=62, JS 3). For open thoracotomy procedures, the combination of IT morphine and sufentanil with a continuous PVB offered slightly higher but acceptable pain scores vs epidural analgesia (Dango 2013 **Level II**, n=84, JS 4).

Hepatic surgery

After liver resection, IT morphine 500 mcg/fentanyl 150 mcg resulted in better analgesia and lower opioid requirements than morphine PCA up to 18 h postoperatively (Roy 2006 **Level II**, n=20, JS 3). Compared to epidural analgesia, IT morphine 200 mcg in liver resections showed comparable pain scores, although there was a reduction in opioid consumption and intubation duration favouring the epidural group (De Pietri 2006 **Level II**, n=50, JS 2). Similarly, in patients for liver resections, IT morphine 500 mcg and fentanyl 15 mcg was inferior to epidural bupivacaine infusion, with twice as much morphine consumption (123 mg vs 59 mg) and more pain (Mondor 2010 **Level II**, n=44, JS 5).

Urological surgery

IT morphine (50–200 mcg ± clonidine) after prostatic surgery resulted in better analgesia and lower opioid requirements than morphine PCA up to 18 h postoperatively (Brown 2004 **Level II**, n=99, JS 5). For transurethral resection of the prostate under spinal anaesthesia, low-dose IT morphine (25 and 50 mcg) resulted in similar pain scores for up to 24 h, but the higher-dose group had more pruritus (15 vs 0%) (Duman 2010 **Level II**, n=70, JS 4).

Other surgery

IT hydromorphone in addition to spinal anaesthesia for knee arthroscopic surgery significantly reduced pain scores for up to 12 h with a 5 or 10 mcg dose vs 2.5 mcg or placebo. Nausea was more frequent (46%) in the 10 mcg group (Lee 2012 **Level II**, n=60, JS 3).

After open nephrectomy, IT morphine (330 mcg) plus IV PCA versus IV PCA alone resulted in better analgesia and reduced systemic opioid requirements with similar adverse effects except for increased pruritus (77% versus 26%) (Kim 2016 **Level II**, n=45, JS 4).

IT morphine at three different doses (100, 200 and 300 mcg) for total abdominal hysterectomy was superior to placebo for analgesia up to 24 h, with the 200 mcg dose equivalent to 300 mcg and superior to 100 mcg in rescue analgesia requirements (Hein 2012 **Level II**, n=144, JS 5). For inguinal hernia repair, IT morphine 100 mcg had similar analgesia to 400 mcg with increased PONV in the higher dose group (Meco 2016 **Level II**, n=48, JS 4).

For endovenous laser ablation in lower extremity venous insufficiency/varicose vein disease, the addition of IT morphine (100 mcg) versus IT fentanyl (25 mcg) to bupivacaine spinal anaesthesia reduced shivering vs placebo control as well as increased time to first analgesia use with no difference between morphine and fentanyl (Onk 2016 **Level II**, n=90, JS 4).

5.7.1.3 | Adverse effects

Typical adverse effects of IT opioids include nausea and vomiting, pruritus and delayed respiratory depression (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338; Meylan 2009 **Level I**, 27 RCTs, n=1,205).

Opioid-induced ventilatory impairment

The definition of respiratory depression in different investigations often lacks uniformity, with many studies using respiratory rate as the primary marker and others using desaturation to different levels and a few others using the need for opioid antagonists. This significantly compromises interpretation of reported event rates. OIVI is a more appropriate term (Macintyre 2011 **NR**). Patients may be hypoxic or hypercapnic with a normal respiratory rate (Bailey 1993 **Level IV EH**, n=20), while others may be able to maintain normocarbia with a lower respiratory rate (Boezaart 1999 **Level II**, n=60, JS 5). In a volunteer study, clinical signs or symptoms including respiratory rate, sedation and pupil size did not reliably indicate hypoventilation or hypoxaemia, unlike peripheral pulse oximetry (Bailey 1993 **Level IV EH**, n=20); although desaturation itself is a late indicator when supplemental oxygen is being administered (Shapiro 2005 **Level IV**, n=1,524). Very large numbers of patient exposures are needed to adequately quantify risk of infrequent events (eg OIVI) thus most studies and meta-analyses will have a limited capacity to report meaningfully on such adverse effects (see also Section 4.3.1.4).

When measured in opioid-naïve volunteers, respiratory depression peaked at 3.5 to 7.5 h following IT morphine at 200 to 600 mcg doses (Bailey 1993 **Level IV EH**, n=20). Volunteers given 600 mcg had significant depression of the ventilatory response to CO_2 up to 19.5 h later.

In patients following major surgery, a 7.6% incidence of respiratory depression was reported in three RCTs (n=172) for IT morphine vs IV PCA morphine (OR 7.86; 95%CI 1.54 to 40.3) (Meylan 2009 **Level I**, 27 RCTs, n=1,205). In patients having spinal surgery, IT morphine only resulted in respiratory depression (6/231) versus placebo (0/162) (RR 3.48; 95%CI 0.41 to 29.32) (Pendi 2017 **Level I**, 8 RCTs, n=393). In patients having minor surgery, major respiratory depression (endpoint "*SpO2 85 to 90%*" in addition to respiratory rate <12) occurred in 3 of 290 (1.0%) patients receiving IT bupivacaine alone and 15 of 410 (3.7%) receiving IT bupivacaine/morphine (OR 3.49; 95%CI 1.25 to 9.73) (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). In the same analysis, the incidence of OIVI in patients receiving IT fentanyl (0.4%) was no different to control (0%). Thus,

indirect comparisons suggest that the risk of OIVI is more pronounced with IT morphine than with IT fentanyl.

A meta-analysis for a range of procedures, comparing IT morphine doses of <300 mcg, ≥300 mcg and placebo reported a greater risk of respiratory depression (respiratory rate <8 to 12) with the higher dose group of IT morphine (9%) with no increased risk with lower morphine dose (1%) vs systemic opioids (2%) (Gehling 2009a **Level I**, 28 RCTs, n=1,414). This difference was not statistically significant but this may reflect the relatively small number of patients in the higher dose group (n=87). The incidence of pruritus was increased for all doses (low dose RR 1.8; 95%CI 1.4 to 2.2 vs high dose RR 5.0; 95%CI 2.9 to 8.6); the risk of nausea and vomiting was increased only in those patients given <300 mcg morphine.

For Caesarean section, when IT opioids (all types of opioids and all doses) were combined with local anaesthetic for analgesia, the rate of respiratory depression was low and not significantly different from controls (Dahl 1999 **Level I**, 15 RCTs, n=535). In a large case series clinically detected respiratory depression in the 24 h following 150 mcg IT morphine was noted in 0.26% of patients (Kato 2008 **Level IV**, n=1,915). In a closed claims study from the USA, a maternal death from IT opioid overdose is reported (Clayton 2018 **CR**).

A prospective audit of IT morphine (200 to 800 mcg) for pain relief following a range of surgical procedures reported a high degree of patient satisfaction and effective analgesia in the first 24 h (Gwirtz 1999 **Level IV**, n=5,969). The incidence of pruritus was 37%, nausea and vomiting 25% and respiratory depression 3% ($PaCO_2$ >50 mmHg and/or respiratory rate <8).

Overall, considering the increased risk of OIVI with IT morphine, the lowest effective dose of IT opioid should be used and surveillance for OIVI should continue for at least 18–24 h following a single dose (Bailey 1993 **Level IV**; Bujedo 2012 **NR**). A current guideline by the ASA recommends a minimum monitoring period of 24 h after administration of single injection IT morphine, with monitoring of at least once per hour for the first 12 h and then at least once every 2 h for the next 12 h (ASA 2016 **GL**). The monitoring should consist of level of consciousness, adequacy of ventilation (rate and depth of respiration) and pulse oximetry. Higher risk patients may require additional monitoring and for a longer period of time. This document also discusses in further detail identification of at-risk patients and strategies for prevention, detection and management of OIVI in patients with neuraxial opioids.

A similar guideline has been published by the Society for Obstetric Anesthesia and Perinatology (SOAP) for the use of neuraxial opioids in Caesarean section patients (Bauchat 2019 **GL**).

Pruritus

Pruritus is a frequent adverse effect of opioids by all routes. The rate following IT morphine is significantly higher than that for patients receiving IV PCA morphine (OR 3.85; 95%CI 2.40 to 6.15) (Meylan 2009 **Level I**, 27 RCTs, n=1,205) and dose-dependent (Sultan 2016 **Level I**, 11 RCTs, n=480). The itch is thought to be caused by stimulation of spinal and supraspinal mu-opioid receptors which includes the trigeminal nucleus and explains the frequency of facial itch (Kumar 2013 **NR**). The incidence of pruritus with IT morphine was 29.2% vs 4.4% with bupivacaine alone (OR 6.92; 95%CI 4.51 to 10.6; NNH 4) (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). IT fentanyl had an incidence of pruritus of 27.3% vs 0% with bupivacaine alone. Pregnant women report greater rates of pruritus of 60–100%, which may be due to an interaction of oestrogen with opioid receptors (Kumar 2013 **NR**). While the incidence of pruritus is consistently high, the number requiring treatment is lower; in post-Caesarean section patients receiving 100 mcg IT morphine, 64% of patients reported pruritus with the proportion requiring treatment being 18% (Mikuni 2010 **Level II**, n=75, JS 3). In patients having Caesarean section under spinal anaesthesia, IT morphine 100 mcg was vs oral opioid (oxycodone SR). The IT morphine group had similar overall

pain scores but reported better satisfaction at 24 h and fewer high pain scores but experienced more pruritus (87 vs 56%) (McDonnell 2010 **Level II**, n=111, JS 5).

There may be a connection between serotonin (5-HT) levels and pruritus, as IT morphine increases serotonin plasma concentrations in a dose-dependent fashion by 283% (10 mcg) vs 556% (200 mcg) with pruritus rates of 55% and 75% respectively (Aly 2018 **Level II**, n=40, JS 5). $5HT_3$-receptor antagonists decrease the incidence of pruritus related to IT opioids with an NNT of 6 (OR 0.44; 95%CI 0.29 to 0.68) (Bonnet 2008 **Level I**, 15 RCTs, n=1,337). This analysis included a high number of Caesarean section patients, who reported higher rates of pruritus. In a subgroup analysis, the antipruritic effect was significant in the morphine group, but not with fentanyl. A similar analysis based purely on Caesarean section patients receiving IT morphine did not identify a decrease in incidence in pruritus overall with prophylactic $5HT_3$ antagonists, but found a reduction in the incidence of severe pruritus and a NNT of 3 for reduction of established pruritus (George 2009 **Level I** [PRISMA], 9 RCTs, n=1,152) (6 RCTs overlap with Bonnet 2008). Ondansetron (4 to 8 mg) reduces pruritus after IT morphine in non-obstetric cases (RR 0.63; 95%CI 0.45 to 0.89) (7 RCTs [1 RCT epidural morphine], n=576) (Wang 2017 **Level I** (PRISMA), 10 RCTs, n=811). However, the result for Caesarean section was not significant with a high degree of heterogeneity (3 RCTs, n=253). Reasons for an inconclusive result in the obstetric group highlighted by the authors include the co-administration of a lipid soluble opioid fentanyl, the delay in administration of ondansetron until after IT morphine because of concerns of placental transfer and altered pharmacokinetic handling of ondansetron in parturient women. Specifically, in pruritus caused by IT fentanyl and IT sufentanil IV ondansetron 8 mg did not reduce the incidence of pruritus, but the need for rescue medication (RR 0.57; 95%CI 0.35 to 0.91) (Prin 2016 **Level I**, 6 RCTs, n=555).

There is limited data and conflicting results regarding the use of opioid antagonists in treating pruritus following IT opioids. However, with parenteral opioids, overall IV naloxone reduces the incidence of pruritus (OR 0.40; 95%CI 0.21 to 0.79) and nausea (OR 0.62; 95%CI 0.43 to 0.89) but not vomiting (Murphy 2011 **Level I**, 8 RCTs, n=800). Other methods that have been described for prevention include nalbuphine (Tubog 2019 **Level I** [PRISMA}, 17 RCTs, n=1,052), mirtazapine (an SSRI antidepressant) and dopamine antagonists such as droperidol (Kumar 2013 **NR**). SC methylnaltrexone 12 mg, a mu-opioid receptor antagonist that works peripherally and does not cross the blood brain barrier, reduced nausea, but had no effect on pruritis or urinary retention (Zand 2015 **Level II**, n=72, JS 5). Similarly, SC methylnaltrexone 12 mg versus placebo did not reduce pruritus from IT morphine 100 mcg after Caesarean section (84% vs 88%) (Paech 2015 **Level II**, n=37, JS 5).

Other treatments for established pruritus include pentazocine, a mixed opioid agonist-antagonist with kappa receptor effects, which was more effective in treating pruritus post Caesarean section than ondansetron 4 mg (Tamdee 2009 **Level II**, n=208, JS 5). IV pentazocine 15 mg vs placebo had also a prophylactic effect on pruritus after IT opioids for Caesarean section (RR 0.69; 95%CI 0.52 to 0.90) (Hirabayashi 2017 **Level II**, n=122, JS 5). Diphenhydramine 25 mg has also been reported to be as effective as ondansetron 4 mg (Siddik-Sayyid 2010 **Level II**, n=113, JS 5).

Preoperative acupuncture vs sham acupuncture maintained for 48 h postoperatively was ineffective in reducing pruritus caused by IT morphine for Caesarean section (Mazda 2018 **Level II**, n=30, JS 5).

