4

Analgesic medicines

Section Editor:
Prof Stephan A Schug

4.1 | Paracetamol

4.2.1 | Systemic nonselective nonsteroidal anti-inflammatory drugs

4.2.2 | Systemic cyclooxygenase-2 selective inhibitors (Coxibs)

Contributor: Dr Jeffrey F Mott

4.2.3 | Nonsystemic NSAIDs

Contributor: Dr Daniel Lee

4.3.1 | Systemic opioids

Contributor: Prof Stephan A Schug

4.3.2 | Neuraxial opioids

Contributor: Dr Reginald Edward

4.3.3 | Peripheral opioids

Contributor: Dr Zoe Vella

4.4 | Local anaesthetics and other membrane stabilisers

Contributor: Prof David A Scott

4.5 | Inhalational agents

4.6 | NMDA-receptor antagonists

Contributor: Prof Stephan A Schug

4.7 | Antidepressant medicines

4.8 | Anticonvulsant medicines

4.9 | Alpha-2 agonists

Contributor: Dr A. Reza Feizerfan

4.10 | Salmon calcitonin and bisphosphonates

Contributor: Dr Noam Winter

4.11 | Cannabis, cannabinoids and cannabimimetics

Contributor: Dr Paul Emery

4.12.1 | Systemic corticosteroids

Contributor: Prof Tomas Corcoran

4.12.2 | Regional corticosteroids

Contributor: Dr Irene Ng

4.13 | Other regional analgesic medicines

Contributor: A/Prof Laurence Weinberg

4.14 | Complementary and alternative medicine

Contributors: Dr Phoon Ping Chen, Dr Yin Ling Or, Dr Chuan-Whei Lee

4.1 | Paracetamol

Paracetamol and its intravenous prodrug propacetamol are the only remaining aniline derived drugs used in clinical practice; it is an effective analgesic (see below) and antipyretic. It is absorbed rapidly and well from the small intestine after oral administration with a bioavailability of between 63 and 89% (Oscier 2009 **NR**). It can also be given rectally and IV (see below and Chapter 5).

4.1.1 | Mechanism of action

Despite extensive use since its discovery in the 19th century the mechanism of action of paracetamol is still not fully understood. In contrast to opioids, paracetamol has no known endogenous binding sites and, unlike NSAIDs, causes only weak inhibition of peripheral cyclooxygenase (COX) activity, with apparent selectivity for COX-2 (Graham 2013a **NR**). Given its limited peripheral actions the most likely mechanism is a central effect and may involve multiple pathways:

- When paracetamol is de-acetylated to p-aminophenol it can undergo conjugation with arachidonic acid by fatty acid amide hydrolase to AM404 in the CNS (Ghanem 2016 **NR**). AM404 has multiple potential mechanisms of action in the CNS. Firstly, it is a weak cannabinoid receptor agonist as well as a reuptake inhibitor of the endocannabinoid anandamide. Secondly, it is a potent TRPV1 receptor agonist and a TRPV1 mutation is associated with paracetamol non-responsiveness in healthy humans volunteers (Pickering 2020 **Level II EH**, n=47, JS 4)
- Paracetamol has been shown to prevent prostaglandin production at the cellular transcriptional level predominantly in the CNS, independent of COX activity (Mancini 2003 **BS**). This may also be AM404 mediated as AM404 reduces PGE-2 release from activated microglia (Saliba 2017 **BS**). This effect is independent of cannabinoid and TRPV1 receptor effects.
- Indirect effects on the serotonergic system appears to be important. In volunteers, coadministration of tropisetron or granisetron blocked the analgesic effects of paracetamol (Pickering 2008 **EH**; Pickering 2006 **EH**). In children undergoing tonsillectomy who all received paracetamol, a fixed dose of morphine and betamethasone, administration of ondansetron was associated with significantly more morphine in recovery vs droperidol but no change in codeine over the first 24 h (Ramirez 2015 **Level II**, n=69, JS 4)

4.1.2 | Efficacy

For paediatric specific information see 10.4.1.1

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 discussed and in Chapter 5 and 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 3.5; 95%CI 2.7 to 4.8), 600/650 mg (NNT 4.6; 95%CI 3.9 to 5.5) and 1,000 mg (NNT 3.6; 95%CI 3.2 to 4.1) show no statistically significant difference (Moore 2015b **Level I** [Cochrane], 53 RCTs, n=5,679). Paracetamol by all routes of administration has an opioid-sparing effect on PCA-morphine consumption (MD over 24 h -6.3 mg; 95%CI -9.0 to -3.7), although this effect is inferior to nsNSAIDs and coxibs (Maund 2011 **Level I**, 60 RCTs, n unspecified).

Oral paracetamol 500 mg and 1,000 mg given 1 h prior to surgery reduced the pain intensity of propofol injection for 500 mg (median NRS of 2/10; IQR 0 to 3] and for 1,000 mg (4/10; 2 to 5) vs placebo (8/10; 7 to 10) (Nimmaanrat 2019 **Level II**, n=324, JS 5).

IV Paracetamol is also an effective analgesic after surgery with an NNT of 4.0 (95%CI 3.5 to 4.8) over 4 h and an NNT of 5.3 (95%CI 4.2 to 6.7) over 6 h (Tzortzopoulou 2011 **Level I** [Cochrane], 36 RCTs, n=3,896). When paracetamol is used as an adjunct to opioid analgesia, opioid requirements are reduced by 30% over 4 h after a single IV dose. For hip and knee arthroplasty, there is a reduction in pain scores for each of the first 3 PODs (POD 1: WMD -0.95; 95%CI -1.2 to -0.7) and opioid consumption (POD 1: WMD -3.1; 95%CI -4.1 to -2.1) (Yang 2017a **Level I** [PRISMA], 4 RCTs, n=865).

IV paracetamol given perioperatively reduces PONV when administered 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 before 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 0.52; 95%CI -0.98 to -0.06) and PONV (RR 0.50; 95%CI 0.31 to 0.83) (Doleman 2015b **Level I** [PRISMA], 7 RCTs, n=544).

Paracetamol is superior to placebo for migraine (NNT 12 for pain-free response at 2 h) and reaches the efficacy of sumatriptan when combined with 10 mg metoclopramide (Derry 2013a **Level I** [Cochrane], 11 RCTs, n=2,942). In episodic tension-type headache (TTH), paracetamol is mildly effective at 2 h (NNT for mild pain or pain free 10; 95%CI 7.9 to 14) (Stephens 2016 **Level I** [Cochrane], 23 RCTs, n=8,079). Paracetamol is also superior to placebo for postpartum perineal pain (OR 2.14; 95%CI 1.59 to 2.89) (Chou 2013 **Level I**, 10 RCTs, n=1,377) but less effective than NSAIDs (Wuytack 2016 **Level I** [Cochrane], 3 RCTs, n=342). Paracetamol does not appear to be effective for acute low back pain (Saragiotto 2016 **Level I** [Cochrane], 3 RCTs, n=1,825).

The combination of paracetamol and NSAIDs is more effective than either paracetamol or NSAID alone (Martinez 2017 **Level I** [NMA], 2 RCTs, n=85 [paracetamol/NSAID]; 60 RCTs, n=3,259 [NSAIDs]; 20 RCTs, n=699 [paracetamol]; Ong 2010 **Level I**, 21 RCTs, n=1,909). This in particular is shown for the combination of paracetamol and ibuprofen in the setting of wisdom tooth removal (Bailey 2013 **Level I** [Cochrane], 7 RCTs, n=2,241).

A combination of 1,000 mg paracetamol with 130 mg caffeine is more effective than paracetamol alone (OR 1.12; 95%CI 1.05 to 1.19) in a range of painful conditions with no safety concerns (Palmer 2010 **Level I** [QUOROM], 8 RCTs, n=2,510).

Combinations of paracetamol with opioids such as codeine, tramadol or hydrocodone show increased efficacy (see Section 5.1.3.1.).

4.1.3 | Adverse effects

For paediatric specific information see 10.4.1.3

Paracetamol has fewer adverse effects than NSAIDs and can be used when the latter are contraindicated (eg patients with a history of renal impairment, asthma or peptic ulcers).

4.1.3.1 | Hepatic effects

The risk of hepatotoxicity from therapeutic doses (maximum 4 g/24 h) is not supported by current data (Dart 2007 **Level IV SR**, 791 studies, n=40,202). The higher number of findings in the retrospective vs the prospective studies suggests that some of these cases may be inadvertent overdoses. Similar safety has also been shown in a paediatric population with no cases of liver disease, need for antidote or transplantation, or death (95%CI 0.000 to 0.009) and only 0.031% of cases (95%CI 0.015 to 0.057) with major or minor hepatic adverse effects (Lavonas 2010

Level IV SR, 62 studies, n=32,414). In conclusion, hepatotoxicity from therapeutic doses of paracetamol is extremely rare (Caparrotta 2018 **NR**; Graham 2013a **NR**).

Guidelines based on individual case reports only recommend that paracetamol should be used with caution or in reduced doses in patients with low body weight (< 50 kg), active liver disease, history of heavy alcohol intake, older age, malnutrition, Gilbert's syndrome and glucose-6-phosphate dehydrogenase deficiency (NPS MedicineWise 2015 **GL**; Queensland Health 2014 **GL**; NSW TAG 2008 **GL**); however, consistent evidence of increased risk in these settings is lacking (Caparrotta 2018 **NR**; Graham 2013a **NR**). Therapeutic doses of paracetamol are an unlikely cause of hepatotoxicity in patients who ingest moderate to large amounts of alcohol. In subjects who consume alcohol, no elevation of alanine aminotransferase levels was noted with up to 4 g/d of paracetamol for at least 4 d (Rumack 2012 **Level I** [PRISMA], 5 RCTs, n=551); no cases of hepatic failure or death were observed in any published prospective trial of moderate to heavy drinkers. In patients newly abstinent after abusing alcohol, therapeutic doses of paracetamol had no effect on parameters of liver function (Dart 2010 **Level II**, n=142, JS 5).

There is no evidence that patients who have depleted glutathione stores (eg patients who are malnourished or who have cirrhosis, hepatitis C or HIV) are at increased risk of liver dysfunction when exposed to therapeutic doses of paracetamol (Caparrotta 2018 **NR**; Graham 2013a **NR**). However, there is a potential association between acute liver failure and therapeutic paracetamol doses in paediatric patients with myopathies (Ceelie 2011 **Level IV**, n=2).

Paracetamol overdose is a common cause of acute liver failure (Caparrotta 2018 **NR**; Graham 2013a **NR**); in the USA 30,000 patients are hospitalised every year for paracetamol overdose, of which >50% are unintentional and 17% result in hepatotoxicity (Blieden 2014 **NR**). In a multiethnic Asian population, the hepatotoxicity rate was lower at 7.3% (Marzilawati 2012 **Level IV**, n=1,024). Treatment should be with acetylcysteine; there is no obvious advantage of IV over oral administration (Green 2013 **Level III-3 SR**, 16 studies, n=5,164). Treatment delays increase the incidence of hepatotoxicity; a detailed systematic review on interventions for treatment of paracetamol poisoning (Chiew 2018 **Level I** [Cochrane], 11 RCTs, n=700) and treatment guidelines have been published (Chiew 2020 **GL**).

4.1.3.2 | Renal effects

Newly diagnosed chronic kidney disease patients had an increased risk of end-stage renal disease with paracetamol use (OR 2.92; 95%CI 2.47 to 3.45) and higher risk with increasing dose exposure (Kuo 2010 **Level III-2**, n=19,163).

4.1.3.3 | Cardiovascular effects

Paracetamol may interact with warfarin to increase the International Normalised Ratio (INR) (with doses >2 g/d over several d) (Hughes 2011 **Level IV SR**, 5 studies, n unspecified).

There is also a potential association between premature closure of ductus arteriosus and maternal paracetamol use in pregnancy (Allegaert 2019 **Level IV SR**, 12 studies, n=25). Given paracetamol has been shown to be as effective as ibuprofen for closure of a patent ductus arteriosus in preterm neonates (Ohlsson 2018 **Level I** [Cochrane], 8 RCTs, n=916), it seems reasonable to recommend that (as with all medications) use should be limited to the minimum dose and duration that is clinically necessary.

The overall effect of oral paracetamol on long term blood pressure remains unclear; observational studies (4 studies, n=155,910) show a variable association between paracetamol use and increased hypertension but RCTs (6 RCTS, n=152) have inconsistent results (Turtle 2013 **Level III-3 SR**, 6 RCTs and 4 studies, n=156,062).

For information on IV paracetamol and hypotension of see Section 5.2.1.

4.1.3.4 | Respiratory effects

In children, exposure to paracetamol was associated with an increased incidence of asthma (pooled OR 1.63; 95%CI 1.46 to 1.77) (Etminan 2009 **Level III-3 SR**, 19 studies, n=425,140). There are also claimed associations between the use of paracetamol in pregnancy and subsequent asthma in childhood (OR 1.19; 95%CI 1.12 to 1.27) (Fan 2017 **Level III-3 SR**, 13 studies, n=1,043,109). For details see Section 10.4.1.3.

4.1.3.5 | Carcinogenic effects

A review of epidemiological studies of paracetamol and cancer found mixed studies with respect to renal cell carcinoma and very limited positive studies with plasma cell disorders and leukaemia and otherwise a null effect on other types of cancer (Weiss 2016 **NR**).

4.1.3.6 | Neurodevelopmental effects

Epidemiological studies show an association between paracetamol usage in pregnancy and ADHD, use of paracetamol >29 d (HR 2.2; 95%CI 1.50 to 3.24), but not use for <8 d (HR 0.90; 95%CI 0.81 to 1.00) (Ystrom 2017 **Level III-3**, n=112,973). For details see Section 9.1.1.1.

Caution should be used with interpretation of all these retrospective analyses because of the possible effect of unknown or unmeasured confounding factors; the relevance to use limited to an acute situation is also unclear.

KEY MESSAGES

1. Paracetamol is an effective analgesic for acute pain; the incidence of adverse effects is comparable to placebo (**U**) (**Level I** [Cochrane Review]).
2. Paracetamol given in addition to PCA opioids reduces opioid consumption but does not result in a decrease in opioid-related adverse effects (**U**) (**Level I**).
3. Hepatotoxicity with therapeutic doses of paracetamol is extremely rare (**U**) (**Level IV**) and not associated with alcohol consumption (**U**) (**Level I** [PRISMA]).

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

☑ Emerging evidence suggests that maternal paracetamol use may influence premature closure of the fetal ductus arteriosus **(N).**

4.2 | Nonselective NSAIDs and coxibs

4.2.1 | Systemic nonselective nonsteroidal anti-inflammatory drugs

The term NSAIDs refers to both nonselective NSAIDs (nsNSAIDs) and coxibs (COX-2 selective inhibitors). NSAIDs have a spectrum of analgesic, anti-inflammatory and antipyretic effects and are effective analgesics in a variety of acute pain states. Many effects of NSAIDs can be explained by inhibition of prostaglandin synthesis in peripheral tissues, nerves and the CNS (Botting 2006 **NR**). However, NSAIDs and aspirin may have other mechanisms of action independent of any effect on prostaglandins, including effects on basic cellular and neuronal processes. Prostaglandins are produced by the enzyme prostaglandin endoperoxide synthase, which has both COX and hydroperoxidase sites. Subtypes of the COX enzyme have been identified; the "constitutive" COX-1 and the "inducible" COX-2; COX-3 does not appear to play a significant role in fever or inflammation in humans (Kam 2009 **NR**; Botting 2006 **NR**; Gajraj 2005 **NR**; Simmons 2004 **NR**).

Prostaglandins regulate many physiological functions including gastric mucosal protection, bronchodilation, renal tubular function and intrarenal vasodilation. Production of endothelial prostacyclin leads to vasodilation and prevents platelet adhesion, whereas thromboxane, produced from platelets by COX, results in platelet aggregation and vasoconstriction. With the exception of prostacyclin synthesis (mediated largely through COX-2), such physiological roles are mainly regulated by COX-1 and this is the basis for many of the adverse effects associated with nsNSAID use. Tissue damage induces COX-2 production leading to synthesis of prostaglandins that result in inflammation, peripheral sensitisation of nociceptors and consequently increased pain perception. COX-2 induction within the spinal cord plays a role in central sensitisation. COX-2 may also be "constitutive" in some tissues, including the kidney, cardiovascular system and brain and is overexpressed in some cancers (Kam 2009 **NR**).

NSAIDs are reversible COX inhibitors with the exception of aspirin, which binds covalently and acetylates the enzyme irreversibly. In platelets, the enzyme cannot be replenished leading to prolonged inhibition of platelet function with minimal inhibition of endothelial prostacyclin; this confers cardiovascular protection at low dosages of aspirin. NsNSAIDs are "nonselective" COX inhibitors that inhibit both COX-1 and COX-2. The coxibs have been developed to inhibit selectively, but not specifically, COX-2 (Botting 2006 **NR**; Gajraj 2005 **NR**; Simmons 2004 **NR**).

4.2.1.1 | Efficacy

Single doses of oral nsNSAIDs are effective in the treatment of pain after surgery (Moore 2015b **Level I** [Cochrane], RCTs ≈460, n≈50,000). For a list of NNTs for each medicine see Table 5.1. However, while useful analgesic adjuvants, they are often inadequate as the sole analgesic agent in the treatment of severe postoperative pain (Cepeda 2005 **Level II**, n=1,003, JS 5).

They are also effective analgesics in chronic low-back pain (Enthoven 2016 **Level I** [Cochrane], 13 RCTs, n= 4,807), renal colic (Afshar 2015 **Level I** [Cochrane], 50 RCTs, n=5,734), primary dysmenorrhoea (Marjoribanks 2015 **Level I** [Cochrane], 80 RCTs, n=5,820), migraine (Rabbie 2013 **Level I** [Cochrane], 9 RCTs, n=4,473); Derry 2013b **Level I** [Cochrane], 5 RCTs, n=1,356), acute ankle sprains (van den Bekerom 2015 **Level I**, 28 RCTs, n unspecified), biliary colic (Colli 2012 **Level I**, 11 RCTs, n=1,076) and acute muscle injury (Morelli 2018 **Level I** [PRISMA], 41 RCTs, n= 5,343).

For more information on use in migraine see Section 8.6.5.2 and in paediatrics Section 10.9.3.

Nonselective NSAIDs are integral components of multimodal analgesia (Young 2012 **NR**; Buvanendran 2009 **NR**; Kehlet 1997 **NR**). When given in combination with IV PCA morphine after surgery, nsNSAIDs result in better analgesia, reduced opioid consumption (MD over 24 h -10.2 mg; 95%CI -11.7 to -8.7) and a lower incidence of PONV (OR 0.70; 95%CI 0.53 to 0.88) (Maund 2011 **Level I**, 60 RCTs, n unspecified). Similar findings were made in the paediatric setting (Michelet 2012 **Level I**, 27 RCTs, n=985).

The combination of paracetamol and NSAIDs is more effective than paracetamol or NSAID alone (Martinez 2017 **Level I** [NMA], 2 RCTs, n=85 [Paracetamol/NSAID]; 60 RCTs, n=3,259 [NSAIDs]; 20 RCTs, n=699 [paracetamol]; Ong 2010 **Level I**, 21 RCTs, n=1,909). This is particularly well documented for the combination of paracetamol and ibuprofen in the setting of wisdom tooth removal (Bailey 2013 **Level I** [Cochrane], 7 RCTs, n=2,241).

Administration of ketorolac to patients with rib fractures reduced the incidence of pneumonia (OR 0.14; 95%CI 0.04 to 0.46) and reduced requirements for ICU admission and ventilation (Yang 2014 **Level III-2**, n=619). The perioperative use of nsNSAIDs, predominantly rectal diclofenac and indomethacin, for endoscopic retrograde cholangiopancreatography (ERCP) reduces the risk of post-ERCP pancreatitis vs placebo (RR 0.54; 95%CI 0.45 to 0.64) (Liu 2019 **Level I** [PRISMA], 19 RCTs, n=5,031).

In cancer surgery, initial data suggested benefits of intraoperative use of nsNSAIDs in breast cancer patients (reduced recurrence rate and lower mortality) and in lung cancer patients (lower metastases risk and longer survival) (Forget 2013 **Level III-2**, n=720). In breast cancer surgery, intraoperative administration of nsNSAIDs (ketorolac or diclofenac) was associated with an improved disease-free survival (HR 0.57; 95%CI 0.37 to 0.89) and better overall survival (HR 0.35; 95%CI 0.17 to 0.70) (Forget 2014 **Level III-2**, n=720). However, a more recent case control study found an effect with ketorolac, but not diclofenac (Desmedt 2018 **Level III-2**, n=1,834). Despite epidemiological associations with NSAIDs reducing prostate cancer risk, pre-operative courses of celecoxib 400mg BD did not appear to increase tumor cell apoptosis in surgical specimens (Flamiatos 2017 **Level II**, n=28, JS 5). NSAID administration (primarily ibuprofen) after colorectal surgery was associated with a reduced recurrence in a historical case series (aHR 0.84; 95%CI 0.72 to 0.99) (Schack 2019 **Level III-3**, n=2,308).

4.2.1.2 | Adverse effects

Adverse effects of nsNSAID are more common with long-term use; the major concerns relate to the gastrointestinal, renal and cardiovascular systems. In the perioperative and acute period, the main concerns are renal impairment, interference with platelet function, wound and bone healing and peptic ulceration or bronchospasm in individuals at risk. Certain risks are accentuated in the perioperative period because of pre-existing comorbidities, concurrent medications, haemodynamic disturbances, fluid shifts, activation of the neurohumoral stress response and deficient enteral feeding.

In general, the risk and severity of nsNSAID-associated adverse effects is increased in elderly people (Juhlin 2005 **Level II**, n=14, JS 4; Pilotto 2003 **Level III-2**, n=2,251). For this reason, opioids are sometimes used in preference to NSAIDs. A cohort study of elderly patients with arthritis (mean age 80 y) started on nsNSAIDs, coxibs or opioids challenges the assumption that opioids are safer in that population, showing increased rates of fracture, hospital admission and all-cause mortality in the opioid cohort and similar or higher rates of cardiovascular, renal and gastrointestinal adverse effects (Solomon 2010 **Level III-2**; n=12,840). Overall the nsNSAID cohort appeared to have the lowest risk for adverse effects.

Gastrointestinal effects

Chronic nsNSAID use is associated with peptic ulceration and bleeding and the latter may be exacerbated by the antiplatelet effect (Bhala 2013 **Level I**, 754 RCTs, n=353,809). All long-term nsNSAID regimens increase the risk of upper gastrointestinal complications (diclofenac RR 1.89; 95%CI 1.16 to 3.09; ibuprofen RR 3.97; 95%CI 2.22 to 7.10; naproxen RR 4.22; 95%CI 2.71 to 6.56). The combination of an nsNSAID with an SSRI further increases the risk of upper gastrointestinal bleeding (Anglin 2014 **Level III-2 SR**, 19 studies, n>393,268). In patients with rheumatoid arthritis, steroids and NSAIDs appear to be additive in increasing gastric ulceration (Tsujimoto 2018 **Level III-2**, n=1,704).

Acute gastroduodenal damage and bleeding can also occur with short-term nsNSAID use; the risk is increased with higher doses, a history of peptic ulceration, use for >5 d and in elderly people (Strom 1996 **Level III-3**, n=10,272 [uses of parenteral ketorolac]). After 5 d of naproxen and ketorolac use in healthy elderly subjects, ulcers were found on gastroscopy in 20 and 31% of cases respectively (Goldstein 2003 **Level II**, n=168, JS 4; Stoltz 2002 **Level II**, n=94, JS 4; Harris 2001 **Level II**, n=17 [terminated due to high incidence of gastrointestinal ulcers in both nsNSAID groups], JS 4). Importantly, such endoscopic findings do not correlate with dyspeptic symptoms; these consequently cannot be relied upon as an indicator of potential harm (Dib 2014 **Level III-2**, n=1,231).

The relative risk of hospital admission for perforations, ulcers and bleeds associated with nsNSAIDs is estimated as 5.3 vs people not consuming nsNSAIDs (Lanas 2003 **Level III-2**, n=3,532). Use of ketorolac and piroxicam carried the highest risk. Concurrent use of a proton-pump inhibitor (PPI) significantly reduced the incidence of nsNSAID-related peptic ulcer disease (Targownik 2008 **Level III-2**, n=35,339). However, concurrent use of a PPI and nsNSAID (diclofenac) was still associated with an increased risk of clinically significant upper or lower gastrointestinal adverse effects vs coxib alone (RR 4.3; 95%CI 2.6 to 7.0) (Chan 2010b **Level II**, n=4,484, JS 5). Suppression of gastric acid by PPI to reduce nsNSAID-induced gastropathy may increase the risk of enteropathy lower in the gastrointestinal tract (Blackler 2014 **NR**), possibly from changes in gut flora (Minalyan 2017 **NR**).

Colonic diverticular bleeding is also increased by aspirin (RR 1.73; 95%CI 1.31 to 2.30) and other nsNSAIDs (RR 2.24; 95%CI 1.63 to 3.09) (Yuhara 2014 **Level III-2 SR**, 6 studies, n 52,000).

Renal effects

Renal prostaglandins regulate tubular electrolyte handling, modulate the actions of renal hormones and maintain renal blood flow and glomerular filtration rate in the presence of circulating vasoconstrictors. The adverse renal effects of chronic nsNSAID use are common and well recognised. In some clinical conditions, including hypovolaemia, dehydration and major surgery, high circulating concentrations of the vasoconstrictors angiotensin II, noradrenaline and vasopressin increase production of intrarenal vasodilators including prostacyclin; maintenance of renal function may then depend on prostaglandin synthesis and thus can be sensitive even to brief nsNSAID administration (McDowell 2014 **NR**).

In patients with normal preoperative renal function, NSAIDs vs placebo may slightly increase serum creatinine (MD 3.23 micmol/L; 95%CI -0.80 to 7.26), however effects on acute kidney injury and need for renal replacement therapy are uncertain (Bell 2018 **Level I** [Cochrane], 26 RCTs, n=8,943). The risk of adverse renal effects of nsNSAIDs and coxibs is increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension, use of other nephrotoxic agents including angiotensin-converting enzyme (ACE) inhibitors (Juhlin 2005 **Level II**, n=14, JS 4), IV contrast media and aminoglycosides (RCA 1998 **Level IV**). Of note, a trial of naproxen following cardiac surgery was stopped because of an increased rate of renal failure (7.3 vs 1.3%) (Horbach 2011 **Level II**, n=161, JS 5). This is confirmed by an analysis of a French pharmacovigilance database, which showed that acute renal failure caused by drug interactions between NSAIDs

and ACE inhibitors, angiotensin-receptor blockers or diuretics was a common issue (Fournier 2014 **Level IV**, n=11,442 [notifications of adverse drug reactions]).

After nephrectomies, evidence is limited and contradictory with a continuous infusion of ketorolac for 24 h after laparoscopic donor nephrectomy having no significant effect on renal function for up to 18 mth postoperatively (Grimsby 2014 **Level II**, n=111, JS 3), but a retrospective case series of donor nephrectomies found a reduction in renal function at 12 mth despite less pain and a shorter LOS (Takahashi 2017 **Level III-2**, n=251). Another retrospective case series found no associations at 1 wk, 1 y or 5 y (Tabrizian 2019 **Level III-2**, n=862).

In the PRECISION trial, long-term use of ibuprofen for treatment of arthritis was associated with significantly more serious renal events than celecoxib (HR 0.61; 95%CI 0.44 to 0.85), but not naproxen (HR 0.79; 95% CI, 0.56 to 1.12) (Nissen 2016 **Level II**, n=24,081, JS 5).

Overall in the general population, NSAID (including coxib) usage is associated with an increased risk of AKI (OR 1.73; 95%CI 1.44 to 2.07) as well as exacerbation in patients with CKD (OR 1.63; 95%CI 1.22 to 2.19) (Zhang 2017a **Level III-3 SR**, 10 studies, n=1,609,163).

For more information on paediatric effects see Section 10.4.2.3.

Cardiovascular effects

Most publications looking at the risk of cardiovascular adverse effects associated with nsNSAID use also include information relating to risks with coxibs (see the more detailed discussion under Section 4.3.2 below).

For some years it has been known that ibuprofen may impede access of aspirin to platelet COX-1 and may abrogate the protective effect of aspirin (Hudson 2005 **Level III-2**, n=18,503; MacDonald 2003 **Level III-2**, n=7,107). Subsequent research indicates that a degree of inhibition may occur with most nsNSAIDs and even some coxibs; while not blocking COX-1, they may block aspirin from reaching it (Nalamachu 2014 **NR**). This is backed up by an ad hoc analysis of data from the PRECISION trial which showed worse cardiovascular outcomes of aspirin/ibuprofen vs aspirin/celecoxib (HR 1.27; 95%CI 1.06 to 1.51) (Reed 2018 **Level III-2**, n=23,953). Impaired aspirin inhibition of platelet function is described in multiple studies for ibuprofen, flufenamic acid, mefenamic acid, piroxicam, nimesulide and dipyrone, while there is conflicting evidence with respect to naproxen, celecoxib, rofecoxib and sulindac, and no inhibition was seen with diclofenac, etoricoxib, ketorolac, ketoprofen, meloxicam or paracetamol (Polzin 2013 **Level III-2**; Meek 2013 **EH**; Saxena 2013 **EH**). The FDA issued a caution specifically about the concomitant use of aspirin and ibuprofen, which states that ibuprofen should be "*given at least 8 hours before or at least 30 minutes after immediate release aspirin*" (FDA 2006 **GL**).

Platelet effects and bleeding

Nonselective NSAIDs inhibit platelet function on aggregometry with naproxen and ibuprofen showing a mild antiplatelet effect for up to 72 and 48 h respectively where meloxicam and celecoxib show essentially no antiplatelet activity (Scott 2014 **BS**).

More recent studies and meta-analyses seem to show less impact of nsNSAIDs on bleeding compared to older ones, perhaps reflecting improvements in surgical technique and reduced total blood loss. A recent meta-analysis found no increased haematoma risk in plastic surgery (OR 1.39; 95%CI 0.82 to 2.37) (Walker 2019 **Level I** [PRISMA] 15 studies, n=3,064) and in another meta-analysis perioperative ketorolac did not increase the rate of postoperative bleeding (OR 1.1; 95%CI 0.61 to 2.06) (Gobble 2014 **Level I**, 27 RCTs, n=2,314). In a cohort study in paediatric neurosurgery, ketorolac was not associated with an increase in clinically significant bleeding events (OR 0.69; 95%CI 0.15 to 3.1) or radiographic haemorrhage (OR 0.81; 95%CI 0.43 to 1.51) (Richardson 2016 **Level III-2**, n=1,451). In contrast, in a previous meta-analysis the rate of surgery-related bleeding was 2.4% after nsNSAIDs vs 0.4% with placebo (Maund 2011 **Level I**, 6 RCTs [bleeding], n=695). In another meta-analysis the use of nsNSAIDs showed a significant increase in

risk of severe bleeding from 0 to 1.7% vs placebo (NNH 59) (Elia 2005 **Level I**, 52 RCTs, n=4,893). A retrospective analysis using data from 2003 to 2016 looking at transfusion risk for hip fractures found a small increase in risk of transfusion with preoperative nsNSAID use within 90 d of surgery (RR 1.07; 95%CI 1.04 to 1.10) (Glassou 2019 **Level III-2**, n=74,791). Other older evidence showing an increased risk of bleeding includes ibuprofen in total hip arthroplasty (THA) (Fransen 2006 **Level II**, n=902, JS 5), tenoxicam in otorhinolaryngological surgery (Merry 2004 **Level II**, n=1,001, JS 5) and diclofenac vs rofecoxib in gynaecological and breast surgery (Hegi 2004 **Level II**, n=50, JS 5).

Bleeding after tonsillectomy is of clinical significance but occurs infrequently; nsNSAID use and post tonsillectomy bleeding remains controversial and the evidence conflicting. The most recent meta-analysis found no statistically significant increase of any outcome related to bleeding with the perioperative use of nsNSAIDs in tonsillectomy (Riggin 2013 **Level I**, 36 RCTs, n=3,193). This was found for most severe bleeding outcome (OR 1.30; 95%CI 0.90 to 1.88), bleeding requiring reoperation (OR 1.32; 95%CI 0.59 to 2.95), bleeding requiring readmission (OR 1.08; 95%CI 0.54 to 2.15), bleeding managed conservatively (OR 1.56; 95%CI 0.91 to 2.66) and secondary haemorrhage (OR 0.90; 95%CI 0.40 to 2.01). There is also no increased bleeding outcome in the paediatric subgroup of this meta-analysis (19 RCTs, n=1,747), which is in line with another meta-analysis in children only (OR 1.69; 95%CI 0.71 to 4.01) (Lewis 2013 **Level I** [Cochrane], 15 RCTs, n=1,101) (see also Section 10.4.2.3 for details). However, neither of these meta-analyses include a subsequent multicentre RCT which was unable to show non-inferiority of ibuprofen to paracetamol with respect to bleeding requiring surgery in paediatric patients (1.2% vs 2.9%; p=0.12 for noninferiority) (Diercks 2019 **Level II**, n=741, JS 5). The above meta-analysis (Riggin 2013 **Level I**, 46 RCTs, n=4,878) could not identify a specific risk for any nsNSAID including aspirin (OR 4.23; 95%CI 0.64 to 27.66) (3 RCTs, n=1,610) and ketorolac (OR 2.01; 95%CI 0.62 to 6.54) (8 RCTs; n=579). These findings are contradicted by a previous larger meta-analysis on aspirin (OR 1.94; 95%CI 1.09 to 3.42) (Krishna 2003 **Level I**, 7 RCTs, n=1,368) and a systematic review on ketorolac (Chan 2014 **Level III-2 SR** [PRISMA], 10 studies, n=1,357). The latter found an overall increased risk of bleeding post tonsillectomy with ketorolac (RR 2.04; 95%CI 1.32 to 3.15), which was also found in adults (RR 5.64; 95%CI 2.08 to 15.27) (3 studies, n=246) but not in children (RR 1.39; 95%CI 0.84 to 2.30) (7 studies, n=1,111).

For more information on paediatric effects see Section 10.4.2.3 and on post-tonsillectomy pain see Sectioin 8.6.7.3.

Hypersensitivity and NSAID-exacerbated respiratory disease (NSAID-ERD)

NSAIDs, especially nsNSAIDs, are one of the most common causes of drug-induced hypersensitivity reactions. Acute reactions include rhinitis, asthma, urticaria, angioedema and anaphylaxis, while delayed reactions include fixed drug eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis, maculopapular reactions, pneumonitis, nephritis or aseptic meningitis (Kowalski 2019 **GL**). This guideline advises on classification, diagnosis and management.

NSAID-ERD has a community prevalence of 1.8% and affects 10-20% of adults with asthma and 5% of children with asthma (Kowalski 2019 **GL**). Bronchospasm usually occurs within 1 to 2 h of exposure and precipitation is related to COX-1 activity with both COX-2 selective NSAIDs (eg celecoxib and etoricoxib) and COX-2 preferential inhibitors (eg nimesulide and meloxicam) being usually well tolerated. See also Section 4.2.2.2 below.

Bone and ligament healing

Ever since the first study in 1976 showed impaired osteoblastic activity with indomethacin in rodent bone models of fracture there has been concern about the effect of NSAIDs on bone healing. The most recent meta-analysis of cohort studies shows an association between long-term NSAID usage and delayed union or disunion (OR 2.07; 95%CI 1.19 to 3.61), but not with low dose or short duration (<2 wk) (OR 1.68; 95%CI 0.63 to 4.46) or in paediatric populations (OR

0.58; 95%CI 0.27 to 1.21) (Wheatley 2019 **Level III-2 SR**, 19 studies, n=15,242 bones). Given the non-randomised cohort nature of this evidence it may well be that patients are taking NSAIDs for longer for a painful non-healing fracture rather than NSAIDs being a causative agent and a firm conclusion is unlikely without a large and well-designed randomised control trial.

In a meta-analysis which included primarily anterior cruciate ligament (ACL) reconstructions (93%) no difference in surgical failure was seen (3.6 vs 3.7%) (Constantinescu 2019 **Level III-2 SR**, 4 studies, n=4,451)

Anastomotic leakage and colorectal surgery

Rodent models of anastamotic leakage have for some time shown reduced collagen formation in rodents given diclofenac leading to concerns about the effect of NSAIDs on anastamotic leak rate in humans (Klein 2012 **BS**). The two most recent meta-analyses of primarily cohort studies (Modasi 2019 **Level III-2 SR** [PRISMA], 8 studies, n=9,835; Huang 2018 **Level III-2 SR**, 17 studies, n=26,098) (overlap 4 studies) show an increased anastamotic leak rate with nsNSAIDs (OR 2.02; 95%CI 1.62 to 2.50 respectively OR 1.79; 95%CI 1.47 to 2.18). Subgroup analysis was unable to show any increase with either selective COX-2 inhibitors (OR 1.17; 95%CI 0.50 to 2.74) or ketorolac (OR 1.36; 95%CI 0.89 to 2.06)). A high risk of publication bias was detected.

NSAIDs do, however, improve recovery of gastrointestinal function with evidence for faster return of flatus (MD -17.73 h; 95%CI -21.26 to -14.19), stool (MD -9.52 h; 95%CI -14.74 to -4.79), and oral feeding tolerance (MD -12.00 h; 95%CI -18.01 to -5.99 h) (Chapman 2019 **Level I** [PRISMA], 6 RCTs, n=563). NSAIDs also reduce the recurrence rate of colorectal adenomas after endoscopic resection (RR 0.68; 95%CI 0.63 to 0.73) (Wang 2015a **Level I**, 9 RCTs, n=8,521).

Central nervous system effects

CNS effects of NSAIDs are poorly defined, but range from symptomatic adverse effects such as headache or dizziness through to possible disease modification in conditions such as Parkinson's disease and dementia (Auriel 2014 **NR**). Evidence on effects on cognitive decline is conflicting with long-term NSAID use showing a small protective effect in one metanalysis of cohort studies (RR 0.87; 95 %CI 0.81 to 0.94) (Wang 2016b **Level III-2 SR** [PRISMA], 11 studies, n=36,165), but no protective effect in another looking at low dose aspirin (Veronese 2017 **Level III-2 SR** [PRISMA], 3 RCTs & 5 studies, n=36,196).

4.2.2 | Systemic cyclooxygenase-2 selective inhibitors (Coxibs)

Coxibs selectively inhibit the inducible COX enzyme, COX-2, and relatively spare constitutive COX-1 (see above). The coxibs available at present are celecoxib, etoricoxib, polmacoxib and parecoxib (the injectable prodrug of valdecoxib). By sparing physiological tissue prostaglandin production while inhibiting inflammatory prostaglandin release, coxibs offer the potential for effective analgesia with fewer adverse effects than nsNSAIDs. However, as noted above, some constitutive physiological synthesis of prostaglandins is also mediated through COX-2, and coxibs may still inhibit COX-1 to some extent.

4.2.2.1 | Efficacy

Coxibs are as effective as nsNSAIDs for postoperative pain (Moore 2015b **Level I** [Cochrane], ≈460 RCTs, n≈50,000), osteoarthritis (Smith 2016 **Level I** [PRISMA], 9 RCTs, n= 2,937) and chronic low-back pain (Chung 2013 **Level I** [PRISMA], 25 RCTs, n=5,935). NNTs are comparable to those for nsNSAIDs for the treatment of moderate to severe acute pain. For a list of NNTs for each medicine see Table 5.1.

When given in combination with opioids after surgery, coxibs show reduced opioid consumption similar to nsNSAIDs (MD over 24 h -10.9 mg; 95%CI -12.8 to -9.1) but no significant reductions in pain scores or opioid-related adverse effects (Maund 2011 **Level I**, 60 RCTs, n unspecified). When given as a single dose preoperatively, coxibs provide a reduction in mean postoperative analgesic requirements at 24 h (MD -0.68; 95%CI -0.95 to -0.33) (Nir 2016 **Level I** [PRISMA], 13 RCTs, n=1,079).

After total knee arthroplasty (TKA), use of coxibs in the perioperative period reduces pain scores, opioid consumption, PONV and pruritus and improves range of motion without increased blood loss (Lin 2013 **Level I**, 8 RCTs, n=571). Continuation of coxibs for 6 wk postoperatively resulted in ongoing improved analgesia and reduced opioid consumption with improved rehabilitation conveying benefits on knee flexion for up to 1 y (Schroer 2011 **Level II**, n=107, JS 5). The risk-benefit ratio for coxibs as a discharge medication after orthopaedic surgery is superior to that for nsNSAIDs (Roberts 2012 **Level I** [PRISMA], 23 RCTs, n unspecified).

Pain relief at rest and on movement and satisfaction were improved when oral celecoxib was added to thoracic PCEA using local anaesthetic and opioid (Senard 2010 **Level II**, n=40, JS 5).

Celecoxib given pre-operatively is effective at reducing 24 h parenteral MED consumption (MD 4.13 mg; 95%Cl 5.58 to 2.67), pain scores at 24 h (MD -1.02/10; 95%CI -1.54 to -0.50) and reducing postoperative nausea and vomiting by 44% and 38% respectively (Khan 2016 **Level I**, 14 RCTs, n=994).

A meta-analysis of parecoxib in orthopaedic surgery in elderly patients shows a reduction in perioperative cognitive dysfunction up to 7 d (RR 0.32; 95%CI 0.16 to 0.63), but not at 3 mth (RR 0.40; 95%CI 0.16 to 1.02) (Huang 2019 **Level I** [PRISMA], 2 RCTs, n=200); these results should be viewed with caution as outcome measures were not robust. A similar effect was shown with celecoxib after arthroplasty (Zhu 2018b **Level II**, n=178, J 5).

4.2.2.2 | Adverse effects

Gastrointestinal effects

In the PRECISION trial celecoxib/esomeprazole was associated with significantly less gastrointestinal events than ibuprofen/esomeprazole (HR 0.43; 95%CI 0.27 to 0.68) and naproxen/esomeprazole (HR 0.51; 95%CI 0.32 to 0.81) (Yeomans 2018 **Level II**, n=24,081, JS 5). Despite a possible dosing inequality this is supported by a trial of naproxen 500 mg BD + PPI vs Celecoxib 100 mg BD + PPI in patients with a recent GI bleed (Chan 2017 **Level II**, n=514, JS 5). Rebleed rates were 5.6% (95%CI 3.3 to 9.2) in the celecoxib group and 12.3% (95%CI 8.8 to 17.1) in the naproxen group (HR 0.44; 95%CI 0.23 to 0.82). Etoricoxib in osteoarthritis similarly shows superiority to nsNSAIDs in terms of GI event rates (RR 0.67; 95%CI 0.59 to 0.76) (Feng 2018 **Level I** [PRISMA], 9 RCTs, n=39,442).

Short-term use of parecoxib/valdecoxib, as required to treat acute pain, results in gastroscopic ulcer rates similar to placebo in elderly patients at increased risk (Goldstein 2003 **Level II**, n=168, JS 4; Stoltz 2002 **Level II**, n=94, JS 4; Harris 2001 **Level II**, n=17 [terminated due to high incidence of gastrointestinal ulcers in both nsNSAID groups], JS 4). This contrasts with increased rates of ulceration with nsNSAIDs in the same setting.

Despite relative safety in comparison to nsNSAIDs, long term usage of COX-2 inhibitors is still associated with an increased GI event rate in cohort studies of non-use versus etoricoxib (RR 4.85; 95%CI 2.64 to 8.93), rofecoxib (RR 2.02; 95%CI 1.56 to 2.61) and celecoxib (RR 1.53; 95%CI 1.19 to 1.97) (Martin Arias 2019 **Level III-2 SR** [PRISMA], 28 studies, n=1,255,401). These results might be unexpected given that both rofecoxib and etoricoxib are more COX-2 selective than celecoxib, however current understanding of gastrointestinal injury includes multiple mechanisms such as mitochondrial uncoupling and ion-trapping that may be unrelated to COX inhibition (Bjarnason 2018 **NR**). In a pooled analysis of COX-2 inhibitor use in osteoarthritis an increase in

gastrointestinal events is seen vs placebo (RR 1.19, 95% CI 1.03 to 1.38) (Curtis 2019 **Level I** [PRISMA], 40 RCTs, n unspecified).

Renal effects

COX-2 is constitutively expressed in the kidney and is highly regulated in response to alterations in intravascular volume. COX-2 has been implicated in maintenance of renal blood flow, mediation of renin release and regulation of sodium excretion (Cheng 2004 **NR**; Kramer 2004 **NR**).

A meta-analysis of perioperative parecoxib found no increase in renal failure vs placebo ((Schug 2017 **Level I**, 26 RCTs, n=9,282). In contrast (and as with nsNSAIDs), a statistically significant increased risk of renal failure was reported following administration of coxibs in cardiac surgery patients (NNH 73) (Elia 2005 **Level I**, 3 RCTs [cardiac surgery], n=803).

In the PRECISION trial long-term ibuprofen was associated with significantly more serious renal events than celecoxib (HR 0.61; 95%CI 0.44 to 0.85), but naproxen was not worse than celecoxib (HR 0.79; 95%CI 0.56 to 1.12) (Nissen 2016 **Level II**, n=24,081, JS 5).

Analysis of the effects of different coxibs on renal function showed heterogeneity within the class as rofecoxib was associated with increased risk of renal dysfunction, while celecoxib was not (Zhang 2006 **Level I**, 114 RCTs, n=116,094).

A subsequent meta-analysis of cohort studies of the general population showed a non-statistically significant trend to a lower AKI incidence with COX-2 selectivity (OR 1.84; 95%CI 1.54 to 2.19 [no COX-2 selectivity] vs OR 1.41; 95%CI 1.07 to 1.87 [COX-2 selectivity]) (Zhang 2017a **Level III-2**, 10 studies, n=1,609,163).

Cardiovascular effects

Cardiovascular risk with coxibs seems very dependent on the coxib in question. This may reflect non-COX dependent effects that NSAIDs may have on the cardiovascular system (Walker 2018 **NR**).

In acute pain management, short-term use of parecoxib after noncardiac surgery does not increase the risk of cardiovascular adverse effects (Schug 2017 **Level I**, 26 RCTs, n=9,282). Similarly, short-term use of other NSAIDs (meloxicam, ketorolac, celecoxib for a mean of 3 d) after lower limb total joint replacement did not increase the risk of myocardial infarction postoperatively vs nonuse (aOR 0.95; 95%CI 0.5 to 1.8) (Liu 2012 **Level III-2**, n=10,873). However, an increase in the incidence of cerebrovascular and cardiovascular events has been reported in patients given parecoxib, then valdecoxib, after CABG surgery (Furberg 2005 **Level I**, 2 RCTs, n=2,098). The FDA has contraindicated the use of all NSAIDs in the immediate postoperative period following CABG surgery (FDA 2007 **GL**). A subsequently performed retrospective observational study with ketorolac has not confirmed these concerns (Oliveri 2014 **Level III-2**, n=1,309).