Nausea and vomiting

Postoperative nausea is common after IT morphine, especially in obstetrics. Consensus guidelines exist for PONV management; however, these do not address IT opioids specifically (Gan 2014 **GL**). Following minor surgical procedures, the addition of IT morphine significantly increased the risk of nausea from 29.4% to 39.4% (OR 1.66; 95%CI 1.05 to 2.64) (NNH 9.8) and vomiting from 16.6% to 26.2% (OR 1.88; 95%CI 1.20 to 2.94) (NNH 10) vs IT local anaesthetic with systemic analgesics (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). Following major surgery,

comparing IT opioids to systemic opioids there was a nonsignificant increase in the incidence of nausea (30.5 vs 24.2%; OR 1.22; 95%CI 0.77 to 1.95) and no difference in the incidence of vomiting (23.8 vs 22.6%; OR 1.05; 95%CI 0.63 to 1.73) (Meylan 2009 **Level I**, 27 RCTs, n=1,205). A low dose of IT morphine (100 mcg) caused no vomiting vs 400 mcg (23%) for inguinal hernia repair (Meco 2016 **Level II**, n=48, JS 4).

Following Caesarean section with IT morphine and fentanyl, ondansetron and transdermal scopolamine were equally effective in reducing emesis from 59.3% (control) to 41.8% (ondansetron) and 40% (scopolamine), although scopolamine use was associated with more anticholinergic adverse effects (Harnett 2007 **Level II**, n=240, JS 4). The combination of ondansetron with either dexamethasone or droperidol had a better antiemetic effect after gynaecological surgery with IT morphine vs droperidol/dexamethasone (Sanchez-Ledesma 2002 **Level II,** n=90, JS 4), although this combination was superior to either alone (Wu 2007 **Level II**, n=120, JS 5).

Urinary retention

The incidence of urinary retention was not increased in patients receiving IT morphine for major surgery (Gehling 2009b **Level I**, 28 RCTs, n=1,414; Meylan 2009 **Level I**, 27 RCTs, n=1,205); however, in patients having spinal anaesthesia for minor surgery, IT morphine increased the risk of urinary retention (OR 3.9; 95%CI 1.94 to 7.86) (NNH 6.5) (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338).

Other adverse effects

In women in labour, reactivation of oral herpes simplex labialis was more frequent (38%) following IT morphine for labour analgesia than IV PCA morphine (16.6%) (Davies 2005 **Level II**, n=98, JS 4).

Cardiovascular effects of IT opioids have generally not been reported. In a retrospective cohort study, IT hydromorphone used in patients having elective colorectal resection with restricted fluid therapy found a higher rate of hypotension (mean arterial blood pressure <60 mmHg or systolic blood pressure <110 mmHg) in those receiving hydromorphone (4.3%) vs the control group up to 12 h (Hubner 2013 **Level III-2**, n=163). This normalised by 24 h and was not associated with any identified adverse outcomes. IT morphine (7 mcg/kg) in surgical aortic valve replacement decreased mean arterial pressure and heart rate while preserving cardiac output, pulmonary capillary wedge pressure and central venous pressure (Elgendy 2017 **Level II**, n=44, JS 5).

Caution has been advised regarding the use of IT opioids in patients who are at risk of spinal cord ischaemia (eg thoracic aortic stenting/surgery) (Fedorow 2010 **NR**), although its use has been described (Chaney 1996 **Level IV**). Such caution is based primarily on laboratory data although there is a case report (Kakinohana 2003 **CR**).

5.7.1.4 | Adjuvant medicines

A variety of adjuvant medicines have been used with IT analgesia, including clonidine, dexmedetomidine, ketamine, neostigmine and midazolam. Many medicines are not licensed for use as spinal analgesic agents; however adequate evidence from the literature may make their use acceptable (for more detail see Chapter 4).

Clonidine and Dexmedetomidine

The addition of clonidine to IT morphine causes a small increase in analgesia duration by 1.63 h (95%CI 0.93 to 2.33) and reduces the amount of systemic morphine consumption over 24 h by 4.45 mg (95%CI 1.40 to 7.49) (Engelman 2013 **Level I** [PRISMA], 7 RCTs, n=503). Incidence of hypotension was also increased (OR 1.78; 95%CI 1.02 to 3.12).

For major abdominal cancer surgery, IT dexmedetomidine 5 mcg added to IT morphine 500 mcg and bupivacaine did not improve analgesia vs the IT morphine/bupivacaine group (Abdel-Ghaffar 2016 **Level II**, n=90, JS 5). Both groups with adjuncts experienced better analgesia than bupivacaine alone.

Magnesium

Magnesium most likely contributes to analgesia by acting as a noncompetitive NMDA-receptor antagonist in the spinal cord. There was no benefit with IT versus intraperitoneal magnesium in animal experiments (Messeha 2016 **BS**). Magnesium with opioid with or without local anaesthetic prolongs the time to first analgesia requirement in non-obstetric populations (SMD 1.38; 95%CI 0.6 to 2.11) but not obstetric patients (Morrison 2013 **Level I**, 15 RCTs, n=980). This may be an effect of fewer studies in the obstetric group. There is no increase in incidence of hypotension. There was a high degree of heterogeneity making any firm conclusion difficult.

KEY MESSAGES

1. Intrathecal morphine improves analgesia and is opioid-sparing for up to 24 hours after major surgery including abdominal (**S**), orthopaedic (**N**), spinal (**N**) (**Level I** [PRISMA]) and cardiothoracic surgery (**N**) (**Level II**).
2. Adding intrathecal morphine to intrathecal bupivacaine/fentanyl or intrathecal bupivacaine/sufentanil prolongs pain relief after labour (**N)** (**Level I** [PRISMA]).
3. The addition of intrathecal fentanyl (**N**) (**Level I** [PRISMA]) and morphine to spinal anaesthesia prolongs time to first analgesic request after Caesarean section (**N)** (**Level I**).
4. Intrathecal morphine in comparison to peripheral regional analgesia techniques offers similar analgesic benefits, but increases adverse effects (nausea, vomiting, pruritus) after lower limb arthroplasty (**N**) (**Level I**).
5. The incidence of opioid-induced ventilatory impairment, pruritus and PONV is higher with intrathecal morphine compared with intravenous PCA opioids (**S**) (**Level I**).
6. Pruritus with intrathecal opioids is dose-dependent (**N**) (**Level I**) and can be effectively prevented and treated with $5HT_3$ antagonists in non-obstetric patients, but only treated but not prevented in obstetric patients (**Q**) (**Level I**)
7. Pruritus with intrathecal opioids cannot be treated with methylnaltrexone (**N**) (**Level II**).
8. The addition of intrathecal clonidine to intrathecal morphine results in slightly longer analgesia and reduced opioid requirements (**U**) (**Level I**).
9. The addition of intrathecal magnesium to opioids and/or local anaesthetics results in slightly longer analgesia in non-obstetric patients (**U**) (**Level I**).

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

☑ The absence of consistent dose-responsiveness to the efficacy of intrathecal opioids and the increase in adverse effects with higher doses suggests that the lowest effective dose (typically 50-200 mcg morphine) should be used (**Q**).

☑ Patients receiving intrathecal opioids should be monitored for opioid-induced ventilatory impairment for the anticipated duration of opioid effects, eg 18 to 24 hours after intrathecal morphine (**S**).

☑ Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at normal clinical intrathecal doses (**U**), however caution is recommended in patients who are at risk of spinal cord ischaemia **(U)**.

5.8 | Other regional and local analgesic techniques

Regional and local analgesic techniques have evolved recently, with a large number of new ultrasound-guided blocks. There have been developments in our understanding of anatomy and proof-of-concept studies on neuromodulation for acute pain management. Regional and local analgesic techniques should be used in conjunction with oral multimodal analgesic techniques.

Adjuvant agents to local anaesthetics are considered in other sections: eg alpha-2-agonists in Section 4.9.2 and corticosteroids in Section 4.12.2 and opioids in Section 4.2.3.

5.8.1 | Needle and catheter localising techniques

Techniques used to precisely identify correct needle location and hence local anaesthetic and catheter placement include anatomic landmarks, peripheral nerve stimulation (PNS) and ultrasound (US) guidance. Radiologic imaging and direct vision during surgery have also been used. In comparison with PNS, blocks performed using US guidance are more likely to be successful (RR 0.41 [for block failure]; 95%CI 0.26 to 0.66), faster to perform (mean 1 min less to perform with US), have faster onset (29% shorter onset time; 95%CI 45 to 12%) and longer duration (Abrahams 2009 **Level I**, 13 RCTs, n=941). US guidance is associated with an increase in success rate of nerve blocks vs all non-US techniques (RR 1.11; 95%CI 1.06 to 1.17) and vs PNS alone (RR 1.11; 95%CI 1.05 to 1.17) (Gelfand 2011 **Level I**, 16 RCTs, n=1,264). US-guided techniques, vs other needle-localisation techniques, are associated with higher success rates, faster onset of block and lower vascular puncture rate (McCartney 2010 **Level I**, 25 RCTs, n=2,187). Duration of analgesia is longer with US-guided blocks than those performed with PNS guidance (SMD 25%; 95%CI 12 to 38) (Abrahams 2009 **Level I**, 13 RCTs, n=941).

Stimulating catheters have been compared with nonstimulating catheter techniques in establishing continuous FNBs for postoperative analgesia following TKA. There was no difference in quality of postoperative analgesia between these two insertion techniques (Barrington 2008 **Level II**, n=82, JS 5; Morin 2005 **Level II**, n=141, JS 3). Stimulating catheters have also been compared with nonstimulating catheter techniques at other anatomical locations with inconclusive results (Stevens 2007 **Level II**, n=43, JS 4; Dauri 2007 **Level II**, n=70, JS 3; Rodriguez 2006 **Level II**, n=48, JS 3).

US guidance has been compared with stimulating and non-stimulating techniques for continuous infraclavicular brachial plexus block. The combination of US and PNS guidance (with stimulating catheters) resulted in the highest primary success and reduced secondary catheter failure (Dhir 2008 **Level II**, n=66, JS 3). In the placement of popliteal sciatic nerve catheters, US guidance alone resulted in similar analgesic outcomes for up to 48 h vs US and PNS (stimulating catheter) guidance (Robards 2013 **Level II**, n=21, JS 3). In patients having total knee arthroplasty (TKA), the combination of US guidance and PNS (needle and/or stimulating catheter) was not different to US guidance alone in analgesic efficacy over 48 h (Farag 2014 **Level II**, n=437, JS 4); stimulating catheter use was associated with a longer procedural time.

An analysis of the German Network of Regional Anaesthesia database between 2007 and 2012 revealed effects of being awake (n=25,004), sedated (n=15.121) or anaesthetised (n=2,529) on complications of regional anaesthesia (Kubulus 2016 **Level III-2**, n=42,654). There were no differences in the rates of LAST or pneumothorax. For peripheral nerve blocks, both sedation (aOR 1.82; 95%CI 1.50 to 2.21) and general anaesthesia (aOR 1.33; 95%CI 1.01 to 1.78) were associated with an increased risk of a bloody tap. The risk for multiple skin puncture was lower in sedated (aOR 0.78; 95%CI 0.71 to 0.85) and higher in anaesthetised patients (aOR 1.28; 95%CI 1.12 to 1.46).

5.8.2 | Continuous and single-injection peripheral nerve blocks

Percutaneous perineural catheter placement enables an infusion of local anaesthetic increasing the duration of analgesia and associated benefits. Continuous peripheral nerve blockade (CPNB) is indicated for treatment of acute postoperative pain, vascular insufficiency, chronic pain conditions and cancer-related pain. CPNB is used in hospital, ambulatory and in trauma settings (Ilfeld 2011a **NR**; Ilfeld 2011b **NR**).

5.8.2.1 | Continuous peripheral nerve block compared to single-injection techniques

Compared with single-injection techniques, CPNB improve pain control, decrease opioid requirements, reduce nausea and improve patient satisfaction postoperatively (Bingham 2012 **Level I**, 21 RCTs, n=702). 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 included limits these statements. These findings are consistent with some but not all recent studies.

Following total knee arthroplasty (TKA), three analgesic modalities were compared: continuous FNB, single-injection FNB and LIA by surgeon (Choi 2016 **Level II**, n=120, JS 5). There were no differences between study groups in pain scores on the morning of POD 2 (primary outcome) or 48 h opioid consumption. However, both continuous FNB and LIA resulted in superior pain control vs the single-injection group on POD 1. Three continuous FNB infusion regimens were evaluated following TKA: ropivacaine 0.2%, ropivacaine 0.1% and sodium chloride 0.9 % as placebo in a trial that was terminated early because of changes in institutional pathways (Albrecht 2014 **Level II**, n=99, JS 5). This pilot data demonstrated no difference in the primary outcome 'time to discharge readiness'. Continuous FNB was not superior (pain scores at 48 h) to single injection FNB following TKA (Dixit 2018 **Level II**, n=85, JS 4). There was no difference in opioid consumption and functional recovery.

Following TKA, single injection adductor canal block (ACB) (combined with sciatic nerve block and posterior capsule LIA by surgeon) was vs continuous ACB (Turner 2018 **Level II**, n=60, JS 5). Local anaesthetic adjuvants included clonidine 33.4 mcg, buprenorphine 150 mcg, dexamethasone 2 mg, and epinephrine. Single injection ACB provided comparable analgesia for 32 h, but continuous ACB improved pain scores beyond 42 h. Following TKA, single injection ACB (2 groups, 1 included IV dexamethasone) was compared to continuous ACB (Lee 2018, **Level II**, n=180, JS 3). Initial local anaesthetic dosage for ACB was ropivacaine 0.5% 20 mL vs periarticular infiltration with ropivacaine 0.5% 30 mL. Single injection ACB (with and without systemic dexamethasone) was non-inferior to continuous ACB for 24 h opioid consumption with continuous ACB patients consuming more opioids 0 to 24 h. Possible reasons include catheter migration, poor placement and superior injectate spread of the single-injection technique.