Absolute long-term cardiovascular risk with chronic usage of NSAIDs remains unclear as the recent large prospective studies were non-inferiority trials without a placebo arm. Studies are conflicting as to cardiovascular risk with individual drugs.

In a review of epidemiological data, rofecoxib showed increased cardiovascular risks vs other coxibs and nsNSAIDs (Gunter 2017 **Level III-2 SR**, 26 studies, n=228,389). In the PRECISION trial in patients with arthritis, there was no difference in cardiovascular event rates between long-term celecoxib and ibuprofen or naproxen (HR [celecoxib vs. naproxen] 0.90; 95%CI 0.71 to 1.15; HR [celecoxib vs. ibuprofen] 0.81; 95%CI 0.65 to 1.02) (Nissen 2016 **Level II**, n=24,081, JS 5). The SCOT trial randomised patients over 60 y with arthritis to either continue their current NSAID or be changed to celecoxib found no difference in cardiovascular risk (HR 1.1; 95%CI 0.81 to 1.55) (MacDonald 2017, **Level II**, n=7,297, JS 3).

A Bayesian meta-analysis found odds ratios for myocardial infarction of 1.24 (95%CI 0.91 to 1.82) for celecoxib, 1.48 (95%CI 1.00 to 2.26) for ibuprofen, 1.50 (95%CI 1.06 to 2.04) for diclofenac, 1.53 (95%CI 1.07 to 2.33) for naproxen, and 1.58 (95%CI 1.07 to 2.17) for rofecoxib (Bally 2017 **Level III-2**, n=446,763 [61 460 myocardial infarctions]). This data directly conflicts with a

previous meta-analysis that found no increased cardiovascular risk with naproxen, diclofenac or etoricoxib (Trelle 2011 **Level I**, 31 RCTs, n=116,429).

Once daily administration of celecoxib eg 400 mg (RR 1.1; 95%CI 0.6 to 2.0) was associated with a lower cardiovascular risk than giving 400 mg as divided doses of 200 mg twice daily (RR 1.8; 95%CI 1.1 to 3.1) (Solomon 2008 **Level I**, 6 RCTS, n=7,950).

All NSAIDs approximately double the risk of congestive heart failure (Bhala 2013 **Level I**, 54 RCTs, n=353,809). However, this analysis pooled all coxib data so that data from rofecoxib and celecoxib was not differentiated. A subsequent meta-analysis of coxibs which looked at heart failure in osteoarthritis found no increase in congestive heart failure (RR 1.18; 95%CI 0.24 to 5.71), but increased risk of peripheral oedema (RR 1.61; 95%CI 1.09 to 2.40) and generalized oedema (RR 1.91; 95%CI 1.08 to 3.39) (Curtis 2019 **Level I** [PRISMA], 40 RCTs, n unspecified). In a nested cohort study which matched 92,163 heart failure admissions with 8,246,403 controls, all NSAIDs except celecoxib were associated with an increased risk of heart failure (Arfe 2016 **Level III-2**, n=8,566,955).

A small increase in the risk of atrial fibrillation with NSAID usage (RR 1.12; 95%CI 1.06 to 1.18) has been documented (Krijthe 2014, **Level III-2**, n=8,423).

In comparison with a historical cohort, the use over a 10 mth period of parecoxib and valdecoxib 40 mg daily for 2–3 wk was associated with an increase in the rate of vascular free flap failure from 7–29%, then falling to 4% after these medicines were no longer used (Al-Sukhun 2006 **Level III-3**, n=180). These retrospective data, which are subject to potential confounding factors, are supported by one study in rats showing a harmful effect of parecoxib on flap survival (Ren 2013 **BS**), which did not occur with celecoxib (Wax 2007 **BS**). A retrospective cohort study using ketorolac after head and neck free flaps found no bleeding complications and no increased risk of free flap failure (Schleiffarth 2014 **Level III-2**, n=138 [free flaps]).

Platelet effects and bleeding

Platelets express only COX-1, not COX-2, and as a consequence, coxibs do not impair platelet function (Munsterhjelm 2006 **Level II EH**, n=18, JS 4). This is consistent with a study on platelet aggregometry with meloxicam and celecoxib show essentially no antiplatelet activity (Scott 2014 **BS**). COX-2 selective NSAIDs show no difference in the risk of postoperative bleeding events (RR 0.92; 95%CI 0.63 to 1.33), intraoperative blood loss (WMD -4.38 ml; 95%CI -14.69 to 5.92), postoperative blood loss (WMD -13.89 ml; 95%CI -30.24 to 2.47), and 24 h postoperative haemoglobin loss (WMD 0.47 g/dL; 95%CI 0.14 to 1.09) vs nsNSAIDs, other analgesics, or placebo (Teerawattananon 2017 **Level I**, 16 RCTs, n=1,704).

Allergic reactions and NSAID-exacerbated respiratory disease

Patients with anaphylactoid reactions to dipyrone and nsNSAIDs (mainly propyphenazone and diclofenac) tolerated oral challenges with rofecoxib and celecoxib (Quiralte 2004 **Level IV**, n=33).

Coxibs, administered at analgesic doses, do not produce bronchospasm in patients with NSAID-exacerbated respiratory disease (Morales 2013 **Level I** [PRISMA], 14 RCTs, n=426).

Bone and ligament healing

At present, data on the effect of coxibs on bone healing are mainly restricted to animal models, where they undoubtedly affect bone remodelling (Kurmis 2012 **NR BS**). Celecoxib after THA reduced the frequency and severity of heterotopic bone formation (Lavernia 2014 **Level III-2**, n=170**;** Oni 2014 **Level III-2**, n=214). There is no good evidence of any clinically significant inhibitory effect of coxibs on bone healing (Kurmis 2012 **NR**; Gerstenfeld 2004 **NR**; Bandolier 2004 **NR**).

In a small single centre trial of celecoxib, ibuprofen or tramadol for rotator cuff repairs celecoxib was associated with an increased rate of re-tears (11/30 [37%]) vs ibuprofen (2/27 [7%]) and tramadol (1/25 [4%]) groups (Oh 2018 **Level II**, n=180, JS 5). This matches animal model data from rabbits (Lu 2015 **BS**).

Anastomotic leakage

There is no increased leakage rate with perioperative coxibs (Modasi 2019 **Level III-2 SR** [PRISMA], 8 studies, n=9,835; Huang 2018 **Level III-2 SR**,17 studies, n=26,098) (overlap 4 studies). See 4.2.1.2 for more detail.

KEY MESSAGES

Efficacy of systemic NSAIDs

1. Nonselective NSAIDs are effective in the treatment of acute postoperative pain, renal colic, migraine, primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]), acute muscle injury (**N**) (**Level I** [PRISMA]) and chronic low-back pain (**U**) (**Level I** [PRISMA]) and acute ankle sprain (**U**) (**Level I**).
2. Coxibs are as effective as nonselective NSAIDs in the treatment of acute pain (including postoperative pain) (**S**) (**Level I** [Cochrane Review]), chronic low-back pain (**U**) (**Level I** [PRISMA]) and osteoarthritis (**N**) (**Level I** [PRISMA]).
3. Nonselective NSAIDs given in addition to paracetamol improve analgesia compared with either medicine given alone (**S**) (**Level I**), in particular ibuprofen combined with paracetamol (**U**) (**Level I** [Cochrane Review]).
4. The risk-benefit ratio for coxibs as a discharge medication after orthopaedic surgery is superior to that for nonselective NSAIDs (**U**) (**Level I** [PRISMA]).
5. Nonselective NSAIDs given in addition to PCA opioids reduce opioid consumption and the incidence of nausea and vomiting (**U**) (**Level I**).
6. Coxibs given in addition to PCA opioids reduce opioid consumption but do not result in a decrease in opioid-related adverse effects (**U**) (**Level I**), except after total knee arthroplasty, where they reduce pain scores and adverse effects and improve outcomes (**U**) (**Level I**).
7. Celecoxib given as a single pre-operative dose is effective at reducing opioid usage, pain scores at 24 hours and postoperative nausea and vomiting (**N**) (**Level I**).

Adverse effects of systemic NSAIDs

8. In patients with normal preoperative renal function nonselective NSAIDs slightly increase serum creatinine, but effects on acute kidney injury and need for renal replacement therapy are uncertain due to lack of evidence (**W**) (**Level I** [Cochrane Review]).
9. Nonselective NSAIDs may increase the risk of any bleeding-related outcome after tonsillectomy in adults (**U**) (**Level I**); however, not in paediatric patients (**U**) (**Level I** [Cochrane Review]) except in a large non-inferiority RCT where need for surgical intervention was increased with ibuprofen versus paracetamol (**Q**) (**Level II**). There is an increase in bleeding complications with aspirin in adults and children (**U**) (**Level I**) and with ketorolac in adults only (**U**) (**Level III-2** [PRISMA]).
10. Nonselective NSAIDS, but not coxibs may cause bronchospasm in individuals known to have NSAID-exacerbated respiratory disease (**U**) (**Level I** [PRISMA]).
11. Coxibs and nonselective NSAIDs exert individual and non-class effects on the cardiovascular system with rofecoxib appearing to be worse than other coxibs and nonselective NSAIDs (**N**) (**Level I**). Celecoxib is no worse than naproxen or ibuprofen (**N**) (**Level II**) and better than ibuprofen when combined with aspirin (**N**) (**Level II**).

12. Short-term use of parecoxib (**S**) (**Level I**) and other NSAIDs (**U**) (**Level III-2**) compared with placebo does not increase the risk of cardiovascular adverse effects after noncardiac surgery.
13. Use of parecoxib followed by valdecoxib after coronary artery bypass graft surgery increases the incidence of cardiovascular and cerebrovascular effects and is therefore contraindicated (**U**) (**Level I**).
14. Perioperative nonselective NSAIDs may increase the risk of minor and major bleeding after surgery compared with placebo (**W**) (**Level I**).
15. Coxibs do not impair platelet function and are not associated with increased perioperative blood loss (**S**) (**Level I**).
16. In patients with normal renal function, parecoxib perioperatively does not increase renal failure (**N**) (**Level I**).
17. NSAIDs hasten bowel recovery after colorectal surgery (**N**) (**Level I**).
18. With regard to renal function, celecoxib is safer than ibuprofen with long-term use (**N**) (**Level II**).
19. Short-term use (5–7 days) of coxibs results in gastric ulceration rates similar to placebo and lower than nonselective NSAIDs (**U**) (**Level II**).
20. The protective effects of low-dose aspirin are reduced by concomitant administration of some NSAIDs, in particular ibuprofen (**S**) (**Level II**).
21. Nonselective NSAIDs, but not coxibs increase the risk of anastomotic leak after colorectal surgery (**N**) (**Level III-2**).
22. NSAIDs taken for less than 2 weeks or in low dose or in paediatrics do not increase the risk of malunion after fracture (**N**) (**Level III-2**).
23. Chronic administration of both nsNSAIDs and coxibs is associated with an increased risk of renal impairment (**N**) (**Level III-3 SR**).

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

☑ The risk of adverse renal effects of nonselective NSAIDs and coxibs may be increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension and use of other nephrotoxic agents including angiotensin-converting enzyme inhibitors (**W**).

4.2.3 | Nonsystemic nonsteroidal anti-inflammatory drugs

Local NSAIDs by any route (transdermal patch or gel, wound infiltration) for non-ophthalmic surgery as part of multimodal analgesic regimens may improve pain control and postoperative function placebo or systemic administration based on low to moderate quality evidence (Brubaker 2016 **Level I** [PRISMA], 9 RCTs, n=532).

4.2.3.1 | Intra-articular

Following arthroscopy, intra-articular (IA) nsNSAIDs such as tenoxicam and ketorolac result in improved pain relief after surgery (Romsing 2000 **Level I**, 16 RCTs, n=844 [7 RCTs IA]). Compared with systemic administration, IA nsNSAIDs (4 RCTs) showed a pain reduction of 20/100 (95%CI 13 to 26) and a 50 to 65% reduction in supplementary analgesic requirements over 24 h. In contrast, when IA nsNSAIDs were compared with IA placebo, two of three RCTs showed no significant analgesic benefit. More recent studies do not permit differentiation of the effect of IA NSAIDs from other components in the injected solution.

In human chondrocytes single-dose equivalent concentrations of ketorolac caused significant chondrotoxicity (Abrams 2017 **BS**). Intraarticular ketorolac for THJR showed no increased risk of loosening, even with long-term follow-up (mean 7.3 y) (Nizam 2015 **Level IV**, n=100).

4.2.3.2 | Wound infiltration

Infiltration of the surgical wound with local anaesthetic/nsNSAID vs local anaesthetic and IV nsNSAID showed no difference in analgesia in three of five RCTs (overall WMD -6/100; 95%CI -19 to 6); similarly, wound infiltration with local anaesthetic/nsNSAID vs local anaesthetic/placebo showed no analgesic benefit in four of five studies (Romsing 2000 **Level I**, 16 RCTs, n=844 [10 RCTs wound]). This lack of a local effect was confirmed in more recent studies, eg with lornoxicam after thyroidectomy (Kilbas 2015 **Level II**, n=80, JS 4).

4.2.3.3 | Local infiltration analgesia

Local infiltration analgesia (LIA) involves the intraoperative periarticular infiltration of large volumes of local anaesthetic combined with a variety of adjuvants typically including an alpha-2 agonist/vasoconstrictor, an opioid and/or an anti-inflammatory agent. The majority of investigations into the effectiveness of LIA in acute pain management following hip or knee arthroplasty fail to separate out the components of the mixture and some protocols also use catheter-based “top-up” regimens of varying composition. The lack of appropriate systemic comparators further complicates analysis of the role of the individual components. Ketorolac is the most frequently used nsNSAID in the LIA mixture. A systematic review identified no RCTs enabling a comparison of the efficacy of systemic vs periarticular administration of nsNSAIDs as a component of LIA in THA (Andersen 2014a **Level I** [PRISMA], 27 RCTs [hip], n=756).

The peak plasma concentrations of ketorolac after use of 30 mg as a component of LIA were comparable to those of similar doses administered IM (0.3-2.2 mg/L) (Affas 2014 **PK**).

4.2.3.4 | Intravenous regional analgesia

Ketorolac 60 mg in combination with local anaesthetic for IV regional analgesia (IVRA) demonstrated longer time to first analgesia request vs local anaesthetic IVRA with either IV ketorolac or IV placebo following minor upper limb procedures (Reuben 1995 **Level II**, n=60, JS 2). However, pain scores were low overall and this study was not blinded. Ketorolac 60 mg added

to local anaesthetic for IVRA or infiltrated into the wound provided superior analgesia for up to 2 h following tourniquet release vs no ketorolac use (Reuben 1996 **Level II**, n=60, JS 3). Again, pain scores were low for all groups and there was no separate parenteral dose of ketorolac. When varying doses of ketorolac were added to IVRA for hand surgery, a linear dose-response relationship from 5 to 20 mg was found; between 20 and 60 mg, there appeared to be no additional analgesic benefit (Steinberg 1998 **Level II**, n=75, JS 3). With IVRA doses of ≥20 mg vs doses <20 mg, time to first analgesia was prolonged and pain scores were significantly lower for up to 2 h following tourniquet release. There was no comparison with ketorolac administered as a separate parenteral dose.

Overall, no conclusion can be drawn regarding a specific benefit of adding ketorolac to IVRA over parenteral administration by a separate route.

4.2.3.5 | Nerve block

Parecoxib/ropivacaine improved quality and duration of brachial plexus block vs placebo/ropivacaine and ropivacaine/IV parecoxib (Liu 2013 **Level II**, n=150, JS 5).

4.2.3.6 | Topical

Application to skin

In adult patients with acute pain resulting from strains, sprains or sports injuries, topical diclofenac, ibuprofen, ketoprofen, piroxicam and indomethacin are effective vs placebo, whereas benzydamine is not significantly better than placebo (Derry 2015a **Level I** [Cochrane] 61 RCTs, n=8,386). Topical compounds with good efficacy are diclofenac with an NNT (for 50% pain reduction over placebo) of 3.7 (95%CI 3.2 to 4.3), ketoprofen of 3.9 (95%CI 3.0 to 5.3), piroxicam of 4.4 (95%CI 3.2 to 6.9) and ibuprofen of 4.6 (95%CI 3.3 to 8.0). Different formulations may differ in efficacy; gels seem to be superior to creams with a diclofenac gel preparation having the lowest NNT of 1.8 (95%CI 1.5 to 2.1) and ketoprofen gel one of 2.5 (95%CI 2.0 to 3.4). The rate of systemic adverse effects with the topical NSAIDs is low and does not differ from placebo. The rate was also lower than with the same oral NSAID although there was limited data on direct comparison.

Topical NSAIDs were of limited efficacy in lateral elbow pain, providing short-term functional improvement for up to 2 wk (Pattanittum 2013 **Level I** [Cochrane], 8 RCTs, n=301). The overall quality of included studies was poor and findings heterogeneous. No comparisons with oral NSAIDs were included.

There is insufficient evidence to differentiate between routes of administration of NSAIDs in the treatment of acute low back pain (Roelofs 2008 **Level I** [Cochrane], 65 RCTs, n=11,237).

Topical application of diclofenac results in tissue levels that are higher and plasma levels that are lower vs oral administration (Zacher 2008 **Level I**, 19 RCTs, n>3,000). Topical NSAIDs were associated with fewer gastrointestinal adverse effects but more local skin irritation than systemic NSAIDs (Klinge 2013 **Level I**, 6 RCTs, n=600).

Ophthalmological applications

There is no strong evidence for pain reduction with topical NSAIDs for traumatic corneal abrasions, but some evidence for a reduced requirement for rescue analgesia at 24 h as a proxy for pain reduction (RR 0.46; 95%CI 0.34 to 0.61) (Wakai 2017 **Level I** [Cochrane], 9 RCTs, n=637). After cataract surgery, topical NSAIDs reduce anterior chamber inflammation and thereby provide postoperative analgesia (Duan 2017 **Level I** [PRISMA], 19 RCTs, n=7,234); diclofenac, nepafenac, ketorolac, and bromfenac are in particular effective. After a number of other ophthalmological procedures, multiple studies show contradictory results with topical NSAIDs.

Mucosal applications

Microgranules containing flurbiprofen 8.75 mg provided better pain relief and reductions in difficulty in swallowing for sore throat than placebo with fast onset (1 min) and long duration (6 h) (Russo 2013 **Level II**, n=373, JS 5). Flurbiprofen spray (8.75 mg) rapidly reduced symptoms of sore throat and provided significantly more relief for up to six h vs placebo, with no difference in adverse effects vs placebo over 3 d (de Looze 2016 **Level II**, n=505, JS 5); similar results (non-inferior to the spay) were found with use of a 8.75 mg flurbiprofen lozenge (Radkova 2017 **Level II**, n=440, JS 5). Flurbiprofen was also useful in post-tonsillectomy pain with reduction in pain scores and reduced requirement for additional analgesia (Muderris 2016 **Level II,** n=84, JS 4).

KEY MESSAGES

1. Topical NSAIDs are effective in treating acute strains, sprains or sports injuries with systemic adverse effects comparable to placebo; gel formulations show superior efficacy over creams (**S**) (**Level I** [Cochrane Review]).
2. Topical NSAIDs are of limited analgesic efficacy for traumatic corneal abrasions, but reduce rescue analgesia requirements (**W**) (**Level I** [Cochrane Review]).
3. Topical NSAIDs reduce anterior chamber inflammation and thereby pain after cataract surgery (**N**) (**Level I** [PRISMA])**.**
4. The efficacy of NSAIDs for peri- or intra-articular injection as a component of local infiltration analgesia compared with systemic administration remains unclear (**U**) (**Level I** [PRISMA]).
5. Intra-articular nonselective NSAIDs may provide more effective analgesia following arthroscopy than IV administration (**U**) (**Level I**).
6. Flurbiprofen spray (or lozenges) provide long-lasting pain relief for sore throat after upper respiratory tract infection (**N**) (**Level II**).

4.3 | Opioids

Opioids can bind to receptors in the brain, spinal cord and periphery, and can be administered systemically or locally (eg intrathecal, intra-articular).

4.3.1 | Systemic opioids

Opioids remain the mainstay of systemic analgesia for the treatment of moderate to severe acute pain.

While opioids are conventionally regarded as acting on opioid receptors, some opioids achieve analgesic effects by additional mechanisms or via alternate interactions with opioid receptors (Raffa 2014a **NR**). The first of this class to be labelled as an "atypical opioid" was tramadol with its effects on noradrenergic and serotonergic inhibitory systems on top of a weak mu-agonism (by an active metabolite) (Raffa 1992 **BS**). The term atypical opioids (although another term "multigesics" has also been suggested) (Pergolizzi Jr 2017 **NR**) is increasingly used for buprenorphine, cebranopadol, tapentadol and tramadol (Schug 2019 **NR)**; of these cebranopadol is undergoing early clinical investigations (Lambert 2015 **NR BS**), while the other three are approved in many countries.

4.3.1.1 | Choice of systemic opioid

All full conventional opioid agonists given in equianalgesic doses produce the same analgesic effect (McQuay 1991 **NR**), although accurate determination of equianalgesic doses is difficult due to interindividual variabilities in kinetics and dynamics (Gammaitoni 2003 **NR**). Equianalgesic conversion dose tables are often used to assist in the change from one opioid to another. However, such tables are based largely on single-dose studies in opioid-naïve subjects and may not be as relevant when conversions are made after repeated doses of an opioid have been given (either in the acute or chronic pain setting) and do not consider incomplete cross-tolerance and patient-specific factors (Weschules 2008a **NR**). Care must be taken when opioid rotations are undertaken based on such tables alone without consideration of clinical factors because this carries a significant risk of toxicity and even fatality (Webster 2012 **NR**). When healthcare professionals (physicians, pharmacists, and nurse practitioners/physician assistants) were surveyed, there was a large variation in mean opioid conversions (Rennick 2016 **Level IV**, n=319). A detailed analysis of equianalgesic doses and suggestions for opioid rotations based on these calculations has been published (Treillet 2018 **Level IV SR**, 20 studies, n unspecified). FPMANZCA provides an opioid calculator including references and background material on a website (FPMANZCA 2019a **GL**), which is also available as an app ("Opioid Calculator") for smartphones. Opioid rotations to methadone require particular care due to the risk of accumulation and subsequent toxicity (McLean 2015 **Level IV SR**, 25 studies, n=1,229).

In general, there is little evidence, on a population basis, to suggest that there are any major differences in efficacy or the incidence of adverse effects between any of the pure agonist opioids, although the results of individual studies are inconsistent. However, for pharmacokinetic and other reasons, some opioids may be better in some patients (Woodhouse 1999 **Level II**, n=82, JS 4). Comparisons of the different opioids are commonly done in patients using PCA (see Section 6.3.1 for these comparisons).

While the data to support the concept of opioid rotation originate from cancer pain (Mercadante 2011 **Level III-2 SR**, 31 studies, n unspecified; Quigley 2004 **Level IV SR** [Cochrane], 52 studies, n unspecified), it may be a useful strategy in the management of acute pain in patients with

intolerable opioid-related adverse effects who are unresponsive to treatment and in opioid-tolerant patients (see also Section 9.7).

The efficacy of various opioids administered by the different routes used in the management of acute pain is discussed in detail in Chapter 5. The following sections describe other relevant aspects of selected atypical and conventional opioids.

4.3.1.2 | Conventional opioids

Codeine

Codeine is classified as a weak opioid. However, it is only a very weak mu-receptor agonist and its analgesic action depends on the metabolism of about 10% of the dose to morphine, via the CYP2D6 cytochrome P450 isoenzyme (Lotsch 2005 **NR**).

Over 100 allelic variants of CYP2D6 have been identified, resulting in wide variability in enzyme activity (Somogyi 2007 **NR**). Individuals carrying two wild-type alleles display normal enzyme activity and are known as extensive metabolisers; intermediate metabolisers are heterozygotes with two variant alleles known to decrease enzymatic capacity; and poor metabolisers have no functionally active alleles and have minimal or no enzyme activity (Stamer 2007a **NR**). In Caucasian populations, 8–10% of people are poor metabolisers; however, 3 to 5% are ultrarapid metabolisers (Madadi 2009 **Level III-2**, n=72; Stamer 2007a **NR**). Those who are ultrarapid metabolisers (carriers of the *CYP2D6* gene duplication) have significantly higher levels of morphine and morphine metabolites after the same dose of codeine (Kirchheiner 2007 **Level IV**, n=23).

There are large interethnic differences in the frequencies of the variant alleles. For example, the proportion of ultrarapid metabolisers is higher (up to 29%) in Middle Eastern and Northern African populations and lower (0.5%) in Asians (Stamer 2007b **NR**); the proportion of poor metabolisers is lower in Asians and African Americans (Yee 2013b **Level IV**, n=75; Holmquist 2009 **NR**).

A case-control study including a case of a newborn dying while breastfed by a mother taking codeine has highlighted that breastfed infants of mothers who are ultrarapid metabolisers are at increased risk of life-threatening CNS depression (Madadi 2009 **Level III-2**, n=72). A number of similar cases have been reported and health professionals and mothers of breastfeeding infants should be aware of this risk (Madadi 2008 **Level IV**, n=35). CYP2D6 genotyping predicts subjects with reduced or increased metabolism to morphine but must be combined with additional phenotyping to accurately predict patients at risk of morphine toxicity (Lotsch 2009 **Level III-2**, n=57).

Death or OIVI has occurred after codeine treatment. Although rare, the risk is highest in children who are ultrarapid metabolisers, after they have undergone tonsillectomy, adenoidectomy, or both, as many of these have sleep-disordered breathing and are therefore more sensitive to opioids (Friedrichsdorf 2013 **Level IV**, n=3; Kelly 2012 **Level IV**, n=4; Racoosin 2013 **NR**). The USA Food and Drug Administration (FDA) now requires a boxed warning of the risk posed by codeine after a child has undergone tonsillectomy or adenoidectomy (FDA 2013 **GL**). The European Medicines Agency has responded similarly (EMA 2013 **GL**); as has the WHO in removing codeine from its tiered analgesic ladder for treatment of (persistent) pain in children (WHO 2012 **GL**). Guidelines on this issue have been published (Crews 2014 **GL**). See also Sections 1.7.3.2 and 10.4.4.5.

The principal metabolite of codeine is codeine-6-glucuronide, which has a similar low potency to the parent medicine and is renally excreted (Lotsch 2005 **NR**).

Dextropropoxyphene

Oral dextropropoxyphene 65 mg alone is a poorly effective analgesic in postoperative pain (NNT 7.7) (Collins 2000 **Level I** [Cochrane], 6 RCTs [dextropropoxyphene only], n=440). Dextropropoxyphene is often used in combination with paracetamol but this combination does not lead to better pain relief vs paracetamol alone and increases the incidence of dizziness (Li Wan Po 1997 **Level I**, 26 RCTs, n=2,231).

The use of this compound is discouraged, not only because of its low efficacy but also because of a number of risks related to its use (Barkin 2006 **NR**). These include QT-interval prolongation and possibility of Torsades des Pointes (TdP) and cardiogenic death. This is exacerbated by complex pharmacokinetics (particularly in the elderly) with the risk of accumulation of dextropropoxyphene and its metabolite nordextropropoxyphene, leading to CNS, respiratory and cardiac depression (Davies 1996 **NR**). However, in therapeutic doses (125±25 mg) no prolongation of the QT-interval >500 ms was observed (Keller 2018 **Level IV**, n=92).

In line with many other developed countries including New Zealand, the Therapeutics Goods Administration (TGA) in Australia decided in November 2011 to remove the registration of dextropropoxyphene (Buckley 2013 **NR**). Despite a number of appeals by the manufacturer, the medication has since been withdrawn from sale in Australia.

Diamorphine

Diamorphine (diacetylmorphine, heroin) is rapidly hydrolysed to monoacetylmorphine (MAM) and morphine (Miyoshi 2001 **NR**); diamorphine and MAM are more lipid-soluble than morphine and penetrate the CNS more rapidly. It is MAM and morphine that are thought to be responsible for the analgesic effects of diamorphine.

There was no difference between parenteral diamorphine and morphine in terms of analgesia and adverse effects after hip surgery (Robinson 1991 **Level II**, n=40, JS 4) and between parenteral diamorphine and pethidine for labour analgesia (Wee 2014 **Level II**, n=484, JS 4). Epidurally administered diamorphine resulted in a longer time to first PCA use and lower total 24 h morphine requirements vs the same dose given by intramuscular (IM) injection (Green 2007 **Level II**, n=60, JS 4). Intranasal (IN) diamorphine has been used as an analgesic for acute pain in children attending EDs (Kendall 2015 **Level IV**, n=226). Here peak morphine plasma concentrations were higher and occurred earlier when diamorphine was administered IV vs IN (Kidd 2009 **Level III-1**, n=24).

Dihydrocodeine

Dihydrocodeine is a semisynthetic derivative of codeine and has similar mu-opioid agonist activity. However, unlike codeine, inhibition of CYP2D6 by quinine does not alter its analgesic effect, even though the CYP2D6-dependant active metabolite, dihydromorphine, has a much higher mu-opioid receptor affinity than the parent medicine (Lotsch 2005 **NR**). Orally administered, it has around twice the potency of codeine and one-sixth the potency of morphine (Leppert 2010 **NR**).

Fentanyl

Fentanyl is a highly potent phenylpiperidine derivative, structurally related to pethidine. It is metabolised almost exclusively in the liver to minimally active metabolites. Less than 10% of unmetabolised fentanyl is renally excreted. Fentanyl is commonly used in the treatment of acute pain, especially when its lack of active metabolites and fast onset of action may be of clinical benefit (Grape 2010 **NR**). The fast onset is the result in particular of its high lipophilicity (octanol:water partition coefficient >700); this leads to a transfer half-life of 4.7 to 6.6 min between plasma and CNS (Lotsch 2013 **NR**) (see also Section 5.4.1). The pharmacokinetics of fentanyl are influenced by impaired liver function and CYP3A4 inhibitor and inducer use (Kuip 2017 **NR**). Data on fentanyl causing opioid-induced hyperalgesia (OIH) are limited and conflicting

with 4 RCTs supporting the induction and 2 RCTs opposing it (Lyons 2015 **Level I**, 6 RCT, n unspecified).

There is insufficient evidence to judge the efficacy of fentanyl in neuropathic pain (Derry 2016b **Level I** [Cochrane], 1 RCT, n=163).

There is an increasing rate of fentanyl (and its analogues) abuse, primarily in the USA, but also now seen in other countries (Jannetto 2019 **NR**). This is paralleled by an increase in fentanyl overdose deaths; in the USA there was a 72% increase from 2014 to 2015 reaching 9,580 deaths caused by synthetic opioids, primarily fentanyl (including illicitly manufactured/non-pharmaceutical). The high mortality is partially due to admixture of fentanyl with other drugs of abuse, in particular heroin; sources are illegal importation and diversion of fentanyl-containing medication (Kuczynska 2018 **NR**). In 2015, a cluster of fentanyl-laced heroin deaths was reported in Melbourne, Australia, the first report of this nature outside North America (Rodda 2017 **Level IV**, n=9 [fentanyl related deaths out of 4,000 deaths investigated]).

Hydromorphone

Hydromorphone is a derivative of morphine that is approximately five times as potent as morphine. The main metabolite of hydromorphone is hydromorphone-3-glucuronide (H3G), a structural analogue of morphine-3-glucuronide (M3G). Like M3G (see below), H3G is dependent on the kidney for excretion, has no analgesic action and can lead to dose-dependent neurotoxic effects (Smith 2000 **NR**; Wright 2001 **NR**; Murray 2005 **NR**).

Hydromorphone is an effective strong opioid analgesic with similar efficacy and adverse effects as other strong opioids (Quigley 2002 **Level I** [Cochrane], 36 RCTs [acute pain], n=2,521). It provides slightly better clinical analgesia than morphine with similar adverse effects (Felden 2011 **Level I**, 8 RCTs, n=1,004). In cancer pain, its efficacy was similar to oxycodone and morphine (Bao 2016 **Level I** [Cochrane], 4 RCTs, n=504). There is insufficient evidence to judge the efficacy of hydromorphone in neuropathic pain (Stannard 2016 **Level I** [Cochrane], 4 RCT, n=604).

Methadone

Methadone is a synthetic opioid commonly used for the maintenance treatment of patients with an addiction to opioids and in patients with chronic pain. It is commercially available as a racemic mixture of R- and L-enantiomers but it is the R-enantiomer that is responsible for most, if not all, its mu-opioid receptor-mediated analgesic effects (Fredheim 2008 **NR**; Lugo 2005 **NR**).

It has good oral bioavailability (70 tot 80%), high potency and long duration of action and a lack of active metabolites (Lugo 2005 **NR**). It is also a weak NMDA-receptor antagonist and monoamine (5HT and noradrenaline [norepinephrine]) reuptake inhibitor and has a long and unpredictable half-life (mean of 22 h; range 4 to 190 h) leading to an increased risk of accumulation (Weschules 2008b **NR**). Therefore, it is of limited use for acute pain treatment. Its use as an analgesic in general requires caution and guidelines have been published (ACMT 2016 **GL**). Recommendations include that it should not be prescribed on an as-needed basis, that the risk of overdose during the initial induction period for chronic use is high and that titration should be very slow. A baseline ECG and a follow-up ECG at 30 d should be obtained in patients at risk for QT prolongation (eg on other medications that prolong QT interval, with structural heart disease or a history of arrhythmias). Patients need extra education on potential risks of methadone treatment.

Dose conversion is complex and depends on many factors including absolute doses of other opioids and duration of treatment (McLean 2015 **Level IV SR**, 25 studies, n=1,229). In cancer pain management, methadone has similar analgesic effects to morphine (Nicholson 2017 **Level I** [Cochrane], 6 RCTs, n=388) (see also 10.4.4.9). There is very limited, very low-quality evidence supporting the efficacy and safety of methadone for chronic neuropathic pain (McNicol 2017 **Level I** [Cochrane], 3 RCTs, n=105).

Methadone is metabolised primarily by the cytochrome P450 group of enzymes, in particular 3A4 and to a lesser extent by CYP 1A2, 2D6, 2D8, 2C9/2C8, 2C19 and 2B6 (Kapur 2011 **NR**). Over 50 drug-drug interactions with methadone are described. Concurrent administration of other medicines that are CYP450 inducers may increase methadone metabolism and lower methadone blood levels (eg carbamazepine, rifampicin, phenytoin, St John's wort [*Hypericum perforatum*] and some antiretroviral agents) leading to potential reduced efficacy or even withdrawal. Conversely, medicines that inhibit CYP450 (eg other antiretroviral agents, some selective serotonin-reuptake inhibitors [SSRIs], grapefruit juice and antifungal agents) may lead to raised methadone levels and an increase in adverse effects or overdose (Fredheim 2008 **NR**) See also Section 8.6.8.2 for interactions in patients with human immunodeficiency virus (HIV).

Methadone use, but not use of other opioids, was associated with an increased incidence of hypoglycaemia in a dose-dependent fashion (for doses > 80 mg/d OR 3.1; 95%CI 2.5 to 3.6) (Flory 2016 **Level III-2**, n=641). This was also found in an analysis of reports from the USA's Food and Drug Administration Adverse Event Reporting System, which showed an association between methadone use and hypoglycaemia in comparison to all other opioids except tramadol (Makunts 2019 **Level IV**, n=12,004,552).

High-dose methadone has been associated with prolonged QT intervals and other cardiac complications (Torsade de pointes, changes in QT dispersion, pathological U waves, Taku-Tsubo syndrome (stress cardiomyopathy), Brugada-like syndrome, and coronary artery diseases) (Alinejad 2015 **NR**) (see below).

In the setting of postoperative pain, methadone was associated with high rates of postoperative complications with the use of a mean dose of 0.14 ± 0.07 mg/kg (Dunn 2018 **Level IV**, n=1,478). Respiratory depression was recorded in 36.8%, hypoxemia in 79.8% and 1.5% required reintubation. QTc prolongation occurred in 58.8% and arrhythmias in 29.9% as well as two in-hospital deaths (0.14%).

Morphine

Morphine remains the standard against which other opioids are compared. Morphine-6-glucuronide (M6G) and M3G, the main metabolites of morphine, are formed by morphine glucuronidation, primarily in the liver. M6G is a mu-opioid receptor agonist that crosses the blood-brain barrier more slowly than morphine (De Gregori 2012 **NR**). It contributes such a large extent to morphine analgesia in patients with both normal (85% of the effect after parenteral and up to 95% after oral administration) and impaired (98% of the effect) renal function, that morphine could be regarded as a prodrug to M6G (Klimas 2014 **NR**). M6G also has other morphine-like effects including respiratory depression (van Dorp 2006b **NR**; Dahan 2008b **NR**). M3G has very low affinity for opioid receptors, has no analgesic activity and animal studies have shown that it may be responsible for the neurotoxic symptoms (not mediated via opioid receptors), such as hyperalgesia, allodynia and myoclonus, sometimes associated with high doses of morphine (Lotsch 2005 **NR**).

Clinical trials have investigated M6G as an analgesic agent after a variety of different types of surgery. It was more effective than placebo (Smith 2009 **Level II**, n=201, JS 4; Romberg 2007 **Level II**, n=42, JS 3) and in some trials as effective as morphine (Cann 2002 **Level II**, n=144, JS 4; Hanna 2005 **Level II**, n=100, JS 3), although withdrawal due to insufficient analgesia was higher in another (Binning 2011 **Level II**, n=249, JS 5); this is possibly due to a slower onset of effect of M6G. However, in the clinical setting of titration of IV morphine to postoperative analgesia, the kinetics of morphine and its metabolites had only limited value in explaining the analgesic effects of morphine (Hammoud 2011 **Level IV**, n=214), which is an effective approach to early postoperative pain (Aubrun 2012 **NR**).

Excellent pain relief was also obtained after IT administration of 100 or 125 mcg M6G in patients after hip replacement surgery, but there was a high incidence (10%) of late respiratory depression (9 to 12 h after the dose was given) requiring treatment with naloxone, and a high incidence of nausea (76–88%) and vomiting (60–64%) (Grace 1996 **Level II**, n=75, JS 5).

The incidence and severity of nausea and vomiting as well as the need for antiemetics was less with M6G than with morphine (Binning 2011 **Level II**, n=249, JS 5; Cann 2002 **Level II**, n=144, JS 4). In healthy volunteers, morphine 0.15 mg/kg and M6G 0.2 mg/kg resulted in similar reductions in ventilatory response to carbon dioxide (CO_2) (Romberg 2003 **Level III-1 EH**).

Both M6G and M3G are dependent on the kidney for excretion. Impaired renal function, the oral route of administration (first-pass metabolism), higher doses and increased patient age are predictors of higher M3G and M6G concentrations (Faura 1998 **Level IV PK SR**, 57 studies, n=1,232; Klepstad 2003 **Level IV**, n=300) with the potential risk of severe long-lasting sedation and respiratory depression.

There is insufficient evidence to judge the efficacy of morphine in neuropathic pain (Cooper 2017 **Level I** [Cochrane], 5 RCTs, n=236). Oral morphine is effective in treating cancer pain with similar efficacy vs other opioids (Wiffen 2016 **Level I** [Cochrane], 62 RCTs, n=4,241).

Oxycodone

Oxycodone is a semisynthetic opioid and directly contributes the majority of drug effect itself while being metabolised primarily to noroxycodone by CYP3A4 (≈45%) and by CYP2D6 to oxymorphone (≈19%) (Kinnunen 2019 **NR PK**). Oxymorphone is more potent than oxycodone as a mu-receptor agonist (14 times) and has a higher receptor affinity (40 times) and may contribute to the overall analgesic effect of oxycodone (Samer 2010b **Level II EH**, n=10 [5-arm cross over], JS 5); noroxycodone, the major metabolite, is only a weak mu-receptor agonist (Lalovic 2006 **NR**; Coluzzi 2005 **NR**).

The dependence of oxymorphone concentrations on CYP2D6 activity and its high potency explains the impact of CYP2D6 polymorphism on oxycodone's pharmacodynamics and pharmacokinetics (Samer 2010b **Level II EH**, n=10 [5-arm cross over], JS 5). Ultrafast metabolisers experience better analgesic effects and higher toxicity, while poor metabolisers experience less analgesic effect. However, in acute postoperative pain, CYP2D6 genotype had no influence on oxycodone requirements (Zwisler 2010 **Level III-3**; Crews 2014 **GL**).

These findings mean also that drug-drug interactions can influence the efficacy of oxycodone (Samer 2010a **Level II EH**, n=10 [cross over], JS 5). This is particularly true for CYP2D6 ultrafast metabolisers but also can be influenced by CYP3A inhibitors such as ketoconazole, which increases the efficacy and toxicity of oxycodone. Therefore, use of a CYP3A inhibitor in an ultrafast CYP2D6 metaboliser is a potentially dangerous combination.

Animal studies have shown that oxycodone is actively taken up into the brain, resulting in a brain concentration that is up to six times that of free plasma levels (Bostrom 2008 **PK**); this may explain the discrepancies between its poorer mu-receptor affinity compared to morphine but its higher potency (Olkkola 2013 **NR**). In general anaesthesia, oxycodone showed a significant dose-dependent respiratory depressant effect measured by reduced minute ventilation, which was significantly more than that of comparable doses of morphine (Chang 2010 **Level II**, n=54, JS 4).

Overall oxycodone has a faster onset of action than morphine, better oral bioavailability, longer duration of action, fewer concerns about metabolites and a lower rate of adverse effects (Olkkola 2013 **NR**). There is increasing use of oxycodone in the perioperative setting based on these pharmacological properties (Kokki 2012 **NR**). With regard to analgesic efficacy in acute pain, IV oxycodone seems superior to fentanyl (6 RCTs) and sufentanil (2 RCTs) and comparable to morphine (3 RCTs), but these results may partially reflect use of doses which were not equianalgesic (Raff 2019 **Level I**, 11 RCTs, n=721). The incidence of adverse effects was lower with

oxycodone vs fentanyl (possibly also a reflection of non-equianalgesic doses) and comparable for oxycodone vs morphine and sufentanil. Patient satisfaction was comparable for all opioids except for sufentanil, which showed consistently lower patient satisfaction vs oxycodone. Similar results are reported by a parallel systematic review which also acknowledges similar limitations (Tan 2018 **Level I**, 8 RCTs, n=506) (6 RCTs overlap). In cancer pain management, oxycodone is comparable in efficacy and adverse effects to other strong opioids; very low-level evidence suggests lower risk of hallucinations with oxycodone vs morphine (Schmidt-Hansen 2018 **Level I** [Cochrane], 23 RCTs, n=2,144). With regard to adverse effects in the setting of cancer pain treatment, there were no differences between oxycodone vs other opioids except for less sleepiness with oxycodone vs morphine (Ma 2016a **Level I** [PRISMA], 11 RCTs, n=1,211) (5 RCTs overlap). In neuropathic pain, there is very low-quality evidence that oxycodone is effective in the treatment of painful diabetic neuropathy (4 RCTs, n=637) and postherpetic neuralgia (1 RCT, n=50) (Gaskell 2016b **Level I** [Cochrane], 5 RCTs, n=687).

Pethidine

Pethidine (meperidine) is a synthetic opioid with decreasing use worldwide due to multiple disadvantages compared to other opioids, and equally effective analgesic alternatives. Despite a common belief that it is the most effective opioid in the treatment of renal colic, it was no better than morphine (O'Connor 2000 **Level II**, n=103, JS 5) or hydromorphone (Jasani 1994 **Level II**, n=73, JS 4). Pethidine and morphine also had similar effects on the sphincter of Oddi and biliary tract and there was no evidence that pethidine was better in the treatment of biliary colic (Latta 2002 **NR**).

Pethidine induced more nausea and vomiting than morphine when used parenterally in the ED (Silverman 2004 **Level III-3**, n=193) and in the first 2 h after gynaecological surgery (Ezri 2002 **Level II**, n=200, JS4). Pethidine use postoperatively was associated with an increased risk of delirium in the postoperative period in comparison to other opioids (Swart 2017 **Level III-2 SR**, 3 studies [pethidine], n=877).

Accumulation of its active metabolite, norpethidine (normeperidine), is associated with neuroexcitatory effects that range from nervousness to tremors, twitches, multifocal myoclonus and seizures (Simopoulos 2002 **Level IV**, n=355). Impaired renal function increases the half-life of norpethidine; therefore, patients with poor renal function are at increased risk of norpethidine toxicity. Naloxone does not reverse and may increase the problems related to norpethidine toxicity.

Overall, the use of pethidine should be discouraged in favour of other opioids in adults (Latta 2002 **NR**) and in the paediatric setting (Benner 2011 **NR**).

Remifentanil

Remifentanil is an unusual opioid with a very fast onset of effect (<1 min) and an extremely short duration of action due to rapid metabolism by nonspecific esterases (Parashchanka 2014 **NR**). It is mainly used as a component of anaesthesia and carries a high risk of OIH; its use as an analgesic has primarily been studied in the setting of labour analgesia (Devabhakthuni 2013 **NR**) (see Section 9.1.3.1).

Sufentanil

Sufentanil (a derivative of fentanyl with rapid onset, short duration of action and no active metabolites) was originally used in the anaesthetic setting; its use has been introduced into the postoperative acute pain setting by the development of SL PCA (Frampton 2016 **NR**) (see Section 6.5.3).

4.3.1.3 | Atypical opioids

Buprenorphine

Buprenorphine is a semisynthetic derivative of thebaine, an alkaloid of opium and a potent, but *in vitro* partial, mu-opioid receptor agonist (Raffa 2014b **NR**) with high receptor affinity and slow dissociation from the mu-receptor and different downstream effects (G protein and adenylcyclase activation) than conventional opioids (Ehrlich 2019 **NR**; Davis 2012 **NR**; Pergolizzi 2010 **NR**). Furthermore, buprenorphine is a potent kappa-opioid receptor antagonist, an agonist at the nociceptin or opioid-receptor-like 1 (ORL-1) receptor and binds to the delta-opioid receptor. Buprenorphine, in particular the SL formulation, is increasingly used in the setting of acute pain management (Macintyre 2017 **NR**).

Buprenorphine shows biphasic pharmacokinetics with an initial distribution half-life of around 2–3 h and a terminal half-life of around 24 h; two-thirds of the medicine is excreted unchanged, mainly in faeces, while the remaining one-third is metabolised predominantly in the liver and gut wall via glucuronidation to an inactive metabolite, buprenorphine-3-glucuronide, and via CYP3A4 to norbuprenorphine, which has 40 times less analgesic effect than buprenorphine (Kress 2009 **NR**). However, in line with findings in animal experiments, an exploratory clinical investigation found respiratory depression more strongly associated with norbuprenorphine than with buprenorphine (Strang 2018 **EH PK**, n=11). Onset of effect is slower than for many other opioids; using experimental pain stimuli, the time to peak effect after administration of an IV bolus dose of buprenorphine was 70–90 min (Yassen 2006 **Level III-3 EH**).