5.8.3 | Upper limb blocks

5.8.3.1 | Interscalene and suprascapular nerve block

Compared with a single-injection interscalene block continuous interscalene blockade with ropivacaine 0.2% following shoulder surgery (rotator cuff surgery, arthroplasty) improved pain outcomes, sleep, patient satisfaction, reduced time to discharge readiness and a greater degree of shoulder movement (Salviz 2013 **Level II**, n=71, JS 3; Yang 2013 **Level II**, n=56, JS 4; Mariano 2009 **Level II**, n=32, JS 5; Ilfeld 2006 **Level II**, n=32, JS 3). Because of close proximity to the neuraxis, a test dose of local anaesthetic through an interscalene catheter should precede a continuous infusion.

Performing interscalene blockade in adults under general anaesthesia is controversial with case reports of block-related mechanical injury to the spinal cord (Benumof 2000 **CR**). Phrenic nerve block is the most common adverse effect of interscalene block. Strategies to reduce the likelihood or magnitude of phrenic nerve block include reducing local anaesthetic dosage, using US guidance, injecting at the C7 vertebral level and use of suprascapular or axillary block (Verelst 2013 **NR**). Suprascapular block resulted in reduced pain vs placebo or subacromial local anaesthetic infusion (Jeske 2011 **Level II**, n=45, JS 4). For shoulder arthroscopy, interscalene block vs combined suprascapular and axillary block resulted in superior analgesia in PACU, but inferior analgesia at 24 h (Dhir 2016 **Level II,** n=60, JS 5). Suprascapular nerve block (anterior approach deep to omohyoid muscle) was compared with interscalene block for shoulder arthroscopy using a composite outcome of pain and grip strength (Wiegel 2017 **Level II,** n=336, JS 5). Different local anaesthetic dosages used in the two study groups (interscalene, ropivacaine 150 mg; suprascapular, ropivacaine 100 mg) resulted in reduced motor block with the suprascapular block and non-inferiority for pain outcomes. Following shoulder arthroplasty, vital capacity at 24 h (primary outcome) was reduced for continuous interscalene (by 991 mL) vs supraclavicular (by 803 mL) block (Auyong 2017 **Level II,** n=75, JS 5). However, anterior suprascapular block had the least effect on vital capacity (reduced by 464 mL) indicating a potential advantage in using this approach in patients with pulmonary disease, while there were no differences in analgesic outcomes.

5.8.3.2 | Other brachial plexus blocks

The incidence of insensate limb with continuous infraclavicular brachial plexus block was higher when the same total dosage of 0.4% ropivacaine was compared with 0.2% ropivacaine. There was no difference in analgesia but satisfaction scores were higher in patients who received the 0.2% infusion (Ilfeld 2009 **Level II**, n=50, JS 3). Following hand surgery, continuous brachial plexus block (axillary approach) (0.1 or 0.2% ropivacaine) did not improve pain outcomes vs single-injection technique with a long-acting local anaesthetic (Salonen 2000 **Level II**, n=60, JS 4). This is also true in comparison with continuous infraclavicular blocks (Mariano 2011 **Level II**, n=20, JS 3).

5.8.4 | Lower limb blocks

Patient falls following major surgery is a key concern. After TKA, inpatient falls occurred in 1.6% and this event was associated with increasing age and higher comorbidity burden, whereas PNB did not increase the risk (OR 0.85; 95%CI 0.71 to 1.03) (Memtsoudis 2014 **Level IV**, n=191,570). Following TKA, continuous lumbar plexus block was associated with an increased risk of inpatient falls vs single-injection block or no block (OR 3.85; 95%CI 1.52 to 9.72) (NNH 59) (Johnson 2013 **Level III-3 SR**, 10 studies, n=4,014). The risk of falls with FNB was not different from ACB following total knee arthroplasty, but patients receiving ACB had significantly increased quadriceps motor strength (Elkassabany 2016 **Level II**, n=62, JS 5).

5.8.4.1 | Femoral nerve block

Continuous femoral nerve block (FNB) either as a continuous or single-injection technique IV PCA analgesia alone is associated with improved analgesia on movement, reduced morphine consumption and decreased incidence of nausea following total knee arthroplasty (Paul 2010 **Level I**, 23 RCTs, n=1,016). Compared with periarticular infiltration of local anaesthetic (LIA), continuous FNB for total knee arthroplasty resulted in reduced opioid consumption and improved functional indicators at 6 wk (Carli 2010 **Level II**, n=40, JS 4). A similar study (infiltration vs continuous FNB) reported no significant difference in opioid consumption; however, 37% of

patients who received the FNB experienced quadriceps weakness vs 0% in the infiltration group (Chaumeron 2013 **Level II**, n=60, JS 5). Continuous FNB combined with single injection sciatic block resulted in better pain relief vs IT morphine (Alvarez 2017 **Level II**, n=40, JS 2). For more information on any differences between the local anaesthetics used for FNBs see Section 4.4.2.

5.8.4.2 | Fascia iliaca compartment and lateral femoral cutaneous nerve block

Single-injection fascia iliaca compartment block (FICB) provided similar postoperative analgesia to FNB following anterior cruciate ligament repair (Farid 2010 **Level II**, n=23, JS 3); and to '3-in-1' nerve block following knee joint arthroscopy and meniscal repair (Wallace 2012 **Level II**, n=60, JS 3). Suprainguinal FICB was opioid-sparing following THA vs no block (Desmet 2017 **Level II**, n=88, JS 5). However, effect on mobilisation was not recorded, which is relevant because FICB may have resulted in motor block delaying early mobilisation. Following a posterior approach to total hip arthroplasty under spinal anaesthesia, US-guided lateral FNB with 8 mL ropivacaine 0.75% vs placebo had no effect on analgesic outcomes at 4 h (Thybo 2016 **Level II**, n=100, JS 5). All patients received paracetamol and ibuprofen.

Continuous FICB provided similar postoperative analgesia to continuous FNB over 48 h following TKA (Brisbane 2010 **Level II**, n=98, JS 2).

5.8.4.3 | Adductor canal and distal femoral triangle block

Recent anatomical studies point to the importance of the nerve to vastus medialis innervating the anteromedial knee capsule (Burckett-St Laurant 2016 **BS**). Research into the anatomy of the adductor canal and femoral triangle has supported the development of US-guided motor-sparing techniques. Since 2014, there has been a vast literature published on adductor canal block (ACB) compared to different combination therapies. However, interpreting the results of RCTs with ACB as an intervention is confounded by lack of consistency in how the block is implemented. It is likely in many RCTs that the ACBs were performed in the femoral triangle and not in the adductor canal. There has been extensive dialogue on this topic with one group describing how the apex of the femoral triangle (and hence the adductor canal which is located between the femoral triangle apex and the adductor hiatus) can be defined using US (Wong 2017 **BS**) The apex of the femoral triangle can be located using US where the medial borders of the adductor longus and sartorius intersect. This knowledge permits block placement at a consistent location where the nerve to vastus medialis and saphenous nerve are closely located. In contrast, but also to maintain consistency, other investigators perform ACB exactly halfway 'mid-thigh' between the anterior iliac spine and the cephalad border of the patella (Jaeger 2012 **Level II**, n=42, JS 5). Subsequent studies have defined the optimal anatomical location further. The 'mid-thigh' location was compared to a true adductor canal approach, where the superficial femoral artery descends towards the adductor hiatus (Sztain 2018 **Level II**, n=50, JS 4). The median pain score on POD 1 was reduced with the proximal vs the distal block (0.5/10 vs 3.0/10), however the worst pain scores were not different. Continuous distal ACB provided noninferior analgesia to a proximal approach following total knee arthroplasty (Meier 2018 **Level II**, n=73, JS 5). Combined distal femoral triangle/obturator blockade was superior to LIA in patients having total knee arthroplasty (Runge 2018 **Level II**, n=74, JS 5). The median 20-h morphine consumption was 6 mg (IQR 2 to 18) vs 20 mg (12 to 28) respectively with no difference in LOS.

Adductor canal block compared to placebo

ACB reduced opioid consumption and pain scores vs placebo after TKA (Hanson 2014 **Level II**, n=80, JS 5; Grevstad 2014 **Level II**, n=50, JS 5; Jenstrup 2012 **Level II**, n=75, JS 4; Jaeger 2012 **Level II**, n=42, JS 5). Single injection ACB with 10 mL bupivacaine 0.25% vs 0.9% saline on top of LIA with 100 mL

ropivacaine 0.2% resulted in clinically relevant improvements in analgesia outcomes (opioid consumption, pain scores) at 36 h (Nader 2016 **Level II**, n=40, JS 5).

Adductor canal compared to femoral nerve blockade

In a volunteer study, ACB produced 8% loss of quadriceps strength vs 49% with FNB (Jaeger 2013 **Level II EH**, n=12, JS 5); this is similarly reported as minimal loss of quadriceps strength with ACB vs FNB in another volunteer study (Kwofie 2013 **Level II EH**, n=16, JS 5).

ACB vs FNB results in similar control of postoperative pain following TKA (no differences in pain at rest and with mobilisation, rescue opioid requirements and patient satisfaction) with reduced likelihood of quadriceps weakness and improved mobilisation leading to better functional recovery (Kuang 2017 **Level I** [PRISMA], 9 RCTs, n=609; Hussain 2016 **Level I**, 6 RCTs, n=447) (6 RCTs overlap).

Studies published subsequent to the meta-analyses or not included confirm these findings. Pre-block maximum voluntary isometric contraction (MVIC) of the quadriceps increased at 60 min in patients who received ACB 24 h after TKA with ropivacaine 0.75% 30 mL vs placebo (median 170% vs 93%) (Sorensen 2016 **Level II**, n=64, JS 5). Despite overall better motor function associated with ACB, decrease in MVIC (defined as MVIC <75% of pre-block values) occurred in 5/64 patients and 4 of these were unable to perform the 'Timed Up and Go' test. This underscores the importance of a thorough functional assessment and falls prevention program. Continuous FNB vs continuous ACB showed no difference in analgesic outcomes and early recovery, although quadriceps motor strength with ACB was increased (Seo 2017 **Level III-1**, n=43). Time to discharge did not differ with continuous ACB vs continuous FNB following unicompartmental knee arthroplasty despite more patients satisfying discharge criteria on POD 2 in the ACB group (Sztain 2015 **Level II**, n=30, JS 3). More patients randomized to ACB, despite significantly worse dynamic pain scores on day of surgery and POD 1, ambulated >30 m than patients in FNB group.

Adductor canal block compared to LIA

There was no significant difference in the 'Timed Up and Go' test (46, 45 and 52 s) on POD 2 (primary outcome) in an RCT comparing LIA/placebo blocks with LIA/ACB with LIA/ACB/IT morphine (Biswas 2018 **Level II**, n=201, JS 5). However, pain control was improved in patients randomised to LIA/ACB/IT morphine. Combined ACB/LIA reduced pain on walking on POD 1 vs ACB block alone or LIA alone (Sawhney 2016 **Level II,** n=151, JS 5). ACB was compared to LIA following TKA with an opioid sparing effect at 24 h (6 vs 13 mg) and at 48 h (10 vs 25 mg) and reduced pain score at 6 to 16 h (by 1.2 to 1.5/10) (Kampitak 2018 **Level II**, n=60, JS 5). See also Section 5.8.2.1 below.

Adductor canal block compared to other peripheral nerve block combinations

Patients received continuous ACB and LIA for total knee arthroplasty and were randomized to receive in addition: obturator, tibial or both nerve blocks (Kampitak 2019 **Level II**, n=90, JS 4). Patients who received all three blocks had superior analgesia and reduced opioid use (2 mg vs 4 mg and 6 mg morphine at 24 h) and mobilisation outcomes. Continuous ACB vs sham catheter inserted on POD 1 decreased opioid consumption, pain scores in 20 h following insertion (on POD 2) and improved function at 3 wk (Leung 2018 **Level II**, n=165, JS 4). Epidural analgesia was used as the analgesic technique in the first 24 h and multimodal analgesia (e.g. NSAID or Cox II inhibitors) was not used. Due to withdrawals only 70 patients completed the study which may have introduced bias.

Adductor canal block – dosage and infusion considerations

There was no meaningful difference in quadriceps strength to 4 h with 10 mL vs 30 mL ropivacaine 0.1% for ACB (Jaeger 2015b **Level II EH**, n=26, JS 5). Both volumes produced

meaningfully reduced tonic heat pain response indicating successful saphenous block. The ED_{95} (minimum effective anesthetic volume in 95% of the subjects) to fill the distal adductor canal estimated on MRI was 20 mL (Jaeger 2015a **Level III-2 EH**, n=40). The ED_{50} (minimum effective anesthetic volume in 50% of the subjects) needed for a 30% decrease in quadriceps strength was determined used the Dixon-Massey up-and-down method in patients having arthroscopic knee surgery as being 46.5 mL (95% confidence interval, 45.01-50.43 mL) (Johnston 2017 **Level III-2**, n=26). This volume is significantly higher than standard dosages used in clinical practice.

Bilateral continuous ACB was established in volunteers with one limb of each subject randomly assigned to a continuous infusion of 8 mL/h or automated hourly boluses of 8 mL (Monahan 2016 **Level II EH**, n=24, JS 5). Tolerance to transcutaneous electrical stimulation in the territory of the anterior branch of the medial femoral cutaneous nerve was evaluated at 8 h with equivalent cutaneous analgesia (non-inferiority). There were no differences in secondary endpoints such as cutaneous analgesia at later time points or motor blockade. Continuous infusion 7 mL/h was compared to intermittent boluses (23 mL/3 h) with no difference in opioid consumption and other analgesic outcomes following TKA (Jaeger 2018 **Level II**, n=110, JS 5).