The debate on buprenorphine being a partial or full mu-opioid receptor agonist in clinical practice continues (Holyoak 2019 **NR**) and is complicated by its multiple mechanism of action. While *in-vitro* experiments have characterised buprenorphine as a partial agonist, clinically it behaves like a full mu-receptor agonist; in 23 of 24 studies identified in a systematic review, buprenorphine achieved analgesia comparable to full mu-opioid agonists (morphine, fentanyl, sufentanil and oxycodone) (Raffa 2014b **Level I**, 24 studies, n unspecified). The authors conclude that in clinically relevant doses, buprenorphine behaves like a full mu-opioid receptor agonist *in-vivo*. A subsequent systematic review found SL buprenorphine comparable to IM or IV morphine in acute pain management without any differences in pain control achieved, need for rescue analgesia or secondary outcomes (Vlok 2019 **Level I** [PRISMA], 9 RCTs, n=826). This is confirmed in a paediatric population with IV buprenorphine vs IV morphine showing similar analgesic effects, but a longer duration of analgesia with buprenorphine (Murray 2018 **Level I**, 4 RCTs, n=193). An overarching meta-analysis of buprenorphine vs morphine by any route of administration in any population finds no difference in pain intensity at <1 h (WMD 0.18; 95%CI -0.45 to 0.81), conflicting evidence for other points of time (1 to 48 h) and no difference overall at all time points combined (WMD 0.29; 95%CI -0.62 to 0.03) (White 2018 **Level I** [PRISMA], 28 RCTs, n=2,210) (all 9 RCTs overlap with Vlok 2019 and all 4 RCTs with Murray 2018). All other outcomes for analgesia and adverse effects (including respiratory depression) are not different except for less pruritus with buprenorphine (OR.0.31; 95%CI 0.12 to 0.84).

In animals as well as humans, in therapeutic doses there also appears to be no antagonism of other concurrently administered mu-agonist medicines and combined use should be effective (van Niel 2016 **NR**; Pergolizzi 2010 **NR**). In patients on opioid substitution therapy (OST) with daily SL buprenorphine (12 to 16 mg), high doses of IV hydromorphone (16 and 32 mg) and to a lesser extent IV buprenorphine (32 mg) achieved analgesic effects in an acute pain model (cold pressor test) (Huhn 2019 **Level II EH**, n=17, JS 4). In contrast, patients on OST with SL buprenorphine (2 to 22 mg/d) achieved no relief of experimental pain (cold pressor or electrical stimulation) with IV Morphine (55 mg achieving plasma concentrations of 92 to 201 ng/mL), but reduced respiratory rates (Athanasos 2019 **Level II EH**, n=12, JS 2).

There is a ceiling effect for respiratory depression but not for analgesia in healthy volunteers (in the dose range tested of 200 to 400 mcg) (Dahan 2006 **Level III-2 EH**; Dahan 2005 **Level III-2 EH**). In clinical practice, transdermal (TD) buprenorphine has not been associated with any fatality in the National Poison Data System of the USA (Coplan 2017 **Level IV**). When used for OST, methadone use increased the risk of overdose death vs buprenorphine (RR 6.23; 95%CI 4.79 to 8.10) (Marteau 2015 **Level III-2**, n=2,418 [overdose deaths] in n=19,935,537 [prescriptions]). However, even with buprenorphine the overdose death rate was not zero, but 0.022/1000 prescriptions (vs 0.137/1000 prescriptions of methadone). In an analysis of overdose deaths, buprenorphine alone can cause fatal respiratory depression, although in most cases (90%) other medications, in particular benzodiazepines and other sedatives, were found (Selden 2012 **Level IV**, n=97). Similarly, in elderly opioid-naïve patients acute pain treatment with titration of SL buprenorphine (200 mcg steps with total doses of 200 to 3,000 mcg) resulted in cases of OIVI without a fatal outcome; all patients had risk factors such as advanced age, concurrent comorbidities, or the ingestion of other potential central nervous system depressants (Richards 2017 **Level IV**, n=6). A meta-analysis comparing buprenorphine with morphine finds no difference in the incidence of respiratory depression (defined as respiratory rate <8 to 12/min) (OR.2.07; 95%CI 0.78 to 5.51) or sedation (OR.1.44; 95%CI.0.76 to 2.74) (White 2018 **Level I** [PRISMA], 28 RCTs, n=2,210).

Should buprenorphine-induced respiratory depression occur, then complete reversal with naloxone is possible (Pergolizzi 2010 **NR**), although higher than usual doses and a longer duration infusion of naloxone are required (van Dorp 2006a **Level III-2 EH**; Yassen 2006 **Level III-3 EH**; Boom 2012 **NR**). This is confirmed in the case series referred to above, were naloxone bolus doses up to 2.2 mg and infusions for up to 20 h were used (Richards 2017 **Level IV**, n=6).

In animal models of pain, buprenorphine appears to have good efficacy for neuropathic pain (Hans 2007 **NR**). In the clinical setting, case reports have suggested that buprenorphine is effective in peripheral (Licina 2013 **Level IV**, n=4) and central neuropathic pain (Guetti 2011 **Level IV**). However, a specific effect cannot be supported or refuted based on current evidence (Wiffen 2015 **Level I** [Cochrane], 0 RCTs, n=0).

Buprenorphine may also have a reduced tendency to cause opioid-induced hyperalgesia (OIH) (Lee 2011 **NR**). In patients in opioid-substitution programs, buprenorphine reduced pain thresholds less than methadone (Compton 2001 **Level III-2 EH**, n=54). Using experimental pain stimuli in humans, buprenorphine, unlike conventional mu-opioid agonists, has been shown to be antihyperalgesic, which may be related in part to its kappa-opioid antagonist activity (Koppert 2005 **Level II EH**, n=15, JS 4). During major lung surgery under remifentanil infusion, perioperative buprenorphine infusion (25 mcg/h for 24 h) vs equianalgesic morphine infusion resulted in less hyperalgesia and allodynia around the incision and longer time until rescue analgesia requirements with no long-term benefits at 3 mth (Mercieri 2017 **Level II**, n=64, JS 5). However, in healthy volunteers, IV infusions of buprenorphine (0.3 mg) and morphine (10 and 20 mg) showed no differences in antihyperalgesic or analgesic effects; only IV buprenorphine (0.6 mg) enhanced the descending nociceptive inhibitory control (Ravn 2013 **Level II EH**, n=32, JS 5). Similarly, patients on OST with SL buprenorphine (2 to 22 mg/d) were hyperalgesic in the cold pressor test vs controls (buprenorphine 17 2 s vs control 34 6 s) (Athanasos 2019 **Level II EH**, n=12, JS 2).

Withdrawal symptoms, which may be seen if the medicine is ceased after long-term treatment, are milder and more delayed in onset (≥72 h) than other opioids (Kress 2009 **NR**). In a direct comparison of buprenorphine vs morphine withdrawal, withdrawal symptoms were far less with buprenorphine (subjectively and objectively) (Tompkins 2014 **Level III-1**, n=7). There is also less neonatal abstinence syndrome (NAS) in babies of mothers under buprenorphine vs methadone substitution (Jones 2012 **NR**). In the USA National Poison Data System, calls describing intentional abuse of an opioid were lower for TD buprenorphine than any conventional opioid;

specifically, prescription adjusted rates for abuse were much higher for TD fentanyl vs TD buprenorphine (aRR 10.8; 95%CI 4.46 to 25.9) (Coplan 2017 **Level IV**, n= 2,687 [calls]).

Buprenorphine can be safely used in patients with renal impairment and has less immunosuppressive effect in animal experiments than pure mu-opioid agonists (Davis 2012 **NR**; Pergolizzi 2010 **NR**). However, buprenorphine has the potential to prolong the QT interval (Klivinyi 2018 **NR**). High doses of buprenorphine patch (above 40mcg/h) may cause QT wave prolongation that is reversible with MOR antagonist; clinical significance of this is unclear (Merivirta 2015 **Level III-1**, n=110).

For use in OST and implications for perioperative management see Section 9.8.3.2

Tapentadol

Tapentadol is a combined mu-agonist and noradrenaline-reuptake inhibitor (Tzschentke 2014 **NR**). In contrast to tramadol, it has no relevant functional serotonin-reuptake inhibition and no active metabolites (Raffa 2012 **NR**). Therefore, serotonin syndrome with its use alone has not been reported in 2 systematic reviews (Channell 2018 **Level IV SR**, 13 RCTs & 3 studies & 8 CRs, n unspecified; Gressler 2017 **Level IV SR**, 13 RCTs & 9 studies, n=12,138) (significant overlap). However, in spontaneous adverse drug event (ADE) reporting to the TGA 16 cases consistent with serotonin syndrome were reported (14 with coadministration of serotonergic medications) (Abeyaratne 2018 **Level IV**, n=104 [reports for tapentadol]). A probable serotonin syndrome in the setting of tapentadol overdose in combination with amitriptyline and duloxetine has also been published (Walczyk 2016 **CR**). There is no effect on heart rate or blood pressure due to noradrenaline-reuptake inhibition in doses up to the maximum recommended 500 mg/d, even in patients with hypertension and/or on antihypertensives (Biondi 2014 **Level I**, 3 RCTs *[post hoc* analysis], n=1,464).

Elimination is by glucuronidation; severely impaired hepatic function may require dose adjustment (Xu 2010 **PK**).

Although in humans tapentadol has 18-fold lower affinity for the mu-receptor than morphine, it is only three times less potent as an analgesic due to its dual mechanism of action with synergy shown in site-specific administration studies (Christoph 2013 **BS**). With regard to tapentadol, the concept of "mu-load" (the % contribution of the opioid component to the adverse effect magnitude relative to a pure/classical mu-opioid at equianalgesic doses) has been discussed, suggesting that while conventional opioids have by definition a mu-load of 100%, atypical opioids have a mu-load <100%; for tapentadol using respiratory depression and constipation the mu-load is calculated ≤ 40% (Raffa 2018 **NR**).

The effect of tapentadol as a noradrenaline-uptake inhibitor on descending pathways of pain inhibition has been confirmed in diabetic neuropathy, where tapentadol use increased conditioned pain modulation (Niesters 2014b **Level II**, n=24, JS 5). This mechanism of action suggests benefits in neuropathic pain (Vinik 2014 **Level II**, n=318, JS 5; Freo 2019 **NR**), but tapentadol also showed efficacy in nociceptive and inflammatory-pain models (Schiene 2011 **NR**) including postoperative pain (Lee 2014b **Level II**, n=352, JS 5) and cancer pain (Mercadante 2017 **Level IV SR**, 8 studies, n=792). In the setting of acute pain, tapentadol IR achieves similar analgesia to oxycodone IR, mostly in a 5:1 dose ratio, but with oxycodone resulting in an increased incidence of the gastrointestinal adverse effects nausea (OR 2.23; 95%CI 1.72 to 2.90), vomiting (OR 2.19; 95%CI 1.09 to 4.42) and constipation (OR 3.16; 95%CI 1.42 to 7.01) (each in 3 RCTs) (Hartrick 2010 **Level I**, 5 RCTs, n=2,831). A subsequent systematic review confirmed these results; tapentadol IR in doses of 50, 75 and 100 mg (with 75 mg being superior to 50 mg) provides similar analgesia to oxycodone IR 10 mg (Xiao 2017 **Level I** [PRISMA}, 9 RCTs, n=3,961) (4 RCTS overlap). The rate of nausea (RR 0.64; 95%CI 0.48 to 0.85), vomiting (RR 0.37; 95%CI 0.24 to 0.56) and constipation (RR 0.44; 95%CI 0.32 to 0.62) was lower with tapentadol IR 50 mg and nausea (RR 0.41; 95%CI 0.41 to 0.93) and constipation (RR 0.38; 95%CI 0.25 to 0.54) with 75 mg.

Data in the setting of a number of chronic pain conditions show similar or superior efficacy to conventional opioids with reduced rates of gastrointestinal adverse effects such as nausea, vomiting and constipation leading to reduced rates of treatment discontinuation (Riemsma 2011 **Level I**, 42 RCTs, n unspecified). In a network meta-analysis of opioids for chronic pain treatment, tapentadol was identified as top-ranking due to low rates of overall adverse effects, in particular constipation, and lowest withdrawal rate for adverse effects (Meng 2017 **Level I** [PRISMA] [NMA], 32 RCTs, n unspecified).

Despite increasing use of this analgesic in many countries of the world (in particular the USA [approved 2008], Australia [2010] and Europe [2011]), only 4 (possibly 5 as double reporting of one case could not be excluded) single drug tapentadol overdose deaths could be identified (Channell 2018 **Level IV SR**, 13 RCTs, 3 studies & 8 CRs, n unspecified). Relative safety of tapentadol vs conventional opioids has been confirmed by data from the USA Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program; there was no reported death due to tapentadol between 2010 and 2016 and it had the lowest rate of overdose deaths, major medical effects, serious adverse events and hospitalisations (data corrected for amounts dispensed) (Murphy 2018 **Level IV**, n=64,538 [reports]). Post-marketing surveillance by the manufacturer could also not identify any overdoses with fatal outcomes (Stollenwerk 2018 **Level IV**, n=10,758 [case reports]). In an experimental setting, tapentadol (100 mg) vs oxycodone (20 mg) (equianalgesic doses) had less respiratory depressant effects, but not 150 mg (van der Schrier 2017 **Level II EH**, n=18, JS 5).

Although a controlled medicine in all countries, tapentadol shows a lower rate of abuse and diversion than oxycodone and hydrocodone and a rate comparable to tramadol (Dart 2012 **Level IV**). Diversion rates of tapentadol in the USA corrected for use (monitored by RADARS) were lower for tapentadol IR (0.03/1,000 prescriptions) and tapentadol CR (0.016) than scheduled oral opioids (0.172) (Dart 2016 **Level III-2**, n=38,388 [cases of diversion]). A subsequent analysis by the same system (adjusted for dosing units dispensed) confirms the lowest rate of diversion (comparable to tramadol) and lower, but not the lowest, rate of intentional abuse in reports to poison centres (tramadol and hydrocodone being lower) (Vosburg 2018 **Level III-3**, n multiple denominators). Rates of doctor shopping were higher for oxycodone vs tapentadol (OR 3.5; 95%CI 2.8 to 4.4) (Cepeda 2013b **Level III-2**) and rates of abuse lower for tapentadol vs oxycodone (OR 0.35; 95%CI 0.21 to 0.58) (Cepeda 2013a **Level III-2**).

Tramadol

Tramadol is commonly referred to as an atypical centrally acting analgesic because of its combined effects as an opioid agonist and a serotonin- and noradrenaline-reuptake inhibitor (Bravo 2017 **NR**; Raffa 2012 **NR**; Raffa 1992 **NR**). Although an effective analgesic, it may not provide adequate pain relief if used as the sole agent for the management of moderate to severe acute pain at the currently recommended doses (Thevenin 2008 **Level III-1**). However, compared to a variety of strong opioids (morphine, fentanyl, oxycodone, pethidine) when administered by PCA, tramadol had comparable analgesic efficacy (Murphy 2010 **Level I**, 12 RCTs, n=782). As discharge medication after surgery, the risk of prolonged tramadol use was similar, if not slightly higher than other short acting opioids (Thiels 2019 **Level III-2**, n= 444,764).

Limited low-quality evidence supports tramadol's analgesic effect in cancer pain, although it is not as effective as morphine in this indication (Wiffen 2017b **Level I** [Cochrane], 10 RCTs, n=958). Tramadol is an effective treatment for neuropathic pain with NNT of 4.4 (95%CI 2.9 to 8.8) (Duehmke 2017 **Level I** [Cochrane], 6 RCTs, n=438).

IV tramadol/IV morphine vs IV morphine has a minor opioid-sparing effect (WMD 6.9 mg; 95%CI 211.3 to 22.5), but does not reduce pain intensity (WMD -0.9/100; 95%CI (-7.2 to 5.2) nor adverse effects (nausea, vomiting, sedation) (Martinez 2015 **Level I** [PRISMA], 14 RCTs, n=713).

The (+) enantiomer of tramadol is the stronger inhibitor of serotonin reuptake and the (-) enantiomer the more potent inhibitor of noradrenaline reuptake; tramadol is metabolised by CYP2D6 and the resultant active metabolite O-desmethyltramadol (M1) is a more potent mu-opioid receptor agonist than the parent drug (Lee 1993 **NR**). Patients who are poor metabolisers get less analgesic effect from tramadol (Stamer 2003 **Level III-2**), while ultrarapid metabolisers may be at increased risk of opioid-induced adverse effects including OIVI (Desmeules 1996 **Level II**, n=10, JS 3; Stamer 2008 **CR**). See also Section 1.7.3.2.

Coadministration with other medicines that inhibit CYP2D6 may also influence the effectiveness of tramadol. For example, pretreatment with paroxetine in healthy extensive metabolisers reduced the hypoalgesic effect of tramadol in an experimental pain model (Laugesen 2005 **Level II EH**, n=16 [4-way cross over], JS 5). Inhibition of $5HT_3$ receptors by ondansetron also decreased the analgesic effect of tramadol, as measured by increased tramadol requirements, in particular early after ondansetron administration (Stevens 2015 **Level I** [PRISMA] 6 RCTs, n=340), although this may also be a pharmacokinetic interaction (Hammonds 2003 **NR**). This has been confirmed in a subsequent RCT in hemithyroidectomy patients; here co-administration of IV tramadol (1.5 mg/kg) with ondansetron (0.1 mg/kg) vs tramadol alone reduced time to request for rescue analgesia (76.3 min vs 164.1) and analgesic efficacy at 0 to 60 min postoperatively (at 60 min: 2.51/10 (SD ± 0.66) vs 1.16/10 (± 0.68), but improved PONV scores (Murmu 2015 **Level II**, n=134, JS 4)

Tramadol's adverse-effect profile is different from other opioids. In the RADARS System Poison Center Program, tramadol had the second-lowest rates of overdose deaths, major medical effects, serious adverse events and hospitalisations (data corrected for amounts dispensed) (Murphy 2018 **Level IV**, n=64,538 [reports]). The risk of respiratory depression is lower than with conventional opioids at equianalgesic doses (Mildh 1999 **Level II EH**, n=8 [cross over], JS 5; Tarkkila 1998 **Level II**, n=36, JS 4; Tarkkila 1997 **Level II**, n=36, JS 4) and it does not depress the hypoxic ventilatory response (Warren 2000 **Level II EH**, n=20 [cross over], JS 5). However, in a large series of tramadol overdoses in Iran, mainly due to deliberate self-harm or abuse, 3.6% experienced apnoea and required respiratory support or naloxone use (Hassanian-Moghaddam 2013 **Level IV**, n=525 [overdoses]). The mean time to presentation was 7.7 h (range 1 to 24 h); the mean dose causing apnoea was 2,125 mg (range 200 to 4,600 mg), significantly higher than in those not experiencing apnoea (1,383 mg; range 100 to 6,000 mg). One death in each group was reported. A further series of tramadol overdoses reported hypertension (38.4%), tachycardia (24.8%), respiratory depression (20%) (median dose 2,750 mg), seizure (14.5%) and no serotonin toxicity (Habibollahi 2019 **Level IV**, n=359 [overdoses]). Similar findings are reported from the USA; respiratory depression with relative higher doses than other symptoms (median dose 2,500 mg) and seizures, tachycardia, mild hypertension, but no serotonin toxicity (Ryan 2015 **Level IV**, n=71). Significant respiratory depression has also been described in a patient with severe renal failure, most likely due to accumulation of the metabolite M1 (Barnung 1997 **CR**).

There is a risk of inducing serotonin toxicity when tramadol is combined with other serotonergic medicines, in particular SSRIs (Nelson 2012 **Level IV SR**, 1 study & 9 CR, n=14). However, despite the widespread use of both medicines, there are only very few case reports (14 cases in above SR) on this interaction. The interaction might be complex, as SSRIs are often CYP2D6 inhibitors (eg sertraline, paroxetine and fluoxetine) and can thereby increase tramadol concentrations (Miotto 2017 **NR**). This might also mean that poor CYP2D6 metabolisers are at an increased risk of this interaction (Nelson 2012 **Level IV SR**, 1 study & 9 CR, n=14). Furthermore, administration of tramadol to elderly patients in the postoperative period was a risk factor for delirium (Swart 2017 **Level III-2 SR**, 1 study [tramadol]: Brouquet 2010 **Level IV**, n=133).

Tramadol has less effect on gastrointestinal motor function than morphine (Lim 2001 **Level II**, n=101, JS 5; Wilder-Smith 1999b **Level II**, n=62, JS 5; Wilder-Smith 1999a **Level II**, n=30, JS 5; Wilder-Smith

1997 **Level II**, n=10 [cross over], JS 5). Nausea and vomiting are the most common adverse effects and occur at rates similar to morphine (Lim 2001 **Level II**, n=101, JS 5; Radbruch 1996 **NR**), although an increased rate in comparison to a variety of strong opioids (morphine, fentanyl, oxycodone, pethidine) occurs with PCA use (OR 1.52; 95%CI 1.07 to 2.14) (Murphy 2010 **Level I**, 12 RCTs, n=782). The incidence of pruritus was reduced with tramadol (OR 0.43; 95%CI 0.19 to 0.98).

Tramadol did not increase the incidence of seizures compared with other analgesic agents in two observational studies (Gasse 2000 **Level III-2**, n=11,383; Jick 1998 **Level III-2**, n=10,916). Seizures were reported in tramadol intoxication, mainly due to deliberate self-harm or abuse, with recurrent seizures in 7 and 11.7% of patients (Hassanian-Moghaddam 2013 **Level IV**, n=525; Shadnia 2012 **Level IV**, n=100). Potential risk factors for seizure, other than overdose, were a history of traumatic brain injury, seizure activity secondary to hypoxia and combination with medications that lower seizure threshold (Miotto 2017 **NR**). Calls to the National Poison Data System of the American Association of Poison Control Centers were more likely to report seizures with tramadol vs tapentadol (RR 7.94; 95%CI 2.99 to 20.91) (Tsutaoka 2015 **Level III-2**, n=8,783 [calls]). The low rate of recurrence does not justify the prophylactic use of an anticonvulsant after an initial seizure (Shadnia 2012 **Level IV**, n=100).

An analysis of reports from United States Food and Drug Administration Adverse Event Reporting System showed an association between tramadol use and hypoglycaemia in comparison to all other opioids except methadone (Makunts 2019 **Level IV**, n=12,004,552).

Although withdrawal from tramadol is uncommon, abrupt cessation can lead to withdrawal symptoms, which can have features of classical opioid withdrawal or atypical withdrawal seen with SNRI antidepressants (similar to those described with venlafaxine withdrawal); gradual tapering is recommended and treatment with lorazepam and clonidine if necessary (Miotto 2017 **NR**).

Finally, tramadol has a lower abuse and misuse potential than conventional opioids, as reconfirmed by an expert committee on drug abuse of the German government (Radbruch 2013 **GL**); this is in line with previous findings and tramadol's status as a noncontrolled drug in most countries. However, in countries with low availability of conventional opioids, tramadol has a higher rate of abuse. This has been reported from China (Wang 2018b **Level III-2 SR**, 80 studies, n= 118,904) and Africa (Salm-Reifferscheidt 2018 **NR**) (eg Egypt [Bassiony 2018 **Level IV**, n=1,135], Ghana [Fuseini 2019 **NR**] and Nigeria [Idowu 2018 **Level IV**, n=249]). A detailed assessment of issues related to tramadol use and abuse internationally has been released by the WHO (WHO 2018 **NR**).

4.3.1.4 | Determinants of opioid dose

Interpatient opioid requirements vary greatly (Macintyre 1996 **Level IV**) and opioid doses therefore need to be titrated to suit each patient. Reasons for variation include patient age and gender, genetic differences and psychological factors as well as opioid tolerance.

Patient age

Age, rather than patient weight, appears to be a better determinant of the amount of opioid an adult is likely to require for effective management of acute pain. There is clinical and experimental evidence of a two-fold to four-fold decrease in opioid requirements as patient age increases (Gagliese 2008 **Level IV**, n=246; Coulbault 2006 **Level IV**, n=74; Gagliese 2000 **Level IV**, n=99; Macintyre 1996 **Level IV**, n=1,010; Burns 1989 **Level IV**, n=100). The decrease in opioid requirement is not associated with reports of increased pain (Macintyre 1996 **Level IV**, n=1,010; Burns 1989 **Level IV**, n=100).

This age-related decrease in opioid requirement appears mainly due to differences in pharmacodynamics or brain penetration rather than systemic pharmacokinetic factors (Minto 1997 **Level IV**, n=65; Scott 1987 **Level IV PK**; Macintyre 2008b **NR**). See also Section 9.2.3.

Gender

In general, females report more severe pain than males with similar disease processes or in response to experimental-pain stimuli (Hurley 2008 **NR**). This is more complicated than initially thought; in experimental-pain settings, women have lower pressure pain thresholds than men with no difference for cold and ischaemic pain (Racine 2012a **Level IV SR**, 122 studies, n unspecified). Temporal summation, allodynia and secondary hyperalgesia may be more pronounced in women than in men (Racine 2012b **Level IV SR**, 129 studies, n unspecified). In acute pain, there is more a difference in pain perception than pain sensitivity (Ravn 2012 **Level IV EH**, n=100).

Evidence for differences of opioid responses in the acute pain setting varies. Across all studies in acute clinical pain with mu-opioids there is no association between gender and opioid response, however with PCA use there is greater analgesic effect in women (ES 0.22; 95%CI 0.02 to 0.42) (Niesters 2010 **Level I**, 25 RCTs, n unspecified). The effect is even more pronounced with morphine PCA (ES 0.36; 95%CI 0.17 to 0.56) and is similar in experimental-pain settings (ES 0.35; 95%CI 0.01 to 0.69). Likely explanations are interactions between oestrogen and opioid receptors (Lee 2013b **NR**). This is supported by preclinical data which show that hormones interact with the opioid system and that these interactions may produce meaningful sex-based differences in the subjective experience of opioids, but the direction of effect is variable and inconsistent (Huhn 2018 **BS SR**).

While response to opioids may differ, both the degree and direction of variation depend on many variables (Campesi 2012 **NR**; Dahan 2008a **NR**). This variation as well as other known and unknown factors involved in the very large interpatient differences in opioid requirements seen clinically, means that gender cannot be used as a basis for opioid-dose alteration and confirms the need to titrate doses to effect for each patient.

Genetics

Genetic variability may also affect a patient's response to opioids (see Section 1.7.3).

Psychological factors

The effect of psychological factors such as anxiety on opioid requirements is contradictory (see Section 1.2). Behavioural and psychological aspects associated with opioid tolerance and addiction are discussed in Sections 9.7 and 9.8.

4.3.1.5 | Adverse effects of opioids

Common opioid-related adverse effects are sedation, pruritus, nausea, vomiting, slowing of gastrointestinal function and urinary retention. Meta-analyses have shown that the risk of adverse effects from opioids administered by PCA is similar to the risks from traditional methods of systemic opioid administration, with the exception of pruritus, which is increased in patients using PCA (Hudcova 2006 **Level I** [Cochrane] 55 RCTs, n=3,861).

However, there may be differences in the routine clinical setting (Dolin 2005 **Level IV SR**, 165 studies, n≈20,000; Cashman 2004 **Level IV SR**, 165 studies, n≈20,000). The following incidences (means) were associated with the use of PCA opioids: respiratory depression 1.2 to 11.5% (using decreased respiratory rate and oxygen desaturation, respectively, as indicators), nausea 32%, vomiting 20.7%, pruritus 13.8% and excessive sedation 5.3%. The incidences reported for IM opioid analgesia were: respiratory depression 0.8 to 37% (using the same indicators), nausea 17%, vomiting 21.9%, pruritus 3.4% and excessive sedation 5.2%.

Clinically meaningful opioid-related adverse effects are dose-related. There was an increased risk of 0.9% for nausea and 0.3% for vomiting for every 1 mg increase in PCA-morphine consumption after surgery (Marret 2005 **Level I**, 22 RCTs, n=2,307). In a later prospective evaluation of the incidence of nausea and vomiting in elderly surgical inpatients (requiring a length of stay (LOS) >2 d and no PONV prophylaxis), there was also a direct correlation between increasing

opioid dose and the incidence of both nausea and vomiting (Roberts 2005 **Level IV**, n=193). In patients after laparoscopic cholecystectomy, once a threshold dose was reached (≈10 mg MED/d), every further 3–4 mg increase of MED/d was associated with one additional meaningful adverse effect or patient-day with such an event (Zhao 2004 **Level II**, n=193, JS 5).

Opioid-related adverse effects in surgical patients were associated with increased LOS in hospital and total hospital costs; the use of opioid-sparing techniques can be cost-effective (Oderda 2007 **Level III-2**; Barletta 2012 **NR**; Philip 2002 **NR**). Postsurgical patients who experienced an opioid-related adverse effect had a 55% longer LOS, 47% higher costs, 36% increased risk of readmission and 3.4 times higher risk of inpatient mortality (Kessler 2013 **Level III-2**, n=37,031). Similar results were found in the analysis of a large national hospital database (Oderda 2013 **Level III-2,** n=319,898). More specific information was found in a subsequent study; 10.6% of surgical patients experienced an opioid-related adverse event (Shafi 2018 **Level III-2**, n=135,379). Risk factors were higher opioid doses (MED 46.8 mg vs 30.0 mg) and opioid use for a longer duration (median 3.0 d vs 2.0 d). Opioid-related adverse events were associated with increased inpatient mortality (OR 28.8; 95%CI 24.0 to 34.5 [2.9% increase in absolute mortality]), prolonged LOS (OR 3.1; 95%CI 2.8 to 3.4), high cost of hospitalization (OR 2.7; 95% CI 2.4 to 3.0), higher rate of 30 d readmission (OR 1.3; 95%CI 1.2 to 1.4) and US$ 8,225 per event increase in cost. Similarly, in previously opioid-naive patients receiving opioids after surgery 9.1% experienced opioid-related adverse effects with an increased risk with prolonged IV administration and resulted in 29% higher costs of hospitalization, 55% longer postoperative LOS, 29% lower odds of discharge home and 2.9 times the odds of death (Urman 2019 **Level III-2**, n= 12,218 [patients receiving opioids]).

Identifying patients at high risk of opioid-related adverse effects using clinical and demographic parameters is possible (Minkowitz 2014a **Level III-2**, n=6,285; Minkowitz 2014b **Level III-3**, n=3,697); identification of such high-risk patients enabled reduction of adverse effects and hospital costs.

Opioid-induced ventilatory impairment

OIVI is a more appropriate term to describe the effects of opioids on ventilation than respiratory depression alone (Macintyre 2011 **NR**). It encompasses the respiratory depression caused by opioids (decreased central CO_2 responsiveness resulting in hypoventilation) and elevated partial pressure of carbon dioxide in arterial blood [$PaCO_2$]) (Boom 2012 **NR**) but also the depressed consciousness (decreased arousal and protection) and the subsequent upper airway obstruction (associated with lower airway motor tone) resulting from excessive opioid use. This combination is the most feared adverse effect of opioids, potentially with fatal consequences.

The most frequently reported risk factors for OIVI were older age, female gender, sleep-disordered breathing, obesity, renal impairment, pulmonary disease (in particular COPD), cardiac disease, diabetes, hypertension, neurologic disease, two or more comorbidities, opioid dependence, concomitant administration of sedatives, different routes of opioid administration and CYP450 enzyme polymorphisms, but patients without such risk factors can also develop OIVI (Gupta 2018b **Level IV SR**, 13 studies, n=871,912; Overdyk 2014 **Level IV**, n=134 [case reports]). Postoperative OIVI occurred in 5/1,000 cases with 85% in the first 24 h (95% CI 4.8 to 5.1) (Gupta 2018a **Level IV SR** [PRISMA], 12 studies, n=841,424). Increased risk is linked to cardiac disease (OR 1.7; 95%CI 1.2 to 2.5), pulmonary disease (OR 2.2; 95%CI 1.3 to 3.6), OSA (OR 1.4; 95%CI 1.2 to 1.7) and higher daily MED (24.7±14 mg vs 18.9±13.0 mg). Age, gender, BMI and ASA status are not identified as risk factors in this systematic review. In a closed claims study of postoperative OIVI, 88% of events occurred within 24 h postoperatively; risk factors included multiple prescribers (33%), concurrent administration of sedating medications (34%), and inadequate nursing assessments or response (31%) (Lee 2015b **Level IV**, n=92 [episodes of OIVI]). Other studies confirm that most postoperative events of OIVI occur in the first 24 h: within 24 h 88% (within

12 h 58%) (Weingarten 2015 **Level III-2**, n=134 [naloxone administrations]), 81% (34% within 6 h) (Ramachandran 2011 **Level IV**, n=33 [episodes of OIVI]) and 78% (57% within 12 h) (Taylor 2005 **Level III-2**, n=62 [episodes of OIVI]).

OIVI can usually be avoided by careful titration of the dose against effect and careful observation and monitoring. A variety of clinical indicators have been used to indicate OIVI caused by opioids; not all may be appropriate or sensitive.

A number of studies investigating hypoxia in the postoperative period in patients receiving opioids for pain relief have found that measurement of respiratory rate as an indicator of respiratory depression may be of limited value and that hypoxaemic episodes often occur in the absence of a low respiratory rate (Kluger 1992 **Level III-2**, n=40; Wheatley 1990 **Level III-2**, n=30; Catley 1985 **Level III-2**, n=32; Jones 1990 **NR**). As respiratory depression is almost always preceded by sedation, the best early clinical indicator is increasing sedation (Jungquist 2017 **NR**; Macintyre 2011 **NR**; Vila 2005 **NR**; Ready 1988 **NR**). This has also been acknowledged in recommendations of current guidelines (Jungquist 2020 **GL**; Chou 2016 **GL**).

Introduction of a numerical pain treatment algorithm in a cancer setting was followed by a review of opioid-related adverse effects (Vila 2005 **Level III-3**, n=25). Use of this algorithm, in which opioids were given to patients in order to achieve satisfactory pain scores, resulted in a two-fold increase in the risk of respiratory depression. Importantly, the authors noted that respiratory depression was usually not accompanied by a decrease in respiratory rate. Of the 29 patients who developed respiratory depression (either before or after the introduction of the algorithm), only 3 had a respiratory rate of <12 breaths/min but 27 (94%) had a documented decrease in their level of consciousness (Vila 2005 **Level III-3**, n=29). This study highlights the risk of titrating opioids to achieve a desirable pain score without appropriate patient monitoring.

In a review of PCA, case reports of respiratory depression in patients with obstructive sleep apnoea (OSA) were examined (Macintyre 2008a **NR**). It would appear that the development of respiratory depression might have been missed because of an apparent over-reliance on the use of respiratory rate as an indicator of respiratory depression; the significance of excessive sedation was not recognised.

In an audit of 700 acute pain patients who received PCA for postoperative pain relief, respiratory depression was defined as a respiratory rate of <10 breaths/min and/or a sedation score of 2 (defined as “asleep but easily roused”) or more. Of the 13 patients (1.86%) reported with respiratory depression, 11 had sedation scores of at least 2 and, in contrast to the statements above, all had respiratory rates of <10 breaths/min (Shapiro 2005 **Level IV**, n=700). In a closed claims report, 62% of patients with postoperative OIVI (with 77% fatality or severe brain injury) experienced somnolence before the event (Lee 2015b **Level IV**, n=92 [events of OIVI]): the authors emphasise that assessment of sedation levels by nurses needs to be improved; 97% were judged preventable with better monitoring and response. These studies confirm that assessment of sedation is a more reliable way of detecting opioid-induced respiratory depression, although monitoring respiratory rate is still important.

Oxygen saturation levels may not be a reliable method of detecting respiratory depression in the postoperative setting. In addition to the use of supplemental oxygen delaying OIVI diagnosis, there may be reasons other than opioids for hypoxaemia. For example, when measurement of oxygen saturation was used as an indicator of respiratory depression, the incidence was reported to be 11.5% in patients receiving PCA and 37% in those given IM opioids (Cashman 2004 **Level IV SR**, 165 studies, n≈20,000). However, the same authors showed that patients given IM opioids reported significantly more pain (moderate to severe pain in 67.2% and severe pain in 29.1% compared with 35.8% and 10.4% respectively in PCA patients), suggesting that these patients received much lower doses of opioids (Dolin 2002 **Level IV SR**, 165 studies, n≈20,000). Continuous pulse oximetry (1 RCT, 3 studies) improves recognition of desaturations (< 90%) (OR 15.7; 95% CI

10.6 to 23.2), with a non-significant decrease in transfers to the ICU (RR 0.66; 95%CI 0.42 to 1.01) (Lam 2017 **Level IV SR** [PRISMA}, 2 RCTs, 7 studies, n unspecified).

Increases in $PaCO_2$ are the most reliable way of detecting respiratory depression. Continuous monitoring of transcutaneous CO_2 for 24 h after major abdominal surgery showed that patients given IV PCA morphine had significantly higher CO_2 levels than those receiving epidural local anaesthetic/fentanyl infusions (McCormack 2008 **Level III-2**, n=30; Kopka 2007 **Level III-2**, n=28). Continuous capnography vs continuous pulse oximetry (1 RCT & 2 studies) identifies more events of respiratory depression (OR 5.83; 95%CI 3.54 to 9.63) (11.5% vs 2.8%) (Lam 2017 **Level IV SR** [PRISMA}, 2 RCTs & 7 studies, n unspecified).

Alternative monitors include continuous non-invasive respiratory-volume monitoring, which was described as identifying at-risk patients with a significant drop in minute ventilation or apnoeic/hypopnoeic episodes with high sensitivity (93%) and specificity (86%) (Voscopoulos 2014 **Level IV**, n=132).

Pharmacological strategies to reduce OIVI without affecting analgesia, eg by respiratory stimulants, have been investigated (Kimura 2014 **NR**; van der Schier 2014 **NR**).

Cardiac effects

The use of methadone has been linked to the development of prolonged QT interval with a risk of TdP and cardiac arrest (Alinejad 2015 **NR**; Mujtaba 2013 **NR**). Methadone has this effect due to inhibition of the cardiac-ion channel KCNH226 and the effect is dose-dependent. Most case reports of TdP in patients taking methadone have identified the presence of at least one other risk factor in addition to methadone (Justo 2006 **Level IV**, n=40 [TdP cases in 14 reports]; Fredheim 2008 **NR**). Risk factors include female gender, heart disease, other medicines with effects on the QT interval (eg tricyclic antidepressants [TCAs], antipsychotics, diuretics) or methadone metabolism, congenital or acquired prolonged QT syndromes, liver impairment and hypokalaemia (Mujtaba 2013 **NR**; Fredheim 2008 **NR**).

Of patients under substitution therapy receiving 60–100 mg/d methadone, 23% developed prolonged QT intervals during treatment vs none of the buprenorphine patients taking 16 to 32 mg 3 times/wk (Wedam 2007 **Level II**, n=165, JS 5). In the methadone group, the QT interval continued to increase over time, even with stable doses.

There is as yet no consensus regarding the benefits or otherwise of obtaining an electrocardiogram (ECG) in patients prior to starting methadone, although it may be that the threshold for doing so should be lower in patients with other concomitant risk factors, including those receiving higher doses of methadone (Cruciani 2008 **NR**). Overall, guidelines targeting the prevention of death from methadone can only offer weak recommendations due to lack of good data (Chou 2014 **GL**); a Cochrane review was unable to identify any studies suitable for inclusion (Pani 2013 **Level I** [Cochrane] 0 RCTs, n=0).

The use of dextropropoxyphene also carries a risk of TdP (Barkin 2006 **NR**) (see above). Similarly, higher doses of oxycodone were linked to prolonged QT intervals (Fanoe 2009 **Level III-2**). Beside these opioids, buprenorphine and pethidine have also been associated with prolonged QT intervals (Klivinyi 2018 **NR**).

Nausea and vomiting

Nausea and vomiting are frequent adverse effects of opioid analgesia in a range of settings. PONV and its prevention have been studied the most extensively; hence the following discussion will focus on this data. PONV is common and related to opioid administration in a dose-dependent manner (Marret 2005 **Level I**, 22 RCTs, n=2,307; Roberts 2005 **Level IV**, n=193), although many other more relevant risk factors for PONV have also been identified (Apfel 2012 **Level IV SR**, 22 studies, n=95,154). Opioids are a risk factor for PONV (OR 1.39; 95%CI 1.20 to 1.60) but less so than female gender,

history of previous PONV or motion sickness, inhalational anaesthesia and nonsmoking status. The biological mechanisms of PONV have not yet been completely unravelled (Horn 2014 **NR**).

Guidelines on the prevention and management of PONV have been published (Gan 2014 **GL**).

Medicines used as components of multimodal analgesia and that are opioid-sparing may also reduce PONV. Opioid-sparing and a reduction in PONV has been shown with concurrent administration of gabapentin (Grant 2016b **Level I** [PRISMA], 44 RCTs, n=3,489) and pregabalin (Grant 2016a **Level I** [PRISMA], 23 RCTs, n=1,693), nsNSAIDs (Maund 2011 **Level I**, 43 RCTs [PONV], n unspecified), ketamine (Assouline 2016 **Level I** [PRISMA], 19 RCTS, n=1,453) and lidocaine (Weibel 2018 **Level I** [Cochrane], 68 RCTs, n=4,525). See also sections covering these medications.

Opioid-sparing with no decrease in PONV is reported for paracetamol and coxibs (Maund 2011 **Level I**, 43 RCTs [PONV], n unspecified). However, paracetamol given IV preoperatively or intraoperatively reduces PONV; this effect is associated with improved analgesia, not reduced opioid requirements (Apfel 2013 **Level I** [PRISMA], 30 RCTs, n=2,364). Preoperative vs postoperative paracetamol reduces postoperative vomiting (RR 0.50; 95%CI 0.31 to 0.83) (Doleman 2015b **Level I** [PRISMA], 7 RCTs, n=544) (see also Section 4.1).

Eight medicines effectively prevent PONV vs placebo: droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron (Carlisle 2006 **Level I** [Cochrane], 737 RCTs, n=103,237). The authors conclude that evidence for differences between the medicines was unreliable due to publication bias. Despite limited data to compare adverse effects, droperidol was more sedative and headache more common after ondansetron.

Scientific fraud by Yoshitaka Fujii has influenced this meta-analysis on the efficacy of antiemetics, in particular the efficacy of granisetron and ramosetron is overestimated by inclusion of 168 fraudulent RCTs by his group (Carlisle 2012 **Level I**, 534 RCTs, n unspecified). Ramosetron remains effective vs placebo (but less than reported previously) and maintains a statistical, but clinically questionable, advantage over ondansetron (Mihara 2013 **Level I**, 12 RCTs, n=1,372).

The efficacy of various single compounds in reducing incidence of PONV in the first 24 h has been confirmed in updated meta-analyses; dexamethasone 4–5 mg IV (NNT 3.7), 8–10 mg IV (NNT 3.8) (De Oliveira 2013b **Level I** [PRISMA], 60 RCTs, n=6,696); droperidol ≤1 mg IV (NNT 3.5 to 5 for high-risk patients) (Schaub 2012 **Level I**, 25 RCTs, n=2,957); metoclopramide 10 mg IV (NNT 7.8) (De Oliveira 2012b **Level I** [PRISMA], 30 RCTs, n=3,328); perphenazine (Schnabel 2010 **Level I**, 11 RCTs, n=2,081); $5HT_3$-antagonists ondansetron, granisetron, tropisetron and dolasetron (Tang 2012 **Level I**, 85 RCTs, n=15,269), palonosetron (Singh 2016a **Level I** [PRISMA], 22 RCTs, n unspecified) and TD hyoscine (scopolamine) (Apfel 2010 **Level I**, 25 RCTs, n=3,298). All 5-HT_3 antagonists are superior to placebo in reducing incidence of PONV (125 RCTs, n=16,667 patients) (Tricco 2015a **Level I** [NMA], 450 RCTs, n=80,410).

NK1 receptor antagonists are also used in treatment and prophylaxis of PONV (George 2010 **NR**). Aprepitant (80 mg) reduces the incidence of nausea vs placebo (pooled RR 0.60; 95%CI 0.47 to 0.75) (3 RCTs, n=224) and vomiting (pooled RR 0.13; 95%CI 0.04 to 0.37) (3 RCTs, n=224) (Liu 2015 **Level I** [PRISMA], 14 RCTs, n unspecified). However, neither 40 mg (3 RCTs, n=1,171) nor 125 mg (2 RCTs, n=1,085) are superior to ondansetron (4 mg). After craniotomy, IV fosaprepitant (150 mg) was significantly more effective than IV ondansetron (4 mg) (6 vs 50% vomiting) (Tsutsumi 2014 **Level II**, n=64, JS 5) and more effective than IV droperidol (1.25 mg) (Atsuta 2017 **Level II**, n=200, JS 5).

Propofol (1 mg/kg) close to the end of surgery reduced PONV significantly vs placebo (Kim 2014a **Level II**, n=107, JS 4). Caffeine (500 mg IV) was ineffective in preventing PONV and increased rates of nausea (Steinbrook 2013 **Level II**, n=136, JS 3).

Combinations of antiemetics may be more effective than one medicine given alone. Prophylaxis with the combination of a $5HT_3$-receptor antagonist and dexamethasone was

associated with lower use of rescue antiemetics than $5HT_3$-receptor antagonist or dexamethasone alone (Tricco 2015a **Level I** [NMA], 450 RCTs, n=80,410; Kovac 2006 **Level I**, 49 RCTs, n=12,752), also after strabismus surgery in children (Shen 2014 **Level I**, 13 RCTs, n=2,006). Similarly, the combination of droperidol and ondansetron was additive (Chan 2006 **Level II**, n=400, JS 5). Other combinations that were more effective than either medicine given alone were cyclizine and granisetron (Johns 2006 **Level II**, n=960, JS 5), dexamethasone and haloperidol (Chu 2008 **Level II**, n=400, JS 5) and dexamethasone and dolasetron (Rusch 2007 **Level II**, n=242, JS 5). The addition of metoclopramide to dexamethasone also led to better PONV prophylaxis but, compared with dexamethasone 8 mg alone, only if doses of 25 mg and 50 mg metoclopramide were used, not 10 mg (Wallenborn 2006 **Level II**, n=3,140, JS 4). Oral aprepitant 80 mg added to ondansetron reduced the rate of postoperative vomiting in bariatric surgery patients for 72 h (Sinha 2014 **Level II**, n=125, JS 5).