5.8.4.4 | Sciatic nerve block

After lower extremity surgery (Ilfeld 2002 **Level II**, n=30, JS 4) and foot surgery (White 2003 **Level II**, n=24, JS 5), continuous popliteal sciatic nerve analgesia resulted in better pain relief, lower opioid requirements and fewer adverse effects compared with opioids alone. The benefit of sciatic nerve block in addition to FNB for analgesia following TKA remains unclear (Paul 2010 **Level I**, 23 RCTs, n=1,016).

Interspace between the Popliteal Artery and the Capsule of the Posterior Knee (iPACK) block

iPACK block is a motor sparing block following TKA. It is likely iPACK results in blockade of a plexus formed by the posterior division of the obturator nerve and the tibial nerve that innervates the posterior knee capsule (Tran 2019 **BS**). ACB and iPACK block when added to periarticular injection had lower pain scores on ambulation on POD 1 (Kim 2019a **Level II**, n=86, JS 5). ACB/iPACK block vs ACB resulted in improved pain scores from 8 h to POD 2 (Sankineani 2018 **Level III-2**, n=120).

5.8.4.5 | Lumbar plexus

Continuous FNB was compared to continuous posterior lumbar plexus block following THA. There was no difference in postoperative pain scores, however patients who received FNB had more motor block impairing ambulatory function (Ilfeld 2011c **Level II**, n=50, JS 3). Lumbar plexus block resulted in a modest improvement in pain in the early postoperative period following hip arthroscopy (YaDeau 2012 **Level II**, n=84, JS 5). Lumbar plexus block vs ACB provided similar analgesia following unicondylar knee arthroplasty 6 h later (Henshaw 2016 **Level II**, n=150, JS 5). There were no other differences in analgesia outcomes in first postoperative 24 h. Quadriceps motor strength was better in the ACB group.

5.8.5 | Truncal blocks

Truncal blocks are increasingly used to provide analgesia after surgery; the number of techniques for these blocks is continuously increasing and most are performed with US guidance; a detailed systematic review on the current developments of these techniques with regard to anatomy, clinical outcomes and complications has been published (Abrahams 2016 **Level IV SR**, n unspecified).

5.8.5.1 | Paravertebral blocks

Paravertebral block (PVB) is a technique that is likely to benefit from US guidance because the landmark technique has been associated with a high proportion of misplaced catheters (Luyet 2012 **Level IV**, n=31), and US guidance can improve the needle trajectory (Abdallah 2014a **NR**). All forms of PVB combined (single-injection, multi-level injection and continuous infusion) demonstrate superior analgesia for up to 48 h following breast surgery than systemic analgesia, with a lower incidence of PONV (RR 0.26; 95%CI 0.13 to 0.5) and few specific adverse effects (Schnabel 2010 **Level I** [PRISMA], 15 RCTs, n=877). PVBs with general anaesthesia or propofol sedation reduce pain scores at rest and movement (22 RCTs, n=1,714) and reduce opioid consumption (16 RCTs, n=1,406) up to 72 h after breast surgery (Terkawi 2015 **Level I** [PRISMA], 24 RCTs, n=1,822). Addition of fentanyl (11 RCTs) and multilevel injection (5 RCTs) improve quality of analgesia. Reduced nausea and vomiting and small decrease in hospital LOS are also observed. A further study confirmed an improved quality of recovery (Abdallah 2014b **Level II**, n=64, JS 5).

For breast cancer surgery, PVB (6 RCTs, n=419) reduces CPSP (OR 0.61; 95%CI 0.39 to 0.97) (NNT 11) (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027). See also Section 1.4.6.1.

For thoracotomy, paravertebral or epidural techniques provide superior analgesia vs IT, interpleural, IC and systemic opioid techniques; PVB causes less hypotension than epidural analgesia and reduce the incidence of pulmonary complications with systemic analgesia (Joshi 2008 **Level I**, 74 RCTs, n unspecified). Following thoracotomy, there is moderate-quality evidence that shows comparable analgesic efficacy at rest and after coughing with PVB vs epidural analgesia (Yeung 2016 **Level I** [Cochrane], 14 RCTs, n=698). There is low to very low-quality evidence that showed no significant difference in mortality and major complications. There is moderate-quality evidence that PVB has a superior minor complication risk vs thoracic epidural analgesia including hypotension (RR 0.16; 95%CI 0.07 to 0.38) (8 RCTs, n=445), nausea and vomiting (RR 0.48; 95%CI 0.30 to 0.75) (6 RCTs, n=345), pruritus (RR 0.29; 95%CI 0.14 to 0.59) (5 RCTs, n=249) and urinary retention (RR 0.22; 95%CI 0.11 to 0.46) (5 RCTs, n=258). These results are consistent with a parallel meta-analysis showing that continuous PVB reduces the incidence of nausea, vomiting, hypotension and urinary retention when vs thoracic epidural analgesia, wound infiltration or IV opioids while providing comparable post-cardiothoracic surgery analgesia (Scarfe 2016 **Level I** [PRISMA], 23 RCTs, n= 1,120) (12 RCTs overlap).

Paravertebral block for midline sternotomy and open liver resection

Most of the evidence for PVB is following breast surgery or thoracotomy, but there are a limited number of studies following midline cardiac surgery (eg 2 of 18 RCTs comparing PVB and TEA in (Scarfe 2016 **Level I**, 23 RCTs, n= 1,120). A comparison of continuous bilateral thoracic PVB with bilateral continuous SC lidocaine infusions in patients undergoing cardiac surgery found no difference in postoperative morphine requirements (Lockwood 2017 **Level II**, n=50, JS 5). Appropriately, the authors highlight the risk of local anaesthetic systemic toxicity (LAST) with continuous bilateral PVBs in patients with ischaemic heart disease and extensive medical comorbidities. The risk of LAST is confirmed in patients having coronary artery bypass surgery with continuous bilateral thoracic PVB, where plasma ropivacaine concentrations consistent with toxicity and one case of toxicity occurred with dosages in the range recommended by manufacturers (Ho 2016 **Level IV PK**, n=8).

Following elective open liver resection, patients were randomised to receive either TEA or bilateral T7 or T8 PVB with ropivacaine (0.2%) infused for 3 d (Schreiber 2016 **Level II**, n=87, JS 3). There was a statistically significant, but clinically modest reduction in pain score in the epidural group.

5.8.5.2 | Intercostal and interpleural block

Following a single intercostal block (ICB) using 0.5% bupivacaine, segmental analgesia can last up to 20 h (Perttunen 1995 **Level II**, n=45, JS 2). Multilevel ICBs improve analgesia vs systemic opioids alone, particularly during POD 1 (Detterbeck 2005 **Level I**, 12 RCTs [ICB vs systemic opioids], n=477); pulmonary function tests are better preserved, although pulmonary complications are not consistently reduced. There are no consistent differences in analgesia outcomes for multilevel ICBs in comparison with epidural analgesia (Detterbeck 2005 **Level I**, 5 RCTs [ICB vs epidural], n=140), although duration of follow-up was not specified and individual studies were small. Following thoracotomy, surgically delivered ICBs with liposomal bupivacaine provided improved analgesia on POD 1 and 3 vs TEA (technique unspecified) with hydromorphone PCA used as rescue in both groups (Khalil 2015, **Level III-2,** n=85).

Analgesia can be achieved using a subpleural catheter placed in the space posterior to the parietal pleura alongside the paravertebral area, or more laterally in the IC region. Following posterolateral thoracotomy, patients receiving TEA had superior pain control vs continuous subpleural analgesia (Kanazi 2012 **Level II**, n=42, JS 4; Debreceni 2003 **Level II**, n=50, JS 5). However, similar analgesia was achieved for up to 5 d with epidural vs IC catheter local anaesthetic infusions (Luketich 2005 **Level II**, n=91, JS 3).

Multilevel US-guided IC nerve blocks provided superior pain relief for 24 h vs systemic analgesics alone after percutaneous nephrolithotomy (Ozkan 2013 **Level II**, n=40, JS 5).

The incidence of pneumothorax following multilevel ICBs has been estimated at 0.07% based on data from approximately 100,000 injections (Moore 1975 **Level IV**, n=10,941 [patients]).

Interpleural local anaesthetic infusion has not been found to be superior to systemic opioid analgesia in thoracotomy patients (Detterbeck 2005 **Level I**, 11 RCTs [interpleural], n=287). Interpleural analgesia (intermittent bolus injection technique) was compared to continuous TEA following minimally invasive thoracoscopic surgery (Ishikawa 2012 **Level II**, n=40, JS 1); pain scores were not different between the groups. Interpleural analgesia is superior to systemic analgesia following open cholecystectomy but not following laparoscopic cholecystectomy or nephrectomy (Dravid 2007 **NR**).

5.8.5.3 | Paravertebral block variants (erector spinae plane block, retrolaminar block)

The erector spinae plane block (ESPB), an US-guided technique with plane of injection between the thoracic vertebral transverse process (often mid-thoracic) and the erector spinae muscle was described in 2016 for a chronic pain indication (Forero 2016 **CR**). The premise of erector spinae plane block and retrolaminar blocks are that spinal ventral and posterior rami are accessed with local anaesthetic injected posterior to, instead of injection anterior to the costotransverse ligament. For retrolaminar blocks the local anaesthetic is injected between erector spinae muscle and the thoracic lamina. It is debated whether the ESPB is a paravertebral variant involving nerve roots (Tsui 2019a **Level IV**, n=242) vs a myofascial plane block. Paravertebral spread of 15 mL radiocontrast was demonstrated during fluoroscopic study through continuous ESPB (Ueshima 2018 **Level IV**, n=3). In unembalmed cadavers, US-guided 20 mL injectate into ESP at T5 involved dorsal rami in 80%, ventral rami in 20%, but dorsal ganglion in only 10% (Ivanusic 2018 **Level IV BS**, n=10 [cadavers]). A second cadaver study assessed an injection on opposite sides into ESP and retrolaminar space with 20 mL injectate at T5; spread to the epidural and neural foraminal spaces over 2 to 5 levels was demonstrated with MRI and anatomical dissection (Adhikary 2019 **Level IV BS**, n=3 [cadavers]).

For ESPB, single-shot techniques were used in 80.2%, intermittent boluses in 12% and continuous infusions in 7.9% (Tsui 2019a **Level IV SR**, 85 studies, n=242). Multimodal analgesia was used in 91% of cases. Sensory changes were reported in 35% of cases; 35% reported reduced

opioid use. For retrolaminar blocks the local anaesthetic is injected between erector spinae muscle and the thoracic lamina.

ESPB versus systemic analgesia after breast (1 RCT: Gurkan 2018 **Level II**, n=50, JS 2) and cardiac surgery (1 RCT: Krishna 2019 **Level II**, n=106, JS 4) as well as after laparoscopic cholecystectomy (1 RCT: Tulgar 2018 **Level II**, n=30, JS 1) improves analgesia and/or reduces rescue requirements (De Cassai 2019 **Level I** [PRISMA], 4 RCTs, n=242). Following cardiac surgery with median sternotomy, continuous bilateral ESPB vs TEA resulted in similar pain scores for the first 12 h and improved pain scores between 24 h and 48 h (1 RCT: Nagaraja 2018 **Level II**, n=50, JS 3).

RCTs not included in this SR are in line with these results. For modified radical mastectomy, similar results were demonstrated for ESPB vs routine pain management (Singh 2019 **Level II**, n=40, JS 4). Following open epigastric hernia repair, ESPB vs sham block reduced pain scores and decreased perioperative analgesic requirements (Abu Elyazed 2019 **Level II**, n=60, JS 3). Following total abdominal hysterectomy, bilateral ESPB vs sham block did not result in a clinically significant reduction in postoperative fentanyl consumption, but achieved clinically significant pain reduction for 12 h (Hamed 2019 **Level II**, n=60, JS 4).

ESPB vs TAP block following laparoscopic cholecystectomy leads to reduction of opioid requirements and pain intensity (Ciftci 2020 **Level II**, n=60, JS 3; Altiparmak 2019a **Level II**, n=68, JS 4).

For video-assisted thoracoscopic surgery, EPSB vs serratus plane block reduced pain intensity from 4 to 6 h and increased time to rescue analgesia (Gaballah 2019 **Level II**, n=60, JS 4).

5.8.5.4 | Pectoralis nerves and serratus plane blocks

US-guided pectoralis nerves (PECS) blocks and serratus anterior plane (SAP) blocks are regional analgesia techniques of the thorax (Battista 2020 **NR**). PECS and SAP blocks were developed as a less invasive alternative to PVB for breast surgery. In PECS I blocks the injectate is injected between pectoralis major and minor only. PECS II blocks refer to an US-guided block of the medial and lateral pectoral nerves (target plane between pectoralis major and minor muscles) combined with lateral cutaneous branch of the intercostal nerves (target plane between the pectoralis minor and serratus anterior muscles).

PECS I blocks vs placebo in the setting of multimodal analgesia did not reduce pain scores in PACU following tissue preserving breast cancer surgery (Cros 2018 **Level II**, n=128, JS 5).