Droperidol and, to a lesser extent, ondansetron may lead to prolonged QT intervals. Concerns about the potential for serious cardiac arrhythmias secondary to QT prolongation associated with administration of droperidol led to a "black box" warning by the USA FDA in 2001. Following this there has been a significant reduction in the use of this medicine, even though the warning was felt by many to be unwarranted (Habib 2008b **NR**). Mild QT prolongation can occur with anaesthesia and surgery. Saline and 0.625 and 1.25 mg IV droperidol were associated with similar QT prolongation in the postoperative period (White 2005 **Level II**, n=120, JS 5). Similarly, 1.25 mg droperidol did not prolong QT interval (Toyoda 2013 **Level II**, n=72, JS 3). A large review (Nuttall 2007 **Level III-3**) of surgical patients in the periods 3 y before (n=139,932) and 3 y after (n=151,256) the FDA black box warning merged anaesthesia database information with information from ECG and other databases as well as patients' case notes, and recorded all patients who had documented prolonged QT intervals, TdP or death within 48 h of their surgery. Despite a reduction in the use of droperidol from 12 to 0% of patients following the warning, there was no difference in the incidence of QT prolongation, ventricular tachycardia, or death within 48 h of surgery and no clearly identified case of TdP related to use of droperidol (Nuttall 2007 **Level III-3**). The authors concluded that for low-dose droperidol, the black box warning was "*excessive and unnecessary*". The scientific basis of the decision in favour of a black box warning has been questioned as a range of data show that the incidence of QT prolongation and TdP development is similar for low-dose droperidol and other compounds used to treat PONV (Halloran 2010 **NR**). The authors of guidelines for the management of PONV also express concerns about the FDA caution and state "*due to the 2001 black box warning, droperidol is not the first choice for PONV prophylaxis in many countries*" (Gan 2014 **GL**).

Haloperidol has also been associated with QT prolongation and TdP (Habib 2008a **NR**). Using data from studies published up until 1988, a meta-analysis showed that haloperidol is also an effective antiemetic (Buttner 2004 **Level I**, 23 RCTs, n=1,468). Subsequent studies have confirmed its effectiveness vs placebo (Aouad 2007 **Level II**, n=93, JS 4), ondansetron (no differences in efficacy, adverse effects or QT intervals) (Rosow 2008 **Level II**, n=244, JS 2; Aouad 2007 **Level II**, n=93, JS 4; Lee 2007 **Level II**, n=90, JS 5) and droperidol (equally effective) (Wang 2008 **Level II**, n=150, JS 5). Haloperidol/ondansetron was more effective than ondansetron alone (Grecu 2008 **Level II**, n=268, JS 3) and haloperidol/dexamethasone was also more effective than either medicine given alone (Wang 2012 **Level II**, n=135, JS 3; Chu 2008 **Level II**, n=400, JS 5), again with no difference in adverse effects or QT intervals. Compared with droperidol, the only advantage of haloperidol may be "*that there is no black box warning*" (Ludwin 2008 **NR**).

Dolasetron (IV and oral formulations) is contraindicated by the Canadian authorities for any therapeutic use in children and adolescents aged <18 y and the prevention or treatment of PONV in adults because of the risk of QT prolongation (Health Canada 2006 **GL**). This age restriction is not limited to Canada but applies in a number of other countries including the UK. The effect of

therapeutic doses of dolasetron (and ondansetron) on QT prolongation is, however, minimal (6% from baseline) (n=1,429) (Obal 2014 **Level III-3**, n=1,429); a case of prolonged QT interval has been reported after overdose (Rochford 2007 **CR**). More patients receiving granisetron/dexamethasone experience an arrhythmia vs placebo (OR 2.96; 95 %CI 1.11 to 7.94), ondansetron (OR 3.23; 95 %CI 1.17 to 8.95), dolasetron (OR 4.37; 95% CI 1.51 to 12.62), tropisetron (OR 3.27; 95 %CI 1.02 to 10.43), and ondansetron/dexamethasone (OR 5.75; 95% CI 1.71-19.34) (Tricco 2015b **Level I** [NMA], 31 RCTs, n=6,623).

Low-dose naloxone (1 mcg/kg/h) reduces opioid-related postoperative nausea (RR 0.80; 95%CI 0.67 to 0.95), but has no effect on vomiting (RR 0.83; 95%CI 0.63 to 1.09) (Barrons 2017 **Level I** [PRISMA], 9 RCTs, n=946).

Mirtazapine vs placebo reduces PONV (RR 0.44; 95%CI 0.32 to 0.62) (3 RCTs) and has similar effects to ondansetron (1 RCT), while it also reduces anxiety (Bhattacharjee 2019 **Level I** [PRISMA], 7 RCTs, n=581).

Supplemental IV crystalloid infusions reduce the risk of PONV and the need for rescue antiemetics (Jewer 2019 **Level I** [Cochrane], 41 RCTs, n=4,424). IV dextrose perioperatively vs control does not reduce the risk of PONV, but does reduce the need for rescue antiemetics (Kim 2018 **Level I** [PRISMA], 7 RCTs, n=701).

Supplemental oxygen (FiO_2 80%) in the postoperative period does not reduce PONV (Orhan-Sungur 2008 **Level I**, 10 RCTs, n=1,729), but high inspired oxygen concentrations intraoperatively reduce PONV in patients receiving inhalational anaesthetics without prophylactic antiemetics (Hovaguimian 2013 **Level I**, 22 RCTs, n=7,001).

PC6 acupoint stimulation (by any means: acupuncture, electro-acupuncture, transcutaneous electrical acupoint stimulation, transcutaneous nerve stimulation, laser stimulation, capsicum plaster, acu-stimulation device, and acupressure) reduces the incidence of nausea (RR 0.68; 95%CI 0.60 to 0.77) (40 RCTs, n=4,742), vomiting (RR 0.60; 95%CI 0.51 to 0.71) (45 RCTs, n=5,147) and rescue antiemetic requirements (RR 0.64; 95%CI 0.55 to 0.73) (39 RCTs, n=4,622) based on low quality evidence (Lee 2015a **Level I** [Cochrane], 59 RCTs, n=7,667). Compared to antiemetics (metoclopramide, cyclizine, prochlorperazine, droperidol, ondansetron and dexamethasone) the effects on all three above outcomes were similar. Acupuncture/acupressure is the only nonpharmacological intervention included in the PONV management guideline developed by the Society for Ambulatory Anesthesiology, endorsed by ANZCA (Gan 2014 **GL**).

Ginger (*Zingiber officinale*) reduces the severity (SMD −0.25; 95%CI −0.46 to −0.04), but not the incidence of PONV (Toth 2018 **Level I** [PRISMA], 10 RCTs, n=918).

Aromatherapy vs placebo has no effect on incidence of PONV, but may reduce need for rescue antiemetic requirements; both statements are based on low-quality evidence (Hines 2018 **Level III-1 SR** [Cochrane], 16 RCTs and CCTs, n=1,036).

Impairment of gastrointestinal motility

Opioids are well described as inducing constipation with chronic use (Ahmedzai 2006 **NR**). Opioids impair return of bowel function after surgery (Barletta 2012 **NR**). A daily dose of hydromorphone IV >2 mg was the most obvious risk factor for postoperative ileus (Barletta 2011 **Level IV**, n=279). Other risk factors were longer IV opioid use and postoperative ileus was a risk factor for prolonged hospital LOS. After laparotomy and laparoscopic cholecystectomy and colectomy, patients with postoperative ileus received higher opioid doses (median MED 285 mg vs. 95 mg); in postoperative patients with an ileus, opioid doses above the median were associated with increased LOS (3.8 d to 7.1 d), total costs (US$ 8,458 to 19,562), and readmission after laparoscopic surgeries (4.8% to 5.2%) (Gan 2015 **Level III-3**, n= 138,068).

Overall, treatment of opioid-induced constipation due to chronic intake with opioid antagonists (methylnaltrexone, naloxone, naloxegol, alvimopan, axelopran, or naldemedine)

(NNT 3.4 to 7) (23 RCTs) is more effective than laxatives (lubiprostone [NNT 15] or prucalopride) (4 RCTs) (Nee 2018 **Level I** [PRISMA], 27 RCTs, n=8,881); the effects of the various opioid antagonists are similar, while the two laxatives are only slightly better than placebo. A network meta-analysis identified SC methylnaltrexone as the most effective opioid antagonist to treat opioid-induced constipation (Sridharan 2018 **Level I** [NMA], 23 RCTs, n unspecified) (17 RCTs overlap).

The peripheral-acting opioid antagonists alvimopan and methylnaltrexone are effective in reversing opioid-induced slowing of gastrointestinal transit time and constipation and alvimopan is an effective treatment for postoperative ileus (McNicol 2008 **Level I** [QUOROM], 22 RCTs, n=2,358) (4 RCTs overlap with Nee 2018); insufficient evidence exists about the efficacy or safety of naloxone or nalbuphine. The efficacy of alvimopan has been confirmed in subsequent studies summarised in a review (Kraft 2010 **NR**). After radical cystectomy in an RCT not included in any of the above systematic reviews, alvimopan resulted in faster gastrointestinal recovery, shorter hospital LOS and reduced incidence of postoperative ileus (7 vs 26%) with reduced resulting morbidity (8.4 vs 29.1%) without increased adverse effects (Lee 2014a **Level II**, n=280, JS 3).

A combined formulation of controlled-release (CR) oxycodone and naloxone is available in many jurisdictions. Compared with CR oxycodone alone in patients with chronic nonmalignant pain, the combination formulation resulted in similar analgesic efficacy but less bowel dysfunction (Lowenstein 2010 **Level II** [pooled analysis of 2 RCTs], n=578, JS 5). It has been suggested that these benefits were transferable to acute pain settings (Kuusniemi 2012 **NR**). This was not confirmed after laparoscopic hysterectomy where oxycodone/naloxone CR had no beneficial effect on constipation or other opioid adverse effects vs oxycodone CR (Comelon 2013 **Level II**, n=85, JS 5). IV administration of the crushed combination resulted in reduced drug liking and other subjective effects (Colucci 2014 **Level II EH**, n=24, JS 3).

Urinary retention

Opioids cause urinary retention due to presumed central and peripheral mechanisms. Opioid antagonists reverse this effect; naloxone reversed opioid-induced urinary retention in 100% of patients, while the peripheral opioid antagonist methylnaltrexone IV was effective in 42% of study participants (Rosow 2007 **Level III-1 EH**, n=13). These data suggest that at least part of the bladder dysfunction caused by opioids is peripherally mediated.

Premedication with gabapentin reduces urinary retention caused by opioids (NNT 7) (Tiippana 2007 **Level I** [QUOROM], 22 RCTs, n=1,909). This effect is most likely related to the opioid-sparing effect of gabapentin.

Pruritus

The mechanism of opioid-induced pruritus, which is particularly common after neuraxial opioid administration, is not fully understood but central mu-opioid receptor-mediated mechanisms are thought to be the primary cause (Ganesh 2007 **NR**). However, a serotonergic mechanism has also been suggested (Aly 2018 **Level II,** n=40, JS 4) (see also Section 4.3.1.5).

Naloxone, naltrexone, nalbuphine and droperidol are effective in the treatment of opioid-induced pruritus, although minimum effective doses remain unknown (Kjellberg 2001 **Level I**, 22 RCTs, n=1,477 patients); doses >2 mcg/kg/h of naloxone are more likely to lead to reversal of analgesic effects. Low-dose continuous naloxone (0.25–1 mcg/kg/h) has the best evidence (Miller 2011 **NR**). Nalbuphine specifically is more effective than placebo (3 RCTs), control (3 RCTs) and diphenhydramine (1 RCT) in reducing pruritus (Jannuzzi 2016 **Level I**, 9 RCTs, n=1,128). Furthermore, ondansetron reduces the incidence of opioid-induced pruritus after neuraxial administration only in non-obstetric patients (RR 0.63; 95%CI 0.45 to 0.89) (3 RCTs, n=235), but not in obstetric patients (RR 0.84; 95%CI 0.69 to 1.03) (7 RCTs, n=576) (Wang 2017b **Level I** [PRISMA], 10 RCTs, n=811).

Cognitive function and confusion

While opioids can be the cause of cognitive dysfunction, confusion and delirium, it is surprising that, after cardiac surgery, IM morphine 5 mg was superior to IM haloperidol 5 mg in treating delirium (Atalan 2013 **Level II**, n=53, JS 2). This suggests that undertreated pain is a relevant consideration. Similarly, in elderly patients after hip fracture repair, opioids were not an important predictor of postoperative delirium (Sieber 2011 **Level IV**, n=236).

The risk of delirium and/or changes in cognitive function has been compared in patients receiving different PCA opioids. There was no statistically significant difference in the rates of confusion between morphine and fentanyl (14.3 vs 14.3%) but there was less depression of cognitive function with fentanyl (Herrick 1996 **Level II**, n=96, JS 2). No differences in cognitive function were reported in patients receiving tramadol vs morphine (Silvasti 2000 **Level II**, n=60, JS 4) or fentanyl (Ng 2006 **Level II**, n=30, JS 5) but cognition has been found to be poorer with hydromorphone vs morphine (Rapp 1996 **Level II**, n=61, JS 4).

Pethidine use postoperatively was associated with an increased risk of delirium in the postoperative period in comparison to other opioids (Swart 2017 **Level III-2 SR**, 3 studies [pethidine], n=877). Tramadol has been identified as a risk factor for postoperative delirium in the elderly following abdominal surgery (Swart 2017 **Level III-2 SR**, 1 study [tramadol]: Brouquet 2010 **Level III-2**, n=118).

Tolerance and hyperalgesia

In the absence of disease progression, a decrease in the effectiveness of opioid analgesia has traditionally been attributed to opioid tolerance. It is now known that administration of opioids can lead to both opioid-tolerance (a desensitisation of antinociceptive pathways to opioids) and, paradoxically, to OIH (a sensitisation of pronociceptive pathways leading to pain hyper-sensitivity) and that both these phenomena can significantly reduce the analgesic effect of opioids (Mao 2015 **NR**; Low 2012 **NR**; Lee 2011 **NR**). The mechanisms underlying the development of tolerance and OIH are still not fully understood but, as with neuropathic pain, are thought to include activation of the glutaminergic system via the NMDA receptor, GABA receptors and possibly the innate neuroimmune system (Arout 2015 **BS NR**) as well as peripheral mu-opioid receptors (Weber 2017 **NR**).

It may be useful here to distinguish “pharmacological tolerance” (ie tolerance, as defined in Section 9.7.1 “the predictable and physiological decrease in the effect of a drug over time”) and “apparent tolerance”, where both tolerance and OIH contribute to a decrease in the effectiveness of opioids (Chang 2007 **NR**; Mao 2008 **NR**). The clinical significance of this mix, and the relevant contribution of pharmacological tolerance and OIH to apparent tolerance in any particular patient is difficult, if not impossible, to determine (Low 2012 **NR**). However, inadequate pain relief because of pharmacological tolerance may improve with opioid dose escalation, while improvements in analgesia in the presence of OIH may follow a reduction in opioid dose (Mao 2008 **NR**; Chu 2008 **NR**; Chang 2007 **NR**).

A formal diagnosis of hyperalgesia may require QST, that is, serial assessment of the responses to varying intensities of a nociceptive stimulus, in order to determine pain thresholds (Mitra 2008 **NR**). QST before and after starting chronic opioid therapy may assist in the differentiation between OIH and pharmacological tolerance (Chu 2008 **NR**) but this is unlikely to become common practice in the acute pain setting. OIH is identified by reduced pain tolerance to noxious thermal (hot and cold) stimuli, but not electrical stimuli, in patients with chronic opioid exposure for pain management and for opioid use disorder treatment (here more evident) (Higgins 2019 **Level III-3 EH SR** [PRISMA], 26 studies, n=2,706); pain detection thresholds remain unchanged. However, an attempt to identify a QST method to detect hyperalgesia in chronic pain patients on long-term opioids failed, as none of the measures could be used as a definitive

standard (Katz 2015 **Level IV EH SR**, 14 studies, n unspecified). The pain types investigated include cold, heat, pressure, electrical, ischaemic and injection; only heat pain sensitivity showed promise.

Studies of OIH are confounded by factors such as pain modality tested, route of administration and type of opioid (Weber 2017 **NR**). Psychological factors such as pain-related distress and catastrophising might also affect pain sensitivity in those taking opioids for chronic pain (Edwards 2011 **Level III-2**, n=276; Eyler 2013 **NR**). Illicit substance use, affective characteristics, or coping styles may also play a role here (Higgins 2019 **Level III-3 EH SR** [PRISMA], 26 studies, n=2,706). Additionally, increasing opioid dose will worsen OIH (Colvin 2019 **NR**). Practical clinical challenges include lack of consensus on "the" diagnostic test, and overlap with tolerance, drug withdrawal and neuropathic pain.

It is probable that the degree of OIH varies between opioids. Remifentanil in particular (Fletcher 2014 **Level I** [PRISMA], 27 RCTs, n=1,494; Kim 2014b **Level IV EH SR**, number of studies unspecified, n unspecified; Rivosecchi 2014 **Level IV SR**, 35 studies, n unspecified) (significant overlap between all three SRs), but also morphine, in high doses, may be more likely to result in OIH than some other opioids; experimental data and a very limited number of case reports have shown an improvement when morphine doses were reduced or a change to methadone, fentanyl or sufentanil was made (Angst 2006 **NR**). Similarly, it appears that opioids differ in their ability to induce tolerance. Medicines such as methadone, fentanyl and sufentanil promote receptor internalisation and thereby receptor recycling; in contrast, the activation of opioid receptors by morphine leads to little or no receptor internalisation and thereby increased risk of development of tolerance (Joo 2007 **NR**). The difference between opioids is one reason why opioid-rotation may be a useful strategy in the clinical setting in attempts to improve pain relief (see Section 9.7.6.4).

In the setting of postoperative pain, high intraoperative doses of opioids resulted in higher postoperative pain intensity than controls at 1 h (MD 9.4/100; 95%CI 4.4 to 14.5), 4 h (MD 7.1/100; 95%CI 2.8 to 11.3) and 24 h (MD 3/100; 95%CI 0.4 to 5.6) and higher postoperative morphine use over 24 h (SMD 0.7; 95%CI 0.37 to 1.02) (Fletcher 2014 **Level I** [PRISMA], 27 RCTs, n=1,494). These results are mainly influenced by remifentanil due to limited data with other opioids. Overall, the effect of remifentanil is dose dependent (Angst 2015 **NR**).

From a target concentration 2.5 ng/ml of a remifentanil infusion for 30 min, gradual withdrawal (by 0.6 ng/ml target concentration every 5 min) induced no OIH (pain similar to placebo) vs abrupt cessation measured with the heat pain test, but not the cold pressor test (Comelon 2016 **Level II EH**, n=19, JS 5). This was confirmed in a clinical setting of thyroidectomy, where gradual tapering of a remifentanil infusion (from 0.3 to 0.1 mcg/kg/min over at least 30 min) reduced postoperative pain at 1 and 2 h and rescue analgesia requirements (Han 2015 **Level II**, n=62, JS 5).

NMDA-receptor antagonists (mainly ketamine [8 RCTs] but also magnesium [5 RCTs] and amantadine [1 RCT]) reduce the development of acute tolerance/OIH associated with remifentanil use (Wu 2015 **Level I** [QUOROM], 14 RCTs, n=729). Pregabalin had an attenuating effect (Lee 2013a **Level II**, n=93, JS 5; Jo 2011 **Level II**, n=60, JS 5) as did propofol in a subgroup analysis (6 RCTs, n=341) of a systematic review (Fletcher 2014 **Level I** [PRISMA], 27 RCTs, n=1,494) and N_2O (Wehrfritz 2016 **Level II EH**, n=21, JS 5; Echevarria 2011 **Level II**, n=50, JS 4). Low-dose naloxone (0.25 mcg/kg/h intraoperatively) also reduced postoperative opioid requirements when combined with high dose remifentanil (and improved time to bowel recovery) (Xiao 2015 **Level II**, n=75, JS 5). In an experimental setting, propranolol infusion reduced the size of area of secondary hyperalgesia induced by remifentanil to being not significantly different from control (Chu 2012 **Level II EH**, n=10 [cross over], JS 4). In animal experiments, the effects of gabapentin and ketamine on fentanyl-induced hyperalgesia were supra-additive (Van Elstraete 2011 **BS**).

The challenge faced by the health professional is that if inadequate pain relief is due to OIH, a reduction in opioid dose may help; if it is due to opioid tolerance, increased doses may provide better pain relief (Colvin 2019 **NR**; Huxtable 2011 **NR**; Mao 2008 **NR**). There are case reports of patients with cancer and chronic noncancer pain taking high doses of opioid who developed OIH and whose pain relief improved following reduction of their opioid dose (Chang 2007 **CR**; Angst 2006 **CR**); there are no data in the acute pain setting.

When a patient who has been taking opioids for a while (either legally prescribed or illicitly obtained) has new and ongoing tissue injury with resultant acute pain, a reasonable initial response to inadequate opioid analgesia, after an evaluation of the patient and in the absence of evidence to the contrary, is a trial of higher opioid doses (Huxtable 2011 **NR**; Chang 2007 **NR**). If the pain improves, this would suggest that the inadequate analgesia resulted from tolerance; if pain worsens, or fails to respond to dose escalation, it could be a result of OIH (Chang 2007 **NR**). Fortunately, some of the strategies that may be tried in an attempt to attenuate opioid tolerance in the acute pain setting may also moderate OIH (see below).

Other reasons for increased pain and/or increased opioid requirements should also be considered. These include acute neuropathic pain, pain due to other causes including postoperative complications, major psychological distress and aberrant drug-seeking behaviours (see Sections 9.7 and 9.8) (Edwards 2011 **Level III-2**; Macintyre 2015 **NR**; Gourlay 2008 **NR**).

The clinical relevance of the phenomena of opioid tolerance and OIH in the setting of perioperative analgesia remains under discussion (Colvin 2019 **NR**) (See also Section 9.7.2 and 9.8.1).

Tolerance to adverse effects of opioids

Tolerance to the adverse effects of opioids also occurs; tolerance to sedation, cognitive effects, nausea and respiratory depression can occur reasonably rapidly but there is little, if any, change in miosis or constipation (Chang 2007 **NR**).

KEY MESSAGES

1. Dextropropoxyphene has low analgesic efficacy (**U**) (**Level I** [Cochrane Review]).
2. Tramadol is an effective treatment for neuropathic pain (**S**) (**Level I** [Cochrane Review]).
3. Droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine, granisetron (**U**) (**Level I** [Cochrane Review]), supplemental crystalloid infusions (**N**) (**Level I** [Cochrane Review]), palonosetron and mirtazapine (**N**) (**Level I** [PRISMA]) are effective in the prevention of postoperative nausea and vomiting.
4. PC6 acupoint stimulation by multiple techniques reduces postoperative nausea and vomiting (**S**) (**Level I** [Cochrane Review]).
5. Neurokinin-1 receptor antagonists aprepitant (**S**) (**Level I** [PRISMA]) and fosaprepitant (**U**) (**Level II**) are effective in the prevention of postoperative nausea and vomiting.
6. Opioids in high doses, in particular remifentanil, can induce hyperalgesia and/or acute tolerance (**S**) (**Level I** [PRISMA]).
7. Propofol (**U**) (**Level I** [PRISMA]), NMDA-receptor antagonists (**U**) (**Level I** [QUOROM]), pregabalin (**U**) (**Level II**), nitrous oxide (**N**) (**Level II**) and gradual tapering of remifentanil dose (**N**) (**Level II**) attenuate acute tolerance and/or hyperalgesia induced by remifentanil.

8. NSAIDs, gabapentin, pregabalin, systemic lidocaine and ketamine are opioid-sparing medications and reduce opioid-related adverse effects (**S**) (**Level I** [PRISMA]).
9. Paracetamol given preoperatively and intraoperatively reduces postoperative nausea and vomiting; this effect is associated with improved analgesia, not reduced opioid requirements (**S**) (**Level I** [PRISMA]).
10. Opioid antagonists (methylnaltrexone, naloxone, naloxegol, alvimopan, axelopran, or naldemedine) are effective (more so than laxatives) and safe to treat opioid-induced constipation (**S**) (**Level I** [PRISMA]).
11. Alvimopan is an effective treatment for postoperative ileus (**U**) (**Level I** [QUOROM]).
12. Haloperidol, perphenazine and transdermal scopolamine are effective in the prevention of postoperative nausea and vomiting (**U**) (**Level I**).
13. The incidence of clinically meaningful adverse effects (nausea, vomiting) of opioids is dose-related (**U**) (**Level I**).
14. Paired combinations of $5HT_3$ antagonists, droperidol or dexamethasone provide superior prophylaxis of postoperative nausea and vomiting than either compound alone (**U**) (**Level I**).
15. Naloxone, naltrexone, nalbuphine and droperidol are effective treatments for opioid-induced pruritus (**U**) (**Level I**).
16. Opioids administered by PCA, in particular morphine, show higher analgesic efficacy in females than in males (**U**) (**Level I**).
17. Tapentadol has similar efficacy to conventional opioids with a reduced rate of gastrointestinal adverse effects (nausea, vomiting, constipation) (**S**) (**Level I**).
18. Tramadol has a lower risk of respiratory depression and impairs gastrointestinal motor function less than other opioids at equianalgesic doses (**U**) (**Level II**).
19. Pethidine is not superior to morphine or hydromorphone in treatment of pain of renal colic (**U**) (**Level II**).
20. Morphine-6-glucuronide is an effective analgesic (**U**) (**Level II**).
21. In the management of acute pain, one opioid is not superior to others but some opioids are better in some patients (**U**) (**Level II**).
22. High doses of methadone can lead to prolonged QT interval (**U**) (**Level II**).
23. Opioid antagonists are effective treatments for opioid-induced urinary retention (**U**) (**Level III-1**).
24. Pethidine use is associated with an increased risk of delirium in the postoperative period compared to other opioids (**S**) (**Level III-2 SR**).
25. In clinically relevant doses, there is a ceiling effect for respiratory depression with buprenorphine but not for analgesia (**U**) (**Level III-2**).
26. Tapentadol has lower rates of abuse and doctor shopping than oxycodone (**S**) (**Level III-2**).

27. Opioid-related adverse effects in the postoperative period are associated with increased inpatient mortality, length of hospital stay, costs and rates of readmission (**S**) (**Level III-2**).
28. Assessment of sedation is a more reliable way of detecting early opioid-induced ventilatory impairment than a decreased respiratory rate (**S**) (**Level III-3**).
29. The evidence for significant QT prolongation and risk of cardiac arrhythmias following low-dose droperidol, haloperidol and dolasetron is weak (**U**) (**Level III-3**).
30. Opioid-induced ventilatory impairment occurs in particular in the first 24 h after surgery and important risk factors are cardiac and pulmonary disease, obstructive sleep apnoea and use of higher opioid doses (**N**) (**Level IV SR** [PRISMA]).
31. Continuous pulse oximetry in patients receiving opioids postoperatively increases detection rate of desaturation, but continuous capnography is superior in identifying episodes of opioid-induced ventilatory impairment (**N**) (**Level IV SR** [PRISMA]).
32. In adults, patient age rather than weight is a better predictor of opioid requirements, although there is a large interpatient variation (**U**) (**Level IV**).
33. Impaired renal function and the oral route of administration result in higher levels of the morphine metabolites morphine-3-glucuronide and morphine-6-glucuronide with increased risk of sedation and respiratory depression (**U**) (**Level IV**).
34. CYP2D6 ultrarapid metabolisers are at increased risk of codeine toxicity (**N**) (**Level IV**).

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

☑ Opioid-induced ventilatory impairment is a more appropriate term to describe the effects of opioids on ventilation as it encompasses the central respiratory depression caused by opioids and also the depressed consciousness and the subsequent upper airway obstruction resulting from excessive opioid use (**U**).

☑ The use of pethidine and dextropropoxyphene should be discouraged in favour of other opioids (**S**).

4.3.2 | Neuraxial opioids

Opioid receptors were described in the spinal cord of the rat in 1976 (Pert 1976 **BS**) and the same year a potent analgesic effect of directly applied IT morphine was reported in these animals (Kontinen 2019 **NR**; Yaksh 1976 **BS**). Opioid analgesia is spinally mediated via presynaptic and postsynaptic receptors in the substantia gelatinosa in the dorsal horn (Yaksh 1981 **BS**). Spinal opioid receptors are 70% mu, 24% delta and 6% kappa (Treman 2001 **NR**); with 70% of all mu and delta receptors being presynaptic (predominantly small primary afferents) and commonly co-located, with kappa being more commonly postsynaptic. Opioid-mediated antinociception may be further augmented by descending inhibition from mu-opioid-receptor activation in the periaqueductal area of the brain, which may be potentiated by neuraxial opioids. In addition to this, a local anaesthetic action has been described for pethidine (meperidine) that may contribute to the clinical effect when administered IT (Jaffe 1996 **BS**). The first clinical use of IT morphine was for analgesia in cancer patients (Wang 1979 **Level IV**).

The use of neuraxial opioids has been reviewed in paediatric patients (Berger 2019 **NR**) (see sections 10.6.4 for use in paediatric cardiac and general surgery and section 10.6.6 for use in paediatric scoliosis surgery) and obstetric populations (Armstrong 2016 **NR**). Its use is widespread in the obstetric and gynaecological setting for provision of analgesia in labour, Caesarean section and hysterectomy (Hein 2017 **Level IV**, n=32 [obstetric units in Sweden]). See also Section 9.1.3.3.

Although dose-response analyses are not always clear, it is suggested that neuraxial opioids have a ceiling effect for analgesia, with optimal single-injection morphine doses (balancing risk-benefit) of 50 to 150 mcg IT and 2.5 to 3.75 mg via epidural route (Saltan 2011 **NR**).

4.3.2.1 | Efficacy of intrathecal opioids

IT opioids have been used for surgical procedures ranging from lower limb orthopaedic surgery to CABG surgery because of their ability to provide prolonged postoperative analgesia following a single dose vs systemic administration. IT opioids may be given alone or in conjunction with a local anaesthetic. In acute pain, the use of continuous subarachnoid infusions of opioids for postoperative analgesia is uncommon.

The lipid solubility of opioids largely determines the speed of onset and duration of IT analgesia; hydrophilic opioids (eg oxycodone, morphine, hydromorphone) have a slower onset of action and longer half-lives in CSF with greater dorsal horn bioavailability and greater cephalad migration vs lipophilic opioids (eg fentanyl) (Bujedo 2014 **NR**; Bernards 2003 **NR**).

Single injection IT opioids

Early clinical studies used very high IT morphine doses (ie ≥500 mcg). However adequate postoperative analgesia with fewer adverse effects may be obtained with significantly less morphine; although at lower doses there is not a clear dose-response relationship for pain relief or some adverse effects (see below) (Meylan 2009 **Level I**, 27 RCTs, n=1,205).

Low doses of IT morphine are effective in prolonging local anaesthetic block or reducing the dose of local anaesthetic required for spinal anaesthesia with reduced adverse effects and improved recovery (Popping 2013 **Level I** [PRISMA], 28 RCTs; n=1,393; Popping 2012 **Level I** [PRISMA], 55 RCTs; n=3,338)

When combined with low-dose bupivacaine for Caesarean section, 100 mcg IT morphine produced analgesia comparable with doses as high as 400 mcg, with significantly less pruritus (Girgin 2008 **Level II**, n=100, JS 4). A single dose of IT morphine (100 mcg) added to a spinal anaesthetic for Caesarean section prolongs the time to first postoperative analgesic administration by 16 to 20 h (Dahl 1999 **Level I**, 15 RCTs, n=535). Sufentanil (2 RCTs) and fentanyl (8 RCTs) showed little or no analgesic benefit in doses of 25 mcg or less. No differences in pain reported or analgesia use was detected when comparing 100 mcg to 50 mcg IT morphine for Caesarean section, although pruritus was more common in the higher-dose group (Carvalho 2013 **Level II**, n=130, JS 4).

IT morphine added to bupivacaine for postoperative analgesia following abdominal hysterectomy reduced IV PCA morphine consumption vs placebo, with no benefit of 300 mcg vs 200 mcg (Hein 2012 **Level II**, n=144, JS 5).

The addition of IT fentanyl 25 mcg to low-dose spinal bupivacaine for anorectal surgery resulted in more pruritus but lower mean recovery and discharge times, with fewer analgesic requests in the fentanyl group (Gurbet 2008 **Level II**, n=40, JS 3). Tramadol (10 and 25 mg) administered IT with bupivacaine produces extension of spinal analgesia and prolonged postoperative analgesia similar to comparative doses of fentanyl (10 and 25 mcg) for Caesarean section (Subedi 2013 **Level II**, n=80, JS 5) and appendectomy (Afolayan 2014 **Level III-1**, n=186).

IT sufentanil dose provided shorter postoperative analgesia (mean 6.3 h) than IT morphine dose (mean 19.5 h) with no difference in adverse effects (Karaman 2006 **Level II**, n=54, JS4).

In a non-blinded comparison of IT morphine 100 mcg and IT pethidine 10 mg for analgesia following Caesarean section, patients receiving morphine had longer analgesia and fewer intraoperative adverse effects than the pethidine group but experienced more pruritus (Kumar 2007 **Level II**, n=60, JS 2). IT pethidine 25 mg added to lidocaine with adrenaline for spinal anaesthesia had quicker onset with higher sensory block and more prolonged time to significant pain (≥4/10) (9.6 h) vs IT fentanyl 25 mcg (6.3 h) or placebo (2.1 h) (Farzi 2014 **Level II**, n=195, JS 5).

Combination IT opioids

The addition of 10 mcg sufentanil to 400 mcg IT morphine did not potentiate postoperative analgesia or reduce intraoperative opioid requirements in patients undergoing major colorectal surgery (Culebras 2007 **Level II**, n=80, JS 5).

IT opioid infusions

In the ICU, IT infusion of morphine has been reported as a method to control burns pain and thereby avoiding the adverse effects of systemic opioids (Zuehl 2018 **CR**). IT morphine has also been administered in bolus doses via a 22-G IT catheter placed at L 3/4 to provide analgesia after thoracotomy (mean dose over 48 h 2.56 mg (SD 0.88) with no serious complications or sequelae at 6 mth follow-up (Ward 2014 **Level IV**, n=84).

For further details on effectiveness and adverse effects related to the use of IT opioids see Section 4.3.2.3 below and 5.7.1.2.

4.3.2.2 | Efficacy of epidural opioids

The behaviour of epidural opioids is also governed largely by their lipid solubility. The greater sequestration of lipid soluble opioids into epidural fat and slow rerelease back into the epidural space means that elimination from the epidural space is prolonged, resulting in relatively smaller fractions of medicine reaching the CSF (Bernards 2003 **NR**). Lipophilic opioids (eg fentanyl) have a faster onset but shorter duration of action vs hydrophilic opioids (eg morphine) (Bujedo 2014 **NR**; Bernards 2004 **NR**; de Leon-Casasola 1996 **NR**).

A meta-analysis of randomised studies involving epidural opioids, mostly in combination with local anaesthetics, found no differences in VAS pain scores at any time after surgery between opioids, although there was a higher rate of nausea and vomiting (OR 1.95; 95%CI 1.14 to 3.18) with morphine vs fentanyl (Youssef 2014 **Level I** [PRISMA], 24 RCTs, n=1,513). No studies directly compare epidural morphine and fentanyl alone for postoperative analgesia.

Epidural diamorphine

Diamorphine (diacetylmorphine, heroin) is rapidly hydrolysed to MAM and morphine. Diamorphine and MAM are more lipid soluble than morphine and penetrate the CNS more rapidly, although it is MAM and morphine that are thought to be responsible for the analgesic effects of diamorphine (Miyoshi 2001 **NR**). Epidural administration of diamorphine is common in the UK and is effective whether administered by intermittent bolus dose or infusion (McLeod 2005 **Level II**, n=62, JS 5).

Epidural fentanyl

The evidence that epidural fentanyl acts via a spinal rather than systemic effect is conflicting and it has been suggested that any benefit when comparing epidural with systemic fentanyl alone is marginal (Bernards 2004 **NR**; Wheatley 2001 **NR**). However, the conflicting results may be due to differing techniques of administration. A lumbar epidural infusion of fentanyl appears to produce analgesia by uptake into the systemic circulation, whereas a bolus dose of fentanyl produces analgesia by a selective spinal mechanism (Ginosar 2003 **Level IV EH**, n=10). Thoracic epidural

administration does appear to produce greater spinal analgesia, an effect more pronounced with coadministration with adrenaline, which provides a supra-additive effect possibly via both pharmacokinetic (via vasoconstriction, increasing amount of epidural fentanyl available to spinal cord site of action) and pharmacodynamic (via apha-2 adrenoceptor antinociceptive) mechanisms (Niemi 2013 **NR**). Less intraoperative fentanyl is required when administered via a thoracic epidural catheter vs IV administration for colon surgery, with longer time to first postoperative analgesia request (Sadurni 2013 **Level II**, n=30, JS 4). There is no evidence of benefit of epidural vs systemic administration of alfentanil or sufentanil (Bernards 2004 **NR**).

Epidural hydromorphone

The quality of epidural analgesia with hydromorphone is similar to morphine (Chaplan 1992 **Level II**, n=55, JS 5). In a comparison of epidural and IV hydromorphone, patients required twice as much IV hydromorphone to obtain the same degree of analgesia (Liu 1995 **Level II**, n=16, JS 3).

Epidural morphine

Morphine is the least lipid soluble of the opioids administered epidurally; it has the slowest onset and offset of action (Cousins 1984 **NR**) and the highest bioavailability in the spinal cord after epidural administration (Bernards 2004 **NR**). As morphine has a prolonged analgesic effect, it can be given by intermittent bolus dose or infusion; the risk of respiratory depression may be higher and analgesia less effective with bolus dose regimens (de Leon-Casasola 1996 **NR**). The low lipid solubility makes level of administration of epidural morphine less relevant after blunt chest wall trauma with no difference in any outcome between thoracic and lumbar epidural morphine administration (Hakim 2012 **Level II**, n=55, JS 3).

Extended-release epidural morphine

An extended-release (ER) suspension of morphine has been developed for epidural use (Depodur™) consisting of morphine molecules suspended in liposome complexes (lipofoam). ER epidural morphine (EREM) has been shown to be effective vs placebo after THA (Martin 2006 **Level II**, n=126, JS 5; Viscusi 2005 **Level II**, n=200, JS 5) and, using doses of ≥10 mg, to lead to better pain relief vs standard epidural morphine (4 or 5 mg) and a reduction in the need for supplemental analgesics up to 48 h after THA (Viscusi 2006 **Level III-1**, n=39), lower abdominal surgery (Gambling 2005 **Level II**, n=541, JS 4) and Caesarean section (Carvalho 2007 **Level II**, n=70, JS 5; Carvalho 2005 **Level II**, n=79, JS 3). A pooled analysis of six clinical studies described consistent prolonged pharmacokinetics vs standard epidural morphine, with 25% higher peak plasma concentrations in women, mainly explained by differences in body weight (Viscusi 2009 **PK**).

EREM has provided superior analgesia vs continuous femoral nerve block (FNB) after TKA; however, only at rest at 24 h (Johnson 2011 **Level II**, n=65, JS 3). There were no differences in functional outcomes and adverse effects except for more pruritus with EREM but patients reported greater satisfaction with EREM. In two patients, EREM was used successfully after multiple rib fractures (Ford 2012 **Level IV**). After lumbar spinal surgery, EREM provided similar analgesia with fewer adverse effects than epidural morphine (Vineyard 2014 **Level II**, n=60, JS 3). IT morphine (7.5 mcg/kg) vs EREM (150 mcg/kg) had similar time to first PCA use and similar postoperative morphine IV use 0 to 48 h in children (8 to 17 y) undergoing posterior spinal fusion for scoliosis repair (Cohen 2017 **Level II**, n=71, JS 4). Pain scores differed relating to the kinetics of the epidural preparation and were lower with IT morphine from 0 to 4 h, similar from 8 to 24 h, and lower with extended release epidural morphine from 28 to 36 h.

OIVI is more likely with EREM than IV PCA opioids (OR 5.74; 95%CI 1.08 to 30.5) (Sumida 2009 **Level I**, 3 RCTs, n=464). It has been recommended that the liposome preparation of Depodur™ not be administered while local anaesthetics are present in the epidural space as this may cause early release of the morphine (Viscusi 2009 **PK**). When Depodur™ was administered within 3 to

15 min of a 3 mL test dose of 1.5% lidocaine with adrenaline, higher maximum serum concentration (C_{max}) values for morphine were reported compared with C_{max} values when no lidocaine was administered; there was no difference in morphine C_{max} if the interval was >30 min. The C_{max} of morphine was unchanged when Depodur™ doses were given 15, 30 and 60 min after an anaesthetic dose of epidural bupivacaine (20 mL of 0.25%) (Gambling 2009 **PK**) although, in a later study, peak plasma morphine concentrations were increased when administered 1 h post a high volume anaesthetic dose (20 to 35 mL 2% lidocaine with adrenaline) after Caesarean section, with associated increased morphine-related adverse effects (Atkinson Rallis 2011 **Level II**, n=30, JS 3).

Epidural oxycodone

There is limited safety data for neuraxial oxycodone (Lamminsalo 2019 **Level III-1 PK**, n=30; Olczak 2017 **Level IV**, n=11; Kokki 2016 **BS).** After Caesarean section, patients given epidural oxycodone 3 mg vs epidural morphine 3 mg had higher pain scores up to 24 h with slightly less pruritus (Sng 2016 **Level II**, n=100, JS 4). Epidural oxycodone was superior to IV oxycodone in gynaecological laparotomy, resulting in less rescue analgesia up to 4 h (Piirainen 2018 **Level II**, n=30, JS 5). The addition of epidural oxycodone to ropivacaine in labour analgesia was superior to ropivacaine alone, with lower pain scores for 4 h and longer duration of analgesia (Zhong 2020 **Level II**, n=80, JS 5).

Epidural pethidine

Pethidine is effective when administered epidurally by bolus dose, continuous infusion and by patient-controlled epidural analgesia (PCEA). It is more lipid soluble than morphine (but less than fentanyl and its analogues); thus its onset and offset of epidural analgesic action is more rapid than morphine (Ngan Kee 1998 **NR**). The analgesic effect of smaller doses appears to be spinally mediated but systemic effects are likely after larger doses; in the smaller doses it is not known whether the local anaesthetic properties of pethidine contribute significantly to pain relief (Ngan Kee 1998 **NR**). Epidural pethidine has been used predominantly in the obstetric setting. After Caesarean section epidural pethidine resulted in better pain relief and less sedation than IV pethidine (Paech 1994 **Level II**, n=45, JS 5) but inferior analgesia vs IT morphine, albeit with less pruritus, nausea and drowsiness (Paech 2000 **Level II**, n=144, JS 5).

Epidural sufentanil

Epidural sufentanil has been mainly used in labour analgesia; for details see Section 9.1.3.3.

Epidural buprenorphine

Epidural buprenorphine has been used in a limited number of studies in the past with no recent publications; a detailed review of the neuraxial use of buprenorphine has been published (Kosel 2016 **NR**).

Epidural tramadol

For lumbar epidural analgesia after thoracotomy, tramadol 100 mg vs morphine 4 mg resulted in comparable quality of analgesia of shorter duration with less sedation and arterial oxygenation (Turker 2005 **Level II**, n=40, JS 4). For epidural analgesia in labour, tramadol 5 mg/mL vs fentanyl 3 mcg/mL added to 0.125% ropivacaine had similar efficacy and adverse effects (Fan 2011 **Level II**, n=61, JS 5).

For paediatric use see Section 10.4.4.12.

4.3.2.3 | Adverse effects of neuraxial opioids in general

Opioid-induced ventilatory impairment

The prevalence of OIVI (author-reported) with use of neuraxial diamorphine and morphine after Caesarean section is 61/10,000 (95%CI 51 to 74) (Sharawi 2018 **Level IV SR**, 78 studies [54 RCTs, 21 studies & 3 case reports], n=18,455). However, when classified as clinically significant OIVI, highest prevalence with all doses of neuraxial opioids was 8.67/10,000 (95%CI 4.20 to 15.16) and lowest was 5.96/10,000 (95%CI 2.23 to 11.28). These rates dropped even further with the use of lower but clinically relevant doses of neuraxial morphine: IT dose ≤150 mcg 1.63/10,000 (95%CI 0.62 to 8.77) (31 RCTs [IT]) or epidural dose ≤3 mg 1.08/10,000 (95%CI 0.24 to 7.22) (32 RCTs [epidural]). No cases were reported for IT diamorphine ≤400 mcg or epidural diamorphine ≤5 mg.

Practice guidelines for the prevention, detection and management of respiratory depression caused by neuraxial opioids have been published (ASA 2016 **GL**).

Nausea and vomiting

IV dexamethasone reduces the need for rescue antiemetics for PONV caused by long-acting neuraxial opioids (RR 0.44; 95%CI 0.35 to 0.56) (Grape 2018 **Level I** [PRISMA], 13 RCTs, n=1,111).

4.3.2.4 | Adverse effects of intrathecal opioids

Depending on type and dose of the opioid, a combination of spinal and systemic (supraspinal) mechanisms may be responsible for adverse effects associated with intrathecal opioids. Many of these effects are more frequent with morphine and are to some extent dose-related (Dahl 1999 **Level I**, 15 RCTs, n=535; Cole 2000 **Level II**, n=38, JS 4).

Opioid-induced ventilatory impairment

Late onset respiratory depression (>2 h after administration), which is believed to be a result of the cephalad spread of opioids to the medulla within the cerebrospinal fluid (CSF), is also seen more commonly with hydrophilic opioids such as morphine and hydromorphone and appears to match the time taken for trigeminal analgesia, which is approximately 612 h after administration (Bujedo 2014 **NR**; Saltan 2011 **NR**; Cousins 1984 **NR**).

A single dose of IT morphine (100 mcg) added to a spinal anaesthetic for Caesarean section was associated with low rate of respiratory depression (Dahl 1999 **Level I**, 15 RCTs [12 respiratory depression], n=535). A meta-analysis comparing IT morphine doses <300 mcg, ≥300 mcg and placebo reported a greater risk of respiratory depression with the higher vs the lower doses of morphine (Gehling 2009 **Level I,** 28 RCTs, n=1,314). In combination with bupivacaine, IT morphine (50 to 2,000 mcg) was associated with more respiratory depression than IT fentanyl (10 to 50 mcg) (3.4% vs 0.4%) (Popping 2013 **Level I** [PRISMA], 28 RCTs; n=1,393; Popping 2012 **Level I** [PRISMA], 55 RCTs; n=3,338).

The incidence of respiratory depression with the lipophilic opioid fentanyl given via the epidural route has been reported to be 1.4% (with 0.4% requiring naloxone) (Scott 1995a **Level IV**, n=1,297) but, given IT, fentanyl or sufentanil are likely to be lower risk than the hydrophilic opioids morphine and hydromorphone (Horlocker 2009 **GL**).

Risk factors for respiratory depression include higher doses (>300 mcg morphine), increasing age, obesity and coadministration of systemic opioids or sedatives (Saltan 2011 **NR**). A detailed analysis of sustained hypercapnia events (transdermal CO_2 >50 mm Hg for ≥2 min) after IT administration of hyperbaric bupivacaine 12 mg , fentanyl 15 mcg and morphine 150 mcg for Caesarean section revealed an incidence of 32% (Bauchat 2017 **Level IV**, n=120). Events occurred at a median of 300 min after IT administration with a median number of 3 events and longest duration of 26 min.

Nausea and vomiting

A meta-analysis comparing IT morphine doses <300 mcg vs ≥300 mcg and placebo reports increased nausea (RR 1.4; 95%CI 1.1 to 1.7) and vomiting (RR 3.1; 95%CI 1.5 to 6.4) in the higher dose group (Gehling 2009 **Level I,** 28 RCTs, n=1,314). A single dose of morphine (100 mcg) added to a spinal anaesthetic for Caesarean section was associated with nausea (10%) and vomiting (12%) (Dahl 1999 **Level I**, 15 RCTs [11 nausea & 8 vomiting], n=535).

Pruritus

A meta-analysis comparing IT morphine doses <300 mcg vs ≥300 mcg and placebo reports increased pruritus (RR 1.8; 95%CI 1.4 to 2.2) in the higher dose group (Gehling 2009 **Level I,** 28 RCTs, n=1,314). A single dose of morphine (100 mcg) added to a spinal anaesthetic for Caesarean section was associated with pruritus (43%) (Dahl 1999 **Level I**, 15 RCTs [11 pruritus], n=535). For Caesarean section, IT morphine 50 mcg vs IT morphine 100 mcg resulted in a lower rate of pruritus (70% vs 87%) (Carvalho 2013 **Level II**, n=130, JS 4).

Neurotoxicity

Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at clinically used IT doses (Hodgson 1999 **Level IV**). Other opioid agonists or partial agonists do not have animal or human safety data.

Tolerance

Tolerance to spinal opioid analgesia can develop rapidly. Low-dose mu and delta opioid antagonists can prevent tolerance development and restore morphine IT analgesia in animals (Abul-Husn 2007 **BS**). In an animal model, bolus doses increased nociceptive thresholds for 3 to 5 h followed by delayed hyperalgesia with a lower threshold lasting 1 to 2 d, an effect prevented by coadministration of ketamine (Van Elstraete 2005 **BS**). The clinical implications of single-dose neuraxial opioid administration in regard to the potential development of OIH or tolerance is uncertain. IT fentanyl added to bupivacaine and morphine for Caesarean section was associated with higher pain scores (the authors suggesting acute tolerance) but no difference in 24 h morphine consumption (Carvalho 2012 **Level II**, n=40, JS 5). Adding fentanyl to IT local anaesthesia for Caesarean section improved anaesthesia conditions but was associated with a 60% increase in morphine consumption between 6 and 24 h (Cooper 1997 **Level II**, n=60, JS 2). IT sufentanil was associated with wound hyperalgesia (at 48 h), with a preventive effect demonstrated by addition of 150 mcg IT clonidine (Lavand'homme 2008 **Level II**, n=96, JS 5). Ondansetron is assumed to ameliorate opioid-induced hyperalgesia and tolerance in animal studies; however, IV ondansetron 8 mg vs placebo administered before spinal anaesthesia for Caesarean section (IT bupivacaine 15 mg, IT fentanyl 20 mcg and IT morphine 100 mcg) had no effect on postoperative pain scores or opioid consumption (Greer 2017 **Level II**, n=86, JS 5).

For more details on epidural opioid use see Section 5.6. and in particular 5.6.2.2 and 5.6.2.3

KEY MESSAGES

Intrathecal opioids

1. Intrathecal morphine and intrathecal fentanyl prolong spinal local anaesthetic block, with fentanyl being associated with fewer adverse effects (**U**) (**Level I** [PRISMA]).
2. Intrathecal morphine produces better postoperative analgesia than intrathecal fentanyl or sufentanil after Caesarean section (**U**) (**Level I**).
3. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**U**) (**Level I**).

Epidural opioids

4. Epidural morphine provides similar analgesia to epidural fentanyl when combined with local anaesthetic, although the incidence of nausea is greater with morphine (**U**) (**Level I** [PRISMA]).
5. Extended-release epidural morphine provides analgesia for up to 48 hours (**U**) (**Level II**), however it is associated with more respiratory depression than IV PCA following abdominal surgery (**U**) (**Level I**)
6. Epidural pethidine produces better pain relief and less sedation than IV pethidine after Caesarean section (**U**) (**Level II**).

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

☑ No neurotoxicity has been shown at normal clinical intrathecal doses of morphine, fentanyl and sufentanil (**U**).

☑ Neuraxial administration of bolus doses of hydrophilic opioids carries an increased risk of delayed sedation and respiratory depression compared with lipophilic opioids (**U**).

4.3.3 | Peripheral opioids

Opioid receptors are expressed in peripheral sensory neurons in both animals and humans (Stein 2013 **NR**; Stein 2011 **NR**). Multiple mechanisms have been proposed to explain the clinical observation that peripheral opioids are more effective in the presence of tissue injury or inflammation. Further research into the role of peripheral opioids in clinical models of inflammatory pain is recommended; the acute postoperative period may not allow sufficient time for the upregulation of peripheral opioid receptors.

Peripherally applied opioids (excluding IA, perineural and mucosal administration) for post-operative pain relief vs placebo or systemic administration do not have any clinically relevant effects (Nielsen 2015a **Level I** [PRISMA], 26 RCTs, n=1,531).

However, peripherally applied opioids had an analgesic effect, when injected into areas with preoperative inflammation (Stein 2013 **NR**; Stein 2011 **NR**). Consequently, submucosal injection of morphine (2 mg) into inflamed tissue after tooth extraction (under a standard local anaesthesia) resulted in lower pain on swallowing and prolonged post-operative analgesia vs IM injection and vs injection into non-inflamed tissue of the same dose of morphine (Akural 2016 **Level II**, n=81, JS 5).

4.3.3.1 | Intra-articular

Morphine

IA administration is the most extensively examined clinical application of peripheral opioid therapy (Stein 2013 **NR**). In experimentally induced synovitis in horses, IA morphine reduced clinical and biological signs of inflammation vs IV administration (Lindegaard 2010 **BS**).

IA bupivacaine was less effective than morphine in providing analgesia in patients having "high inflammatory arthroscopic knee surgery", whereas bupivacaine was more effective than morphine in those having "low inflammatory surgery" (Marchal 2003 **Level II**, n=53, JS 5).

IA morphine in a dose of 1 mg is not better than placebo at reducing pain at early, medium or late stages post arthroscopy (7 RCTs, n=297) (Zou 2016 **Level I** [Cochrane], 28 RCTs, n=2,564). One mg morphine IA was not more effective than IA bupivacaine, NSAIDs, sufentanil, fentanyl and pethidine. There was no difference in pain relief between IM morphine vs IA morphine at any time point (2 RCTs, n=73); the latter results are in line with another RCT not included in the meta-analysis (Cepeda 1997 **Level II**, n=112, JS 5).

Morphine/bupivacaine vs bupivacaine alone leads to reduced pain scores (WMD −1.15/10; 95% CI −1.67 to −0.63) without an effect on time to first analgesic request and requirements for supplementary analgesia and with no increase in side effects (Yang 2017b **Level I** [PRISMA], 29 RCTs, n=1,116). However, morphine/bupivacaine vs tenoxicam/bupivacaine following arthroscopy showed increased postoperative analgesia requirements and side effects (Sanel 2016, **Level II**, n=240, JS 5).

Other opioids

IA tramadol (50-100 mg) administered as an adjunct to bupivacaine reduces postoperative pain and increases time to breakthrough analgesia requirements without increasing side effects after arthroscopy (Ryan 2019 **Level I**, 6 RCTs, n=334). The combination of IA pethidine (meperidine)/bupivacaine was found to have synergistic analgesic effect vs either medication alone (Imani 2015 **Level II**, n=60, JS 5). IA fentanyl/bupivacaine demonstrated a trend towards a greater reduction in reported pain scores and postoperative analgesia requirement vs bupivacaine alone or midazolam/bupivacaine (Nahravani 2017, **Level II**, n=45, JS 5). IA administration of morphine/levobupivacaine/tenoxicam provided superior analgesia to a combination of tramadol/levobupivacaine/tenoxicam or saline placebo (Oral 2015 **Level II**, n=90, JS 5). Levobupivacaine 0.25% for arthroscopic knee surgery combined with either fentanyl or tramadol provided superior analgesia vs levobupivacaine alone for day case arthroscopic knee surgery (Sayin 2015 **Level II**, n=80, JS 4). The addition of IA sufentanil to a mixture of ropivacaine and clonidine following anterior cruciate ligament repair provided no additional analgesic benefits (Armellin 2008 **Level II**, n=120, JS 5).

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

There are no comparisons between IA and systemic administration of these opioids alone.

4.3.3.2 | Perineural

An initial meta-analysis found no evidence for analgesic efficacy of peripheral opioids with perineural block by local anaesthetics (Picard 1997 **Level I**, 26 RCTs, n=952). Since its publication, more research has been conducted.

Buprenorphine

The addition of perineural buprenorphine (0.1 to 0.3 mg) to local anaesthetics prolongs the duration of analgesia provided by nerve blocks vs placebo (MD 8.64 h; 95%CI 6.44 to 10.85) (9 RCTs, n= 510), but is associated with significant increases in PONV (RR 5.0; 95%CI 1.12 to 22.27) (3 RCTs, n=210) (Schnabel 2017 **Level I** [PRISMA], 13 RCTS, n=685). In comparison to systemic (IM) administration of buprenorphine, perineural administration prolongs duration of analgesia (MD 6.87 h, 95%CI 4.02 to 9.71) (5 RCTs, n=294) without increasing PONV. The findings are qualified by the description of high risk of publication bias and heterogeneity in the results obtained. A subsequent RCT found no difference in time to first rescue analgesia comparing a femoral nerve block for TKA with either perineural or SC buprenorphine (0.3 mg) (van Beek 2017 **Level II**, n=65, JS 5). Adjuvant buprenorphine (0.3 mg) vs adjuvant dexamethasone (4 mg) and saline in a 20 ml 0.25% levobupivacaine by transverse abdominis plane block (TAPB) for inguinal hernia repair demonstrated a longer time to rescue analgesia and lower mean postoperative tramadol consumption in the first 24 h (Seervi 2019 **Level II**, n=93, JS 4). Perineural administration of buprenorphine (0.15 mg) and dexamethasone (4 mg) vs IV administration of the same doses in conjunction with sciatic and adductor canal blocks for foot and ankle surgery resulted in longer block duration, lower scores for 'worst pain' and less nausea, but no difference in pain scores at 24 h (YaDeau 2015 **Level II**, n=90, JS 5).

Sufentanil

The addition of sufentanil (10 mcg) to bupivacaine for ultrasound guided brachial plexus block for upper limb procedures prolonged the duration of both sensory and motor block in chronic opioid users and non-users (Azimaraghi 2015 **Level II**, n=120, JS 5). No statistically significant difference was found in postoperative pain scores or supplemental analgesic requirements when 100 mcg fentanyl was administered with 0.75% ropivacaine in a femoral nerve block and then per perineural catheter infusion (3 mcg/ml fentanyl in 0.75% ropivacaine, basal infusion rate 10 ml/h) vs ropivacaine alone (Heo 2016 **Level II**, n=82, JS 5).

Tramadol

Tramadol (100 mg) as an adjuvant to brachial plexus block vs placebo prolonged analgesia (MD 125.5 min; 95% CI 73.3 to 175.8), but also sensory and motor block (Shin 2017 **Level I** [PRISMA], 16 RCTS, n=751); there were no comparisons to systemic administration.

Preoperative femoral nerve block for TKA with 20 ml 0.375% ropivacaine and adjuvant tramadol 100 mg was superior in terms of analgesic effect (lower pain scores from 8 to 72 h), longer sensory and motor blockade and reduced requirement for postoperative PCA vs no femoral nerve block, femoral nerve block with ropivacaine only or femoral nerve block with ropivacaine and adjuvant tramadol 50 mg (Tang 2016 **Level II**, n=60, JS 1).

4.3.3.3 | Topical

While opioid receptors have been identified in the cornea and skin, topically applied opioids have not consistently demonstrated efficacy in pain states such as corneal ulceration (fentanyl) (Zollner 2008 **Level II**, n=40, JS 4), partial thickness burns (morphine) (Welling 2007 **Level II**, n=49, JS 5) or chronic skin ulceration (morphine) (Vernassiere 2005 **Level II**, n=18, JS 4).

The clinical use of topical opioids in palliative care for pain control in cutaneous lesions is reported as beneficial in three of six RCTs (Graham 2013b **Level IV SR**, 26 studies, n unspecified). A greater benefit was reported with inflammatory lesions than with vascular ulcers, suggesting an anti-inflammatory role of topical opioids may be as important as a peripheral analgesic benefit. Topical morphine (0.2% gel) and ointment for mucosal and skin lesions in palliative cancer patients reduced base line pain after 7 d of treatment ($NNT_{50\%}$ 1.67) with minimal side effects (Cialkowska-Rysz 2019, **Level II**, n=35, JS 4).

In chemotherapy-induced mucositis an analgesic dose-dependent effect was seen in a small pilot study using 1 mg/mL and 2 mg/mL morphine mouthwash (Cerchietti 2003 **Level III-1**). Benefit was also evident for morphine mouthwash 30 mg every 3 h, with a local anaesthetic-based solution, in mucositis associated with chemoradiotherapy in head and neck cancer patients (Cerchietti 2002 **Level II**, n=26, JS 3). With oral morphine mouthwash (30 mg in 15 mL) for the treatment of mucositis pain, the act of mouth washing was beneficial, with a trend to more benefit with morphine (Vayne-Bossert 2010 **Level II**, n=11, JS 5). Recruitment difficulties meant this trial was concluded before enough subjects were recruited based on the power analysis. Topical morphine mouthwash (2%) for patients with severe mucositis associated with treatment for head and neck cancer was more effective than mouthwash containing viscous lidocaine, magnesium aluminium hydroxide and diphenhydramine, both being administered in 10 ml aliquots every 3 h (Sarvizadeh 2015 **Level II**, n=30, JS 5). There was also a statistically significant reduction in WHO grading scores for mucositis after 6 d of treatment and patients reported increased satisfaction with their treatment. See also Section 8.6.7.7 and 8.9.8.2.

KEY MESSAGES

1. Intra-articular morphine (1 mg) following knee arthroscopy does not improve analgesia compared with placebo (**S**) (**Level I** [Cochrane Review]).
2. Intra-articular morphine/bupivacaine following knee arthroscopy compared to bupivacaine alone improves analgesia without increasing adverse effects (**N**) (**Level I** [PRISMA]).
3. Perineural buprenorphine/local anaesthetic for peripheral nerve blocks compared to local anaesthetic and to systemic buprenorphine/local anaesthetic prolongs duration of analgesia (**N**) (**Level I** [PRISMA]).
4. Perineural tramadol/local anaesthetic for brachial plexus block compared to local anaesthetic alone prolongs duration of analgesia (**N**) (**Level I** [PRISMA]).
5. Peripherally applied opioids (excluding intra-articular, perineural and mucosal administration) show no clinically relevant analgesic effect (**N**) (**Level I** [PRISMA]).
6. Intra-articular tramadol/bupivacaine following knee arthroscopy compared to bupivacaine alone improves analgesia without increasing adverse effects (**N**) (**Level I**).
7. Morphine mouthwash has analgesic effects in chemotherapy-induced mucositis (**N**) (**Level II**).

4.4 | Local anaesthetics and other membrane stabilisers

Local anaesthetics (LA) act primarily by reversibly blocking neuronal voltage-gated sodium channels (VGSC) and thereby temporarily interrupting nerve impulse propagation. LA also have additional systemic effects which may be independent of action on the VGSC due to interaction with potassium channels, calcium channels, N-methyl-D-aspartate (NMDA) receptors, and G-protein coupled receptors (van der Wal 2016 **NR BS**; Lirk 2014 **BS**). The latter, via the $G_{q/11}$ subfamily, may contribute to the anti-inflammatory effects of Las (Hollmann 2000 **NR**). Thus, the use of LAs beyond perineural applications is expanding.

Both amide and ester local anaesthetics have been found to have antimicrobial activity in concentrations used in clinical practice, with tetracaine, bupivacaine and lidocaine having the most marked activity (Razavi 2019 **NR BS**); these are not primary effects and are modified by a range of factors including the admixture of other drugs.

4.4.1 | Systemic local anaesthetics and other membrane stabilisers

IV lidocaine has analgesic, anti-inflammatory and antihyperalgesic properties and attenuates the neuroinflammatory response in perioperative pain and chronic neuropathic pain (van der Wal 2016 **Level IV SR**, 36 in vitro studies & 31 animal studies & 21 clinical studies [3 SRs & 7 RCTs in acute pain; 1 SR & 6 RCTs & 4 studies in chronic pain]). The safe dose and duration of perioperative IV lidocaine infusions has not been clearly established, with only limited total patient numbers and few adverse reactions having been reported in the literature to date (Bailey 2018 **Level I**, 6 RCTs, n=420; Masic 2018 **Level IV SR**, 13 studies, n= 512).

4.4.1.1 | Acute pain

A Cochrane review on IV lidocaine and analgesia (Kranke 2015 **Level I** [Cochrane], 45 RCTs, n=2,802) has been updated with a further 23 RCTs (Weibel 2018 **Level I** [Cochrane], 68 RCTs [66 vs placebo/no comparator; 2 vs epidural], n=4,525) finding small effects and uncertain outcomes. Lidocaine infusions at varying doses (1-5 mg/kg/h) for varying duration in various surgery types (open [22 RCTs] or laparoscopic [20 RCTs] abdominal and others [26 RCTs]) vs placebo or no treatment) reduces pain intensity to a limited extent 1 to 4 h postoperatively (SMD −0.50; 95%CI −0.72 to −0.28; 0.37/10 to 2.48/10) (29 RCTs, n=1,656), at 24 h (SMD −0.14; 95%CI −0.25 to −0.04) (33 RCTs, n=1,847) and at 48 h (SMD −0.11; 95%CI −0.25 to 0.04) (24 RCTs, n=1,404), noting that the results for these later time points represent less than a 1 point reduction in a 10 point pain scale. There is also a reduction of postoperative ileus (RR 0.37; 95%CI 0.15 to 0.87) (4 RCTs, n=273), time to first defaecation (MD −7.92 h; 95%CI −12.71 to −3.13) (12 RCTs, n=684), postoperative nausea 0 to 2 h (RR 0.78; 95%CI 0.67 to 0.91) (35 RCTs, n=1,903), opioid requirements (MD −4.52 MME; 95%CI −6.25 to −2.79) (40 RCTs, n=2,201) and LOS (MD −0.37 d; 95%CI −0.60 to −0.15) (32 RCTs, n=2,077). IV lidocaine vs TEA has no effect on pain intensity and other outcomes (2 RCTS, n=102). The authors describe all these results as "*uncertain*" due to the quality of the evidence being limited by inconsistency, imprecision, and study quality.

In breast surgery, IV lidocaine administered intraoperatively and continued for up to 2 h is not associated with improved pain scores up to 72 h versus placebo controls, but opioid requirements were lower in the lidocaine group (Chang 2017 **Level I** [PRISMA], 3 RCTs, n=167); however, benefit was found in chronic postsurgical pain prevention. See Section 4.4.1.2 below.

After colonic surgery, IV lidocaine was associated with improved pain relief vs controls and also with decreases in proinflammatory cytokines, including interleukin-6 (IL-6), IL-8 and IL-1RA

(a competitive inhibitor of IL-1β) (Kuo 2006 **Level II**, n=60, JS 5). For radical prostatectomy, a combination of intraoperative IV and postoperative SC lidocaine for up to 24 h vs saline reduced pain, morphine consumption and LOS (Weinberg 2016 **Level II**, n=76, JS 5). Following open nephrectomy, intraoperative IV lidocaine or IV ketamine continued for 24 h were both superior to placebo in reducing pain scores and 24 h opioid consumption (lidocaine 27.8 mg ± 5.5 and ketamine 32 mg ± 7.0 vs placebo 47.6 mg ± 5.0) (Jendoubi 2017 **Level II**, n=60, JS 4); IV lidocaine was associated with significantly lower pain scores at rest and with movement over 24 h vs IV ketamine. In radical cystectomy patients, the addition of perioperative IV lidocaine infusion for 6 h resulted in lower pain scores for up to 18 h (Moeen 2019 **Level II**, n=111, JS 5); recovery of bowel function was also improved.

Perioperative IV administration of lidocaine also has a preventive analgesic effect (extending beyond 5.5 half-lives of lidocaine, ie >8 h after cessation of administration) after a wide range of operations (Barreveld 2013a **Level I**, 16 RCTs, n=678) (15 RCTs overlap with Weibel 2018). See also Sections 1.4 and 1.5.

In the emergency department (ED), the efficacy of IV lidocaine in the treatment of nonsurgical acute pain has been reviewed, noting that dosing was not standardised and individual studies were small (Silva 2018 **Level IV SR**, 6 RCTs & 2 studies, n=536; Masic 2018 **Level IV SR** 4 RCTs & 9 studies, n= 512) (4 RCTs overlap); analgesic benefit was superior to placebo or comparable to active controls in renal colic (2 RCTs) and limb ischemia (1 RCT), but inconsistently in acute migraine (2 RCTs) and not in acute radicular low back pain (1 RCT). Although most non-randomised studies demonstrated improved analgesia with IV lidocaine, certainty with these findings is low. Safety data is limited with 20 adverse events (rate 8.9%; 95%CI 5.5% to 13.4%) (6 studies, n=225) reported with use of IV lidocaine in the ED (19 nonserious and 1 classified as serious) (Silva 2018 **Level IV SR**, 6 RCTs and 2 studies, n=536).

IV lidocaine has a potentially analgesic effect in procedural pain in burns (Wasiak 2012 **Level I** [Cochrane], 1 RCT: Wasiak 2011 **Level II**, n=45, JS 5), however its role in this indication requires further investigation.

The use of IV lidocaine in an obese population undergoing laparoscopic gastric reduction surgery reduced pain scores, opioid consumption and improved quality of recovery (Sherif 2017 **Level II**, n=150, JS 5; De Oliveira 2014a **Level II**, n=50, JS 5).

Results for IN lidocaine are conflicting showing significant benefit (Maizels 1996 **Level II**, n=53, JS 2) and no effect (Blanda 2001 **Level II**, n=49, JS 4).

Mexiletine improved pain relief and reduced analgesic requirements after breast surgery (Fassoulaki 2002 **Level II**, n=75, JS 3).

4.4.1.2 | Chronic pain and transition to chronic pain

A meta-analysis found that IV lidocaine reduces chronic postsurgical pain at 3 mth vs placebo (OR 0.29; 95%CI 0.18 - 0.48) (Bailey 2018 **Level I** [PRISMA], 6 RCTs, n=420). In breast surgery patients, IV lidocaine administered intraoperatively and continued for up to 2 h had a lower risk for the development of chronic pain at 3 to 6 mth (RR 0.33; 95%CI 0.14 to 0.78) (Chang 2017 **Level I** [PRISMA], 2 RCTs, n=97) (2 RCTs overlap). See also Sections 1.4 and 1.5.

The membrane stabilisers IV lidocaine and mexiletine have a similar analgesic effect on neuropathic pain of various origins, which is superior to placebo (WMD 10.6; 95%CI -14.5 to -6.7) (Tremont-Lukats 2005 **Level I,** 19 RCTs, n=706) and similar to various comparators (Challapalli 2005 **Level I** [Cochrane], 30 RCTs, n=1,142). There was strong evidence of benefit for use of membrane stabilisers in pain due to peripheral nerve trauma (Kalso 1998 **Level I**, 17 RCTs, n=450). However, in the guidelines for pharmacotherapy for neuropathic pain by the Special Interest Group on Neuropathic Pain (NeuPSIG) of the IASP, there is a strong recommendation against the use of

mexiletine because of negative trials on efficacy and safety concerns (Finnerup 2015 **GL Level I** [PRISMA], 229 RCTs, n unspecified).

Currently, the use of membrane stabilisers for acute neuropathic pain can only be based on extrapolation of the above data.

KEY MESSAGES

1. Perioperative intravenous lidocaine reduces pain and opioid requirements to a limited extent following a range of surgery types, as well as nausea, vomiting, incidence and duration of ileus and length of hospital stay (**W**) (**Level I** [Cochrane Review]).
2. In breast surgery, perioperative lidocaine infusion does not improve pain scores for up to 72 h, but is associated with lower acute opioid requirements and less chronic postsurgical pain at 3 to 6 months (**N**) (**Level I** [PRISMA])
3. Perioperative intravenous lidocaine has a preventive analgesic effect (extending beyond 5.5 half-lives of lidocaine, ie > 8 hrs after cessation of administration) after a wide range of operations (**U**) (**Level I**).

Chronic neuropathic pain and transition to chronic postsurgical pain

4. Both intravenous lidocaine and mexiletine are effective in the treatment of chronic neuropathic pain (**U**) (**Level I** [Cochrane Review]); however, guidelines advise against the use of mexiletine in this indication (**N**) (**GL Level I** [PRISMA]).
5. Perioperative IV lidocaine reduces chronic postsurgical pain at 3 months compared to placebo (**N**) **(Level I** [PRISMA]).

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

☑ The optimal and safe dose and duration of perioperative intravenous lidocaine infusions has yet to be clearly established (**N**).

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use membrane stabilisers including systemic lidocaine in the management of acute neuropathic pain (**U**).

☑ The role and safety of IV lidocaine for analgesia in the emergency department still requires clarification (N).

4.4.2 | Regional local anaesthetics

LAs exert their effect as analgesics by blocking sodium channels and hence impeding neuronal excitation and/or conduction. LAs differ predominantly by potency, duration of action and systemic toxicity.

4.4.2.1 | Short-duration local anaesthetics

Lidocaine is the most widely used short-duration LA in acute pain management. Although the plasma half-life is approximately 90 min, the duration of the LA effect depends very much on site of administration, dose administered and the presence or absence of vasoconstrictors. Although

lidocaine is hydrophilic, it is delivered in high concentrations and therefore usually diffuses well into nerve bundles, resulting in little separation of sensory and motor blocking actions (Covino 1998 **NR**).

The use of lidocaine in ongoing acute pain management is usually restricted to the short-term re-establishment of a LA infusion block. It is generally considered unsuited to long-term (ie days) use because of the development of tachyphylaxis or acute tolerance, although the existing literature documenting the phenomenon of tachyphylaxis with neuraxial use of local anaesthetics is scarce and the mechanisms behind this phenomenon should it occur, is unclear. (Kongsgaard 2016 **Level III-3** [PRISMA], 6 RCTs & 7 studies, n unspecified). Continuous perineural infusions of lidocaine for 24 h resulted in less effective analgesia and more motor block than infusions of the long-acting LA ropivacaine (Casati 2003c **Level II**, n=40, JS 4).

Mepivacaine is a short- to intermediate-duration LA agent, structurally related to bupivacaine and ropivacaine. Its use is largely restricted to intraoperative anaesthesia.

4.4.2.2 | Long-duration local anaesthetics

The three commonly used long-duration LAs, bupivacaine, levobupivacaine and ropivacaine, are structurally related (McLeod 2001 **NR**; Markham 1996 **NR**). Whereas bupivacaine is a racemic mixture of S- and R-enantiomers, levobupivacaine is the S-(or levo-) enantiomer of bupivacaine; ropivacaine is likewise an S-enantiomer.

The issue with relative potency emerges with lower doses and concentrations of LAs. When doses are carefully titrated, a minimum local anaesthetic concentration (MLAC) can be found at which 50% of patients will achieve a satisfactory analgesic block. In obstetric epidural analgesia, two separate studies found the MLAC of bupivacaine was 0.6 times that of ropivacaine (Capogna 1999 **Level II**, n=87, JS 4; Polley 1999 **Level II**, n=83, JS 4). The motor-blocking potency showed a similar ratio of 0.66 (Lacassie 2003 **Level II**, n=60, JS 4).

When comparing bupivacaine with levobupivacaine, the "percentage" bupivacaine solution is by weight of bupivacaine hydrochloride, whereas the percentage levobupivacaine solution is for the active molecule alone. This means that the molar dose of equal "percentage concentration" is 13% higher for levobupivacaine (Schug 2001 **NR**). The sensory MLAC potency ratio of levobupivacaine to bupivacaine is 0.98, although if correction is made for molar concentrations this falls to 0.87 (neither value being significantly different from unity) (Lyons 1998 **Level II**, n=60, JS 3). Levobupivacaine has been shown to have slightly less motor-blocking capacity than bupivacaine with a levobupivacaine/bupivacaine potency ratio for epidural motor block of 0.87 (95%CI 0.77 to 0.98) (Lacassie 2003 **Level II**, n=60, JS 4). Another labour epidural analgesia study has found no difference in MLAC between levobupivacaine and ropivacaine with a ropivacaine/levobupivacaine potency ratio of 0.98 (95%CI 0.80 to 1.20) (Polley 2003 **Level II**, n=83, JS 4).

4.4.2.3 | Epidural local anaesthetics

For postoperative analgesia using epidural infusions, dose-ranging studies established that 0.2% ropivacaine was a suitable concentration (Schug 1996 **Level II**, n=36, JS 5; Scott 1995b **Level II**, n=30, JS 5). 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. In obstetric epidural analgesia, lower concentrations of epidural ropivacaine, typically 0.1%, are used in labour to avoid dense sensory and motor block (Zhang 2018 **SR Level IV**, 30 studies, n=2,851).

The majority of studies find similar analgesic outcomes with postoperative epidural infusions based on these strengths (Casati 2003b **Level II**, n=45, JS 5; Macias 2002 **Level II**, n=80, JS 5; Jorgensen 2000 **Level II**, n=60, JS 3). Motor block is of clinical relevance in low-thoracic or lumbar epidural infusions and has been reported to be less intense with epidural ropivacaine than with

bupivacaine (Merson 2001 **Level II**, n=68, JS 4; Muldoon 1998 **Level II**, n=52, JS 4; Zaric 1996 **Level II**, n=37, JS 3). However, this finding has not been supported by another study (Casati 2003b **Level II**, n=45, JS 5).

The relevance of dose, not concentration or volume of LA infused, was confirmed in two trials. The same dose of a mixture of levobupivacaine in three different concentrations (0.5%, 0.25% and 0.15%) and sufentanil administered during continuous thoracic epidural infusion for thoracotomy resulted in similar efficacy and adverse effects (Mendola 2009 **Level II**, n=138, JS 3) as did two concentrations (0.15 and 0.5%) of levobupivacaine in another RCT (Dernedde 2006 **Level II**, n=82, JS 4). Neither infusions of bupivacaine 0.125% nor ropivacaine 0.2% interfered with neurophysiological assessments after scoliosis surgery (Pham Dang 2008 **Level II**, n=18, JS 4). At concentrations of ≥0.5%, there were no significant differences in onset time and intensity or duration of sensory block between bupivacaine, levobupivacaine or ropivacaine used for epidural analgesia (Casati 2003b **Level II**, n=45, JS 5; Cheng 2002 **Level II**, n=45, JS 3).

Local anaesthetic/opioid combinations

The quality of pain relief from low-dose epidural infusions of plain LA consistently benefits from the addition of opioids, most commonly fentanyl (Walker 2002 **Level I**, 4 RCTs [epidural local anaesthetic/opioid combinations], n=226; Curatolo 1998 **Level I**, 18 RCTs [fentanyl/local anaesthetic], n unspecified); this was confirmed by additional RCTs (Senard 2002 **Level II**, n=60, JS 3; Hubler 2001 **Level II**, n=109, JS 4; Crews 1999 **Level II**, n=64, JS 3; Scott 1999 **Level II**, n=182, JS 5;). For addition of other adjuvants see Sections 4.9, 4.12.2 and 4.13.

Potential dose-sparing benefits are more obvious for LA adverse effects (hypotension and motor block) than for opioid-related adverse effects (Walker 2002 **Level I**, 4 RCTs [epidural LA/opioid combinations], n=226).

Comparisons of PCEA using ropivacaine 0.2%, ropivacaine 0.125% and levobupivacaine 0.125%, all with sufentanil 1 mcg/mL (6 mL background plus 2 mL bolus), showed no differences in pain relief or motor block; patients given 0.2% ropivacaine used similar volumes, thus receiving more total dose of local anaesthetic and the same amount of sufentanil (Sitsen 2007 **Level II**, n=63, JS 4). Similarly, there was no difference in analgesia and no motor block reported in a PCEA comparison of ropivacaine 0.05%, 0.075% and 0.1%, with fentanyl 4 mcg/mL and droperidol 25 mcg/mL added to all solutions (Iijima 2007 **Level II**, n=272, JS 4). In another comparison of PCEA 0.625% bupivacaine with fentanyl 3 mcg/mL and 0.15% ropivacaine alone, there was no difference in pain relief; patient satisfaction was lower with PCEA ropivacaine, even though it led to fewer opioid-related adverse effects (Pitimana-aree 2005 **Level II**, n=70, JS 3).

No studies directly compare fentanyl to morphine when added to LA epidural infusions, although a single retrospective audit of the use of high-thoracic epidural following cardiac surgery suggested improved pain control and lowered infusion rate using ropivacaine 0.2% with morphine 20 mcg/mL vs fentanyl 2 mcg/mL (Royse 2005 **Level III-3**, n=200). For information relating to the use of epidural LA or LA/opioid combinations for postoperative pain see Section 5.6.2 and for labour pain see Section 9.1.3.3.

4.4.2.4 | Peripheral local anaesthetics

A number of studies have compared different LAs or doses of LAs used for peripheral nerve block (PNB) and continuous peripheral nerve block (CPNB). Specific regional and local anaesthetic techniques are discussed in Section 5.8

In a meta-analysis comparing ropivacaine to levobupivacaine for peripheral nerve block, there was no difference in time to onset of anaesthesia or patient satisfaction, but levobupivacaine was found to provide longer block (WMD -2.94 h; 95%CI -5.56 to -0.32) and a lower incidence of postoperative rescue analgesia (OR 2.11; 95%CI 1.18 to 3.74) (Li 2017a **Level I**

[PRISMA], 12 RCTs, n=556); concentrations included ranged from 0.5% to 1.0% and non-equipotent comparisons were included.

At concentrations of 0.5% or greater, there were no significant differences in onset time and intensity or duration of sensory block between bupivacaine, levobupivacaine or ropivacaine in sciatic (Casati 2002 **Level II**, n=50, JS 4), interscalene (Casati 2003a **Level II**, n=47, JS 5) or axillary brachial plexus blocks (McGlade 1998 **Level II**, n=61, JS 5). A comparison of three concentrations (0.1%, 0.2%, 0.3%) of ropivacaine for continuous FNB following TKA found that infusions of 0.2% and 0.3% ropivacaine had equivalent quality of postoperative analgesia (Brodner 2007 **Level II**, n=102, JS 4). After similar surgery, there was no difference in pain relief or motor block between patient-controlled FNB with 0.125% levobupivacaine and 0.2% ropivacaine (Heid 2008 **Level II**, n=60, JS 4).

Comparisons of two different patient-controlled CPNB regimens found different results depending on the location of the block; the regimens were ropivacaine at 4 mL/h 0.4% (bolus 2 mL) or 8 mL/h 0.2% (bolus 4 mL). For continuous popliteal nerve block, the larger volumes of the dilute LA were more likely to cause an insensate limb (Ilfeld 2008 **Level II**, n=50, JS 3); for continuous interscalene nerve block there was no difference between the two solutions (Le 2008 **Level II**, n=50, JS 2) and for continuous infraclavicular nerve block the smaller volumes of the more concentrated LA were more likely to cause an insensate limb (Ilfeld 2009 **Level II**, n=50, JS 3).

Another comparison of patient-controlled continuous interscalene block using 0.25% levobupivacaine, 0.25% ropivacaine and 0.4% ropivacaine reported less effective pain relief with the lower concentration of ropivacaine (Borghi 2006 **Level II**, n=72, JS 5).

Continuous popliteal sciatic nerve block using 0.2% ropivacaine, 0.2% levobupivacaine and 0.125% levobupivacaine resulted in similar pain relief after foot surgery but fewer patients had complete recovery of motor function at 24 and 48 h with 0.2% levobupivacaine (Casati 2004 **Level II**, n=60, JS 5). Many continuous perineural infusion techniques now use low concentrations of ropivacaine (approx. 0.1%) in order to minimize motor block while still providing effective analgesia (see Section 5.8).

Skin infiltration

Increasing the pH of commercial lidocaine (to ≥7.35 by the addition of sodium bicarbonate prior to injection) reduces pain scores on injection for invasive procedures in cross-over studies (WMD -2/10; 95%CI -2.6 to -1.3) (10 RCTs) and in parallel design studies (WMD -1/10; 95%CI -1.4 to -0.4) (7 RCTs) (Cepeda 2010 **Level I** [Cochrane], 23 RCTs, n=1,067). The magnitude of the decrease in pain is larger when the solution contains adrenaline (WMD -2.5/10; 95%CI -3.2 to -1.7) (6 RCTs, n=232).

Warming the solution (to 37–43°C), assessed mostly in adults, reduces pain on SC or intradermal injection overall (WMD -11/100; 95%CI -14 to -7) (18 RCTs, n=831) and when the local anaesthetic is buffered (WMD -7/100; 95%CI -12 to -3) (8 RCTs, n=412) (Hogan 2011 **Level I** [PRISMA], 18 RCTs, n=831).

Local infiltration analgesia

Two main strategies using large volume, low concentration local anaesthetic infiltration techniques are described: tumescent local anaesthesia and local infiltration analgesia (LIA). Tumescent local anaesthesia has been described for soft-tissue surgery such as varicose vein sclerosis, liposuction or cosmetic breast surgery.

The term LIA typically refers to the systematic intraoperative injection of LAs in the periarticular and intra-articular regions. LIA may also be referred to as periarticular infiltration. A “cocktail” is most commonly used for periarticular LIA comprising a local anaesthetic, an alpha-2 agonist/vasoconstrictor, an opioid and an anti-inflammatory agent. The majority of investigations into the effectiveness of LIA in acute pain management following hip or knee arthroplasty fail to separate out the components of the mixture and some protocols use “top-

up" regimes of varying composition (Andersen 2014a **Level I** [PRISMA], 27 RCTs, n=1,644). In THA (n=756), multimodal systemic analgesia or neuraxial techniques (IT morphine or epidural analgesia) have similar analgesic efficacy vs LIA; however, in TKA LIA provided superior analgesia to placebo (n=328). Compared with FNB, epidural analgesia or IT morphine, LIA provided similar or improved analgesia in the early postoperative period, but most trials had a high risk of bias due to different systemic analgesia regimens between groups. Overall, the use of wound catheters for postoperative administration of local anaesthetic following LIA was not supported in the included trials.

Despite the many studies of LIA, final interpretation is hindered by methodological insufficiencies in most studies, especially because of differences in use of systemic analgesia between groups. For more detail see also Section 5.8.7.1.

There is limited data regarding local anaesthetic systemic toxicity (LAST) in patients receiving LIA with hip and knee joint surgery. In a case series of 39 patients receiving up to 300 mg ropivacaine as LIA, there was no clinical toxicity and peak plasma values did not exceed 1.7 mcg/mL; peak levels occurred at approximately 6 h post administration (Affas 2016 **Level IV**, n=39).

In volunteers receiving 41 exposures to tumescent subcutaneous infiltration of lidocaine with epinephrine, recommendations were made for up to 28 mg/kg lidocaine without liposuction and 45 mg/kg with liposuction with peak levels occurring 8 to 16 h after infiltration (Klein 2016 **Level IV EH**, n=14)

Slow-release preparations of local anaesthetics

Encapsulation of bupivacaine within liposomes in clusters of <100 microns diameter (liposomal bupivacaine) results in drug release into adjacent tissues for a number of days following injection, with peak plasma levels occurring 12–36 h after injection (Skolnik 2014 **NR**). Current indications from trial data have not raised any specific safety concerns (Viscusi 2014 **Level I**, 10 RCTs, n=823).

A limited number of RCTs have been conducted with wound infiltration, periarticular infiltration, perineural block and epidural administration (see Section 4.3.2.2 for ER epidural opioid preparations); most RCTs have demonstrated analgesic superiority over placebo for up to 72 h, however benefit over normal formulations of bupivacaine has not been shown (Tong 2014 **Level III-2 SR**, 5 studies, n unspecified). When comparing wound infiltration with liposomal bupivacaine to either ropivacaine or plain bupivacaine, no difference was seen with analgesic outcomes up to 48 h (Kendall 2018 **Level I** [PRISMA], 9 RCTs, n=779).

A systematic review of liposomal bupivacaine use in TKA found (Yayac 2019 **Level IV SR** [PRISMA], 6 SRs & 17 RCTs & 25 studies, n unspecified):

- For liposomal bupivacaine by periarticular infiltration vs conventional LA single injection PNB (3 RCTs, n=555), pain relief is better with PNB (SMD 0.45, 95%CI 0.08 to 0.82), largely driven by benefits on POD 0 and 1; there is no difference in opioid consumption. Differences in complication rates, including falls, are mixed.
- For liposomal bupivacaine by periarticular infiltration vs conventional LA LIA (13 RCTs, n=1,155), slightly lower pain scores are found using AUC over 5 d (SMD = -0.08, 95%CI -0.14 to -0.03), but not using pain scores by time-point up to 3 d (-5.21/100; 95%CI -12.1 to 1.65). There are no differences in opioid consumption nor functional recovery.
- For liposomal bupivacaine by periarticular infiltration vs conventional LA IA infiltration (2 RCTs, n=345), only one study included a direct comparison and found no difference in pain outcomes.

Also in TKA, two overlapping meta-analyses compared liposomal bupivacaine by periarticular infiltration to conventional LA FNB (Liu 2017a **Level III-2 SR** [PRISMA], 1 RCT & 7 studies, n=2,407; Ma 2016b **Level III-2 SR**, 1 RCT & 5 studies, n=1,289) (all 6 studies overlap); 2 FNB studies used continuous

infusions. There is no difference between groups in pain scores to 72 h, PONV or range of motion, but liposomal bupivacaine is associated with decreased LOS (MD -0.43 d; 95%CI -0.60 to -0.27) and reduced total morphine requirements (MD -29.3 mg; 95% CI -57.6 to -1.1) (Liu 2017a **Level III-2 [PRISMA]**, 1 RCT & 7 studies, n=2,407).

In THA, LIA with liposomal bupivacaine vs conventional bupivacaine showed no difference up to 72 h in postoperative opioid consumption, pain scores, opioid-related side effects, time to first ambulation, or LOS (Perets 2018 **Level II**, n=107, JS 4).

Following day-case retropubic sling placement, pain scores were low but liposomal bupivacaine infiltration vs saline improved scores slightly at 4 h post-discharge and the following morning (Mazloomdoost 2017 **Level II**, n=109, JS 4).

4.4.3 | Local anaesthetic toxicity

4.4.3.1 | Direct toxicity

Nerve injury following perineural LA injection may be a consequence of many factors including needle trauma, haematoma, pressure injury, or direct local anaesthetic toxicity (Verlinde 2016 **NR**). In clinical practice it is difficult, if not impossible to separate out these elements, and the likely contribution of direct neurotoxicity is small. All local anaesthetics exhibit neurotoxicity if nerves are exposed to sufficiently high concentrations for a sufficiently long period (Verlinde 2016 **NR BS**). Lidocaine (5%) infused via lumbar subarachnoid microcatheters has been associated with case reports of cauda equina syndrome (Rigler 1991 **Level IV**, n=4; Schell 1991 **Level IV**, n=2). This suggested that high local concentrations of lidocaine were potentially neurotoxic and led to the technique falling into disfavour. The precise mechanisms of direct LA neurotoxicity remain unclear, but are concentration-dependent, and may involve the intrinsic caspase-pathway, PI3k-pathway, and MAPK-pathways (Verlinde 2016 **NR BS**).

Transient neurological symptoms (TNS) is a clinical syndrome associated with spinal (IT) anaesthesia. Patients experience pain or muscle spasms in the buttocks or lower limbs following initial recovery from the spinal anaesthetic. The onset of symptoms is usually within 24 h of the procedure and it fully resolves spontaneously within a few days. Despite its name, there is no evidence that this condition is associated with actual neurologic pathology. A network meta-analysis showed that, compared to lidocaine, the risk ratio (RR) of TNS was lower for bupivacaine, levobupivacaine, prilocaine, procaine, and ropivacaine with RRs in the range of 0.10 to 0.23, while 2-chloroprocaine and mepivacaine did not differ in terms of RR of TNS development vs lidocaine (Forget 2019 **Level I** [Cochrane] [NMA], 24 RCTs, n=2,226); the quality of evidence was considered moderate to low, and the overall incidence of TNS was 10.7%.

Other tissues are susceptible to direct toxicity from local anaesthetics. Myotoxicity has been described clinically (Zink 2004 **NR**) and reproduced experimentally (Yildiz 2011 **BS**), especially for bupivacaine, but is rare and reversible. Local anaesthetics have chondrotoxic effects on articular cartilage, which are worsened by coadministration of corticosteroids (Jayaram 2019 **Level I** [PRISMA], 16 RCTs, n unspecified); ropivacaine at concentrations of 0.5% or less was found to be the least chondrotoxic LA.

4.4.3.2 | Systemic toxicity

There is consistent laboratory data showing that the S-enantiomers of the long-acting amide LAs exhibit less CNS or cardiac toxicity than the R-enantiomers or the racemic mixtures for doses resulting in equivalent sensory nerve conduction block. Defining relative toxicities for these agents is complex because it depends on the parameters measured (eg cardiac, CNS),

the dose, route and species studied. There is lack of scientific data available to determine a safe maximal dose of local anaesthetic. However, the upper limit of a dose should take into account patient weight, age and comorbidities. There is a pharmacokinetic rationale to support fractional dosing by incremental injection of local anaesthetic in addition to identifying unintended intravascular injection.