Combined PECS I and PECS II blocks vs control reduced postoperative pain scores for 24 h and decreased morphine consumption for 12 h following modified radical mastectomy surgery (Bashandy 2015 **Level II**, n=120, JS 3). After mastectomy, PECS II block vs placebo resulted in less pain and reduced opioid requirements during the PACU stay (Versyck 2017 **Level II**, n=140, JS 5). Similarly, for breast cancer surgery, PECS II blocks vs control had an opioid-sparing effect and resulted in better mobilization of the shoulder and patient satisfaction (Neethu 2018, **Level II**, n=60, JS 2). Following radical mastectomy, PECS II block provided superior analgesia to ESPB (tramadol requirements as primary outcome) (Altiparmak 2019b **Level II**, n=38, JS 3).

Postoperative insertion of combined bilateral PECS II blocks and drain site infiltration (35 mL bupivacaine 0.25%) with no block (all participants received paracetamol/tramadol) in patients undergoing median sternotomy cardiac surgery reduced pain scores and requirement for intensive care resources (Kumar 2018, **Level II**, n=40, JS 3). After paediatric cardiac surgery through a thoracotomy, PECS II and SAP blocks vs IC blocks resulted in statistically significant, but clinically modest, improved analgesia (Kaushal 2019 **Level II**, n=108, JS 3).

SAP block was superior (opioid consumption and first request for analgesia) to no block for mastectomy (Rahimzadeh 2018 **Level II**, n=60, JS 2). SAP block vs PVB for modified radical mastectomy was inferior with regard to time to commence PCA use (245 min vs 346 min) and opioid requirements with similar pain scores (Gupta 2017 **Level II**, n=50, JS 5). Similarly, following

modified radical mastectomy PVB vs SAP block prolonged analgesia (11 vs 6 h) (Hetta 2016 **Level II**, n=64, JS 3).

Following video-assisted thoracic surgery, SAP block vs placebo improved 40-item Quality of Recovery (QoR-40) score at 24 h after surgery (Kim 2018a **Level II**, n=90, JS 5). SAP block vs systemic multimodal analgesia reduced pain scores following thoracoscopic surgery for 8 h (Semyonov 2019 **Level II**, n=104, JS 1). SAP block vs TEA had reduced effects on blood pressure (primary outcome) following thoracotomy (Khalil 2017 **Level II**, n=60, JS 3).

5.8.5.5 | Sternal bed blocks

PECS blocks will not block the anterior cutaneous branch of the intercostal nerves. However, transversus thoracis block, a sternal bed block with local anaesthetic injected into the neurovascular plane superficial to the transversus thoracis muscle will result in anterior cutaneous branch block. Injections of ropivacaine 0.5% (total dosage <5 mg/kg) into the 2nd to 6th parasternal intercostal spaces were superior to the same volume of sodium chloride 0.9 % as placebo for treatment of postoperative pain in pediatric patients undergoing cardiac surgery with a median sternotomy (Chaudhary 2012 **Level II**, n=30, JS 4). PECS block combined with transversus thoracis block vs PECS block alone reduced pain intensity following mastectomy (Ueshima 2017a **Level II**, n=70, JS 3).

Surgeon administered sternal bed blocks combined with systemic analgesia vs systemic analgesia alone resulted in clinically relevant reduced pain scores for 24 h following coronary artery bypass graft surgery (CABG) (Dogan Baki 2016 **Level II**, n=81, JS 4). This study included a 6 mth follow-up, where there was no difference in the incidence of chronic pain

5.8.5.6 | Transversus abdominus plane block

Transversus abdominis plane block (TAPB) is used to provide analgesia following abdominal surgery. TAPB are routinely performed with US guidance. Independent of the type of surgery (abdominal laparotomy, abdominal laparoscopy, and Caesarean section) US guided TAPB vs sham or no block reduce IV morphine consumption at 6 h (MD -6 mg; 95%CI −7 to −4) and 24 h (MD −11 mg; 95%CI −14 to −8) vs control or placebo (Baeriswyl 2015 **Level I** [PRISMA], 31 RCTs, n= 1,611). In addition, pain at rest (MD −10/100; 95%CI −15 to −5) and on movement (MD −9/100; 95%CI −14 to −5) at 6 h are reduced, but not PONV or pruritus. These effects are not seen in patients receiving long-acting spinal opioid, and were independent of timing of injection, approach used or the use of systemic multimodal analgesia. A parallel systematic review in all types of surgery (with significant overlap) describes similar effects; TAPB vs placebo reduces pain intensity at 6 h by 1.4/10 (95%CI -1.9 to -0.8), at 12 h by 2.0/10 (95%CI -2.7 to-1.4), at 24 h by 1.2/10 (95%CI -1.6 to -0.8) and opioid requirements at 24 h (MED -14.7 mg; 95%CI -18.4 to -11.0) (Brogi 2016 **Level I** [PRISMA], 51 RCTs, n unspecified). These results remain consistent across surgical types, but analgesic efficacy of TAPB is inferior to IT morphine. These results are also in line with two preceding meta-analyses specifically looking at effects of TAPB in Caesarean section (Mishriky 2012 **Level I**, 9 RCTs, n=524) (4 RCTs overlap with Baeriswyl 2015) and in laparoscopic surgery (De Oliveira 2014 **Level I**, 10 RCTs, n=633) (all 10 RCTs overlap with Baeriswyl 2015). RCTs not included in these meta-analyses have shown contradictory results (Soltani Mohammadi 2014 **Level II**, n=67, JS 5; Rao Kadam 2013 **Level II**, n=42, JS 3).

For a wide range of open and laparoscopic abdominal surgery in adults and children, epidural analgesia vs TAPB provides similar analgesia (MD 0.3/10; 95%CI -0.1 to 0.6), but TAPB reduces the risk of hypotension (RR 0.13; 95%CI 0.04 to 0.38) and LOS (MD: -0.6 d; 95%CI: -0.9 to -0.3) (Baeriswyl 2018 **Level I** [PRISMA], 10 RCTs [TAPB vs epidural analgesia], n=505).

After abdominal hysterectomy, TAPB vs sham block or no block reduce 24 h opioid consumption (3 RCTs, n=126), pain scores at 2 h (6 RCTs, n=274) and 24 h (5 RCTs, n=228), PONV (6 RCTs, n=345) and prolong time to analgesic request (4 RCTs, n=238) (Zhou 2018 **Level I** [PRISMA], 13 RCTs, n=841) (3 RCTs overlap with Baeriswyl 2015). After open hysterectomy, TAPB vs epidural analgesia vs parenteral analgesia provided the best pain relief and the lowest opioid rescue requirements (Mathew 2019 **Level II**, n=60, JS 4).

In adults undergoing lower abdominal surgery, TAPB vs local anaesthetic infiltration provided superior analgesia at 24 h, although pain scores at 2 and 4 h postoperatively were similar (Yu 2014 **Level I**, 4 RCTs, n=196) (3 RCTs overlap with Baeriswyl 2015). TAPB vs local anaesthetic infiltration reduces 24 h morphine consumption (MD -3.85 mg; 95%CI -7.47 to -0.22) (Guo 2015 **Level I**, 5 RCTs, n=127) (3 RCTs overlap with Baeriswyl 2015).

Both landmark and US-guided TAPB have been complicated by liver trauma (Lancaster 2010 **CR**; Farooq 2008 **CR**). For paediatric use, see Section 10.6.1.4.

5.8.5.7 | Quadratus lumborum block

Quadratus lumborum block (QLB) has been proposed as a superior alternative to US-guided TAPB (Elsharkawy 2019 **NR**; Ueshima 2017b **NR**). With QLB, local anaesthetic is injected anterior, posterior or lateral to the posterior abdominal wall muscle quadratus lumborum. Posterior QLB vs placebo or control resulted in reduced morphine requirements and pain intensity after Caesarean section (Krohg 2018 **Level II,** n=40, JS 5; Mieszkowski 2018 **Level II,** n=58, JS 3; Blanco 2015 **Level II,** n=50, JS 5). Posterior QLB vs TAP block reduced morphine requirements while providing comparable analgesia after Caesarean section (Blanco 2016 **Level II,** n=75, JS 4).

Following laparoscopic gynaecological surgery posterior QLB vs control improved pain relief at rest and on movement (Ishio 2017 **Level II,** n=70, JS 2). QLB was not superior to systemic IV lidocaine for the reduction of morphine requirements 24 h after laparoscopic colorectal surgery (Dewinter 2018 **Level II**, n=125, JS 5).

For paediatric use see section 10.6.1.4

5.8.6 | Head and Neck Blocks

5.8.6.1 | Sphenopalatine ganglion block

After endoscopic sinus surgery, sphenopalatine ganglion block vs placebo or control improved pain intensity and PONV (Kim 2019b **Level I** [PRISMA], 8 RCTs, n=441). Topical sphenopalatine ganglion block was associated with improved results for treatment of postdural puncture headache (PDPH) vs epidural blood patch (Cohen 2018 **Level IV**, n=81).

5.8.7 | Periarticular and intra-articular analgesia

The use of intra-articular (IA) infusions of bupivacaine with adrenaline has been cautioned against because of reports of glenohumoral chondrolysis following shoulder arthroscopy (Hansen 2007 **Level III-3**, n=189 [shoulders operated on]; Bailie 2009 **Level IV**, n=23). Chondrotoxic effects have been shown for all local anaesthetics in in-vitro studies of human knee cartilage (Jayaram 2019 **Level III-2 BS** [PRISMA], 16 studies, n unspecified). Chondrotoxicity is worsened by coadministration of corticosteroids; ropivacaine at concentrations of 0.5% or less was found to be the least chondrotoxic LA. See also Section 4.4.3.1.

IA NSAIDs have demonstrated analgesic efficacy over systemic administration in some studies but the overall benefit is less clear (see Section 4.2.3.1). An analgesic effect for IA morphine following arthroscopy vs placebo cannot be shown (Rosseland 2005 **Level I**, 46 RCTs, n=3,166).

5.8.7.1 | Local infiltration analgesia

LIA refers to the systematic intraoperative injection of local anaesthetics in the periarticular and IA regions; LIA may also be referred to as periarticular infiltration. There have been methodology issues in LIA studies: lack of blinding, lack of placebo, lack of supplemental agents in controls (eg ketorolac), variable use of 'top-up' catheters, inferior results with established techniques (peripheral nerve or epidural block) compared to the literature, the use of traditional recovery programs with low activity (limiting the assessment of therapies on early functional recovery) and inadequate pain assessment (Andersen 2014 **Level I**, 27 RCTs, n=1,644). Other limitations of LIA studies have included non-uniform use of both non-opioid and opioid analgesia across treatment groups, poorly defined multimodal analgesia therapies and mobilisation pathways (Kehlet 2011 **NR**). The role of NSAIDs introduced via LIA vs systemic administration is also unclear (see Section 4.2.3.3). Similarly, there seems to be little benefit by adding opioids such as morphine; morphine (0.1 mg/kg) as a component of LIA with ropivacaine/ketoprofen/methylprednisolone/adrenaline in one side of a bilateral TKA vs no morphine did have no effect on pain, swelling or ROM (Iwakiri 2017 **Level II**, n=53, JS 4).

Total knee arthroplasty: LIA compared to placebo or no injection

Compared to placebo or no injection in TKA, LIA (with local anaesthetics in various combinations with NSAID, steroids, opioids, and epinephrine) was associated with reduced pain scores and reduced opioid consumption for up to 32 h (Andersen 2014 **Level I**, 7 RCTs [LIA in TKA vs placebo/no injection], n=328); there was a high risk of bias with unbalanced systemic analgesic regimens between groups. In patients having bilateral arthroplasty, LIA improved pain outcomes vs periarticular placebo on the opposite side (Fajardo 2011 **Level II**, n=30, JS 2; Mullaji 2010 **Level II**, n=40, JS 5; Andersen 2008 **Level II**, n=12, JS 4). Reviews comparing LIA with placebo or no injection report that following TKA LIA achieves superior analgesia and reduced opioid consumption, however the source RCTs were at high risk of bias because of lack of blinding (Xu 2014 **Level I**, 18 RCTs, n=1,858).

Total knee arthroplasty: LIA compared to epidural analgesia

In comparison to LIA in TKA, LEA has similar analgesic effects at rest for <24 h, but LIA achieves better analgesia at 48 and 72 h (MD −1.08/10; 95%CI −1.86 to −0.29 and MD −0.82/10; 95%CI −1.24 to −0.4) (Yan 2016 **Level I**, 9 RCTs [TKA], n=537). Similarly, pain on movement was similar at <24 h, but better controlled by LIA at 48 h and LIA enabled a better range of movements at all time points.

Total knee arthroplasty: LIA compared to peripheral nerve blockade

When comparing FNB to LIA in TKA, most studies report either equal analgesic efficacy or a short-term benefit of LIA (Andersen 2014 **Level I**, 5 RCTs [LIA vs FNB in TKA], n=307; Fan 2016 **Level II**, n=157, JS 2; Ashraf 2013 **Level II**, n=50, JS 3; Ng 2012 **Level II**, n=16, JS 4). Interpretation of results is hindered by the multitude of techniques, leaving the analgesic benefit of LIA *per se* unclear.

LIA achieved similar mean readiness for discharge from hospital of 3.2 d vs combined PCEA/FNB (Yadeau 2013 **Level II**, n=90, JS 3). A single-injection FNB when combined with epidural analgesia resulted in reduced pain vs LIA during the first 24 h (Reinhardt 2014 **Level II**, n=94, JS 5). LIA has superior analgesic outcomes vs epidural analgesia (Andersen 2014 **Level I**, 3 RCTs [LIA vs epidural in TKA], n=204); these trials had high risk of bias because of incomplete blinding and high heterogeneity due to different systemic analgesic regimens between groups. In patients receiving epidural analgesia, there was no added analgesic or functional benefit from LIA vs placebo in the contralateral side for up to 14 d (Joo 2011 **Level II**, n=572, JS 5). When LIA was added to combined FNB and sciatic block (with spinal anaesthesia for the surgery), improved pain relief

was only found at one time point postoperatively (0.6/10 ± 1.5 vs. 1.7/10 ± 2.3) (Hinarejos 2016 **Level II**, n=50, JS 5). As there were no other differences in analgesic outcomes, the authors concluded that adding LIA to their regimen was not necessary

Total hip arthroplasty

In THA, no additional analgesic benefit of LIA vs placebo LIA (systemic multimodal analgesia) is identified (Andersen 2014 **Level I**, 10 RCTs [THA], n=756). Compared with IT morphine and epidural analgesia, LIA was reported to have similar or improved analgesic effects.