The incidence of local anaesthetic systemic toxicity (LAST) has been quantified using registry databases at 0.03% or 0.27/1,000 PNBS (95%CI 0.21 to 0.35) (Gitman 2018 **Level IV**, n=251,325); the most common presenting feature was seizure (53% and 61%; from case reports and registries respectively). The use of ultrasound (US) was associated with a reduced incidence of LAST (OR 0.23; 95%CI 0.088 to 0.59) (Barrington 2013 **Level IV**, n=25,336 [PNBS] in n=20,021 [patients]); this may be due to increased precision of needle placement with US guidance (minimising intravascular placement) (Neal 2016 **Level IV SR**, 27 studies, n=1,867), or the use of lower doses of local anaesthetic. A meta-analysis identifies a significantly decreased risk of vascular puncture using US (RR 0.16; 95%CI 0.05 to 0.47) (Abrahams 2008 **Level I**, 13 RCTs, n=946). These data form the basis for the current Class I-B ASRA recommendations for the use of US to reduce LAST (Neal 2018 **GL**). It should be noted that LAST episodes continue to occur despite precautionary measures, including US use (Gitman 2018 **Level IV SR**, n=47 [episodes of LAST]). Factors associated with increased LAST events were paravertebral (OR 9.20; 95%CI 2.24 to 37.8) and upper limb blocks (OR 4.80; 95%CI 1.23 to 18.7), the use of lidocaine vs ropivacaine (OR 5.64; 95%CI 2.02 to 15.7) and larger doses of local anaesthetic (Barrington 2013 **Level IV**, n=25,336 [PNBS in n=20,021 patients]).

In blinded human-volunteer studies, CNS symptoms were detected at IV doses and plasma levels that were 25% higher for ropivacaine vs bupivacaine (Scott 1989 **Level II EH,** n=12, JS 2) and 16% higher for levobupivacaine than bupivacaine (Bardsley 1998 **Level II EH**, n=14, JS 3). Although these data show that CNS toxicity might occur less frequently or be less severe with the S-enantiomers, all local anaesthetics are toxic. A rapid IV bolus of any of these agents may overwhelm any of the more subtle differences found at lower plasma concentrations.

Severe myocardial depression and refractory ventricular fibrillation have been described as the hallmark of accidental IV administration of moderately large doses of bupivacaine. This has been attributed to the slow dissociation of bupivacaine from the myocardial sodium channel, which is less marked with levobupivacaine and ropivacaine (Mather 2001 **NR**). Animal studies confirm that higher systemic doses of ropivacaine and levobupivacaine are required to induce ventricular arrhythmias, circulatory collapse or asystole (Ohmura 2001 **BS**), with the ranking of toxicity risk being bupivacaine > levobupivacaine > ropivacaine (Groban 2001 **NR**).

Controlled human studies are only possible when looking at surrogate endpoints such as ECG changes or myocardial depression and suggest a similar ranking of adverse effects (Bardsley 1998 **Level II EH**, n=14, JS 5; Knudsen 1997 **Level II EH**, n=12, JS 5; Scott 1989 **Level II EH**, n=12, JS 5), with bupivacaine being the most toxic and levobupivacaine being less toxic and similar to ropivacaine (Stewart 2003 **Level II EH**, n=14, JS 5).

Successful resuscitation from a massive overdose is of greater relevance in clinical practice. A canine study investigating resuscitation (not using lipid emulsion) and survival following local anaesthetic-induced circulatory collapse showed survival rates of 50%, 70% and 90% with bupivacaine, levobupivacaine and ropivacaine respectively (Groban 2001 **BS**).

Case reports of accidental toxic overdose with ropivacaine suggest that outcomes are more favourable and resuscitation more straightforward (in particular requiring less cardiovascular support) than with racemic bupivacaine (Weiss 2014 **CR**; Hubler 2010 **CR**; Kimura 2007 **CR**; Khoo 2006 **CR**; Soltesz 2003 **CR**; Chazalon 2003 **CR**; Huet 2003 **CR**; Klein 2003 **CR**; Pham-Dang 2000 **CR**). This data is prior to the widespread use of guidelines and lipid emulsion therapy, and a review of case-series and registry data over 33 mth from March 2014 identified only 2 reported deaths out of 47

events, one case having delayed therapy and the other related to lidocaine (Gitman 2018 **Level IV SR,** n=47 [episodes of LAST]).

Total plasma levels of LAs tend to rise during the first 48 h of postoperative infusion, although free levels remain relatively low (Scott 1997 **Level IV**, n=11; Emanuelsson 1995 **EH PK**). Thus, in published studies, toxicity due to systemic absorption from epidural or perineural infusions has not been a problem. However, the risk of accidental absolute overdose with postoperative infusions and the increasing use of fascial plane infusions, suggests that the less toxic agents should be used in preference and that the doses administered should be the minimum needed for efficacy.

Lipid emulsion therapy

Lipid emulsion therapy is advocated for the treatment of LAST. The ASRA Practice Advisory on Local Anesthetic Systemic Toxicity recommends the administration of IV lipid emulsion therapy at the first signs of LAST but following airway management (Class I-B recommendation) (Neal 2018 **GL**). Animal experimental data (Weinberg 2003 **BS**; Weinberg 1998 **BS**) has been supported by case reports of successful resuscitation following bupivacaine (Rosenblatt 2006 **CR**), ropivacaine (Litz 2006 **CR**), levobupivacaine (Foxall 2007 **CR**) mepivacaine/prilocaine (Litz 2008 **CR**) and mepivacaine/ bupivacaine (Warren 2008 **CR**) toxicity and published case series of use of IV lipid emulsion therapy (Gitman 2018 **Level IV SR**, n=47 [LAST episodes]; Cave 2014 **Level IV**, n=10 (LAST episodes]; Felice 2008 **Level IV**, n=4).

The mechanism of action of the lipid emulsion may be due to partitioning of local anaesthetic within the emulsion itself (acting as a "lipid sink" or "shuttling") (Fettiplace 2018 **NR**), mitochondrial substrate enhancement in the myocardium (Weinberg 2000 **BS**) and/or a direct inotropic effect (Fettiplace 2014 **BS**). Uncertainties relating to dosage, efficacy and adverse effects (Cave 2014 **Level IV**, n=10 (LAST episodes]) still remain, however, lipid administration appears safe and therefore it is recommended to administer lipid emulsion immediately after airway support has commenced and ventilation is controlled in suspected LAST (convulsions may or may not need control at this point in order to ventilate) (Neal 2018 **GL**); this prevents hypoxia, hypercapnia, and acidosis which are known to potentiate LAST. Guidelines have been established to facilitate management of local anaesthetic toxicity, which include use of lipid emulsion therapy (Neal 2018 **GL**; AAGBI 2010 **GL**). It should be noted that local anaesthetic toxicity might recur following successful initial resuscitation, suggesting a need for continued intensive observation if a large dose of local anaesthetic has been administered (Marwick 2009 **GL**).

LAST is also discussed in Section 5.8.11.3 and in paediatric patients in Section 10.6.3.5 (including adverse effects of lipid emulsion use).

KEY MESSAGES

1. Lidocaine intrathecal is more likely to cause transient neurologic symptoms than bupivacaine, prilocaine and procaine (**S**) (**Level I** [Cochrane Review NMA]).
2. Local anaesthetics have chondrotoxic effects on articular cartilage, with ropivacaine the least toxic (**N**) (**Level I** [PRISMA])
3. Wound infiltration with liposomal preparations of bupivacaine is no more effective than ropivacaine or plain bupivacaine for analgesic outcomes up to 48 hours (**N**) (**Level I** [PRISMA])
4. The quality of epidural analgesia with local anaesthetics is improved with the addition of opioids (**U**) (**Level I**).

5. Ultrasound guidance reduces the risk of vascular puncture during the performance of regional blocks (**S**) (**Level I**).
6. Local anaesthetic systemic toxicity is reduced by the use of ultrasound guidance for regional anaesthesia (**S**) (**Level I**).
7. Continuous perineural infusions of lidocaine result in less effective analgesia and more motor block than long-acting local anaesthetic agents (**U**) (**Level II**).
8. There are no consistent differences between ropivacaine, levobupivacaine and bupivacaine in terms of quality of analgesia or motor block, when given in low doses for regional analgesia (epidural and peripheral nerve block) (**U**) (**Level II**).
9. Cardiovascular and central nervous system toxicity of the stereospecific isomers ropivacaine and levobupivacaine is less severe than with racemic bupivacaine (**U**) (**Level II**).
10. Local anaesthetic systemic toxicity is increased in paravertebral and upper limb blocks, with the use of lidocaine and higher doses of local anaesthetics (**U**) (**Level IV**).
11. Lipid emulsion is effective in resuscitation of circulatory collapse due to local anaesthetic toxicity (**S**) (**Level IV SR**); however, uncertainties relating to dosage, efficacy and adverse effects still remain; therefore, it is appropriate to administer lipid emulsion only once ventilatory support has begun and convulsions are controlled (**S**) (**Level IV**).

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

☑ Case reports following accidental overdose with ropivacaine, levobupivacaine and bupivacaine suggest that resuscitation is less likely to be successful with bupivacaine (**U**).

4.5 | Inhalational agents

4.5.1 | Nitrous oxide

N_2O has been used since the inception of anaesthesia for its modest analgesic and sedative properties. It has minimal respiratory and cardiovascular depression. In many countries it is available as a 50% N_2O /50% oxygen mixture called Entonox®. While it has a long history of use, there is a paucity of good studies examining its effectiveness in comparison with other analgesics (Buhre 2019 **NR**).

In a meta-analysis of inhaled analgesics in labour, subgroup analysis of N_2O shows minimal analgesic difference vs placebo (RR 0.06; 95%CI 0.01 to 0.34) (MD 3.5/100; 95%CI -3.75 to -3.25) (Klomp 2012 (**Level I** [Cochrane], 3 RCTs [N_2O], n=819). A systematic review shows that N_2O in oxygen has some analgesic efficacy in labour (Likis 2014 **Level IV SR**, 58 studies, n=20,266). Only two studies were of good quality. N_2O provides less analgesia than epidural analgesia but more than pethidine, or bath and shower. Maternal satisfaction with the birth experience using N_2O for analgesia is higher than for pethidine or epidural analgesia. The reports of maternal adverse effects in this review are nausea, vomiting, dizziness and drowsiness. Apgar scores are no different for N_2O vs no analgesia. A subsequent systematic review vs multiple comparators, was overall of low quality and did not add to the previous information (Sheyklo 2017 **Level I** [PRISMA], 14 RCTs, n unspecified) (See also Section 9.1.3.2).

N_2O was effective during painful procedures such as venous cannulation (Gerhardt 2001 **Level II**, n=10, JS 5), sigmoidoscopy (Harding 2000 **Level II**, n=77, JS 5), dermatological procedures (Brotzman 2018 **Level IV SR**, 8 studies, n unspecified), extraction of gauze packing strips after Caldwell-Luc operation (Dong 2017 **Level II**, n=47, JS 4), lumbar puncture (Moisset 2017 **Level II**, n=66, JS 5), transrectal prostate biopsy (Cazarim 2018 **Level II**, n=84, JS 4), liver biopsy (Castera 2001 **Level II**, n=100, JS 5) and in relieving acute ischaemic chest pain (O'Leary 1987 **Level II**, n=12, JS 2) and in trauma patients in the prehospital setting (Ducasse 2013 **Level II,** n=60, JS 4). In elderly patients (median age 84 y), N_2O provided better analgesia than morphine during bed sore and ulcer care (Paris 2008b **Level II**, n=34, JS 3). For colonoscopy, there was no difference in pain intensity between continuous and as-required 50% N_2O use (Ball 2015 **Level II**, n=108, JS 5).

While a previous study reported benefits in bone marrow aspiration (Gudgin 2008 **Level III-3**, n=16), a subsequent RCT found no difference in pain and anxiety scores between 50% N_2O in oxygen and an oxygen/air mixture (Kuivalainen 2015 **Level II**, n=60, JS 3). Similarly, for intrauterine device insertion, there was no analgesic effect of 50% N_2O vs oxygen (Singh 2016b **Level II**, n=80, JS 5) and there was no pain relieving or opioid-sparing effect of 65% N_2O vs oxygen for burns dressing changes (do Vale 2016 **Level III-1**, n=15).

For lower gastrointestinal endoscopy, there is no difference in pain scores between N_2O and IV opioid/midazolam, or the ability to successfully complete the procedure (Welchman 2010, **Level I**, 11 RCTs, n=623). The N_2O group has a shorter time to achieve fitness for discharge. Self-administration of 50% N_2O combined with PO morphine vs the same dose of PO morphine alone resulted in better pain control of breakthrough pain in cancer patients at 5 and 15 min (Liu 2018 **Level II**, n=240, JS 5).

As no RCTs compare N_2O and methoxyflurane, an indirect comparison for pain relief in the ED showed no significant differences in efficacy between the two agents (Porter 2018b **Level I** [NMA], 2 RCTs, n=263).

For use in paediatrics see Section 10.7.2 and 10.7.4.

In an experimental setting, a study measuring changes in detection and pain thresholds to electrical tooth stimulation reported the development of acute and chronic tolerance in

response to single and repeated administration of N_2O (38% or 35%) for 30 min (Ramsay 2005 **EH**). The significance of this finding in the clinical setting is unknown.

A *post-hoc* analysis of an RCT (ENIGMA) using telephone interviews at a median of 4.5 y following (mostly abdominal) surgery found that the intraoperative use of N_2O reduced the risk of chronic postsurgical pain in an Asian population (OR 0.48; 95%CI 0.33 to 0.93) (Chan 2011 **Level II**, n=423, JS 5); factors increasing risk included severity of acute postoperative pain, wound length, wound infection and anxiety. These findings were confirmed in a planned subgroup analysis in Asian vs non-Asian patients (RR 0.70; 95%CI 0.50 to 0.98) of a subsequent RCT (ENIGMA II) (Chan 2016 **Level II**, n=2,924 [phone interviews at 12 mth postop], JS 5).

N_2O attenuated remifentanil induced tolerance/hyperalgesia (Wehrfritz 2016 **Level II EH**, n=21, JS 5; Echevarria 2011 **Level II**, n=50, JS 4).

N_2O diffuses more rapidly than nitrogen and can expand enclosed air-containing spaces within the body. Its use is therefore contraindicated in the presence of a pneumothorax, obstruction of middle ear and sinus cavities, recent vitreoretinal surgery, pneumocephalus, bowel obstruction and gas embolism (Shaw 1998 **NR**).

4.5.1.1 | Toxicity

N_2O oxidises the cobalt ion of cobalamin (vitamin B_{12}) preventing it from acting as a coenzyme for methionine synthetase; methionine synthetase also requires 5-methyltetrahydrofolate as a coenzyme (Sanders 2008 **NR**). Methionine synthetase is required for the synthesis of deoxyribonucleic acid and ribonucleic acid and therefore the production of cells in rapidly dividing tissues such as bone marrow and gastrointestinal mucosa, as well as the synthesis of myelin (Sanders 2008 **NR**). Exposure of young children (median age 11 mth) to N_2O anaesthesia for more than 2 h leads to a statistically significant but small increase in total homocysteine plasma concentrations on the first postoperative morning with unclear clinical relevance (Pichardo 2012 **Level IV**, n=32).

Bone marrow and neurological complications have been reported in patients exposed to N_2O. A systematic review identified 100 cases of neurological toxicity, of which 57% resulted from recreational use (Oussalah 2019 **Level IV SR**, 85 studies, n=100 [cases]). Other reasons for exposure were surgery in 25%, occupational exposure in 9%, pain control in 6% and procedural sedation in 1%. Clinical symptoms included paraesthesia in 80%, unsteady gait in 58% and weakness in 43%. The most common diagnoses were subacute combined degeneration (SACD) of the spinal cord in 28%, myelopathy in 26% and generalized demyelinating polyneuropathy in 23%; a T2 signal hyperintensity in the MRI of the spinal cord was seen in 68%. Pathological haematological findings occurred in 72%. The most relevant factor was possible or probable vitamin B_{12} deficiency (diagnosed on the combined indicator of vitamin B_{12} status (cB_{12}) scoring system [Fedosov 2015 **BS**) in 85%. In a univariate risk analysis, the following risk factors were identified: age 40 y (OR 23.3; 95%CI 6.8 to 79.6), vitamin B_{12} level 74 pmol/L (OR 6.06; 95%CI 2.05 to 17.9) and MCV >100 fL (OR 9.8; 95%CI 1.9 to 49.1). Amount of N_2O was not associated with any outcome.

A parallel systematic review of specifically cases of SACD of the spinal cord excluded recreational users (Patel 2018 **Level IV SR**, 32 studies, n=39 [cases]) (significant overlap). Again in 84% of cases vitamin B_{12} malabsorption secondary to a gastrointestinal disorder is the underlying causation. Classical symptoms were proprioceptive and vibratory sensation loss in 67% and burning or tingling paraesthesia in 59%. Again, there was no association to exposure duration. Most notably, supplementation with vitamin B_{12} resulted in complete recovery in 33% and partial improvement in 64%. Mean time to complete resolution was 37 wk (4 wk to 3 y).

The risk may be greater in critically ill patients with increased metabolic demands or poor

nutrition (Amos 1982 **Level IV**, n=70). N_2O-induced bone marrow toxicity leading to megaloblastic anaemia is usually progressive but reversible. The bone marrow changes were almost completely prevented by administration of folinic acid (Amos 1982 **Level IV**, n=70).

The following case reports are included in the systematic reviews above, but highlight specific risk factors: Those at risk of vitamin B_{12} deficiency include some vegetarians (in particular vegans) (Rosener 1996 **CR**), the newborns of vegetarian mothers (McNeely 2000 **CR**), patients with gastrointestinal pathology (Schilling 1986 **Level IV**) or phenylketonuria (Walter 2011 **NR**), elderly people (Nilsson-Ehle 1998 **NR**), patients taking PPIs (Schenk 1999 **Level IV**) or H2 blockers and alcoholics (Sanders 2008 **NR**; Carmel 2000 **NR**). Cases have also been reported in those abusing the drug (eg obtained from whipped cream chargers) or being exposed to N_2O for medical purposes after longer periods of abuse (Lin 2011 **Level IV**, n=3; Rheinboldt 2014 **CR**; Hu 2014 **CR**; Chiang 2013 **CR**; Cheng 2013 **CR**; Ghobrial 2012 **CR**; Sanders 2008 **NR**).

The neuropathy appears to be the result of decreased methionine and subsequent defective myelin formation. Involvement of peripheral, autonomic and central nervous systems may also lead to incontinence, diplopia, confusion or impaired cognitive function (Weimann 2003 **NR**). Despite the lack of any good data assessing efficacy in humans, and even though the bone marrow changes are usually reversible, it may be reasonable to give patients repeatedly exposed to N_2O, vitamin B_{12} and folic or folinic acid supplements (Weimann 2003 **NR**).

Another consequence of N_2O-induced inactivation of methionine synthetase is elevation of plasma homocysteine (a known risk factor for coronary artery and cerebrovascular disease), the levels of which rise after anaesthesia using N_2O (Myles 2008 **Level II**, n=59, JS 3; Badner 1998 **Level II**, n=20, JS 2; Nagele 2008 **Level III-3**, n=140). Patients who are homozygous for polymorphisms in the gene encoding the enzyme that is an antecedent to methionine synthetase are at a higher risk of developing abnormal plasma homocysteine concentrations after N_2O anaesthesia (Nagele 2008 **Level III-3**, n=140). However, the large ENIGMA II study, comparing oxygen 30% with or without N_2O (70%) in patients with known or risk factors for ischaemic heart disease, found no difference in serious adverse effects in the N_2O group vs the non-N_2O group (Myles 2014 **Level II**, n=7,112, JS 3). However, as this study examined patients who were undergoing major surgery that lasted for at least 2 h, the applicability to the setting of analgesia may be limited.

Methionine given preoperatively to patients undergoing N_2O anaesthesia improved the rate of recovery of methionine synthetase and prevented the prolonged postoperative rise in plasma homocysteine concentrations (Christensen 1994 **Level IV**, n=14). Preoperative administration of oral B vitamins (folate, B_6 and B_{12}) (Badner 2001 **Level II**, n=53, JS 3) and of vitamin B_{12} infusions (Kiasari 2014 **Level II**, n=60, JS 5) also prevented the postoperative increase in homocysteine following N_2O anaesthesia.

The information about the complications of N_2O derives from case reports only. There are no controlled studies that evaluate the safety of repeated intermittent exposure to N_2O in humans and no data to guide the appropriate maximum duration or number of times a patient can safely be exposed to N_2O. Nevertheless, the potential problems require highlighting. The suggestions for the use of N_2O outlined below are extrapolations only from the information above.

4.5.1.2 | Suggestions for the use of nitrous oxide as an analgesic

When N_2O is to be used repeatedly for painful short procedures, it may be reasonable to:

- Exclude patients with persistent vitamin B_{12} deficiency;
- Screen patients at risk of vitamin B_{12} deficiency by examination of the blood picture and serum B_{12} concentrations before using N_2O repeatedly;

- Exclude asymptomatic patients with macrocytic anaemia or hypersegmentation of neutrophils until it is established that vitamin B_{12} or folate deficiency is not the cause;
- Exclude females who may be in the early stages of pregnancy, although this will depend on the relative harm of any alternative methods;
- Limit exposure to N_2O to the briefest possible time — restricting the duration of exposure may require strict supervision and limited access to the gas;
- Administer methionine, vitamin B_{12} (both with a good safety profile) and possibly folic or folinic acid to patients repeatedly exposed to N_2O (doses that may prevent the complications of exposure to N_2O have not been established);
- Monitor for clinical signs and symptoms of neuropathy on a regular basis and start treatment with vitamin B_{12} early.

4.5.2 | Methoxyflurane

Methoxyflurane is a volatile anaesthetic agent with analgesic properties. It was first marketed in 1962 and later withdrawn from sale in 2001. The FDA withdrew the medicine because of the risk of nephrotoxicity and hepatotoxicity and stated that it would not consider reintroduction into the market until new clinical trials were undertaken (FDA 2005). Methoxyflurane is no longer licensed for anaesthesia in humans.

Although no longer used as an anaesthetic, methoxyflurane has been registered in Australia and New Zealand (as well as now a number of other countries) for use as an analgesic in low doses since 1975 for relief of trauma-associated acute pain as well as procedural pain (Porter 2018a **NR**; Jephcott 2018 **NR**; Medical Devices International 2009). It is available as a self-administered "Penthrox®" inhaler, which dispenses 0.2 to 0.4% methoxyflurane (Medical Devices International 2009).

As an analgesic in prehospital and ED settings methoxyflurane has been reported as effective (Yeung 2018 **Level III-2 SR** [PRISMA], 2 SRs & 2 studies, n unspecified; Grindlay 2009 **Level IV SR,** 6 studies [analgesia], n unspecified). Methoxyflurane provided inferior analgesia to IV morphine and IN fentanyl in the prehospital setting with minimal adverse effects (Yeung 2018 **Level III-2 SR**, 2 SRs & 2 studies, n unspecified). In ED patients aged ≥12 y it was significantly more analgesic than placebo, with only mild transient adverse effects such as dizziness and headache (Wells 2018 **Level I** [PRISMA, 1 RCT: Coffey 2014 **Level II**, n=300, JS 4). The median time to onset of analgesia was rapid at 4 min and time to peak analgesia was 15 min. Safety was assessed over 14 d following administration and no significant adverse effects were found, including no renal impairment. Use of the Penthrox® inhaler in children reduced pain associated with extremity injuries (Babl 2006 **Level IV**, n=15) but did not provide adequate analgesia for subsequent fracture manipulation (Babl 2007 **Level IV**, n=14). It also provided effective pain relief for adult patients in the prehospital setting, as shown in adults travelling by ambulance to an urban teaching hospital (Buntine 2007 **Level IV**, n=83). Adverse effects included hallucinations, vomiting, confusion and dizziness, and sedation/drowsiness was common (26%) in children (Buntine 2007 **Level IV**, n=83; Babl 2006 **Level IV**, n=15).

As an analgesic for painful procedures outside of the ED, methoxyflurane was first described for obstetric analgesia in 1966 (Bodley 1966 **Level IV**, n=62) and then used as an analgesic for burns dressing (Marshall 1972 **Level IV**, n=60 [procedures in 10 patients]; Firn 1972 **Level IV**, n=94 [procedures in 36 children]; Packer 1969 **Level IV**, n=60 [procedures in 11 patients]). Methoxyflurane was effective for prostate biopsies achieving a low pain score (median 3), mild adverse effects and high patient acceptance (Grummet 2012 **Level IV**, n=42). However, methoxyflurane combined with periprostatic infiltration of local analgesia provided superior analgesia vs methoxyflurane alone (Huang 2016 **Level III-1**, n=72). In patients having colonoscopies, methoxyflurane vs IV

fentanyl/midazolam resulted in similar pain scores but shorter recovery and fitness for discharge times, no respiratory depression, and high degree of patient satisfaction (Nguyen 2013 **Level II** n=250, JS 3). Ten patients in the methoxyflurane group required supplementation with IV sedation.

In patients having bone-marrow biopsies, local anaesthetic infiltration plus methoxyflurane vs placebo inhaler resulted in lower worst pain scores (4.9 vs 6.0) (Spruyt 2014 **Level II**, n=97, JS 4). Adverse effects were mild and of short duration. The overall efficacy was also confirmed in an audit of methoxyflurane use for procedural analgesia in a variety of procedures with reported success in 97% and minimal adverse effects (Gaskell 2016a **Level IV**, n=173 [procedures in 123 patients]).

As no RCTs compare methoxyflurane and N_2O, an indirect comparison for pain relief in the ED showed no significant differences in efficacy between the two agents (Porter 2018b **Level I** [NMA], 2 RCTs, n=263). In an unblinded comparison between self-administered methoxyflurane and IV PCA ketamine/midazolam for burns dressing both achieved similar analgesia with patient preference for methoxyflurane (Gaskell 2016a **Level II**, n= 8 [cross over], JS 3).

4.5.2.1 | Toxicity

Methoxyflurane causes dose-dependent renal toxicity and, as noted above, renal failure was a key reason behind the withdrawal of the medicine from use. Use of an analgesic device delivering higher concentrations of methoxyflurane was reported to have led to two fatalities from renal toxicity (Toomath 1987 **Level IV**). However, the amount of methoxyflurane delivered using the Penthrox® inhaler is said to be significantly less than the dose that has been associated with subclinical nephrotoxicity (Grindlay 2009 **NR**). There have been no reports of toxicity (Grindlay 2009 **NR**) with dosing limited to 6 mL/d or 15 mL/wk (Medical Devices International 2009). A large population database study found no long-term (up to 14 y) adverse effects (heart disease, renal disease, hepatic disease, diabetes, or cancer) in patients who had been given methoxyflurane by an ambulance service (Jacobs 2010 **Level IV**; n=17,629). The maximum dose approved (6 mL/d and 15 mL/wk) is calculated to achieve a minimum alveolar concentration (MAC) of 0.59 MAC-h (Dayan 2016 **NR**). Methoxyflurane ≤2.0 MAC-h results in serum fluoride ≤40 micmol/L, which has not been associated with renal tubular toxicity, thereby suggesting a safety margin of at least 2.7 to 8-fold of the approved dose limits.

There has been one documented case report of acute hepatitis following three administrations of methoxyflurane in an otherwise healthy woman for procedural analgesia (O'Rourke 2011 **CR**).

Methoxyflurane is contraindicated in patients with known or at genetic risk of malignant hyperpyrexia as well as in patients renal impairment (Medical Devices International 2009).

KEY MESSAGES

1. Nitrous oxide has some analgesic efficacy in labour pain (**U**), increases maternal adverse effects (nausea, vomiting, dizziness) (**U**), with no adverse effects on the newborn (**U**) (**Level I** [Cochrane Review]) and increases maternal satisfaction compared to pethidine and epidural analgesia (**U**) (**Level IV SR**).
2. Nitrous oxide has equivalent effectiveness and more rapid recovery compared with intravenous sedation in patients having lower gastrointestinal endoscopy (**U**) (**Level I**).
3. Methoxyflurane, in low doses, is an effective analgesic with rapid onset in the prehospital setting, and a range of procedures in the hospital setting (**U**) (**Level II**) with good safety data (**S**) (**Level IV**); it may have comparable efficacy to nitrous oxide (**N**) (**Level I** [NMA]), but is inferior to IV morphine and IN fentanyl (**N**) (**Level III-2 SR**).
4. Nitrous oxide is an effective analgesic agent in a variety of other acute pain situations (**U**) (**Level II**).
5. Intraoperative use of nitrous oxide reduces the incidence of chronic postsurgical pain in Asian populations (**N**) (**Level II**).
6. Subacute combined degeneration of the spinal cord, myelopathy and generalized demyelinating polyneuropathy are rare but potentially serious complications of nitrous oxide use including in those abusing nitrous oxide (**S**) (**Level IV SR**).
7. Vitamin B_{12} deficiency (identified by vitamin B_{12} level 74 pmol/L and MCV >100 fL) and age 40 years are relevant risk factors in nitrous oxide neurotoxicity; total nitrous oxide exposure may not be a risk factor (**N**) (**Level IV SR**).
8. Early supplementation with Vitamin B_{12} in subacute combined degeneration of the spinal cord exacerbated by nitrous oxide use improves neurological recovery (**N**) (**Level IV SR**).

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

☑ In patients receiving nitrous oxide repeatedly, supplementation with vitamin B_{12}, methionine and folic or folinic acid is a consideration, in particular in those with risk factors (**Q**).

☑ If nitrous oxide is used with other sedative or analgesic agents, appropriate clinical monitoring should be used (**U**).

4.6 | NMDA-receptor antagonists

NMDA-receptor/ion-channel complexes are located peripherally and centrally within the nervous system (Gonda 2012 **NR**). These ionotropic receptors are an important component of glutamergic neurotransmission and thereby involved in multiple functions within the nervous system including learning and memory, cognitive functions, neural development, neuroplasticity, excitotoxicity, addiction, psychiatric disorders and nociception (Li 2016a **NR**).

At the spinal level, NMDA-receptor activation results in the development of central sensitisation manifested clinically as hyperalgesia and allodynia (Petrenko 2014 **NR**; Hocking 2007 **NR**). Activation of NMDA receptors via glutamate release from excitatory synapses augments the propagation of nociceptive information and is therefore linked to acute and chronic pain states as well as opioid-induced tolerance and hyperalgesia.

The NMDA-receptor antagonists ketamine, dextromethorphan, amantadine, memantine and magnesium have been investigated for the management of acute pain (Kreutzwiser 2019 **NR**; Jonkman 2017 **NR**).

4.6.1 | Systemic NMDA-receptor antagonists

4.6.1.1 | Ketamine

In low (subanaesthetic) doses, ketamine acts primarily as a noncompetitive antagonist of the NMDA receptor, although it also binds to many other sites in the peripheral and central nervous systems (Petrenko 2014 **NR**; Sleigh 2014 **NR**; Mion 2013 **NR**). In more detail it is a "high-trapping" antagonist with a slow off-rate, causing a prolonged tonic block; therefore it has higher adverse effect rates than "low-trapping" antagonists with a fast off-rate such as memantine (Sleigh 2014 **NR**). Consequently, ketamine's main role is as an adjuvant in the treatment of pain associated with central sensitisation (Persson 2013 **NR**), such as in severe acute pain, neuropathic pain (Zhou 2011 **NR**) (see Section 8.1.4) and "opioid-resistant" pain (Kreutzwiser 2019 **NR**; Tawfic 2013 **NR**). See also Section 9.7 and for paediatric use Section 10.4.7.

In experimental pain, low-dose ketamine (<1 mg/kg) reduces the area of hyperalgesia (SMD 0.54; 95% CI 0.34 to 0.74) and pain intensity (MD -1.2/10; 95%CI -0.88 to -1.44) (54 RCTs [ketamine]; 43 RCTs [IV administration]) (Thompson 2019 **Level I EH** (PRISMA), 70 RCTs, n=1,069).

In Australia and New Zealand, ketamine is supplied as a racemic mixture (S- and R- enantiomers), although a number of other countries have the more potent pure S-ketamine enantiomeric form available which has twice the analgesic potency, and slightly less adverse cognitive effects in adults (Mion 2013 **NR**).

Perioperative use

Perioperative IV ketamine (IV bolus pooled with IV infusion) used in a large number of operations performed under general anaesthesia versus placebo reduces postoperative opioid consumption over 24 h by 19 % (MD 8 mg morphine equivalents; 95%CI 6 to 9) (65 RCTs, n=4,004) and over 48 h by 19 % (MD 13 mg; 95%CI 10 to 15) (37 RCTs, n=2,449) (Brinck 2018 **Level I** [Cochrane], 130 RCTs, n=8,341). Pain at rest is reduced by 19% at 24 h (MD -5/100; 95%CI -4 to -7) (82 RCTs; n=5,004) and at 48 h by 22 % (MD -5/100; 95%CI -3 to -7) (49 RCTs, n=2,962). Pain during movement is reduced in a similar way. Furthermore, PONV is reduced to a minor degree (23 % vs 27 %; RR 0.88; 95%CI 0.81 to 0.96) (NNT 24; 95%CI 16 to 54) (95 RCTs, n=5,965). The incidence of adverse events with ketamine (5%) versus placebo (4%) is similar (RR 1.2; 95%CI 0.95 to 1.4) (105 RCTs, n=6,538). A dose-dependent analgesic effect is not apparent.

Multiple further systematic reviews in subgroups have been performed with significant overlap of RCTs included.

Adding ketamine to an opioid in the PCA pump has similar benefits to the pooled data above on pain at rest at 24 h (WMD 21.1/100; 98%CI 21.8 to 20.39) (9 RCTs, n=595) and opioid consumption (-28%) (7 RCTs, n=495) and PONV (-44%) (7 RCTs, n=435) (Assouline 2016 **Level I** [PRISMA], 19 RCTS, n=1,453). Respiratory depression (RR 0.31; 98%CI 0.06 to 1.51) (9 RCTs, n=871) and hallucinations (OR 1.16; 98%CI 0.47 to 2.79) (7 RCTs, n=690) are not increased. A parallel meta-analysis on ketamine added to morphine or hydromorphone PCA confirms these results (Wang 2016a **Level I** [PRISMA], 36 RCTs, n=2,502) (12 RCTs overlap).

Morphine/ketamine vs higher doses of morphine alone improves analgesia (MD 2.19/10; 95%CI 1.24 to 3.13) and wakefulness (MD -1.53/10; 95%CI -2.67 to -0.40) and reduces PONV (OR 3.71; 95%CI 2.37 to 5.80) and need for nonopioid rescue analgesia (Ding 2014 **Level I**, 7 RCTS, n=492).

Subanaesthetic doses of IM ketamine (escalating from 5 to 25 mg) injected two to three times 17 h to 4 h before cancer surgery reduced postoperative pain and morphine consumption in comparison to a single injection 4 h before surgery and placebo (Rakhman 2011 **Level II**, n=120, JS 5).

Results with regard to specific types of surgery:

- After thoracotomy, addition of ketamine to IV morphine PCA is opioid-sparing and improved analgesia in all RCTs and increases patient satisfaction in one (Mathews 2012 **Level I**, 5 RCTs, n=243). Improved respiratory outcomes (oxygen saturations and $PaCO_2$) are found in the RCTs assessing these parameters (2 RCTs, n=89). IV ketamine/fentanyl PCA resulted in comparable analgesia to thoracic epidural analgesia (Tseng 2019 **Level II**, n=70, JS 3).
- After knee arthroscopy, IV ketamine reduces pain intensity and opioid requirements as well as malonaldehyde levels as a measure of reperfusion injury (SMD -0.63; 95%CI -1.05 to -0.2) (2 RCTs, n=90), but not PONV (Pan 2019 **Level I** [PRISMA], 7 RCTs, n=300).
- After laparoscopic cholecystectomy, IV ketamine reduces pain intensity and opioid requirements at all time points up to 48 h, while reducing the incidence of PONV, pruritus and ileus (Zhu 2018a **Level I**, 6 RCTs, n=294)**;** Ye 2017 **Level I**, 5 RCTs, n=212) (5 RCTs overlap).
- After Caesarean section under spinal anaesthesia (7 RCTs, n=562), but not under general anaesthesia (5 RCTs, n=391), parenteral ketamine improves pain intensity at 2 h, prolongs time to first analgesic request and reduces opioid requirements without increasing adverse effects except for diplopia in one RCT and nystagmus in 2 RCTs (Heesen 2015 **Level I** [PRISMA], 12 RCTs, n=953).
- After spinal surgery, ketamine reduces pain intensity and opioid requirements for 24 h without increased adverse effects (Pendi 2018 **Level I**, 14 RCTs, n=649). After spinal fusion surgery, perioperative IV ketamine bolus and infusion vs placebo resulted in improved long-term outcomes 1 y after surgery with reduced oral morphine (0 mg vs 20 mg) and other analgesic use, better pain relief at rest and on mobilisation (MD -17/100; 95%CI −30 to −3) and higher rate of return to work (43% vs 28%) (Nielsen 2019 **Level II**, n=147, JS 4).
- After laparoscopic gastric banding in obese patients, intraoperative ketamine infusion reduced pain and PCA opioid requirements (Andersen 2014b **Level I**, 1 RCT, n=60).

Subsequent to these meta-analyses, multiple further RCTs studying the same issue have been performed; overall the outcomes from these studies do not affect the existing conclusions and they are therefore not referenced here.

Low-dose parenteral ketamine may also improve analgesia in patients with opioid-induced tolerance or hyperalgesia. After spinal fusion in opioid-tolerant patients, use of a continuous ketamine infusion resulted in significantly less pain but did not reduce PCA opioid requirements

in one RCT (Urban 2008 **Level II**, n=24, JS 4), however its use reduced opioid requirements and pain scores in the early postoperative period and at 6 wk in another (Loftus 2010 **Level II**, n=101, JS 4). Another trial in the same setting found reduced morphine requirements over 24 h (MD -42 mg; 95%CI -59 to -25), reduced sedation and improved function and disability at 6 mth (Nielsen 2017 **Level II**, n=150, JS 5). Similar results were found after noncancer surgery (Barreveld 2013b **Level II**, n=64, JS 5). A preoperative ketamine bolus for extracorporeal shock-wave lithotripsy reduced opioid requirements in chronic opioid users on low and high doses (Gharaei 2013 **Level II**, n=190, JS 4). However, when opioid-tolerant patients had epidural analgesia and IV PCA after spinal surgery, the addition of ketamine bolus and 24 h infusion conveyed no further benefit vs placebo (Subramaniam 2011 **Level II**, n=30, JS 5); the patients in this study also received gabapentin and antidepressants.

After remifentanil based anaesthesia, perioperative systemic ketamine reduces the development of acute tolerance/OIH associated with remifentanil use (Garcia-Henares 2018 **Level I** [PRISMA], 12 RCTs, n=569). This assessment is based on reduced postoperative pain scores and opioid requirements and increased time to first analgesic request and satisfaction scores in the NMDA-receptor antagonist vs the placebo groups but not on QST.

Use of a low-dose (0.05 mg/kg/h) IV ketamine infusion 24 h postoperatively significantly reduced pain scores (over 48 h) in patients receiving epidural ropivacaine and morphine analgesia following thoracotomy (Suzuki 2006 **Level II**, n=49, JS 5). However, this was not confirmed by a subsequent study, where the addition of IV infusion of ketamine 0.09 mg/kg/h for 48 h to epidural analgesia added no benefit (Joseph 2012 **Level II**, n=60, JS 5).

Perioperative ketamine vs placebo significantly reduces the incidence of CPSP at 3 mth (5 RCTs, n unspecified) but only when administered for >24 h (OR 0.37; 95%CI 0.14 to 0.98) (Chaparro 2013 **Level I** [Cochrane] 14 RCTs [ketamine], n=1,388). At 6 mth (10 RCTs, n=516), perioperative ketamine reduces CPSP (OR 0.63; 95%CI 0.47 to 0.83), which remains significant when infused for <24 h (OR 0.45; 95 %CI 0.26 to 0.78). These effects were predominantly in abdominal surgery. Another meta-analysis found a benefit of perioperative IV ketamine vs placebo in reducing the incidence of CPSP at 3 mth (RR 0.74; 95%CI 0.60 to 0.93) (NNT 12), 6 mth (RR 0.70; 95%CI 0.50 to 0.98) (NNT 14) but not at 12 mth postoperatively (McNicol 2014 **Level I**, 14 RCTs [IV route], n=1,586) (11 RCTs overlap); such beneficial effects were not found with epidural administration of ketamine (3 RCTs, n=302). A subsequent meta-analysis found a benefit only at one mth, but is based on a much smaller number of included RCTs and speculates about the potential benefits of ketamine infusion >72 h and the role of epidural administration (Klatt 2015 **Level I** [PRISMA], 10 RCTs, n=784) (6 RCTs overlap with Chaparro 2013, all 10 RCTs overlap with McNicol 2014).

Ketamine has an effect on the regulation of inflammation by inhibiting inflammatory cell recruitment, cytokine production and downregulating inflammatory mediators (Loix 2011 **NR**). Intraoperative administration of ketamine has an inhibitory effect on the early postoperative IL-6 inflammatory response (MD -71 pg/mL; 95%CI -101 to -41) (Dale 2012 **Level I** [PRISMA], 6 RCTs, n=331).

Other acute pain indications

IV ketamine pretreatment reduces pain from propofol injection vs no pretreatment (OR 0.52; 95%CI 0.46 to 0.57) (Jalota 2011 **Level I**, 7 RCTs, n=910).

Ketamine has also some analgesic efficacy in burns patients (McGuinness 2011 **Level I**, 4 RCTs, n=67) (see also Section 8.5).

In the ICU, ketamine acts as a potent analgesic, sedative agent and bronchodilator with positive effects on haemodynamics (Patanwala 2017 **Level IV SR** [PRISMA], 6 RCTs, n=223 & 6 studies) (see also 8.10.5.5).

Low dose ketamine 0.1 to 0.3 mg/kg IV is considered a safe and efficacious analgesic in the ED either as single therapy or in combination with IV morphine 0.1 mg/kg (Karlow 2018 **Level I**

[PRISMA], 3 RCTs, n=261; Ghate 2018 **Level IV SR** [PRISMA], 6 RCTs, n=544 and 2 studies, n=65) (2 RCTs overlap). See also Section 8.11.1.4.

Ketamine is also a safe and effective analgesic for pain due to trauma in the prehospital setting (Jennings 2011 **Level IV SR**, 2 RCTs & 4 studies, n=340). See also Section 8.12.2.4.

Guidelines for the use of ketamine infusions in acute pain support its use in painful surgery, for opioid-dependent or opioid-tolerant patients undergoing surgery or with acute or chronic sickle cell pain and possibly for patients with sleep apnoea to limit opioid use (Schwenk 2018 **GL**).

Adverse effects with short-term systemic administration of ketamine

Overall, CNS adverse events (eg hallucinations and nightmares) were increased vs placebo in 52 studies, while 53 studies reported no increase (Brinck 2018 **Level I** [Cochrane], 130 RCTs, n=8,341). Pooled incidence of CNS adverse effects is not increased (RR 1.2; 95%CI 0.95 to 1.4) (105 RCTs, n=6,538). The incidence of hallucinations is reported as not increased when ketamine is combined with the opioid in a PCA pump (OR 1.16; 98%CI 0.47 to 2.79) (7 RCTs, n=690) (Assouline 2016 **Level I** [PRISMA], 19 RCTS, n=1,453).

The incidence can be reduced with a gradual dose increase (Okamoto 2013 **Level IV**, n=46). For IV administration, slow IV infusion of 0.3 mg/kg ketamine resulted in lower rates of CNS adverse effects than IV bolus injection (Clattenburg 2018 **Level II**, n=62, JS 5; Motov 2017 **Level II**, n=48, JS 5).

Contrary to common beliefs, IV ketamine does not increase intracranial pressure or reduce cranial perfusion pressure vs opioids (Wang 2014 **Level I**, 5 RCTs, n=198). This is also true for patients with nontraumatic neurological diseases (Zeiler 2014 **Level IV SR**, 16 studies, n=127 [adult] & n=87 [children]).

Chronic pain

Ketamine has efficacy in treatment of chronic neuropathic pain (15 of 23 RCTs positive [ketamine]) (Aiyer 2018 **Level I** [PRISMA], 58 RCTs, n unspecified).

IV ketamine is superior to placebo and comparable to IV lidocaine and IV alfentanil in the treatment of pain after SCI (Teasell 2010 **Level I**, 2 RCTs [ketamine], n=19). See also Section 8.2.1.

IV ketamine reduces phantom limb pain short-term with some possible long-term benefit (Alviar 2016 **Level I** [Cochrane], 2 RCTs [ketamine], n=31; McCormick 2014 **Level I**, 4 RCTs, n=107) (2 RCTs overlap). See also Section 8.1.5.2.

Ketamine by various routes of administration (IV, oral, topical) is also a successful treatment for Complex Regional Pain Syndrome (CRPS) based on limited evidence (Zhao 2018 **Level III-2 SR**, 1 RCT & 14 studies, n=258; Azari 2012 **Level IV SR**, 3 RCTS & 16 studies, n unspecified).

In view of the risks described below, current use of ketamine to treat chronic pain should be restricted to therapy-resistant severe neuropathic pain (Niesters 2014a **NR**; Tawfic 2013 **NR**); recent evidence-based guidelines outline a cautious approach with possibly best indications in spinal cord injury pain and CRPS (Cohen 2018 **GL**). A draft of a practice guideline has been published by FPMANZCA (FPMANZCA 2020 **GL**).

Cancer pain

Ketamine is a viable therapeutic option in treating refractory cancer pain despite limitations in the data available (Bredlau 2013 **Level IV SR**, 5 RCTs and 6 studies, n=483); however, the largest RCT included showed no clinical benefit when ketamine was added to opioids for cancer-pain treatment (Hardy 2012 **Level II**, n=187, JS 5). A subsequent Cochrane review of ketamine as an adjunct to opioids in cancer pain excluded most of the RCTs considered above and regards the current evidence as insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of refractory cancer pain (Bell 2017 **Level I** [Cochrane] 3 RCTs, n=217). See also Section 8.9.3.3.

Adverse effects with long-term systemic administration of ketamine

Ketamine has an abuse potential (Morgan 2012 **NR**) with highest abuse rates in South-East Asia and China (Liu 2016 **NR**; Kalsi 2011 **NR**). Heavy use of ketamine has consequences on cognitive and emotional function (Morgan 2010 **NR**) and there are increasing consequences including traffic accidents under its influence (Liu 2016 **NR**). Acute toxicity leads to confusion, drowsiness, or transient loss of consciousness, while symptoms of chronic toxicity are "ketamine cystitis" and chronic abdominal pain (Yiu-Cheung 2012 **NR**) as well as hepatotoxicity. The latter issues need to be considered when using ketamine in a chronic setting therapeutically (Bell 2012 **NR**) and may limit its indications (Cohen 2018 **GL**; Niesters 2014a **NR**).