5.8.8 | Wound infiltration including wound catheters

Wound catheter local anaesthetic injections provide minor analgesic benefits up to 48 h and reduced hospital LOS in obstetric and gynaecological surgical, but do not improve analgesic outcomes following abdominal or other non-orthopaedic (urological, plastic or thoracic) surgery (Gupta 2011 **Level I**, 32 RCTs, n unspecified). Continuous wound infiltration with ropivacaine vs placebo leads to a reduction in pain scores and opioid consumption (Raines 2014 **Level I**, 14 RCTs, n=756). Following Caesarean section, local anaesthetic wound infiltration (by infusion) reduces opioid consumption (MD −10.29 MME; 95%CI −18.36 to −2.21) (8 RCTs, n=441), but has limited effects on pain scores with movement at 24 h (MD −0.83/10; 95%CI −1.90 to −0.23) (7 RCTs, n=434) (Adesope 2016 **Level I**, 21 RCTs, n=1,435). Local anaesthetic infusions via abdominal wound catheter vs epidural analgesia demonstrate equal analgesic efficacy for up to 48 h with a lower incidence of urinary retention (Ventham 2013 **Level I** [PRISMA], 9 RCTs, n=505); there was however considerable heterogeneity with variability in analgesic regimens, especially in the epidural arms. Epidural analgesia provided better pain relief than continuous wound infiltration at rest at 72 h (4 RCTs, n=289) (Li 2018a **Level** I, 16 RCTs, n unspecified). There were no significant differences in pain score on rest and mobilization at 2 h, 12 h, 24 h and 48 h. The incidence of hypotension in the epidural group was significantly higher than patients receiving wound infusion (14 RCTs, n=1,350). Local anaesthetic infiltration vs a variety of controls for mastectomy did not improve analgesic outcomes (Tam 2015 **Level I** [PRISMA] 13 RCTs, n=1,150).

Infiltration of local anaesthetic into the scalp is used to treat postoperative pain following craniotomy. Preoperative scalp infiltration provides improved pain scores for up to 8 h postoperatively, with postprocedural infiltration improving analgesia for up to 12 h (Guilfoyle 2013 **Level I** [PRISMA], 7 RCTs, n=325).

Early postoperative abdominal pain is improved after laparoscopic cholecystectomy by the use of intraperitoneal local anaesthetic; the effect is better when given at the start of surgery vs instillation at the end of surgery (Boddy 2006 **Level I**, 24 RCTs, n=1,256). Preperitoneal infusion of ropivacaine following colorectal surgery resulted in improved pain relief, opioid-sparing and earlier recovery of bowel function (Beaussier 2007 **Level II**, n=49, JS 5). Based on direct (1 RCT, n=60) and indirect comparisons, continuous preperitoneal local anaesthetic infiltration is recommended in preference to subcutaneous injections and with similar analgesia vs epidural analgesia (Mungroop 2019 **Level I** [PRISMA], 29 RCTs, n=2,059).

In laparoscopic gastric surgery, intraperitoneal local anaesthetic reduces postoperative abdominal pain intensity, the incidence of shoulder pain and opioid consumption (Kahokehr 2011 **Level I** [PRISMA], 5 RCTs, n=273).

5.8.9 | Topical application of local anaesthetics

Topical EMLA® cream (eutectic mixture of lignocaine and prilocaine) is effective in reducing the pain associated with venous ulcer debridement (Briggs 2003 **Level I** [Cochrane], 6 RCTs, n=343). When compared with EMLA® cream, topical amethocaine provides superior analgesia for

superficial procedures in children, especially IV cannulation (Lander 2006 **Level I**, 6 RCTs, n=534). Topical tetracaine, liposome-encapsulated tetracaine and liposome-encapsulated lignocaine are as effective as EMLA® cream for dermal instrumentation analgesia in the ED (Eidelman 2005 **Level I**, 25 RCTs, n=2,096) (see Sections 10.6. and 10.7. for use in children and Section 8.11.2 for use in the ED).

Topical local anaesthetic provides no analgesic benefit when performing flexible diagnostic nasoendoscopy, either alone or in combination with a vasoconstrictor (Conlin 2008 **Level I**, 8 RCTs, n=818; Nankivell 2008 **Level I**, 18 RCTs, n=1,356). Intraurethral instillation of lidocaine gel provides superior analgesia to lubricating gel during flexible cystoscopy (Aaronson 2009 **Level I**, 4 RCTs, n=411). Following tonsillectomy, local anaesthetics provide a modest reduction in post-tonsillectomy pain; administering the local anaesthetic on swabs appeared to provide a similar level of analgesia to that of infiltration (Grainger 2008 **Level I**, 13 RCTs, n unspecified). Topical local anaesthetic gel and/or nebulised local anaesthesia of the nose and pharynx reduced pain associated with nasogastric tube insertion (OR 0.42; 95%CI 0.20 to 0.88) (Kuo 2010 **Level I**, 5 RCTs, n=212).

The lignocaine 5% patch may reduce acute pain intensity following herpes zoster once lesions have healed (McCarberg 2013 **NR**).

5.8.10 | Neuromodulation

There is some emerging evidence that percutaneous peripheral nerve stimulation may be a promising alternative to infusions of local anaesthetics through a perineural catheter (Gabriel 2019 **NR**). In this technique, small gauge insulated electrical leads are placed percutaneously through needle that is placed remotely 0.5 to 3.0 cm from a peripheral nerve using US guidance. The lead is connected to an external stimulator and narrow pulse duration electrical stimulation is applied to selectively activate pain-relieving fibres in a peripheral nerve trunk. This technique does not activate fibres that would result in muscle contractions, loss of strength or loss of proprioception. US-guided percutaneous peripheral nerve stimulation has been used successfully for analgesia following pain refractory to standard therapy following knee arthroplasty (Ilfeld 2017 **Level IV**, n=5). Following ambulatory rotator cuff repair, although initial pain control was inadequate, the later postoperative quality of analgesia (POD 1 to 14) was considered excellent (Ilfeld 2019a **Level II**, n=11, JS 5). Proof of concept studies have used percutaneous femoral nerve stimulation for ambulatory anterior cruciate ligament reconstruction (Ilfeld 2019b **Level II**, n=10, JS 5) and percutaneous sciatic nerve stimulation for ambulatory foot surgery (Ilfeld 2018 **Level II**, n=10, JS 5). Development issues with this technique include optimal lead location and insertion technique, the stimulating protocol and prevention of lead fracture/dislodgement.

5.8.11 | Safety

Regional anaesthesia techniques when performed with vigilance and professionalism are associated with a high degree of safety (Barrington 2013 **Level IV**, n=25,336 [PNBs in 20,021 patients]; Orebaugh 2012 **Level IV**, n=14,498 [PNBs]; Barrington 2009 **Level IV**, n=8,189 [PNBs in 6,950 patients]). Simple strategies such as preprocedural checklists, including block "*time-out*" and a "*pause*", may help reduce the incidence of events as wrong-site blockade (Barrington 2015 **GL;** ANZCA 2015 **GL**).

5.8.11.1 | Anticoagulation

Caution should be used when considering and performing some peripheral nerve or plexus blocks in patients with impaired coagulation (see Section 5.9.2). This particularly applies to where the PNB is performed at a deep location that prevents external compression, should bleeding occur.

5.8.11.2 | Nerve injury

A new onset postoperative nerve injury regardless of severity is of concern to patients and healthcare providers. Methods used to capture, define and report neurologic outcomes vary considerably. A multicentre registry using systematic postoperative contact with all patients reported the incidence of block-related nerve injury as 0.4/1,000 blocks (95%CI 0.08 to 1.1) (Barrington 2009 **Level IV**, n=8,189 [PNBs in 6,950 patients]). A large single-institution database identified four peripheral nerve injuries with sensory loss persisting for 6 to 12 mth, which were not able to be attributed to nonblock causes (≈0.3/1,000) (Orebaugh 2012 **Level IV**, n=14,498 [PNBs]). A single-centre study reported the incidence of postoperative neurologic symptoms >6 mth duration as 0.9/1,000 (95%CI 0.5 to 1.7) (Sites 2012 **Level IV**, n=12,668). Nerve injury may follow surgery independently of nerve block procedures. The baseline risk of nerve injury risk inherent to common elective orthopaedic surgical procedures is now better understood (Neal 2015 **GL**). Awareness of the mechanism, location, and frequency of nerve injuries associated with elective orthopedic surgery may facilitate diagnosis and treatment of peripheral nerve injury. After TKA, the all-cause incidence of perioperative nerve injury was 0.79%; however, this outcome was not associated with PNB (Jacob 2011b **Level III-3**, n=12,329). Similarly, PNB following total hip (Jacob 2011a **Level III-3**, n=12,998) and shoulder arthroplasty (Sviggum 2012 **Level III-3**, n=1,569) was not associated with perioperative nerve injury. Observational studies consistently report that postoperative neurologic dysfunction may be related to patient and surgical factors and that the incidence of neuropathy directly related to peripheral regional anaesthesia is infrequent or rare (Sviggum 2012 **Level III-3**, n=1,569; Jacob 2011a **Level III-3**, n=12,998; Jacob 2011b **Level III-3**, n=12,329; Sites 2012 **Level IV**, n=12,668; Orebaugh 2012 **Level IV**, n=14,498; Barrington 2009 **Level IV**, n=8,189 [PNBs in 6,950 patients]). However, distinguishing surgical, anaesthetic, and patient factors is often difficult. Differential diagnosis should include use of a pneumatic tourniquet (>120 min), which has been associated with nerve injury. These injuries often present as diffuse sensorimotor deficits. Consider delaying placement of regional blocks if assessment of postoperative nerve function is important for the surgeon. Mechanical, ischaemic or neurotoxic injury of the neuraxis or peripheral nervous system associated with regional anaesthesia and pain medicine interventions has been summarised into a practice advisory (Neal 2015 **GL**).

5.8.11.3 | Local Anaesthetic Systemic Toxicity

US guidance has been shown to be associated with a reduced incidence of local anaesthetic systemic toxicity (LAST) following PNB, with an incidence of 0.87/1,000 PNBs and no related deaths (Barrington 2013 **Level IV**, n=25,336 [PNBs in 20,021 patients]). This result is consistent with an analysis of block outcomes over 10 y period, which revealed a significant increase in the rate of LAST with the landmark technique (7 of 5,932) versus 0 of 16,858 cases that were US guided (Melnyk 2018 **Level IV**, n=22,790 [PNBs]). An analysis from the Pediatric Regional Anesthesia Network database indicates that TAPB has a low risk from local anaesthetic systemic toxicity in this patient population (Long 2014 **Level IV**, n=19,994). A review of case reports and registries reporting LAST estimate that its incidence reported from registries to be 0.03% (3 per 10,000) or 0.27 (95%CI 0.21 to 0.35) per 1,000 PNBs (Gitman 2018 **Level IV**, n=251,325). Seizure was the most common presenting feature (53% and 61% from case reports and registries, respectively). It is important to note that presenting

features of LAST may not comply with classic descriptions and be overlooked or disguised by perioperative processes and interventions. There is a trend toward delayed presentation, which may mirror the increased use of US guidance (fewer intravascular injections), local infiltration techniques (slower systemic uptake), and continuous local anaesthetic infusions. Small patient size, sarcopenia and patient co-mobidities potentially increase the risk of LAST. An increasing number of reported events occur outside of the traditional hospital setting and involve non-anaesthetists. Caution must be exercised with all regional techniques as case reports of adverse outcomes, including death, continue to occur (Vadi 2014 **CR** & **NR**), even with local anaesthetic infusion catheters placed under direct vision (Calenda 2014 **CR**). This caution also applies to fascial plane techniques such as TAP block that tend to involve large dosages (Hessian 2013 **Level IV PK**, n=20; Griffiths 2013 **Level IV PK**, n=8) (see also Section 4.4.3.2). Treatment should be directed towards importance of the airway and oxygenation (avoiding hypercarbia and acidosis), seizure control and lipid emulsion therapy (100 mL lipid emulsion 20% for patient 70 kg or over; 1.5 mL/kg for patient less than 70 kg). Mechanisms of lipid emulsion reversal of local anaesthetic systemic toxicity include rapid partitioning, direct inotropy, and post ischaemic conditioning (Neal 2018a **GL**). The American Society of Regional Anesthesia and Pain Medicine (ASRA) has updated its checklist for the management of local anesthetic systemic toxicity (Neal 2018b **GL**). Exact volume and flow rate of lipid emulsion are not essential however avoid giving more than 10 to 12 mL/kg of lipid emulsion, calling for help early, and use of electronic decision support tools are recommended. The pharmacological treatment of local anaesthetic systemic toxicity is different to other cardiac arrest scenarios. It is recommended to reduce individual doses of adrenaline to less than 100 mcg, avoiding vasopressin, calcium channel blockers, beta-blockers and use of other local anaesthetics. A guideline for management of severe local anaesthetic toxicity has been developed by the AAGBI and is endorsed by ANZCA (AAGBI 2010 **GL**).