Other routes of systemic administration and bioavailability

Ketamine is most commonly administered as a continuous low-dose IV infusion, however SC infusion is also used, especially in palliative care, with a bioavailability (similar to IM) of approximately 90% (Clements 1982 **PK**). Sublingual (SL), IN and TD routes have also been used for acute pain management (Peltoniemi 2016 **NR PK**) (see Chapter 5).

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 SL ketamine wafer achieved rapid absorption with a bioavailability of 29% (Rolan 2014 **PK**).

4.6.1.2 | Dextromethorphan

In a meta-analysis of experimental studies (oral administration 11 RCTs; IV administration 1 RCT) (mean dose 0.92 mg/kg [range 0.17 to 2.71 mg/kg]), dextromethorphan has no effect on area of hyperalgesia (4 RCTs) nor on pain intensity (SMD 0.07; 95%CI -0.21 to 0.34) (10 RCTs, n=132) (Thompson 2019 **Level I EH** (PRISMA), 70 RCTs, n=1,069). However, dextromethorphan (30 mg oral) in a model of primary and secondary hyperalgesia (freeze-injury pain model) had antihyperalgesic effects on both phenomena, while it has no anti-nociceptive effect in areas of healthy skin (Martin 2019a **Level II EH**, n=20, JS 5).

In postoperative pain, dextromethorphan reduces pain at 1 h (MD -1.60/10; 95%CI -1.89 to -1.31) (13 RCTs, n=884), 4 to 6 h and 24 h as well as opioid requirements (IV MED MD -10.51 mg; 95%CI -16.48 to -4.53) (14 RCTs, n=848) (King 2016 **Level I**, 21 RCTs, n unspecified).

As dextromethorphan is metabolised by CYP2D6 to the inactive metabolite dextrorphan, the effect of the CYP2D6 inhibitor quinidine before dextromethorphan 50 mg oral administration has been assessed in knee ligament surgery (Ehret 2013 **Level II**, n=48, JS 4). Dextromethorphan concentrations were higher after quinidine than after placebo and resulted in lower rescue analgesia requirements. Oral dextromethorphan/quinidine provided superior pain relief vs placebo in diabetic polyneuropathy (Shaibani 2012 **Level II**, n=379, JS 3).

Dextromethorphan (120 to 180 mg oral administration) reduces chronic phantom limb pain vs placebo (Alviar 2016 **Level I** [Cochrane], 1 RCT [dextromethorphan]: Ben Abraham 2003 **Level II**, n=10 [triple phase cross over], JS 3).

Dextromethorphan may have efficacy in chronic neuropathic pain (4 of 6 RCTs), possibly with less benefit in PHN (Aiyer 2018 **Level I** [PRISMA], 58 RCTs, n unspecified). After IV ketamine treatment of neuropathic pain, oral dextromethorphan extended treatment effects for one mth vs placebo (Martin 2019b **Level II**, n=60, JS 4).

Dextromethorphan oral therapy (titrated to 480 mg/d) for 5 wk was not effective in reversing methadone-induced hyperalgesia (Compton 2008 **Level III-1**).

4.6.1.3 | Magnesium

Magnesium is regarded as an NMDA-receptor antagonist as its primary mechanism of action; however, magnesium also blocks calcium channels and modulates potassium channels and may have an antinociceptive effect through the activation of the nitric oxide (NO) pathway (Srebro 2016 **NR**). It has also anti-inflammatory effects by reducing IL-6 and TNF-alpha plasma levels in the postoperative setting, which might contribute to the effects described here (Aryana 2014 **Level II**, n=90, JS 4).

Magnesium IV as an adjunct to morphine IV analgesia has an opioid-sparing effect (MED WMD -7.4 mg; 95%CI -9.4 to -5.4) without reducing PONV but with improved pain scores at 4–6 h (Murphy 2013 **Level I**, 22 RCTs, n=1,177). This is in line with a parallel meta-analysis, which also describes an opioid-sparing effect (MED WMD -10.52 mg; 99%CI -13.50 to -7.54) and reduction of pain at rest (4 and 24 h) and on movement (24 h) (De Oliveira 2013c **Level I** [PRISMA], 20 RCTs, n=1,257) (most RCTs overlap). Another meta-analysis published in the same year comes to similar conclusions and found no significant adverse effects (Albrecht 2013 **Level I**, 25 RCTs, n=1,461) (most RCTs overlap).

Subsequent to these three meta-analyses, multiple further meta-analyses and RCTs exploring the same issues after different types of surgery or anaesthesia have been performed with significant overlap of RCTs included:

- After orthopaedic surgery, IV magnesium reduces postoperative analgesic consumption, PONV and shivering (Peng 2018 **Level I** [PRISMA], 11 RCTs, n=535). Pain intensity is reduced in 6 of 11 RCTs;
- After laparoscopic cholecystectomy, IV magnesium reduces pain intensity at 2 and 8 h and analgesic consumption (Chen 2018a **Level I**, 4 RCTs, n=463);
- After Caesarean section, a qualitative systematic review showed that IV magnesium may reduce postoperative pain intensity (McKeown 2017 **Level I**, 7 RCTs, n=530);
- In paediatric tonsillectomy, magnesium administered by local infiltration or IV (bolus infusion) has analgesic effects (Xie 2017 **Level I** [PRISMA], 10 RCTs n=665; Cho 2018 **Level I** [PRISMA], 10 RCTs, n=615) (9 RCTs overlap). See also Section 10.4.7.2;
- After spinal anaesthesia, IV magnesium prolonged the duration of sensory block for abdominal hysterectomy and reduced postoperative pain scores in the first 4 h after surgery (Kahraman 2014 **Level II**, n=40, JS 5). After spinal anaesthesia for umbilical hernia repair, IV magnesium prolonged time to first rescue analgesia and was opioid-sparing in the first 24 h after surgery (Kumar 2013 **Level II**, n=60, JS 5). This was also found after spinal anaesthesia for THA, where IV magnesium reduced postoperative pain scores and opioid requirements for 48 h, while increasing serum magnesium concentrations (Hwang 2010 **Level II**, n=40, JS 5). However, IV magnesium did not change magnesium concentrations in the CSF (Mercieri 2012 **Level II**, n=45, JS 3).

Subsequent to these meta-analyses, multiple further RCTs studying the same issue have been performed; overall the outcomes from these studies do not affect the existing conclusions and they are therefore not referenced here.

Magnesium reduces the development of acute tolerance/OIH associated with remifentanil use (Wu 2015 **Level I** [QUOROM], 5 RCTs [magnesium], n=729)

Combining ketamine with IV magnesium reduced 48 h morphine consumption by 30% vs ketamine alone after scoliosis surgery (Jabbour 2014 **Level II**, n=50, JS 5). While pain scores were not different, sleep quality and patient satisfaction were improved with the combination treatment.

IV magnesium may also have other beneficial effects on postoperative recovery; after segmental mastectomy in an outpatient setting, patients receiving IV magnesium had better quality of recovery (QoR) scores at 24 h vs saline (MD 24/40; 99%CI 3 to 33) and reduced opioid requirements after discharge (De Oliveira 2013a **Level II**, n=50, JS 5). There were significant linear relationships between the postoperative systemic magnesium concentrations and 24 h postoperative QoR scores as well as with pain burden (inverse).

IV magnesium sulphate 4 g attenuated tourniquet pain in healthy volunteers (Satsumae 2013 **Level II EH**, n=24, JS 5).

IV magnesium in treatment of acute migraine attacks vs placebo or active comparators is superior at time points 15-45 min (OR 0.23; 95%CI 0.09 to 0.58) (6 RCTs), 2 h (OR 0.20; 95%CI 0.10 to 0.40) [5 RCTs] and 24 h (OR 0.25; 95%CI 0.10 to 0.60) [4 RCTs] (Chiu 2016 **Level I** [PRISMA], 11 RCTs, n=948).

IV magnesium was non-inferior to IV dexamethasone for the prevention of postoperative sore throat after lumbar spinal surgery in the prone position (Park 2015 **Level II**, n=146, JS 5).

IV magnesium has only at best anecdotal evidence for an effect on any outcome of Irukandji syndrome, caused by jellyfish sting in Northern Queensland (Rathbone 2017 **Level IV SR** 1 RCT & 8 studies, n unspecified); the only RCT included showed no beneficial effect (McCullagh 2012 **Level II**, n=39, JS 5).

Oral magnesium daily for 4 wk had no beneficial effect in the treatment of neuropathic pain (Pickering 2011 **Level II**, n=45, JS 5). IV or oral magnesium therapy has been shown to have no effect on reducing painful crisis and hospital LOS in treating sickle cell disease (Than 2019 **Level I** [Cochrane], 5 RCTs, n=386). Oral magnesium (65 mg elemental/d) was also not improving analgesia when added in cancer pain patients treated with oral morphine (Baaklini 2017 **Level** II, n=43, JS 5). IV magnesium vs IV lidocaine provided inferior analgesia for propofol injection pain; IV magnesium/IV lidocaine offered no advantage over IV lidocaine alone (Galgon 2015 **Level II**, n=200, JS 5).

See Section 5.7.1.4 for magnesium use via the IT route and Section 10.4.7.2 for paediatric use.

4.6.1.4 | Amantadine and memantine

A bolus dose of IV amantadine had no effect on postoperative analgesia after abdominal hysterectomy (Gottschalk 2001 **Level II**, n=30, JS 4). However, after radical prostatectomy, perioperative oral amantadine reduced morphine consumption, wound pain on palpation and bladder spasms (Snijdelaar 2004 **Level II**, n=24, JS 4). After spinal surgery, premedication with oral amantadine reduced not only intraoperative fentanyl requirements but also postoperative pain intensity and opioid requirements in the first 48 h by 25% (Bujak-Gizycka 2012 **Level II**, n=60, JS 5).

Oral memantine shows analgesic effects in acute [4 studies], but not in chronic phantom limb pain [4 RCTs] (Loy 2016 **Level IV SR**, 5 RCTs, 2 case series & 1 case report, n unspecified).

Memantine administered perioperatively was not effective in reducing the incidence of postmastectomy pain syndrome (Eisenberg 2007 **Level II**, n=22, JS 5); however, a subsequent trial showed a reduction in postmastectomy pain, analgesic consumption and better emotional state at 3 mths (Morel 2016 **Level II**, n=43, JS 5).

Memantine may have some benefits in neuropathic pain (Pickering 2018 **NR**).

KEY MESSAGES

1. Perioperative IV ketamine reduces opioid consumption, pain intensity and postoperative nausea and vomiting compared to placebo (**S**) (**Level I** [Cochrane Review]); similar outcomes are achieved when ketamine is added to an opioid in a PCA pump (**S**) (**Level I** [PRISMA]).
2. Perioperative IV ketamine reduces the incidence of chronic postsurgical pain in selected procedures (**S**) (**Level I** [Cochrane Review]).
3. NMDA-receptor antagonists reduce the development of acute tolerance/opioid-induced hyperalgesia associated with remifentanil use (**S**) (**Level I** [PRISMA]).
4. IV ketamine reduces ischaemic pain intensity in critical limb ischaemia (**N**) (**Level I** [PRISMA]).
5. IV magnesium as an adjunct to morphine analgesia has an opioid-sparing effect and improves pain scores (**S**) (**Level I** [PRISMA]).
6. IV magnesium is effective in treatment of acute migraine attacks (**N**) (**Level I** [PRISMA]).
7. IV ketamine is effective in the treatment of neuropathic pain following spinal cord injury (**U**) (**Level I**).
8. Morphine/ketamine compared with higher doses of morphine alone improves analgesia and reduces sedation and postoperative nausea and vomiting in postoperative patients (**U**) (**Level I**).
9. IV ketamine does not increase intracranial pressure or reduce cranial perfusion pressure compared to opioids (**U**) (**Level I**).
10. Perioperative dextromethorphan reduces opioid consumption and pain intensity compared to placebo (**N**) (**Level I**)
11. Ketamine is a safe and effective analgesic in the prehospital setting (**U**) (**Level II**).
12. Ketamine reduces postoperative pain and opioid requirements in opioid-tolerant patients (**S**) (**Level II**).
13. IV magnesium extends the duration of sensory block with spinal anaesthesia and reduces subsequent postoperative pain (**N**) (**Level II**).

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

☑ Increasing rates of ketamine abuse are reported, in particular from South-East Asia and China (**S**).

☑ Ketamine toxicity leads to cognitive impairment and abuse to chronic organ toxicity (bladder, liver) (**U**).

4.6.2 | Regional NMDA-receptor antagonists

4.6.2.1 | Ketamine

Neuraxial

Some commercially available preparations of ketamine have a low pH (3.5 to 5.5) and contain an untested preservative (benzethonium chloride) and thus cannot be recommended for IT use in humans (de Lima 2000 **NR**; Hodgson 1999 **NR**). Subarachnoid administration of S(+)-ketamine without preservative caused histological lesions on the spinal cord and meninges in dogs (Gomes 2011 **BS**). Concerns of local neurotoxicity *in vitro* continue to limit the use of neuraxial ketamine, in particular when combined with lidocaine (Werdehausen 2011 **NR**).

The addition of IT racemic ketamine to bupivacaine did not prolong postoperative analgesia or reduce analgesic requirements but led to significantly more nausea and vomiting, sedation, dizziness, nystagmus and "strange feelings" (Kathirvel 2000 **Level II**, n=30, JS 2). IT S(+)-ketamine with bupivacaine for Caesarean section decreased time to onset and increased spread of the block but did not prolong duration vs fentanyl (Unlugenc 2006 **Level II**, n=90, JS 5). However, IT ketamine/morphine was superior to morphine or ketamine alone added to IT bupivacaine for major abdominal cancer surgery with regard to pain intensity, opioid requirements and time to rescue analgesia (Abd El-Rahman 2018b **Level II**, n=90, JS 3).

The combination of epidural ketamine with epidural opioid-based (local anaesthetic) solutions improves pain relief and may reduce overall opioid requirements without increasing the incidence of adverse effects (Subramaniam 2004 **Level I,** 8 RCTs [epidural], n=513; Walker 2002 **Level I**, 4 RCTs [epidural], n=211). Ketamine IV may be as effective as epidural ketamine in reducing hyperalgesia. Epidural racemic ketamine improved early postoperative analgesia when used with bupivacaine for lower limb amputations, although pain at 1 y was not different; perioperative opioids were not used (Wilson 2008 **Level II**, n=47, JS 5).

Ketamine 0.25 to 0.5 mg/kg added to caudal local anaesthetic prolongs time to first analgesic request by a median difference of 5.6 h without prolonged motor block (Schnabel 2011 **Level I** [PRISMA], 13 RCTs, n=884). Although many adverse effects were more frequent in the ketamine group, there was no significant difference to placebo. Caudal ketamine prolonged analgesia when administered with caudal bupivacaine but was less effective than midazolam or neostigmine as caudal adjuvants (Kumar 2005 **Level II**, n=80, JS 5). See also Section 10.4.7.1.

Peripheral sites

Use of ketamine alone or with local anaesthesia for PNB or local infiltration shows contradictory results, possibly due systemic effects. Systemic comparators are not included in most RCTs.

No analgesic benefit for PNB was shown in brachial plexus block for arm surgery (Lee 2002 **Level II**, n=51, JS 4), IA injection (where IV ketamine provided better analgesia) (Rosseland 2003 **Level II**, n=77, JS 5) or wound infiltration such as following Caesarean section (Zohar 2002 **Level II**, n=50, JS 5) or inguinal hernia repair (Clerc 2005 **Level II**, n=36, JS 2). Adding ketamine to lidocaine IVRA did not result in better pain relief vs IV ketamine (Viscomi 2009 **Level II**, n=36, JS 4). When added to lidocaine for axillary brachial plexus block, ketamine (50 mg) only modestly increased duration of sensory and motor block vs placebo (114.8 12.5 min v. 106.2 7.9 min), much less than dexamethasone (174.4 13.1 min) (Zaman 2017 **Level II**, n=78, JS 5). Significant nystagmus, increased heart rate and blood pressure were observed in the ketamine group.

However, in pectoral block for mastectomy, ketamine 1 mg/kg added to 30 ml 0.25% bupivacaine vs bupivacaine alone prolonged time to first analgesic request and reduced opioid requirements (Othman 2016 **Level II**, n=60, JS 3). IA ketamine 1 mg/kg provided analgesia superior to placebo, but inferior to IA ketamine 0.5 mg/kg in 20 ml 0.25% levobupivacaine after

arthroscopic meniscectomy (Isik 2015 **Level II**, n=6, JS 3). In circumcision pain scores were lower with preincisional ketamine vs saline (Tan 2007 **Level II**, n=40, JS 4). Adding 2 mg/kg ketamine to 40 ml bupivacaine 0.25% resulted in comparable analgesia to adding 2 mcg/kg dexmedetomidine to local wound infiltration after abdominal hysterectomy; both mixtures were superior to bupivacaine alone (Mohamed 2018 **Level II**, n=90, JS 5). Following thyroidectomy, wound infiltration with ketamine 1 mg/kg provided superior analgesia to IM ketamine 1 mg/kg and both groups were superior to placebo (Abd El-Rahman 2018a **Level II**, n=90, JS 5). After rhinoplasty, the addition of ketamine 0.5 mg/kg to lidocaine for submucosal infiltration provided superior analgesia to lidocaine alone with both being superior to placebo (Sanli 2016 **Level II**, n=90, JS 4).

Topical administration

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

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

Topical ketamine-amitriptyline did not reduce chemotherapy-induced peripheral neuropathic pain (Gewandter 2014 **Level II**, n=462, JS 5).

4.6.2.2 | Magnesium

Magnesium influences neuronal calcium influx and may exert an analgesic effect on NMDA receptors in the spinal cord (Bailard 2014 **NR**). The long-term effects of perineural or neuraxial magnesium have not been clarified.

Neuraxial magnesium for Caesarean section prolongs duration of sensory and motor block, time to first rescue analgesic requirement and reduces pain intensity and analgesic requirements without an effect on PONV, pruritus, hypotension, shivering or sedation (Wang 2017a **Level I** [PRISMA], 9 RCTs, n=827).

IT magnesium combined with lipophilic opioid, with or without local anaesthetic, prolongs the duration of spinal analgesia in nonobstetric populations, too (SMD 1.38; 95%CI 0.6 to 2.11) (Morrison 2013 **Level I**, 15 RCTs, n=980). There is no increase in adverse effects. There was a high degree of heterogeneity, including magnesium dose, making any firm conclusion difficult. This was supported by a parallel meta-analysis (Pascual-Ramirez 2013 **Level I**, 12 RCTs, n=817) (9 RCTs overlap).

Epidural magnesium (50 mg) added to bupivacaine/morphine (2 mg) improved analgesia after thoracotomy for the first 4 h and reduced rescue analgesia requirements (Farzanegan 2018 **Level III-1**, n=80).

Magnesium added to perineural block prolongs analgesia (MD 125 min; 95%CI 65 to 184), sensory and motor block (Li 2016b **Level I** [PRISMA], 7 RCTs, n=493). Subsequent RCTs have confirmed these findings in femoral nerve block in the prehospital setting (Jebali 2018 **Level II**, n=48, JS 4), TAPB after abdominal hysterectomy (Abd-Elsalam 2017 **Level II**, n=60, JS 4) and sciatic nerve block for toe amputation (Sun 2017a **Level II**, n=70, JS 5), The mechanism of action of magnesium at perineural sites is uncertain and safety and outcome data are limited suggesting caution should be exercised (Bailard 2014 **NR**).

Oral topical magnesium reduces the incidence (RR 0.22; 95%CI 0.12 to 0.39 [at 24 h postoperatively]) and severity of postoperative sore throat after orotracheal intubation (Singh 2019 **Level I** [PRISMA] 7 RCTs, n=726).

Intra-articular (IA) magnesium versus placebo after arthroscopic surgery improves pain control [5 RCTs] and prolongs time to first analgesic request [4 RCTs] (Zeng 2016 **Level I** [PRISMA], 8 RCTs, n=513). The combination magnesium/bupivacaine versus bupivacaine only prolongs only time to first analgesic request [4 RCTs]. Magnesium vs bupivacaine results in similar analgesia [3 RCTs]. No relevant adverse effects were described in any study. Magnesium/levobupivacaine vs levobupivacaine alone and vs placebo after arthroscopic meniscectomy reduced pain intensity and rescue analgesic requirements (Kizilcik 2017 **Level II**, n=96, JS 4).

Magnesium added to lidocaine IVRA improved intra and postoperative analgesia and tourniquet tolerance (Kashefi 2008 **Level II**, n=40, JS 4; Turan 2005 **Level II**, n=30, JS 4).

KEY MESSAGES

1. Neuraxial magnesium reduces pain intensity and analgesic requirements after Caesarean section (**N**) (**Level I** [PRISMA].
2. Oral topical magnesium or ketamine (as gargle or lozenge) reduce the incidence of postoperative sore throat (**N**) (**Level I** [PRISMA].
3. Intra-articular magnesium improves analgesia after arthroscopic surgery compared to placebo (**N**) (**Level I** [PRISMA].
4. Magnesium added to local anaesthetics in peripheral nerve blocks prolongs sensory block and analgesic effects (**N**) (**Level I** [PRISMA].
5. Epidural ketamine (without preservative) added to opioid-based epidural analgesia regimens improves pain relief without reducing adverse effects (**U**) (**Level I**).
6. Caudal ketamine in children, in combination with local anaesthetic or as the sole medicine, improved and prolonged analgesia with few adverse effects (**U**) (**Level I**).

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

☑ Variable results on regional and topical administration of ketamine and magnesium may reflect systemic effects (**N**).

4.7 | Antidepressant medicines

4.7.1 | Acute pain

There are limited published data on the use of antidepressants in the management of acute nociceptive and neuropathic pain.

4.7.1.1 | Tricyclic antidepressants

Amitriptyline given to patients with acute herpes zoster reduced the incidence of postherpetic neuralgia at 6 mth (Bowsher 1997 **Level II**, n=80, JS 5).

Desipramine, but not amitriptyline, given prior to dental surgery increased and prolonged the analgesic effect of a single dose of morphine but both had no analgesic effect on their own (Levine 1986 **Level II**, n=30, JS 3). When used for a fortnight in experimental pain, desipramine had no effect on pain or hyperalgesia (Wallace 2002 **Level II EH**, n=13, JS 4). Amitriptyline given after orthopaedic surgery did not improve opioid analgesia vs placebo (Kerrick 1993 **Level II**, n=28, JS 5).

4.7.1.2 | Serotonin–norepinephrine-reuptake inhibitors

After total knee joint replacement duloxetine (60 mg preoperative and on POD 1) had an opioid-sparing effect (35%) (Ho 2010 **Level II**, n=50, JS 5). In patients with an increased Central Sensitisation Inventory (CSI), duloxetine (30 mg before surgery and for 6 wk thereafter) improved pain control, physical and emotional functioning and patient satisfaction with analgesia for 2 to 12 wk after TKA (Koh 2019 **Level II**, n=40, JS 5). However, duloxetine (60 mg for 2 wk) had no effect on subacute pain with ambulation after TKA, when used as a component of a multimodal analgesia regimen (YaDeau 2016 **Level II**, n=106, JS 5). Venlafaxine (37.5 mg) was as effective as gabapentin (300 mg) in reducing pain at rest and analgesic requirements, when given perioperatively for 10 d in mastectomy (Amr 2010 **Level II**, n=150, JS 4). Venlafaxine was inferior to gabapentin in reducing pain on movement; however, at 6 mth postoperatively, fewer patients in the venlafaxine group reported chronic pain or analgesic use.

4.7.1.3 | Selective serotonin-reuptake inhibitors

In patients with high preoperative pain catastrophising scale (PCS) scores, escitalopram (10 mg preoperatively and for 6 d postoperatively) did not reduce pain on mobilisation at 24 h after total knee replacement (Lunn 2015 **Level II**, n=120, JS 5). On POD 2 to 6, pain at rest and mobilisation was lower in the treatment group.

4.7.2 | Chronic pain

Treatment guidelines for chronic neuropathic pain recommend TCAs and SNRIs, but not SSRIs, as first-line treatment in this indication (Finnerup 2015 **GL Level I** [PRISMA], 229 RCTs, n unspecified).

4.7.2.1 | Tricyclic antidepressants

While TCAs are seen as the first-line therapy in neuropathic pain treatment, data are of disappointing quality. None of the supportive studies are of high quality and low risk of bias (Moore 2015a **Level I** [Cochrane], 17 RCTs, n=1,342). Adverse events were increased with amitriptyline (RR 1.5; 95%CI 1.3 to 1.8) (NNH 5.2; 95%CI 3.6 to 9.1). Similarly, imipramine

(Hearn 2014 **Level I** [Cochrane], 5 RCTs, n=168) and nortriptyline are supported only by very low-quality evidence in this indication (Derry 2015b **Level I** [Cochrane], 6 RCTs, n=310).

In elderly patients, TCAs should possibly be avoided as the use of medications with anticholinergic activity increases risk of cognitive impairment and even mortality in this patient group (Fox 2011 **Level III-2**, n=13,004).

4.7.2.2 | Serotonin–norepinephrine-reuptake inhibitors

Duloxetine (60 to 120 mg/d) provides analgesia for diabetic neuropathy (Lunn 2014 **Level I** [Cochrane], 8 RCTs, n=2,728; Hossain 2016 **Level I** [PRISMA], 8 RCTs, n=4,084) (7 RCTs overlap). RCTs supporting the use of venlafaxine in neuropathic pain have a high risk of bias (Gallagher 2015 **Level I** [Cochrane], 6 RCTs, n=460; Aiyer 2017 **Level I** [PRISMA], 13 RCTs, n=851) (6 RCTs overlap). There is no evidence for an effect of milnacipran in neuropathic pain (Derry 2015b **Level I** [Cochrane], 1 unpublished RCT: [NCT01225068], n=40).

SNRIs also have limited analgesic effects in fibromyalgia (Welsch 2018 **Level I** [Cochrane], 18 RCTs, n=7,903). This has been confirmed specifically for milnacipran (Cording 2015 **Level I** [Cochrane], 6 RCTs, n=4,238). Duloxetine and milnacipran have comparable efficacy in this indication (Lee 2016 **Level I** [NMA], 9 RCTs, n=5,140).

4.7.2.3 | Selective serotonin-reuptake inhibitors

There is only limited evidence for the effectiveness of SSRIs in neuropathic pain (Saarto 2007 **Level I** [Cochrane] 61 RCTs, n=3,293). Similarly, there is no unbiased evidence that SSRIs are superior to placebo in treating the key symptoms of fibromyalgia: namely pain, fatigue and sleep problems (Walitt 2015 **Level I** [Cochrane], 7 RCTs, n=383).

4.7.3 | Specific pain conditions

In postherpetic neuralgia, TCAs are less effective than pregabalin and 5% lidocaine medicated plaster (Snedecor 2014 **Level I**, 28 RCTs, n=4,317). In diabetic polyneuropathy, amitriptyline is the least effective of the medications studied with the worst benefit-risk balance, while venlafaxine and duloxetine were the superior antidepressants here (Rudroju 2013 **Level I**, 21 RCTs, n=4,219).

In fibromyalgia, amitriptyline (NNT 4.9) and the serotonin–norepinephrine-reuptake inhibitors (SNRIs) duloxetine and milnacipran (NNT 10) were the most effective antidepressants (Hauser 2012 **Level I**, 35 RCTs, n=6,766).

In chronic headaches, antidepressants are effective in treatment and prophylaxis with better efficacy of TCAs than SSRIs (Jackson 2017 **Level I** [PRISMA], 21 RCTs, n=2,751; Jackson 2010 **Level I** [PRISMA], 37 RCTs, n=3,176). Use of SSRIs and SNRIs for migraine prophylaxis (Banzi 2015 **Level I** [Cochrane], 12 RCTs, n=585) and prevention of chronic tension type headache is not supported by evidence (Banzi 2015 **Level I** [Cochrane], 8 RCTs, n=412).

In chronic low-back pain, antidepressants neither improve pain nor depression (Urquhart 2008 **Level I** [Cochrane], 10 RCTs, n=706); this was confirmed in a subsequent systematic review of pharmacological interventions in this indication (Kuijpers 2011 **Level I**, 5 RCTs, n=303). However, these results are challenged as they did not differentiate between different antidepressants; SNRIs like duloxetine (Williamson 2014 **Level I**, 3 RCTs, n=982) and TCAs may be effective, while SSRIs are not (Staiger 2003 **Level I**, 7 RCTs, n=440).

There is only poor evidence for an analgesic effect of antidepressants in orofacial pain disorders (Martin 2012 **Level I**, 6 RCTs, n=208) and for an analgesic effect of TCAs or SSRIs in rheumatoid arthritis (Richards 2011 **Level I** [Cochrane], 8 RCTs, n=652).

Duloxetine improves WOMAC scores in osteoarthritis to an extent comparable to other first-line treatments for osteoarthritis (eg NSAIDs) (Myers 2014 **Level I**, 3 RCTs, n=775). Duloxetine results in a greater reduction in pain, improved function and patient rated impression of improvement for treatment of osteoarthritis of the knee after 10 to 13 wk of treatment (Wang 2015b **Level I**, 3 RCTs, n=1,011) (2 RCTs overlap). Therefore, duloxetine is a recommended treatment in updated guidelines for osteoarthritis (eg McAlindon 2014 **GL**).

Currently the use of antidepressants for acute neuropathic pain is mainly based on extrapolation of the above data. Clinical experience in chronic pain suggests that TCAs should be started at low doses (eg amitriptyline 5 to 10 mg at night) and subsequent doses increased slowly if needed, in order to minimise the incidence of adverse effects.

KEY MESSAGES

1. In chronic neuropathic pain and fibromyalgia, tricyclic antidepressants and serotonin–noradrenaline-reuptake inhibitor are effective analgesics (**W**) and more effective than selective serotonin-reuptake inhibitors (**U**) (**Level I** [Cochrane Review]).
2. Tricyclic antidepressants are effective in the treatment of chronic headaches (**U**) (**Level I** [PRISMA]).
3. Duloxetine is as effective as other first-line treatments for pain and disability of osteoarthritis (**U**) (**Level I**).
4. Some antidepressants, in particular duloxetine, may be effective in the treatment of chronic low-back pain (**U**) (**Level I**).
5. Perioperative serotonin-noradrenaline reuptake inhibitors reduce acute pain and opioid requirements in a limited number of studies (**U**) (**Level II**).

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

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use tricyclic antidepressants and serotonin–noradrenaline-reuptake inhibitors in the management of acute neuropathic pain (**U**).

☑ To minimise adverse effects, it is advisable to initiate treatment with tricyclic antidepressants at low doses (**U**).

4.8 | Anticonvulsant medicines

4.8.1 | Acute pain

4.8.1.1 | Alpha-2-delta ligands (gabapentinoids)

Efficacy

Gabapentin (250 mg) as the sole analgesic reduces the intensity of postoperative pain (NNT 11; 95%CI 6.4 to 35) and requirements for rescue analgesia (NNT 5.8) vs placebo (Straube 2010 **Level I** [Cochrane], 4 RCTs, n=387). This is only anticonvulsant which has been shown to be effective in acute postoperative pain on its own; the high NNT, inferior to most analgesics used in this setting, suggests that gabapentin is clinically not useful as sole analgesic for postoperative analgesia.

Gabapentin shows a lower reduction of 24 h opioid consumption in RCTs with low risk of bias (MD -3.1 mg; 95%CI -5.6 to -0.5) than in all RCTs (MD -7.31 mg; 95%CI -9.74 to -5.98), similar to pregabalin in a meta-analysis by the same group (Fabritius 2016 **Level I** [PRISMA], 132 RCTs, n=9,498). The opioid-sparing effect is not significant as an add-on to other non-opioids in trials with low risk of bias; in these the risk of serious adverse events is not significantly increased (RR 1.61; 95%CI 0.91 to 2.86). Similar results were found in an earlier meta-analysis of all RCTs of prophylactic gabapentin with an opioid-sparing effect in the first 24 h of 8.44 mg (95%CI 7.26 to 9.62) and reduced postoperative pain scores at multiple time points between 1 and 24 h by 0.71/10 to 1.68/10 (Doleman 2015a **Level I**, 133 RCTs, n=8,655) (significant overlap). These effects increased with increasing pain scores in the control group suggesting more benefit in more painful surgeries. The analysis identified also reduced pre-operative anxiety, postoperative nausea, vomiting and pruritus, and increased patient satisfaction, but also increased sedation. The authors acknowledge that the absolute effects may be overestimated by publication bias and small study effects.

Single and multiple doses of pregabalin for postoperative analgesia reduces 24 h IV morphine consumption by 10.8 mg (95%CI –13.19 to –8.46) (37 RCTS, n=2,423) across all RCTs assessing this outcome, but only by 5.8 mg (95%CI -8.5 to -3.2) (11 RCTs, n=705) in RCTS with low risk of bias (Fabritius 2017 **Level I** [PRISMA], 97 RCT, n=7,201). Other results for low risk of bias studies are that the opioid sparing effect is more pronounced when no other non-opioids are used (MD -13.7 mg; 95%CI -9.6 to -17.8) (2 RCTs, n=120) and the effects are more pronounced with use of a single dose (MD -10.1mg; 95% CI -2.4 to -18.0) (6 RCTs, n=399) than with multiple dosing (MD 2.4mg; 95%CI -0.5 to -4.9) (5 RCTs, n=306). Serious adverse events (SAEs) in the studies with low risk of bias were rare (22/730) and occurred more with pregabalin than placebo (RR 2.9; 95%CI: 1.2 to 6.8); nausea, sedation and headache were not significantly different between the groups.

In a preceding meta-analysis, operations were classified by the authors according to association with 'pronociceptive' mechanisms (acute hyperalgesia) (eg spine surgery, joint arthroplasty, amputations) and those without such mechanisms (eg abdominal laparoscopic surgery, gynaecological procedures) (Eipe 2015 **Level I** [PRISMA], 43 RCTs, n=3,378) (39 RCTs overlap). Pregabalin (150 to 300 mg) reduces pain at rest and on movement more in the first than in the second group (MD -1.09/10; 95%CI -0.37 to -1.80 vs MD -0.45/10; 95%CI 0.13 to -1.03 and MD -0.94/10; 95%CI -0.65 to -1.23 vs MD -0.31/10; 95%CI 0.15 to -0.77). Across all RCTs, there is a reduction of mean analgesic consumption by 16% (pooled ratio of means 0.84; 95%CI 0.79 to 0.91). PONV is reduced with an NNT of 11 (95%CI 7 to 28). Adverse effects include somnolence (RR 1.72; 95%CI 1.08 to 2.72), sedation (RR 1.51; 95%CI 1.16 to 1.96; absolute risk 41/1,000) and visual disturbances (RR 3.08; 95%CI 1.91 to 4.96; absolute risk 10/1,000).

Multiple meta-analyses have looked at perioperative gabapentin and pregabalin (single and multiple doses) in specific types of surgery with significant overlap with the overarching meta-analyses described above:

- In breast cancer surgery, preoperative use of gabapentin or pregabalin reduces acute postoperative pain and opioid consumption with low to very low quality of evidence of no effect on the rate of CPSP (Rai 2017 **Level I** [PRISMA], 12 RCTs, n=516);
- After open hysterectomy, gabapentin reduces postoperative opioid consumption and pain scores (Li 2017d **Level I** [PRISMA], 14 RCTs, n=879);
- After Caesarean section, gabapentin improves pain scores on movement at 24 h ((MD -11.58/100; 95%CI -23.04 to -0.12) and satisfaction scores increased with no other benefits (Felder 2019 **Level I** [PRISMA], 6 RCTs, n=656);
- After spinal surgery, gabapentin reduces pain scores and morphine consumption over the first 24 h (Han 2017a **Level I** [PRISMA], 10 RCTs, n=827);
- After laparoscopic cholecystectomy, gabapentin decreases analgesic requirements, pain scores and PONV (Sun 2016 **Level I** [PRISMA] 12 RCTs, n=1,192); pregabalin in the same setting has similar effects except no effect on PONV (Zhang 2017c **Level I** [PRISMA], 6 RCTs, n=434);
- After TKA and THA a number of meta-analyses with significant overlap have been performed. Pregabalin reduces pain scores, opioid consumption and PONV after TKA and THA (Li 2017b **Level I** [PRISMA], 7 RCTs, n=823). Specific meta-analyses identify similar benefits with pregabalin in TKA (reduced opioid requirements and PONV and pruritus, but not pain scores) (Han 2017b **Level I** [PRISMA], 7 RCTs, n=962) and gabapentin in TKA (reduced opioid requirements and pruritus) (Han 2016 **Level I** [PRISMA], 6 RCTs , n=859) and THA (reduced pain scores and opioid requirements, but no effect on any adverse effect) (Han 2016 **Level I** [PRISMA] 5 RCTs, n=573). A combined meta-analysis on the effects of pregabalin and gabapentin after TKA found only clinically insignificant reductions of pain (pregabalin only) with 0.5/10 (95%CI 0 to 1.0) at 24 h and 0.3/10 (95%CI 0 to 0.6) at 48 h and a reduction in cumulative opioid consumption at 48 h (MD -23.2mg; 95%CI -40.9 to -5.4mg); the latter effect was only significant with pregabalin (MD -33.14 mg; 95%CI -53.98 to -12.29mg) There was no difference in knee flexion at 48 h, but a reduction in the incidence of PONV (RR 0.7; 95%CI 0.6 to 0.9) and an increase in the risk of sedation (only with pregabalin) (RR 1.4; 95% CI 1.1 to 1.9) (NNH 8.7) (Hamilton 2016 **Level I** [PRISMA], 12 RCTs, n=1,493) (4 RCTs [gabapentin] overlap with Han 2016 and all 7 RCTs [pregabalin] overlap with Han 2017b). In THA, pregabalin 150 mg preoperatively and 75 mg BD postoperatively for 7 d reduced pain and opioid requirements for 7 d with no effects on pain or physical function at 6 wk or 3 mth (Clarke 2015 **Level II**, n=184, JS 5).

A network meta-analysis reports a dose-dependent effect of single-dose preoperative pregabalin and gabapentin on reduction of pain scores and opioid consumption vs placebo (Hu 2018a **Level I** [NMA], 79 RCTs, n=6,201). With regard to pain reduction, pregabalin in a dose ≥150mg and gabapentin ≥900 mg are more effective.

In RCTs designed with PONV as a primary endpoint (8 RCTs, n=838), preoperative gabapentin reduces PONV (RR 0.60; 99%CI 0.50 to 0.72), nausea (RR 0.34; 99%CI 0.20 to 0.56), and vomiting (RR 0.34; 99%CI 0.19 to 0.61) at 24 h (Grant 2016b **Level I** [PRISMA], 44 RCTs, n=3,489). These findings are similar in an analysis of all 44 RCTs; this is accompanied by an increased rate of sedation (RR 1.22; 95%CI 1.02 to 1.47).

In RCTs designed to report PONV, preoperative pregabalin reduces PONV (RR 0.53; 95%CI 0.39 to 0.73), nausea (RR 0.62; 95%CI 0.46 to 0.83), and vomiting (RR 0.68; 95%CI 0.52 to 0.88) at 24 h (Grant 2016a **Level I** [PRISMA], 23 RCTs, n=1,693). There is no increased sedation reported (RR 0.97; 95%CI 0.71 to 1.33), but an increase of postoperative visual disturbance (RR 3.11; 95%CI 1.34 to 7.21).

Used as an adjunct to epidural analgesia, perioperative gabapentin reduced pain scores and epidural analgesic requirements and improved patient satisfaction, despite an increase in dizziness (Turan 2006 **Level II**, n=54, JS 5) but these benefits were not confirmed with thoracic epidural analgesia for thoracotomy (Kinney 2012 **Level II**, n=120, JS 5).

Alpha-2-delta ligands were also studied in the setting of acute burns pain (see Section 8.5.2), acute herpes zoster pain (see Section 8.6.2.2) and acute pain due to Guillain-Barre Syndrome (see Section 8.10.6.7).

The effects of alpha-2-delta ligands on the prevention of CPSP are presented in Section 1.4.6.3.

Abuse potential and toxicity

Alpha-2-delta ligands have a potential for misuse, abuse and toxicity in overdose (Evoy 2017 **Level IV SR** [PRISMA], 59 studies [24 epidemiological, 3 clinical abuse liability, 16 case series or reports of abuse or misuse or dependence, 17 case series or reports of acute overdose]; Bonnet 2017 **Level IV SR** [PRISMA], 106 studies [17 rewarding behaviour, 14 clinical, 38 case series or reports on abuse and dependence, 37 on overdose toxicity or fatalities]; Schjerning 2016 **Level IV SR** [PRISMA], 76 studies [pregabalin only] [17 preclinical, 19 clinical, 13 epidemiological, 27 case series or reports]) (all with significant overlap of studies). Preclinical studies suggest that modulation of the GABA and glutamate systems, with resulting anxiolysis and in particular euphoria, underpin the abuse potential. The prevalence of abuse in the UK general population is 1.1% for gabapentin and 0.5% for pregabalin; consistently patients with opioid use disorder have higher rates: gabapentin 15 to 22% and pregabalin 3 to 68%. Substance use disorder and psychiatric comorbidities are the most important risk factors. Abuse typically involves the intake of supratherapeutic doses to achieve euphoria, with pregabalin appearing more addictive than gabapentin.

Overdose toxicity from gabapentin or pregabalin alone is rarely fatal, but the risk increases in combination with sedatives, particularly opioids. Another contributing factor may be that pregabalin reversed the tolerance to opioids (Lyndon 2017 **BS**). Data from many countries (USA, UK, Germany, Finland, India, South Africa and France) show that over 75% of deaths attributable to alpha-2-delta ligands also involve opioids (Smith 2016 **Level IV SR**, 34 studies, n unspecified). This is in line with findings that the combination of gabapentin and opioid vs opioid alone increased the risk of opioid overdose death (OR 1.99; 95%CI 1.61 to 2.47) (Gomes 2017 **Level III-2**, n=5,875). Mixed adverse outcome data have been reported in hospitalised patients and the postoperative period; as a component of multimodal analgesia, gabapentin increased the risk of respiratory depression (OR 1.47; 95%CI 1.22 to 1.76) (Cavalcante 2017 **Level III-3**, n=8,567) and continuation of alpha-2-delta ligands into the postoperative period was associated with increased need for naloxone administration (RR 6.30; 95%CI 2.4 to 16.7) (Deljou 2018 **Level III-2**, n=128 [naloxone administrations] in n=110,019). On the other hand, in hospitalised patients (only 17% had surgery in the preceding 24 h, but >60% received the opioid for acute pain treatment), alpha-2-delta ligand use vs non-use did not increase frequency of naloxone requirement (Savelloni, 2017 #14922} **Level III-2**, n=153 [naloxone administrations]).

4.8.1.2 | Sodium valproate

Sodium valproate did not improve acute nociceptive pain after surgery (Martin 1988 **Level II**, n=39, JS 3). There are conflicting results on IV sodium valproate in treating acute migraine; it was ineffective in one study (Tanen 2003 **Level II**, n=40, JS 2) and superior to metoclopramide plus sumatriptan in another (Bakhshayesh 2013 **Level II**, n=60, JS 3).

4.8.2 | Chronic pain

Among all anticonvulsants, there is good evidence only for the use of alpha-2-delta ligands in chronic pain conditions including neuropathic pain states such as diabetic polyneuropathy, postherpetic neuralgia and central neuropathic pain as well as fibromyalgia (Wiffen 2013b **Level I** [Cochrane], 91 RCTs, n=17,995). For most other anticonvulsants, the evidence was non-existent, so little or of so low quality that conclusions were not permitted or of reasonable quality showing no or very little effect. This is in line with treatment guidelines for chronic neuropathic pain which recommend alpha-2-delta ligands, but no other anticonvulsants, as first-line treatment in this indication (Finnerup 2015 **GL Level I** [PRISMA], 229 RCTs, n unspecified).

4.8.2.1 | Alpha-2-delta ligands (gabapentin/pregabalin)

Gabapentin

At doses of 1,800 mg to 3,600 mg, gabapentin is effective in treating neuropathic pain, in particular caused by postherpetic neuralgia (NNT 6.7; 95%CI 5.4 to 8.7) (8 RCTs, n= 2,260) and diabetic polyneuropathy (NNT 5.9; 95% CI 4.6 to 8.3) (6 RCTs, n=1,277) (Wiffen 2017a **Level I** [Cochrane], 37 RCTs, n=5,914). Withdrawals due to adverse events were more common with gabapentin (NNH 30; 95%CI 20 to 65) (22 RCTs, n=4,346), while serious adverse events were not more common with gabapentin than with placebo. Pain relief in 20 to 40% of patients is accompanied by improvement of sleep, fatigue, depression, quality of life and function.

Gabapentin was also effective for the treatment of neuropathic pain caused by traumatic or postsurgical nerve injury (Gordh 2008 **Level II,** n=120, JS 5).

Pregabalin

Pregabalin is effective in a dose-dependent fashion in postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain due to spinal cord injury (SCI) and mixed or unclassified post-traumatic neuropathic pain, but only with limited evidence in neuropathic back pain or sciatica, neuropathic cancer pain or polyneuropathy and no effect in HIV neuropathy (2 RCTs, n=674) (Derry 2019 **Level I** [Cochrane], RCTs=45, n=11,906):

- Postherpetic neuralgia: 300 mg/d pregabalin (NNT 5.3; 95%CI 3.9 to 8.1) (4 RCTs, n=713) and 600 mg/d (NNT 3.9; 95%CI 3.1 to 5.5) (4 RCTs, n=732);
- Painful diabetic neuropathy: 600 mg/d pregabalin (NNT 7.8; 95% CI 5.4 to 14) (5 RCTs, n=1,015);
- Mixed or unclassified post-traumatic neuropathic pain: 600 mg/d pregabalin (NNT 7.2; 95%CI 5.4 to 11) (4 RCTs, n=1,367);
- Central neuropathic pain (mainly SCI): 600 mg/d pregabalin (NNT 9.8; 95%CI 6.0 to 28) (3 RCTs, n=562).

In all studies, somnolence and dizziness occurred more in pregabalin than placebo arms in a dose-dependent pattern, but serious adverse events were not different between arms: pregabalin 300 mg (RR 1.2; 95%CI 0.8 to 1.7) (17 RCTs, n=4,112) and pregabalin 600 mg (RR 1.1; 95%CI 0.8 to 1.5) (16 RCTs, n=3,995).

Pregabalin 300 to 600 mg has also beneficial effects in fibromyalgia; substantial pain relief is achieved over 12 to 26 wk of treatment in about 10% more patients than in the placebo arm, accompanied by improvements of other symptoms, quality of life and function (Derry 2016a **Level I** [Cochrane], 8 RCTs, n=3,283).

Alpha-2-delta ligands are also used in chronic pain due to SCI (see Section 8.2.2.5), phantom limb pain (see Section 8.1.5.2) and in patients who are opioid-tolerant (see Section 9.7) or have a substance use disorder (see Section 9.8).