5.8.11.4 | Infection

The strongest recommendations for infection-preventive measures are effective hand hygiene and skin preparation with alcohol-based chlorhexidine solution; as per the UK epic2 National Guidelines (Pratt 2007 **GL**). These guidelines recommend full barrier precautions for central venous catheter placement (cap, mask, sterile gown and gloves; and large drape). Although specific data for aseptic technique in CPNB is lacking, advisories have been developed which advocate similar practices (Hebl 2011 **NR**). In a review of infections associated with CPNB, the use of full surgical-type aseptic technique for CPNB procedures was supported (Capdevila 2009 **NR**). Identified risk factors for local CPNB catheter inflammation include ICU stay, duration of catheter use >48 h, lack of antibiotic prophylaxis, axillary or femoral location and frequent dressing changes (Capdevila 2009 **NR**). The use of a chlorhexidine-impregnated patch designed to inhibit bacterial growth for days as a dressing after femoral nerve catheter insertion did not reduce the low rate of bacterial colonisation but showed a trend towards reduced local skin inflammation (2.1 vs 10.6%) in a most likely underpowered RCT (Schroeder 2012 **Level 2**, n=100, JS 3). Chlorhexidine was also the superior skin disinfectant prior to regional catheter insertion vs povidone iodine (Krobbuaban 2011 **Level II**, n=100, JS 4); a positive skin culture immediately after skin disinfection occurred in 10 vs 35% (NNT 4).

The implications of catheter-related sepsis in patients with implanted prosthetic devices (eg joint arthroplasty) are significant and therefore all reasonable measures should be taken to minimise the risk of infection. The widespread use of US guidance has introduced a potential risk related to contamination. The use of a sterile disposable sheath reduces the risk of contamination of the aseptic field by the transducer. Decontaminating US transducers with 70% isopropyl alcohol was effective at removing pathogenic organisms (Chuan 2013 **Level IV**, n=120 [swabs]).

KEY MESSAGES

1. Topical EMLA cream (eutectic mixture of lignocaine [lidocaine] and prilocaine) is effective in reducing the pain associated with venous ulcer debridement (**U**) (**Level I** [Cochrane Review]).
2. Transversus abdominis plane blocks provide pain relief superior to local anaesthetic infiltration for a range of abdominal surgeries (**N**) (**Level I** [PRISMA].
3. Following thoracotomy, thoracic paravertebral block provides comparable analgesia to thoracic epidural analgesia (**U**) (**Level I**).
4. Continuous peripheral nerve block, compared with single-injection peripheral nerve block, results in improved pain control, decreased need for opioid analgesics, reduced nausea and improved patient satisfaction in some settings, in particular in the first 24 hours postoperatively (**W**) (**Level I**).
5. Femoral nerve block, either single-injection or continuous, provides better analgesia and decreased nausea compared with parenteral opioid-based techniques after total knee arthroplasty (**U**) (**Level I**).
6. Compared with opioid analgesia, continuous peripheral nerve block (regardless of catheter location) provides better postoperative analgesia and leads to reductions in opioid use as well as nausea, vomiting, pruritus and sedation (**U**) (**Level I**).
7. Blocks performed using ultrasound guidance are more likely to be successful, faster to perform, with faster onset and longer duration compared with localisation using a peripheral nerve stimulator (**U**) (**Level I**).
8. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo (**U**) (**Level I**).
9. Following total knee arthroplasty, local infiltration analgesia reduces postoperative pain for up to 32 hours when compared to systemic analgesics alone; however, there is limited benefit in comparison to femoral nerve block (**U**) (**Level I**).
10. Following total hip arthroplasty, there is no additional analgesic benefit for local infiltration analgesia over conventional multimodal analgesia (**S**) (**Level I**) and peripheral nerve blocks have limited or no effect on postoperative pain (**Q**) (**Level II**).
11. Following either knee or hip arthroplasty, there is insufficient evidence to support postoperative administration of local infiltration analgesia via catheter (**U**) (**Level I**).
12. Local anaesthetic injections through wound catheters provide analgesic benefits following gynaecological and obstetric surgery, but not other nonorthopaedic surgery (**U**) (**Level I**).
13. Intraperitonal local anaesthetic after laparoscopic cholecystectomy improves early postoperative pain relief (**U**) (**Level I**).
14. Intraurethral instillation of lignocaine gel provides analgesia during flexible cystoscopy (**U**) (**Level I**).
15. The benefit of routine sciatic nerve block in addition to femoral nerve block for analgesia following total knee joint arthroplasty remains unclear (**U**) (**Level I**).

16. Continuous interscalene analgesia provides better analgesia, reduced opioid-related adverse effects and improved patient satisfaction compared with intravenous PCA or single-injection interscalene block after open shoulder surgery (**U**) (**Level II**).
17. Intermittent bolus administration versus continuous infusion versus of local anaesthetics via adductor canal block catheters does not improve analgesia for total knee arthroplasty in the first 24 hours (**N**) (**Level II**).
18. Erector spinae plane blocks provide postoperative analgesia superior to systemic analgesia after cardiac surgery (**N**) (**Level II**).
19. Quadratus lumborum block reduces pain scores and opioid requirements following Caesarean section compared to placebo or control (**N**) (**Level II**).
20. Intra-articular bupivacaine infusions have been associated with chondrolysis and their use has been cautioned against (**U**) (**Level IV**).
21. Postoperative neurologic dysfunction is often related to patient and surgical factors and the incidence of neuropathy directly related to peripheral regional anaesthesia is rare (**S**) (**Level IV**).
22. Ultrasound guidance of regional blocks is associated with a reduced risk of local anaesthetic systemic toxicity in adults (**N**) (**Level IV**).

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

☑ Continuous peripheral nerve blocks carry a risk of infection; skin preparation with alcohol-based chlorhexidine and full barrier precautions (including face masks) are recommended for insertion of peripheral nerve catheters (**U**).

☑ Ultrasound-guided techniques should be practiced with a high degree of skill and care, including aseptic techniques, as they do not eliminate the risks of injury to tissues and structures, local anaesthetic toxicity or site contamination (**U**).

☑ Caution should be used when considering and performing some peripheral nerve or plexus blocks in patients with impaired coagulation, in particular where the PNB is performed at a deep location that prevents external compression, should bleeding occur (**N**).

5.9 | Regional analgesia and concurrent anticoagulant medications

5.9.1 | Neuraxial block and anticoagulant medication

The low event rate of epidural haematoma means that evidence cannot be based on RCTs but must rely on data from case reports, case series and large audits. An American Society of Regional Anesthesia and Pain Medicine (ASRA) Practice Advisory publication provides a good overview of and guidance on neurological complications of regional anaesthesia (Neal 2008 **GL**).

The population incidence of epidural haematoma following neuraxial block is possibly smaller than that of spontaneous epidural haematoma, however the rate in patients exposed to epidural anaesthesia is more appropriate for comparison. Between 1962 and 1992, 326 case reports of spontaneous epidural haematoma were published (Schmidt 1992 **Level IV**), while between 1906 and 1996 only 51 cases of epidural haematoma following epidural anaesthesia or analgesia were reported (Wulf 1996 **Level IV**).

Anticoagulation (present in 48% of cases) was the most important risk factor for epidural haematoma following insertion of an epidural needle/catheter, followed by coagulopathy (present in 38% of cases) (Wulf 1996 **Level IV**, n=51). This was confirmed by the series of epidural haematomas that followed epidural anaesthesia/analgesia in combination with inappropriate LMWH regimens in the USA, where the incidence was reported to be 1 in 3,000 (Horlocker 2003 **Level IV**).

In view of the increased risk with anticoagulation, ASRA (Horlocker 2010 **GL**) and the European Society of Anaesthesiology (ESA) (Gogarten 2010 **GL**) published a number of consensus statements and recommendations on regional anaesthesia in patients receiving antithrombotic or thrombolytic therapy. Such statements should be viewed as "*a panel of experts*" best faith efforts to offer reasonable pathways to provide safe and quality patient care while allowing for clinical differences based on individual situations (Bergqvist 2003 **NR**). It is recognised that variances from recommendations outlined in the ASRA guidelines "*may be acceptable based on the judgement of the responsible anesthesiologist*" (Horlocker 2010 **GL**). That is, these guidelines will not substitute for an individual risk/benefit assessment of every patient by the individual anaesthetist.

The ASRA guideline was updated in 2018 (Horlocker 2018 **GL**), but the ESA (Gogarten 2010 **GL**) recommendations have not been updated since 2010, despite the fact that new information on both established and newly introduced anticoagulants has become available. Subsequent guidelines developed for interventional spine and pain procedures jointly by ASRA, European Society of Regional Anaesthesia and Pain Therapy (ESRA), the American Academy of Pain Medicine (AAPM), the International Neuromodulation Society (IMS), the North American Neuromodulation Society and the World Institute of Pain (WIP) in 2015 (Narouze 2015 **GL**) were updated in 2018 (Narouze 2018 **GL**). These guidelines classify pain procedures according to potential risk of serious bleeding and emphasize the importance of assessing both procedure and patient-specific risk factors, such that concurrent use of anticoagulant or antiplatelet agents increases the potential procedural risk.

The Society for Obstetric Anesthesia and Perinatalogy (SOAP) published a consensus statement in 2018, too, in the context of increased use of thromboprophylaxis in obstetrics and differences in pharmacokinetics of anticoagulants in the obstetric population, as well as the competing risks to the fetus and from general anaesthesia, issues not directly addressed in the aforementioned guidelines (Leffert 2018 **GL**).

Table 5.2 summarises recommendations from these guidelines for timing of antithrombotic or antifibrinolytic administration in relation to neuraxial blockade including epidural catheter insertion and removal.

Recommendations aim to minimise anticoagulant presence during both insertion and removal of an epidural catheter due to associated risk of spinal haematoma formation. Time intervals between discontinuation of therapeutic anticoagulation and neuraxial block are predominantly pharmacologically based. After 5 half-lives (adjusted for renal impairment, if the anticoagulant is renally excreted), the residual anticoagulant activity will be 3%. Prophylactic doses of parenteral anticoagulants are interrupted for 2 half-lives due to lower levels of anticoagulation, although this may not be the case for non-vitamin K oral anticoagulants (NOACs) as discussed below.

Time intervals for subsequent dosing are based on the time to reach peak effect for each anticoagulant which is subtracted from the 8 h required for platelet plug stabilisation (Rosencher 2007 **GL**; Bouma 2006 **NR BS**).

Pregnancy-related physiological changes may impact UFH and/or LMWH pharmacokinetics. Increased maternal plasma volume may increase their volume of distribution with decreased peak and steady-state concentrations, more rapid renal clearance due to increased blood flow and glomerular filtration rate (GFR) and the free fraction of highly protein bound drugs may be increased due to lower serum albumin concentration in pregnancy (Leffert 2018 **GL**). Consequently, recommendations for the range of drug doses, including intermediate and high doses have been included in the SOAP guideline and Table 5.2.

For some anticoagulants there is a role for coagulation studies and use of anticoagulant reversal agents may be relevant if urgent neuraxial block is required.

- *Unfractionated heparin SC or IV*— Thromboprophylaxis with SC heparin given twice-daily is not a contraindication to neuraxial block after an appropriate time interval (see Table 5.2). IV administration of UFH results in immediate anticoagulant activity. SC administration has lower bioavailability than IV heparin administration with a 1 to 2 h delay in onset of anticoagulant activity. Offset of action is also slower when higher SC doses are used. To identify thrombocytopaenia associated with (heparin-induced thrombocytopenia [HIT]), a platelet count should be checked during therapy continued for more than 5 d and prior to removal of an epidural catheter in patients who have had more than 4 d of heparin therapy. In patients with prior heparin exposure, pre-formed heparin-platelet factor 4 antibodies may exist and the onset of HIT may occur by 2 d. The anticoagulant activity of unfractionated heparin, administered IV or SC can be fully reversed with protamine (1 mg per 100 IU heparin with maximum dose 50 mg).
- *Low molecular weight heparin* — Routine use of anti-Xa monitoring is not recommended and a safe level of residual anti-Xa activity for neuraxial block has not been determined. Concurrent administration of other medicines that may affect haemostasis (eg antiplatelet medicines) should be avoided. Renal impairment prolongs the effect of LMWH (for dosing recommendations in renal impairment see Table 5.3), although only one of the guidelines suggests determination of antifactor Xa activity in patients with renal insufficiency (Narouze 2015 **GL**). Protamine reverses approximately 60% of LMWH activity.
- *Fondaparinux* – This parenteral synthetic pentasaccharide with antiXa activity has a plasma half-life of 21 h and is not reversed by protamine. Neuraxial anaesthesia is not recommended outside of the context of clinical trials and an alternative VTE prophylactic agent should be utilized (Horlocker 2018 **GL**).
- *Oral warfarin* — Established warfarin therapy should be discontinued 5 d prior to neuraxial block and the INR normalised. Preoperative initiation of warfarin therapy requires an INR check prior to neuraxial block if a single dose of warfarin 5 mg was given >24 h preoperatively or a second dose was given. The INR should also be checked prior to

removal of indwelling epidural catheters if warfarin was administered >36 h before. An INR <1.5 is estimated to be a safe level for removal, while an INR >3 requires withholding warfarin and waiting for normalisation or actively reversing warfarin to allow earlier catheter removal. Specific advice on warfarin reversal is available in an updated Australian and New Zealand guideline (Tran 2013 **GL**).

Non-vitamin K oral anticoagulants (NOACs)

Neuraxial techniques should be avoided whilst patients are anticoagulated with NOACs.

- *Rivaroxaban* and *apixaban* are oral direct factor Xa inhibitors with partial renal excretion. They require cessation at least 3 d prior to neuraxial blockade (see Table 5.2 for details) and may be recommenced 6 h post epidural catheter removal or at least 24 h post-surgery. Andexanet alpha has been shown to reduce the anti-Xa activity in patients with major bleeding but is not currently available for use in Australia or New Zealand and has not been trialled in a surgical or procedural setting (Connolly 2019 **Level IV**, n=352).
- *Dabigatran* is an oral direct thrombin inhibitor with 80% renal clearance. It also requires cessation at least 3 d prior to neuraxial anaesthesia and longer periods of interruption for various degrees of renal impairment (Table 5.2) and it may be recommenced 6 h post epidural catheter removal or at least 24 h post-surgery. Idarucizumab is a direct specific reversal agent for dabigatran and is widely available in Australia and New Zealand. A 5 g dose rapidly and completely reverses dabigatran in patients with major bleeding and 92% patients requiring urgent surgery or procedures had normal haemostasis post administration of idarucizumab including some patients requiring urgent neuraxial anaesthesia (Pollack 2017 **Level III-1**, n=503). A dilute thrombin time assay can quantify the dabigatran concentration in plasma and should be tested 24 h after administration of idarucizumab as a minority of patients may show rising dabigatran concentrations potentially requiring a further dose of idarucizumab.
- The timing of NOAC interruption was standardised for the particular anticoagulant, renal function and surgical bleeding risk (Douketis 2019 **Level III-2**, n=3,007). Patients did not receive bridging anticoagulation. Rates of major bleeding (2%) and arterial thromboembolism (<1%) were low. A subgroup of 230 patients received neuraxial anaesthesia and were managed according to the 'high-bleeding risk' protocol in which patients received their last NOAC dose 3 d prior to surgery or 5 d prior for patients on dabigatran with creatinine clearance less than 50 ml/min. Almost all patients (98.8%) had a residual anticoagulant level less than 50 ng/mL. The proportion of these patients with residual anticoagulant level less than 30 ng/mL was 93.1% in the apixaban cohort, 98.9% in the dabigatran cohort and 85.4% in the rivaroxaban cohort. The optimal preoperative anticoagulant level has not been established and some assays show increased result variability below 50 ng/mL. No spinal haematomas were reported in this study. The same NOAC interruption protocol was used for different doses of each NOAC and there was no significant difference in drug levels preoperatively. NOACs have a wide therapeutic index and consequently shorter periods of interruption are not currently recommended for the lower drug doses.

Antiplatelet medications

NsNSAIDs including aspirin alone do not significantly increase the risk of spinal haematoma but should be regarded as a risk factor if combined with other classes of anticoagulants. In such situations, coxibs should be considered. Recommended time intervals between discontinuation or recommencement of other antiplatelet medications and neuraxial block are given in Table 5.2. Note wide variance in recommendations for different agents and significant changes in the

updated guidelines. For some agents the post-operative time interval to recommencement is longer than the recommendation for neuraxial procedures without surgery.

- *Herbal therapy* — Although garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), ginseng (*Panax* spp), dong quai (*Angelica sinensis*) and danshen (*Salvia miltiorrhiza*) have effects on haemostasis, there are currently no specific concerns about their use alone with neuraxial block. However, their combination with other anticoagulants or antithrombotics increases the risks. Dong quai and danshen combined with warfarin require INR check.
- *Fibrinolytics and thrombolytics* — Patients receiving fibrinolytic or thrombolytic medicines should not undergo neuraxial block except in exceptional circumstances; no data are available on a safe time interval after use of such medicines but at least 48 h and normalisation of fibrinogen level are recommended. No definite recommendations are given for the removal of neuraxial catheters after initiation of such therapy, although fibrinogen level might be a useful guide in such situations.

5.9.2 | Plexus and other peripheral regional block and anticoagulant medication

Significant blood loss or haematoma formation, rather than neurological deficit, seems to be the main risk when plexus or other regional blocks are performed in patients taking anticoagulant medications (Horlocker 2010 **GL**). Technical and anatomical considerations are different for pain interventions with both patient-specific and procedure-specific risk factors requiring assessment (Narouze 2018 **GL**).

In a series of peripheral nerve blocks for joint replacement (continuous lumbar plexus, continuous femoral and continuous or single sciatic block), with removal of the catheters at POD 2 or 3, no perineural haematoma was found despite use of warfarin (50.0%), fondaparinux (12.8%), dalteparin (11.6%), enoxaparin (1.8%) and aspirin (23.8%) (Chelly 2008a **Level IV**, n=6,935). A case series of patients receiving rivaroxaban 10 mg with a femoral catheter for total knee joint replacement *in situ* and removal 20 h after intake reported no cases of haematoma formation (Idestrup 2014 **Level IV**, n=504). However, a case series of bleeding complications after removal of femoral and sciatic catheters under LMWH suggests that caution is appropriate (Bickler 2006 **Level IV**, n=3; Horlocker 2010 **GL**).

For obvious reasons, deep blocks may be more at risk of bleeding complications than superficial blocks, where external compression is possible. Case reports of retroperitoneal haematoma after lumbar plexus block in conjunction with anticoagulation are published with either no neurological sequelae (Weller 2003 **CR**) or plexopathy (Klein 1997 **CR**). However, in a case series where lumbar plexus catheters were removed in warfarinised patients (36.2% with an INR >1.4 [range 1.5–3.9]), only one superficial bleeding event occurred (in a patient with INR 3.0) (Chelly 2008b **Level IV**, n=670).

The updated guidelines developed for interventional spine and pain procedures classify procedure–related risks, then upgrade the risk for patients on anticoagulants such that preoperative recommendations are similar to other guidelines but the post-operative resumption of anticoagulants is aligned with postsurgical recommendations of at least 24 h delay (Narouze 2018 **GL**). An expert panel of the Regional Anesthesia and Acute Pain Section of the Canadian Anesthesiologists Society (CAS) published a practice advisory on the bleeding risks for peripheral nerve and interfascial plane blockade, which categorises blocks into low, moderate and high risk (Tsui 2019b **GL**).

KEY MESSAGES

1. Anticoagulation and coagulopathy are the two most important risk factors for the development of epidural haematoma after neuraxial block (**U**) (**Level IV**).

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

☑ Consensus statements of experts guide the timing and choice of regional anaesthesia and analgesia in the context of anticoagulation but do not represent a standard of care and will not substitute the risk/benefit assessment of the individual patient by the individual anaesthetist (**S**).

☑ Caution should be used when considering and performing some peripheral nerve or plexus blocks in patients with impaired coagulation, in particular where the peripheral nerve block is performed at a deep location that prevents external compression, should bleeding occur (**S**).

TABLE 5.2 | Anticoagulation Table

Medication	Dosing	Before epidural insertion	Whilst epidural catheter in place	Prior to epidural catheter removal	After epidural catheter removal
		Minimum time after last anticoagulant or thrombotic/ thrombolytic dose until insertion	Delay from epidural insertion until next anticoagulant or thrombotic/ thrombolytic dose	**Minimum** time after last anticoagulant or thrombotic/ thrombolytic dose until removal of epidural catheter	**Minimum** time after epidural catheter removal and next dose of anticoagulant or thrombotic/ thrombolytic dose
Unfractionated heparin subcutaneous	prophylactic, up to 15000 IU/d	4-6 h or ensure normal APTT	1 h	4-6 h	1 h
Unfractionated heparin subcutaneous	intermediate, >15000 IU/d up to 20000 IU/d	12 h* AND ensure APTT normal	Safety of higher doses not established. Assess individual risks and benefits	12 h* AND ensure APTT normal	1 h
Unfractionated heparin subcutaneous	therapeutic (full dose), > 20000 IU/d s/c	24 h* AND ensure APTT normal	Safety of higher doses not established. Assess individual risks and benefits	24 h* AND ensure APTT normal	1 h
Unfractionated heparin intravenous (IV) infusion	therapeutic (full dose), IV	Discontinue infusion for 4-6 h AND ensure normal APTT	1 h (Wait 24 h if bloody tap)	4-6 h	1-2 h
LMWH (Low molecular weight heparin) Eg: enoxaparin (Clexane®), dalteparin (Fragmin®) subcutaneous	prophylactic (dosing adjusted to renal function see Table 5.3)	12 h	12 h	12 h	4 h
LMWH	therapeutic (full dose)	24 h	12 h	24 h	4 h**
Fondaparinux (Arixtra®) subcutaneous	prophylactic	2 d (longer if higher doses used)	CONTRAINDICATED	CONTRAINDICATED	6 h
Warfarin	therapeutic (full dose)	5 d AND ensure INR < 1.5	CONTRAINDICATED	INR < 1.5	4 h
Apixaban (Eliquis®)	2.5mg BD or 5mg BD				
CrCl > 50 ml/min		3 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl 25-50 ml/min		3 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl < 25 ml/min		Seek specialist advice with haematologist. Drug levels can be measured to assist in decision making.	CONTRAINDICATED	CONTRAINDICATED	CONTRAINDICATED
Rivaroxaban (Xarelto®)	15 or 20mg daily				
CrCl > 50 ml/min		3 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl 30-50 ml/min		3 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl < 30 ml/min		Seek specialist advice with haematologist. Drug levels can be measured to assist in decision making.	CONTRAINDICATED	CONTRAINDICATED	CONTRAINDICATED
Dabigatran (Pradaxa®)					
CrCl > 80 ml/min		3 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl 50-80 ml/min		4 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl 30-49 ml/min		5 d	CONTRAINDICATED	CONTRAINDICATED	At least 6 h
CrCl < 30 ml/min		Seek specialist advice with haematologist. Drug levels can be measured to assist in decision making.	CONTRAINDICATED	CONTRAINDICATED	CONTRAINDICATED

Medication	Dosing	Before epidural insertion	Whilst epidural catheter in place	Prior to epidural catheter removal	After epidural catheter removal
Thrombolytic therapy eg: tissue plasminogen activator tpA		At least 48 h and ensure normal coagulation studies	CONTRAINDICATED	CONTRAINDICATED	If thrombolytics required, check that no lumbar puncture, epidural or spinal anaesthesia in the preceding 10 d
Non-steroidal anti-inflammatory drugs (NSAIDS)	Interruption not required unless combined with other antithrombotics	COX-2 agents have minimal effect on platelet function			
Aspirin (COX inhibitor)	Interruption not required unless combined with other antithrombotics				
Thienopyridines (Inhibition of ADP-induced platelet aggregation)					
Ticlopidine		10 d	May be used without loading dose		6 h if loading dose given, or post-operatively 24 h
Clopidogrel		5-7 d	May be used without loading dose		6 h if loading dose given, or post-operatively 24 h
Prasugrel		7-10 d	CONTRAINDICATED due to rapid onset of action	CONTRAINDICATED	6 h if loading dose given, or post-operatively 24 h
Direct and reversible P2Y12 receptor inhibitors: Ticagrelor		5-7 d	CONTRAINDICATED due to rapid onset of action	CONTRAINDICATED	6 h if loading dose given, or post-operatively 24 h
Direct and reversible P2Y12 receptor inhibitors: Cangrelor		3 h	CONTRAINDICATED due to rapid onset of action	CONTRAINDICATED	8 h
Glycoprotein IIb/IIIa Inhibitors: Abciximab		24-48 h	CONTRAINDICATED due to rapid onset of action	CONTRAINDICATED	4 weeks post-surgery, if emergent use required minimise sensory and motor block to facilitate assessment of neurological function
Eptifibatide, Tirofiban		4-8 h	CONTRAINDICATED due to rapid onset of action	CONTRAINDICATED	4 weeks post-surgery, if emergent use required minimise sensory and motor block to facilitate assessment of neurological function
Selective inhibition of PDE IIIA: Cilostazol		2 d	CONTRAINDICATED	CONTRAINDICATED	6 h post catheter removal or post-operatively 24 h
Dipyridamole	Potential risk in combination with aspirin	24 h (for extended release formulations)			
Selective serotonin re-uptake inhibitors (SSRIs) - antidepressants with inhibition of serotonin-mediated plateletr aggregation	Low risk unless associated with other patient specific risk factors or combined with other antithrombotics	Consider discontinuation or switch to alternative agent			

** SC UFH - delayed excretion with higher doses administered by this route*
*** For post-operative therapeutic LMWH dosing, commencement should be at least 24 h post-surgery with low bleeding risk and 48-72 h post-surgery with high-bleeding risk*

References:
Horlocker 2018, Narouze 2018, Gogarten 2010, Leffert 2018, Douketis 2019

Table 5.3 | Dosing of prophylactic LMWH in renal impairment

Normal dosing (CrCl greater than 30 mL / min)	Renal impairment (CrCl =10 to 30 mL / min)	Renal impairment (CrCl less than 10 mL / min)
TWICE a day regimen: Enoxaparin (Clexane®): 1 mg / kg TWICE a day (max. 150 mg TWICE a day Dalteparin (Fragmin®): 100 units / kg / TWICE a day (max. 15,000 units TWICE a day)	Enoxaparin (Clexane®)*: 1 mg / kg ONCE daily Dalteparin (Fragmin®)*: 100 units / kg ONCEdaily	Use unfractionated heparin
ONCE daily regimen: Enoxaparin (Clexane®): 1.5 mg / kg ONCE daily (max. 180 mg ONCE daily) Dalteparin (Fragmin®): 200 units / kg ONCE daily (max. 25,000 units ONCE daily)		

*The determination of an tiXa levels is recommended for optimal dosing
(*adapted from Sanofi-Aventis Australia 2018; Pfizer Australia 2019*)

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