4.8.2.2 | Carbamazepine

Carbamazepine for the treatment of chronic neuropathic pain has possibly some analgesic efficacy in some patients, but the quality of data is insufficient to draw meaningful conclusions or make comparisons (Wiffen 2014 **Level I** [Cochrane], 10 RCTs, n=480).

4.8.2.3 | Oxcarbazepine

Only very-low level evidence supports limited effectiveness of oxcarbazepine in painful diabetic neuropathy, neuropathic pain from radiculopathy and a mixture of neuropathies (Zhou 2017 **Level I** [Cochrane], 5 RCTs, n=862).

4.8.2.4 | Phenytoin

A meta-analysis could not identify any quality studies to support the use of phenytoin in chronic neuropathic pain or fibromyalgia (Birse 2012 **Level I** [Cochrane], 0 RCTs, n=0).

4.8.2.5 | Valproate

Valproate may affect pain in diabetic polyneuropathy based on very small RCTs of poor quality (Gill 2011 **Level I** [Cochrane] 2 RCTs, n=84).

Valproate is effective for the prevention of episodic migraine (Linde 2013 **Level I** [Cochrane], 10 RCTs, n=652).

4.8.2.6 | Lamotrigine

Lamotrigine shows no analgesic benefit in neuropathic pain in large, high-quality, long-duration RCTs (Wiffen 2013a **Level I** [Cochrane] 12 RCTs, n=1,511).

4.8.2.7 | Lacosamide

Lacosamide is not beneficial for the treatment of neuropathic pain and fibromyalgia (Hearn 2012 **Level I** [Cochrane] 6 RCTs, n=2,022).

KEY MESSAGES

1. Alpha-2-delta ligands (gabapentinoids) are the only anticonvulsants with well-proven efficacy in the treatment of chronic neuropathic pain (**S**) (**Level I** [Cochrane Review]).
2. Pregabalin is the only anticonvulsant with proven but limited efficacy in chronic pain due to fibromyalgia (**S**) (**Level I** [Cochrane Review]).
3. Perioperative alpha-2-delta ligands (gabapentinoids) reduce postoperative pain and opioid requirements, in particular after more painful surgery (**Q**) and reduce the incidence of postoperative nausea and vomiting (**S**) as well as pruritus (**S**), but increase the risk of sedation (**S**) (**Level I** [PRISMA]).
4. Alpha-2-delta ligands have the potential for misuse and abuse, in particular in patients with opioid use disorder or psychiatric comorbidity (**N**) (**Level IV SR**).
5. Overdose toxicity of alpha-2-delta ligands is increased when taken in combination with other agents that cause sedation, particularly opioids (**N**) (**Level IV SR**).

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

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use alpha-2-delta ligands (gabapentin, pregabalin) in the management of acute neuropathic pain (**U**).

4.9 | Alpha-2 agonists

4.9.1 | Systemic alpha-2 agonists

4.9.1.1 | Clonidine

Clonidine is a selective alpha-2 agonist with an alpha-2 to alpha-1 ratio of 200:1 (Chan 2010a **NR**). Systemic perioperative administration of clonidine vs placebo does not reduce pain scores, but has an opioid sparing effect at 24 h (MD 24%; 95%CI 16 to 32) (4 RCTs, n=313) and reduces incidence of PONV (RR 0.35; 95%CI 0.25 to 0.51]) (6 RCTs, n=412) (Sanchez Munoz 2017 **Level I** [PRISMA], 57 RCTs, n=14,790 [PO 29 arms, IM 4 arms, IV 24 arms, TD 2 arms]).

After non-cardiac surgery, 0.2 mg oral clonidine given preoperatively and continued as 0.2 mg/d transdermal clonidine patch for 72 h did not reduce pain scores or opioid consumption vs placebo over these 72 h (Turan 2016 **Level II**, n=624, JS 5). An updated meta-analysis adding this and two further RCTs to a preceding one (Blaudszun 2012 **Level I** [PRISMA], 30 RCTs [clonidine 19 RCTs], n=1,792 [clonidine n=1,156]) confirms no effect of clonidine versus placebo on pain scores at 24 h (7 RCTs, n=802) or 48 h (4 RCTs, n=562) (Turan 2016 **Level I**, 7 RCTs, n=802).

Alpha-2 agonists such as clonidine are more effective than placebo in the management of opioid-withdrawal symptoms (Gowing 2014 **Level I** [Cochrane], 25 RCTs, n=1,668).

4.9.1.2 | Dexmedetomidine

Dexmedetomidine is a highly selective alpha-2 adrenoceptor agonist with an alpha-2 to alpha-1 ratio of 1,620:1 (Chan 2010a **NR**). Systemic intraoperative only administration of dexmedetomidine vs placebo reduces pain intensity at 6 h [WMD −0.93/10; 95%CI −1.34 to −0.53) and at 24 h (WMD=−0.47/10; 95%CI −0.83 to −0.11) as well as opioid consumption (WMD −6.76 mg; 95% CI −10.16 to −3.35) (Wang 2018c **Level I** [PRISMA], 40 RCTs, n=2,401). Dexmedetomidine also reduces the need for rescue analgesia and extends the time to first rescue analgesia. Dexmedetomidine used perioperatively (12 RCTs [intraoperative use only]) in spinal surgery reduces postoperative pain at 2 h postoperatively and reduces analgesic requirement at 12 h (2 RCTs) and 48 h (3 RCTs), but not 24 h (3 RCTs) (Tsaousi 2018 **Level I** [PRISMA], 15 RCTs, n=913) (4 RCTs overlap).

4.9.1.3 | Effects of systemic dexmedetomidine on neuraxial and peripheral blocks

The use of IV dexmedetomidine in patients receiving spinal anaesthesia prolongs time to first analgesic request by at least 60% as well as duration of sensory and motor block by 34% respectively 17% (Abdallah 2013 **Level I** [PRISMA], 7 RCTs, n=364). These results were in principle confirmed by a subsequent systematic review, which analysed separately 8 RCTs published since the previous review (Johnson 2016 **Level I**, 8 RCTs, n=480) and by one subsequent RCT (Kumari 2017 **Level II**, n=60, JS 5). Most of the RCTs utilised an initial bolus dose and a subsequent maintenance infusion for the duration of surgery (11 of the overall 16 RCTs). IN dexmedetomidine had a significant opioid sparing effect after THA (Uusalo 2019 **Level III-3**, n=120).

IV dexmedetomidine (0.5 mcg/kg) but not IV midazolam prolonged spinal bupivacaine sensory block and also provided sedation and additional analgesia in patients undergoing transurethral resection of the prostate (Kaya 2010 **Level II**, n=75, JS 2).

IV dexmedetomidine (2.0 mcg/kg) significantly prolonged analgesia and reduced postoperative opioid requirements after single-shot interscalene brachial plexus block vs placebo and lower doses of dexmedetomidine (0.5 and 1.0 mcg/kg) (Kang 2018a **Level II**, n=72, JS 5).

See also Sections 4.9.2.1 and 4.9.2.2 below.

KEY MESSAGE

1. Alpha-2 agonists such as clonidine are more effective than placebo in the management of opioid-withdrawal symptoms (**U**) (**Level I** [Cochrane Review])
2. The perioperative use of the alpha-2-agonist clonidine systemically (excluding transdermal administration) reduces nausea/vomiting and opioid consumption (**Q**) (**Level I** [PRISMA])
3. The perioperative use of the systemic alpha-2-agonist dexmedetomidine reduces postoperative pain intensity, opioid consumption and requirements for rescue analgesia (**S**) (**Level I** [PRISMA]).
4. The IV administration of dexmedetomidine combined with intrathecal local anaesthetic prolongs time to first analgesic request (**N**) (**Level I** [PRISMA]).
5. The perioperative use of the systemic alpha-2-agonist clonidine for 48 h does not reduce pain intensity (**Q**) (**Level I**).

4.9.2 | Regional alpha-2 agonists

Alpha-2 adrenoceptor agonists act as an analgesic at the level of the dorsal horn of the spinal cord, although there may be peripheral effects as well (Chan 2010a **NR**). Systemic adverse effects are predominantly centrally mediated sedation and hypotension.

4.9.2.1 | Neuraxial

Clonidine

There is no human or animal evidence of neurotoxicity when preservative-free clonidine is administered IT (Hodgson 1999 **NR**). Epidural clonidine is approved by the FDA for relief of chronic cancer pain.

In volunteers, significant analgesia to experimental heat pain was detected with IT doses >25 mcg clonidine, with 50 mcg having similar effects on heat threshold to 5 mg bupivacaine (Ginosar 2013 **Level II EH**, n=11, JS 4). IT clonidine given in doses from 15 to 150 mcg, combined with IT local anaesthetic does not affect the rate of onset of a local anaesthetic block, but significantly prolongs the time to two-segment block regression and prolongs the time to first analgesic request (median 101 min, range 35–310 min) (Elia 2008 **Level I**, 22 RCTs, n=1,445). Treatment effects were noted to be heterogeneous and dose responsiveness could not be demonstrated. IT clonidine also reduces intraoperative pain, but hypotension was more frequent (RR 1.8; 95%CI 1.4 to 2.3) (Elia 2008 **Level I**, 22 RCTs, n=1,445).

The addition of clonidine to IT morphine causes a small increase in duration of analgesia by 1.63 h (95%CI 0.93 to 2.33) and reduced 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). Hypotension is also increased (OR 1.78; 95%CI 1.02 to 3.12).

IT clonidine (30 to 150 mcg) as an adjuvant to neuraxial anaesthesia during Caesarean section prolongs the duration of sensory block by 128 min (95%CI 82 to 175) and motor block by 45 min (95%CI 9 to 81) (Crespo 2017 **Level I** [PRISMA], 12 RCTs, n=1,254). IT clonidine increases sedation (RR 3.92; 95%CI 1.17 to 13.14), but does not increase the risk of hypotension, pruritus or PONV. Neuraxial clonidine (epidural and IT) modestly enhances postoperative analgesia in women

having Caesarean section under neuraxial anaesthesia (Allen 2018 **Level I** [PRISMA], 12 RCTs [IT administration] [complete overlap with Crespo 2017] & 6 RCTs [epidural administration; 2 RCTs bolus followed by infusion, 2 RCTs repeated bolus, 2 RCTs single bolus], n unspecified). Neuraxial clonidine reduces morphine consumption (MD -8.7 mg; 95% CI: -15.3 to -2.0); this effect is less with IT administration (MD -4.3 mg; 95%CI -7.0 to -1.5) than with epidural administration (MD -18.9 mg; 95%CI -34.8 to -3.0). It also increases the time to first analgesic request (MD 150 min; 95%CI 110 to 190) vs placebo, but does not improve pain scores on movement at 0 to 6 h. Neuraxial clonidine increases the risk of intraoperative hypotension (49%) vs placebo (33%) and of intraoperative sedation. Risks for bradycardia, nausea/vomiting and pruritus are inconclusive. There was no case of respiratory depression and neonatal outcome was not different in control and study group.

In obstetrics patients, the time to achieve highest sensory and complete motor block was less and duration of analgesia was longer when clonidine and hyperbaric bupivacaine were administered sequentially, compared to the mixing the two medicines in a single syringe (Sachan 2014 **Level II**, n=60, JS 4).

Low-dose infusion of clonidine alone via thoracic epidural catheters after spinal surgery reduced systemic opioid requirements and nausea without causing significant sedation or hypotension (Farmery 2009 **Level II**, n=65, JS 5). The addition of clonidine to PCEA with ropivacaine and morphine after TKA decreased opioid requirements and improved analgesia without increasing adverse effects (Huang 2007 **Level II**, n=80, JS 3). The addition of clonidine to epidural anaesthesia with ropivacaine after haemorrhoidectomy improved analgesia without causing adverse effects (Baptista 2014 **Level III-2**, n=80).

See also Section 5.7.1.4, for obstetric use Section 9.1.3.3 and for paediatric use Section 10.4.8.1.

Dexmedetomidine

Dexmedetomidine is not approved for epidural or IT administration and animal studies on its neurotoxicity via these routes are contradictory (Ozdamar 2018 **BS**; Konakci 2008 **BS**).

Epidural single-shot dexmedetomidine (0.5 to 1.5 mcg/kg) as an adjuvant to epidural analgesia prolongs analgesia (SMD 3.50 h; 95%CI 1.86 to 5.13) (8 RCTs) and reduces rescue analgesia requirements (SMD -2.00; 95% CI -2.80 to -1.21) (6 RCTs) and pain scores (SMD -0.76; 95%CI -1.46 to -0.06) (4 RCTs) (Zhang 2017b **Level I** [PRISMA]; 12 RCTs, n=660). It increases sedation scores and reduces heart rate minimally with no other significant adverse effects, but reduces postoperative shivering. Pain relief was improved with 0.5 mcg/kg epidural dexmedetomidine versus 0.5 mcg/kg IV administration for open thoracotomy (Zeng 2017 **Level II**, n=73, JS 5).

IT dexmedetomidine in comparison to IT clonidine as adjuvants for IT local anaesthetics results in a minor prolongation of the sensory block (WMD 24.2 min; 95%CI 12.8 to 35.6) and a prolongation of time to first analgesic request (WMD 65.8 min; 95%CI 14.7 to 116.9) with no statistically significant difference in incidence of adverse effects (Zhang 2016 **Level I** [QUOROM], 7 RCTs, n=354).

IT dexmedetomidine vs IT fentanyl prolongs the pain free period (SMD 2.98 h; 95%CI 1.69 to 4.27) without increasing the incidence of adverse events including hypotension and bradycardia (Sun 2017b **Level I**, 9 RCTs, n=639). Similarly, after lower limb orthopaedic surgery, the addition of IT dexmedetomidine vs IT fentanyl to IT bupivacaine significantly prolonged duration of sensory, motor block and postoperative analgesia (Rahimzadeh 2018 **Level II**, n=90, JS 4). In patients undergoing lower limb surgery, IT dexmedetomidine was associated with prolonged motor and sensory block, haemodynamic stability and reduced demand of rescue analgesics at 24 h vs IT clonidine, fentanyl, or saline with bupivacaine (Mahendru 2013 **Level II**, n=60, JS 4).

In patients having lower abdominal surgery using spinal 0.5% bupivacaine, IT dexmedetomidine (5 mcg) vs IT buprenorphine (60 mcg) resulted in a significant prolongation of anaesthesia and analgesia with a reduced need for sedation and rescue analgesics (Gupta 2014 **Level II**, n=60, JS 5). Similarly, in patients undergoing lower abdominal surgery, the quality of anaesthesia was superior with low-dose bupivacaine/dexmedetomidine vs bupivacaine/fentanyl (Nayagam 2014 **Level II**, n=150, JS 4). Dexmedetomidine facilitated the spread of the block and prolonged postoperative analgesia. For major abdominal cancer surgery, the addition of IT dexmedetomidine (5 mcg) to IT morphine (500 mcg)/bupivacaine did not improve analgesia vs IT morphine/bupivacaine (Abdel-Ghaffar 2016 **Level II**, n=90, JS 5). Both groups with adjuncts experienced better analgesia than bupivacaine alone.

Adrenaline (epinephrine)

Adding IT adrenaline to IT local anaesthetics (27 RCTs, n=1,660) prolongs motor block (WMD 64 min; 99%CI 37 to 91), analgesia (WMD 34 min; 99%CI 6 to 62) and time to 2 segments regression (WMD 20 min; 99%CI 11 to 28) (Tschopp 2018 **Level I** [PRISMA] [trial sequential analysis], 70 RCTs, n=3,644). For epidural analgesia (37 RCTs, n=1,781), no effects can be identified either due to lack of an effect (pain intensity, hypotension) or insufficient numbers (motor block, urinary retention). These findings are in line with those of a preceding meta-analysis which also presented dose dependent effects of IT adrenaline (de Oliveira 2012a **Level I** [PRISMA], 24 RCTs, n=1,271) (significant overlap). Doses of ≤100 mcg prolong sensory and motor block duration but also cause more hypotension and PONV than higher doses. IT adrenaline at doses >100 mcg prolongs sensory and motor block more than the lower dose but is not associated with a greater incidence of hypotension and PONV vs IT local anaesthetic alone. The effect of IT adrenaline in prolonging analgesia duration was not seen when added to IT local anaesthetic/opioid combinations (de Oliveira 2012a **Level I** [PRISMA], 24 RCTs, n=1,271).

The influence of caudal adrenaline and/or clonidine on the absorption characteristics of caudal levobupivacaine were evaluated in 240 paediatric patients (Chalkiadis 2013 **PK**). Adrenaline (5 mcg/mL) decreased the rate of levobupivacaine systemic absorption, reducing peak concentrations by half. Clonidine (2 mcg/mL) resulted in faster systemic absorption of levobupivacaine and a similar concentration time profile to levobupivacaine alone.

In postoperative thoracic epidural infusion, the addition of adrenaline to fentanyl and ropivacaine or bupivacaine improved analgesia (Niemi 2003 **Level II**, n=33, JS 5; Niemi 2002 **Level II**, n=12, JS 5; Sakaguchi 2000 **Level II**, n=77, JS 2). The efficacy of thoracic epidural pethidine infusions after thoracotomy was not improved by addition of adrenaline (Bryson 2007 **Level II**, n=50, JS 5).

With lumbar epidural infusions, no analgesic benefit was seen with added adrenaline at 2 mcg/mL or 4 mcg/mL (Forster 2008 **Level II,** n=63, JS 3; Forster 2003 **Level II**, n=46, JS 5).

In labour epidural analgesia, adrenaline (5 mcg/mL) added to low-dose bupivacaine infusions decreased pain scores and resulted in longer redosing intervals with no change in labour duration (Connelly 2011 **Level II**, n=60, JS 4).

4.9.2.2 | Peripheral nerve block

Clonidine

A meta-analysis evaluated the benefits of clonidine as an adjuvant to local anaesthetics for various peripheral nerve and plexus blocks (Popping 2009 **Level I**, 20 RCTs, n=1,054). Clonidine doses ranged from 30 to 300 mcg with most patients receiving 150 mcg. Clonidine prolongs the duration of postoperative analgesia (WMD 122 min; 95%CI 74 to 169), sensory block (WMD 74 min; 95%CI 37 to 111) and also prolongs motor block. However, clonidine increases the risk of hypotension (OR 3.61; 95%CI 1.52 to 8.55), bradycardia (OR 3.09; 95%CI 1.10 to 8.64) and sedation (OR 2.28; 95%CI 1.15 to 4.51). There was a lack of evidence of dose-responsiveness for

beneficial or harmful effects. Subsequent studies in supraclavicular blocks report similar findings (Nasir 2017 **Level II**, n=97, JS 4; Chakraborty 2010 **Level II**, n=70, JS 4; Singh 2010 **Level II**, n=50, JS 4). However, the addition of 150 mcg clonidine to 20 mL of levobupivacaine 0.5% in posterior gluteal (Labat) sciatic nerve block did not prolong the duration of analgesia and resulted in more hypotension vs the control group (Fournier 2012 **Level II**, n=60, JS 4).

In an experimental setting controlling for systemic effects of clonidine using bilateral adductor canal blocks, the addition of 150 mcg clonidine to ropivacaine for one side resulted in no difference in block characteristics (quality and duration) on either side (Andersen 2017 **Level II EH**, n=21, JS 5).

Evidence is lacking for the use of clonidine as an adjunct to local anaesthetics for continuous catheter techniques, with no studies showing benefit (McCartney 2007 **Level I**, 3 RCTs [continuous], n=110).

Dexmedetomidine

Animal studies suggest potential dose-dependent neurotoxic effects when dexmedetomidine is combined with ropivacaine for 48 h of continuous FNB in rabbits (Wang 2019 **BS**) and for brachial plexus in high doses in rats (Kang 2018b **BS**).

Dexmedetomidine added to local anaesthetics for various peripheral nerve and plexus blocks increases duration of postoperative analgesia (MD 4.87 h; 95%CI 4.02 to 5.73) (Schnabel 2018 **Level I** [PRISMA], 46 RCTs, n=3,149). Dexmedetomidine increases the risk of intraoperative bradycardia (RR 2.83; 95%CI 1.50 to 5.33) and hypotension (RR 3.42; 95%CI 1.24 to 9.48). Perineural and IV administration of dexmedetomidine results in a similar prolongation of duration of analgesia (MD 0.98 h; 95%CI -0.12 to 2.08) (2 RCTs, n=107). However, for ulnar nerve blocks perineural administration was superior to systemic dexmedetomidine in prolonging block duration (without dexmedetomidine 7.1 h [95%CI 6.6 to 7.6], systemic administration 9.2 h [95%CI 8.6 to 9.8], perineural 14.4 h [95%CI 13.1 to 15.6]) (Andersen 2019 **Level II EH**, n=22, JS 5).

Meta-analyses of data on specific blocks have significant overlap with the overarching meta-analysis (Schnabel 2018 **Level I** [PRISMA], 46 RCTs, n=3,149) and show similar results.

- For thoracic paravertebral blocks (PVB) dexmedetomidine combined with local anaesthetics reduces pain at rest and with movement; for the latter the results were (SMD -1.63/10; 95%CI -2.92 to -0.34) and at 24 h (SMD -1.78/10; 95% CI -2.66 to -0.90) (Wang 2018a **Level I** [QUORUM], 7 RCTs [2 RCTs infusion, 5 RCTs single shot 1 mcg/kg], n=350). It extends duration of analgesia by 202 min (95% CI 33.5 to 369.6) and reduces postoperative analgesic consumption, while increasing the incidence of hypotension (OR 4.40; 95% CI 1.37 to 14.17).
- For TAPB, dexmedetomidine as an adjuvant increases duration and quality of analgesia, while being opioid sparing ((WMD −13.71; 95%CI −17.8 to −9.6) without increasing adverse effects (Sun 2019 **Level I** [PRISMA], 20 RCTs, n=1,212).
- As part of a brachial plexus block perineural dexmedetomidine reduces time to onset of sensory and motor block, prolongs sensory and motor block and prolongs analgesia by at least 63% respectively 266 min (95%CI 191 to 343) (Vorobeichik 2017 **Level I** [PRISMA], 32 RCTs, n=2,007; Hussain 2017 **Level I**, 18 RCTs, n=1,092 [17 RCTs overlap]; Ping 2017 **Level I** [QUOROM], 18 RCTs, n=1,014 [10 RCTs overlap]). In addition, dexmedetomidine has an opioid sparing effect of 10.2 mg (95%CI -15.3 to -5.2) MED in the first 24 h, improves pain control and enhances patient satisfaction, but increases the incidence of bradycardia and hypotension.

A dose-finding study for dexmedetomidine as an adjunct to interscalene brachial plexus block identified 2 mcg/kg as superior over 1 and 1.5 mcg/kg with regard to duration of analgesia (placebo: 808 min ± 180; 1mcg/kg: 1033 min ± 288; 1.5 mcg/kg: 1,042 min ± 188; 2 mcg/kg:

1,224 min ± 238 min), but with an increased risk of hypotension for the two highest dose groups (Jung 2018 **Level II**, n=100, JS 5).

Compared with clonidine the perineural application of dexmedetomidine as a local anaesthetic adjunct in single-injection supraclavicular block produces significant prolongation of sensory block, motor block, and postoperative analgesia (on average by factor 1.2), while increasing the incidence of transient bradycardia (OR 7.4; 95%CI 1.3 to 40.8) and postoperative sedation (OR 11.8; 95%CI 1.9 to 73.6) (El-Boghdadly 2017 **Level I** [PRISMA], 14 RCTs, n=868).

Compared with dexamethasone, dexmedetomidine as a perineural adjunct for supraclavicular plexus block was inferior with regard to duration of analgesia (MD -148 min; 95%CI -259 to -37), while causing more hypotension (RR 6.3; 95%CI 1.5 to 27.5) and sedation (Albrecht 2019 **Level I** [PRISMA], 49 RCTs, n=3,019).

Adrenaline

Adrenaline added to local anaesthetics for locoregional anaesthesia (6 RCTs, n=203) prolongs analgesia (WMD 66 min; 98%CI 32 to 100) (Tschopp 2018 **Level I** [PRISMA] [trial sequential analysis], 70 RCTs, n=3,644).

4.9.2.3 | Intravenous regional anaesthesia

Clonidine

Magnesium sulphate (1.5 g of 50% MgSO4) vs clonidine (150 mcg) as an adjunct to IVRA resulted in longer time to first analgesic request (193.9 ± 38.4 min vs 169.5 ± 33.3 min) and less requirements for rescue analgesia (1.6 ± 0.7 vs 2.1 ± 0.8) (Kaur 2017 **Level II**, n=40, JS 5).

Dexmedetomidine

Addition of dexmedetomidine (typically 0.5 mcg/kg) to lidocaine or prilocaine IVRA increased duration and quality of analgesia (Subramanya 2017 **Level II**, n=60, JS 5; Kumar 2012 **Level II**, n=72, JS 5; Kol 2009 **Level II**, n=75, JS 5; Esmaoglu 2005 **Level II**, n=40, JS 4; Memis 2004 **Level II**, n=30, JS 4). These findings were not supported by a dose-finding study with clonidine (0 to 1.5 mcg/kg) added to IVRA, where no analgesic benefit was found (Ivie 2011 **Level II**, n=52, JS 5).

In patients having carpal tunnel repairs under IVRA, dexmedetomidine IV was compared with dexmedetomidine added to the local anaesthetic for IVRA and with placebo. Both routes of dexmedetomidine had similar effects, with improved postoperative pain scores up to 30 min (Mizrak 2010 **Level II**, n=45, JS 5).

Dexmedetomidine (1 mcg/kg) vs midazolam (50 mcg/kg) as an adjunct to IVRA resulted in similar duration of analgesia (Subramanya 2017 **Level II**, n=60, JS 4).

4.9.2.4 | Intra-articular

Clonidine

Intra-articular (IA) clonidine vs placebo after arthroscopic knee surgery reduces pain scores for 4 hrs, the need for rescue analgesia and postoperative nausea, but increases the risk of hypotension (Sun 2014 **Level I** [PRISMA] 7 RCTs, n=230). Combined femoral-sciatic nerve block offered better analgesia with fewer adverse effects than IA infiltration with bupivacaine/clonidine/morphine in children undergoing anterior cruciate ligament reconstruction (Tran 2005 **Level II**, n=36, JS 2).

Dexmedetomidine

IA dexmedetomidine when added to ropivacaine resulted in a longer time to analgesic request than ropivacaine alone (mean 10.8 h [SD 2.6] vs 5.4 h [SD 1.4]) (Paul 2010 **Level II**, n=30, JS 5). Compared with IV dexmedetomidine, IA dexmedetomidine resulted in a longer time to first

analgesia (dexmedetomidine 312.0 min [SD 120.7]; IV group 102.1 min [SD 54.4]; placebo group 71.0 min [SD 50.1]) (Al-Metwalli 2008 **Level II**, n=60, JS 5). When IA dexmedetomidine, fentanyl and ropivacaine each alone were compared following knee arthroscopy, time to first analgesia was longest with ropivacaine, followed by fentanyl and then dexmedetomidine (mean: 380 min [SD 22], 327 min [SD 17] and 244 min [SD 20] respectively) (Manuar 2014 **Level II**, n=99, JS 2). IA dexmedetomidine (1 mcg/kg) resulted in similar prolongation and quality of analgesia as IA dexamethasone (8 mg) vs bupivacaine alone after meniscal surgery (Moeen 2017 **Level II**, n=60, JS 5).

KEY MESSAGES

1. Neuraxial clonidine improves duration and quality of analgesia and is opioid sparing when used as an adjunct to neuraxial local anaesthetics (in particular after Caesarean section) (**S**) (**Level I)** or to morphine (**U**) (**Level I** [PRISMA]), but increases the risk of hypotension and sedation (**N**) (**Level I** [PRISMA]).
2. Neuraxial dexmedetomidine improves duration and quality of analgesia when used as an adjunct to neuraxial local anaesthetics (**S**) (**Level I** [PRISMA]).
3. Intrathecal adrenaline (epinephrine) when combined with local anaesthetic, but not with intrathecal opioids, prolongs analgesia duration (**U**) (**Level I** [PRISMA]).
4. Dexmedetomidine when added to local anaesthetics for peripheral nerve blocks improves duration and quality of analgesia, but is associated with increased hypotension and bradycardia (**S**) (**Level I** [PRISMA]).
5. Intra-articular clonidine reduces pain scores for 4 hours, need for rescue analgesia and incidence of nausea, but increases hypotension (**N**) (**Level I** [PRISMA])
6. Clonidine improves duration of analgesia and anaesthesia when used as an adjunct to local anaesthetics for peribulbar, peripheral nerve and plexus blocks but is associated with increased hypotension and bradycardia (**U**) (**Level I**).
7. Dexmedetomidine added to intravenous regional anaesthesia improves and prolongs analgesia (**U**) (**Level II**).
8. Epidural adrenaline (epinephrine) in combination with a local anaesthetic improves the quality of postoperative thoracic epidural analgesia (**U**) (**Level II**).

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

☑ The benefits of perineural adjunctive administration of alpha-2-agonists over systemic administration remains unclear (**N**).

4.10 | Salmon calcitonin and bisphosphonates

4.10.1 | Calcitonin

Calcitonin is a 32-amino acid peptide hormone that regulates calcium homeostasis in vertebrates. It also has analgesic properties, primarily through receptor-mediated modulation of serotonergic activity in pain pathways of the CNS (Visser 2005 **NR**). Salmon calcitonin has a greater potency than mammalian forms of the hormone and is therefore reproduced as a synthetic medicine for pharmaceutical use. The adverse effects of calcitonin therapy such as sedation, nausea, skin flushing and diarrhoea may reflect increased serotonergic activity. In rodents, the $5HT_3$ antagonist tropisetron reduced its analgesic efficacy, which may be relevant in humans during the treatment of its adverse effects, nausea and vomiting (Visser 2005 **NR**).

In patients with osteoporotic vertebral compression fractures, salmon calcitonin (IV, SC, IM, IN or rectal) administered within <10 d reduces acute pain at rest and on movement within 1 wk and improves mobilisation (in 7 to 28 d); adverse effects are usually minor and mainly gastrointestinal (Knopp-Sihota 2012 **Level I** [PRISMA], 13 RCTs, n=589). Weekly IM injections of eel calcitonin (elcatonin 20 Units) were more effective than NSAIDs in controlling pain and improving mobility in new (<2 wk) thoracolumbar osteoporotic fractures (Endo 2017 **Level II**, n=228, JS 3). In chronic pain (>3 mth) from pre-existing osteoporotic vertebral compression fractures, the effect was minimal and only statistically significant on movement at 6 mth. In a case series IN salmon calcitonin reduced pain due to fracture of the coccyx (Foye 2014 **Level IV**, n=8).

In acute phantom limb pain, IV (and likely SC) salmon calcitonin was more effective than placebo (Jaeger 1992 **Level II**, n=21 (cross over), JS 3; Turek 2012 **CR**; Bornemann-Cimenti 2017 **CR**). However, it was not effective for chronic phantom limb pain (Eichenberger 2008 **Level II**, n=20 [cross over], JS 5). Epidurally administered calcitonin was found to reduce the incidence of chronic phantom limb pain, allodynia and hyperalgesia at 6 and 12 mth in diabetic patients undergoing lower limb amputation (Yousef 2017 **Level II**, n=60, JS 5).

In CRPS, a meta-analysis concluded that salmon calcitonin (IN, IV) is beneficial (Perez 2001 **Level I**, 5 RCTs [calcitonin], n unspecified). However, the only two placebo-controlled RCTs in this meta-analysis produced conflicting results. A subsequent RCT found that calcitonin was no more effective than paracetamol in improving pain and function in CRPS over a 2 mth period in patients already receiving physical therapy following upper limb trauma (Sahin 2006 **Level II**, n=35, JS 2). A network meta-analysis recommended short term (<2 mth) calcitonin by all routes of administration in CRPS over 12 mth in duration (Wertli 2014 **Level I** [NMA], 3 RCTs [calcitonin], n=116); the RCTs included did not use IASP or Budapest diagnostic criteria for CRPS and the quality of the data have been questioned by other authors (Benzon 2016 **NR**).

Neuropathic pain after SCI was responsive to SC salmon calcitonin (Humble 2011 **Level IV**, n=3).

In lumbar spinal stenosis, salmon calcitonin (IN, IM, SC) has no effect on pain or walking distance vs placebo or paracetamol regardless of method of administration (Peng 2015 **Level I**, 6 RCTS, n=232).

The limited evidence available does not support the effectiveness of SC salmon calcitonin in the treatment of acute and persistent metastatic bone pain (Martinez-Zapata 2006 **Level I** [Cochrane], 2 RCTs, n=90).

With long-term use of salmon calcitonin for treatment of chronic osteoporosis (with unproven efficacy), there is a suggested association with increased cancer incidence; however, this is based on studies with poor-quality cancer assessment methodology (Overman 2013 **NR**). A subsequent meta-analysis further weakened the association and found little biological plausibility linking cancer risk and long-term calcitonin use (Wells 2016 **Level I**, 22 RCTs, n= 11,489).

The FDA has decided to continue the registration of salmon calcitonin, including for chronic use (FDA 2014b).

4.10.2 | Bisphosphonates

IV pamidronate (30 mg daily for 3 d) vs placebo, rapidly reduced pain associated with acute osteoporotic vertebral compression fractures (<21 d after incident) for up to 30 d post treatment (Armingeat 2006 **Level II**, n=35, JS 5). Pamidronate IV was as effective as IV human synthetic calcitonin for this indication (Laroche 2006 **Level II**, n=27, JS 3).

Bisphosphonates reduce subacute and chronic bone pain associated with metastatic carcinoma of the breast (Wong 2012 **Level I** [Cochrane], 9 RCTs, n=2,810). In multiple myeloma there is high quality evidence for benefit in reduction of vertebral fractures and skeletal related events, and low-quality evidence for pain reduction (Mhaskar 2017 **Level I** [Cochrane], 24 RCTs, n=7,293). In advanced prostate cancer, there is no clear benefit to the use of bisphosphonates for reducing pain, but they may prevent further skeletal related events (Macherey 2017 **Level I** [Cochrane], 18 RCTs, n=4,843). Bisphosphonates improve pain control in patients with metastatic bone disease from lung cancer (Lopez-Olivo 2012 **Level I**, 12 RCTs, n=1,767). Zoledronate specifically reduces the likelihood of experiencing a bone pain event in metastatic bone disease in comparison to placebo (RR 0.83; 95%CI 0.76 to 0.89) (Zhu 2013 **Level I**, 12 RCTs, n=4,450). See also Section 8.9.7.7.

There is poor quality evidence for the use of bisphosphonates outside of the aforementioned cancer states (breast, multiple myeloma, prostate, lung), nor is it warranted in patients with short life expectancy (<3 mth) (Porta-Sales 2017 **Level I**, 40 RCTs, n = 16,105).

Bisphosphonates reduce pain in patients with CRPS Type 1, in particular in the early phases of the syndrome (<12 mth) (Chevreau 2017 **Level I**, 4 RCTs, n=181).

In Paget's disease, bisphosphonate use tripled the proportion (31% versus 9%) of participants whose bone pain disappeared (RR 3.42; 95%CI 1.31 to 8.90) (NNT 5) (2 RCTs, n=205) (Corral-Gudino 2017 **Level I** [Cochrane], 20 RCTs [pain], n=3,168). The evidence was limited regarding benefit of specific bisphosphonates, but zoledronate appeared to have marginally better efficacy vs pamidronate and risedronate (2 RCTs, n=436).

In acute pain due to osteoarthritis of the knee, there is no effect on pain, function and radiological progress (Vaysbrot 2018 **Level I**, 7 RCTs, n=3,013).

KEY MESSAGES

1. Bisphosphonates reduce bone pain associated with metastatic breast cancer (**U**), multiple myeloma (**S**) and Paget's disease (**N**) (**Level I** [Cochrane Review]).
2. Salmon calcitonin reduces pain and improves mobilisation in the acute phase after osteoporosis-related vertebral compression fractures (**U**) (**Level I** [PRISMA]).
3. Bisphosphonates reduce pain in patients with CRPS Type 1 in the early phase of the disease (**N)** (**Level I**).
4. Salmon calcitonin reduces acute, but not chronic, phantom limb pain (**U**) (**Level II**).
5. Pamidronate reduces pain associated with acute osteoporotic vertebral compression fractures (**U**) (**Level II**).

4.11 | Cannabis, cannabinoids and cannabimimetics

4.11.1 | Pharmacology

Medicinal preparations made from the cannabis plant contain several hundred chemical substances, which occur in varying concentrations in different plant strains and growth environments. Cannabis plants and their extracts are uniquely rich in phytocannabinoids (Russo 2011 **NR**), of which delta^9-tetrahydrocannabinol (Δ^9-THC) is the best characterised substance and induces most of the psychogenic effects attributed to cannabis. Tetrahydrocannabinolic acid is the nonpsychotropic phytochemical precursor of THC and is of therapeutic interest for the prevention of nausea (Rock 2013 **BS**) and the selective inhibition of COX-2 (Takeda 2008 **BS**). Other prominent THC congeners include cannabidiol and cannabinol. Cannabidiol (CBD) is of interest because it opposes the psychotropic activity of THC and is currently being developed for anticonvulsant therapy (Schubart 2011 **Level IV**, n=1,877; Devinsky 2014 **NR**; Borgelt 2013 **NR**). Cannabinol is also of interest for possible antitumour actions (Guindon 2011 **NR**).

"Cannabinoids" refers to both the phytocannabinoid congeners of Δ^9-THC and to a wide range of synthetic substances that act on a family of G-protein coupled receptors, which are presently designated subtypes CB_1 and CB_2. CB_1 receptors are predominantly distributed throughout the central and peripheral nervous system, where they mediate inhibition of neurochemical transmitter release and are associated with analgesic and mood modifying effects. CB_2 receptors predominantly occur on immune cells, including microglia, and are associated with modulation of cytokine release and have an anti-inflammatory effect (Mackie 2006 **NR**).

The endogenous cannabinoid system can be considered complementary to the endogenous opioid system (Wilson-Poe 2013 **BS**). Endogenous cannabinoid ligands (endocannabinoids) are derived from arachidonic acid. It is postulated that some (chemically noncannabinoid) analgesic agents (including paracetamol and various NSAIDs) may act, at least in part, via cannabinoid receptor mediation, either directly or indirectly via modulation of endocannabinoid metabolism (Graham 2013a **NR**; Manzanares 2006 **NR**) although much of this evidence is from pre-clinical data and some effects may be species-specific (McPartland 2014 **BS SR**).

It is difficult to group together cannabis-derived preparations and other cannabinoids. This is because plant-extract formulations comprise a mixture of active ingredients (eg the oral mucosal metered-dose spray nabiximols [Sativex®; containing THC:CBD≈1:1] in comparison to pure single ingredient cannabinoid preparations, such as dronabinol [Marinol®, synthetic THC, oral capsules] and nabilone [Cesamet®, synthetic analogue of THC, oral capsules]). Nabiximols is registered in Australia and New Zealand among other countries for treatment of spasticity associated with multiple sclerosis (MS).

The acute toxicity of phytocannabinoids is extremely low; nevertheless, clinical studies of the effect-adverse effect profile of cannabis and cannabinoids have demonstrated that desirable actions may be limited in a proportion of patients due to adverse effects, including dysphoria, sedation and impaired psychomotor performance, memory and concentration (Robson 2011 **NR**).

Many patients self-administer cannabis by smoking; the traditional route popularised by nonmedical users (Wilsey 2013 **Level II**, n=39, JS 4; McQuay 2010 **NR**). Transpulmonary administered phytocannabinoids are rapidly and efficiently absorbed; however, newer vaporising delivery techniques are supplanting smoking with its attendant health risks (Zuurman 2008 **Level II**, n=12, JS 4; Eisenberg 2014 **Level IV PK**; Hazekamp 2006 **EH**) including emerging concerns regarding severe pulmonary toxicity and 'vaping' (Schier 2019 **GL**). Oral cannabis and cannabinoid preparations have a poor and highly variable systemic bioavailability (Huestis 2007 **NR**). Likewise the oromucosal spray (of nabiximols) does not achieve a rapid systemic absorption, with a profile

resembling oral administration (Karschner 2011a **Level II PK**, n=9, JS 3; Karschner 2011b **Level II EH**, n=22, JS 3; Zuurman 2008 **Level II EH**, n=12, JS 4; Hazekamp 2006 **EH**).

4.11.2 | Efficacy

4.11.2.1 | Acute Pain

A volunteer study considering acute pain used electrical and heat stimuli in healthy young adult female volunteers found 20 mg oral standardised cannabis extract to be no different to 5 mg oral diazepam (active placebo) in a variety of endpoint measures (Kraft 2008 **Level II EH**, n=18, JS 4). The authors concluded that "*cannabinoids are not effective analgesics for the treatment of acute nociceptive pain in humans*". The authors determined the plasma concentrations of the Δ^9-THC and cannabidiol components and found that they varied more than seven-fold between subjects.

Similarly, in the clinical setting, there is no evidence for a role of synthetic or purified cannabinoids in the management of acute pain (Stevens 2017 **Level I** [PRISMA], 7 RCTs, n=310). Five RCTs found cannabinoids to be equivalent to placebo, one inferior and one superior. There were no synergistic or additive analgesic effects when used in combination with opioids.

4.11.2.2 | Chronic Pain

In a variety of chronic pain conditions, including neuropathic pain, fibromyalgia, arthritis and other/mixed groups the efficacy of all commercially available cannabinoids in all study designs and considering all IMMPACT recommended outcomes were analysed (Stockings 2018 **Level IV SR** [PRISMA], 47 RCTs & 57 studies, n=9,958). Across the RCTs, the pooled event rate for 30% pain reduction is 29.0% for cannabinoids vs 25.9% for placebo (OR 1.46; 95%CI 1.16 to 1.84) ($NNT_{30\%}$ 24; 95%CI 15 to 61) (8 RCTs, n=1,734); this outcome is achieved in 72% of patients (95%CI 66%-78%) in observational studies with no comparison group. Across the RCTs the pooled event rate for 50% pain reduction is 18.2% vs 14.4% (OR 1.43; 95%CI 0.97 to 2.11) (5 RCTs, n=753). With regard to other outcomes in RCTs, there were no effects on physical functioning, quality of life, overall emotional functioning or depressive or anxiety symptoms, but some low level evidence for reduction in sleep problems (moderate level evidence with nabiximols only) and an improved Global Impression of Change (GIC) (perceived "much" to "very much" improved 18.9% vs 11.8% (OR 1.62; 95%CI 1.34 to 1.96) (NNT 38; 95%CI 27 to 62) (13 RCTs, n unspecified). There is moderate-to high-grade evidence supporting use of nabiximols to achieve modest reductions in pain as adjunctive therapy in MS-related pain. Adverse events occurred in 81.2% of cannabinoid-treated patients vs 66.2% of placebo treated patients (OR 2.33; 95%CI 1.88 to 2.89) (NNH 6 (95%CI 5 to 8) (10 RCTs, n=1,959); severe adverse events resulting in study withdrawal occurred in 15.8% vs 4.6% (OR 3.47; 95%CI 2.64 to 4.56) (NNH 40; 95%CI 35 to 49) (19 RCTs, n=3,265).

These findings are largely consistent with a preceding meta-analysis with significant overlap of RCTs included (Aviram 2017 **Level I** [PRISMA], 43 RCTs, n= 2,437) and an overview of systematic reviews not including the above meta-analyses (Hauser 2018 **Level I** [PRISMA], 10 SRs, unspecified number of RCTs).

In addition to these meta-analyses of effects on all chronic pain conditions, there are also assessments of specific conditions published (with significant overlap of included RCTs):

- In neuropathic pain there is no high-quality evidence for the efficacy of any cannabis-based medicine (Mucke 2018a **Level I** [Cochrane], 16 RCTs, n=1,750). Low quality evidence shows a 50% or greater pain reduction versus placebo in 21% vs 17% (RD 0.05; 95%CI 0.00 to 0.09) ($NNT_{50\%}$ 20; 95%CI 11 to 100) (8 RCTs, n=1,001). Moderate quality evidence shows a 30% or greater pain reduction in 39 vs 33% (RD 0.09; 95%CI 0.03 to 0.15) ($NNT_{30\%}$ 11; 95%CI 7 to 33) (10 RCTs, n=1,586). For adverse events, evidence is of low quality and shows

an increase in nervous system adverse events 61% versus 29% (RD 0.38; 95%CI 0.18 to 0.58) (NNH 3; 95%CI 2 to 6) (9 RCTs, n=1,304) and psychiatric disorders 17% vs 5% (RD 0.10; 95%CI 0.06 to 0.15) (NNH 10; 95% CI 7 to 16) (9 RCTs, n=1,314).

- In fibromyalgia, there is no convincing evidence that nabilone (the only cannabinoid in both RCTs) is of any value in treating this condition (Walitt 2016 **Level I** [Cochrane], 2 RCTs, n=72).
- In cancer pain, very low-quality evidence shows no benefit of nabiximols or THC (the only cannabinoids in the included RCTs) on any outcome including pain, sleep problems and opioid consumption with increased adverse events (GI and nervous system) (Hauser 2019 **Level I** [PRISMA], 5 RCTs, n=1,534). Even for improvement of anorexia or cachexia in a palliative care setting, there is no convincing, unbiased, high quality evidence for an effect of cannabinoids (Mucke 2018b **Level I** [PRISMA], 9 RCTs, n=1,561).
- In MS, cannabinoids may have modest effects for pain or spasticity based on high quality evidence (Nielsen 2018 **Level III-3 SR** [PRISMA], 11 SRs based on 32 studies).

Smoking cannabis has only short-term effects in studies with potential bias (Phillips 2010 **Level I** [PRISMA], 14 RCTs, n=1,764). With regard to smoked cannabis, the authors caution that there is a risk of bias due to difficulties in blinding patient exposure; in one trial 92% guessed treatment allocation correctly.

A 4 y prospective cohort study looking at the effect of non-prescribed cannabis use in people with chronic non-cancer pain using opioids identified that its use increased pain severity, pain interference and generalized anxiety disorder scores and decreased pain self-efficacy scores (Campbell 2018 **Level III-2**, n=1,514). Cannabis use did not have an opioid sparing or opioid cessation effect.

4.11.3 | Adverse effects

Transient adverse effects of cannabis and cannabinoids are variable and include impaired cognition, dizziness and sedation. In short-term exposure (mean treatment duration of 2 wk) medical cannabis was not associated with a higher incidence of serious adverse effects vs control (RR 1.04; 95%CI 0.78 to 1.39), with dizziness being reported as the most commonly reported nonserious event in cannabinoid-treated patients (15.5%) (Wang 2008a **Level I**, 23 RCTs, n=3,141).

Longer-term studies in patients with MS have indicated no new safety concerns after several years of administration. Nabiximols (Sativex®) treatment in patients with MS was not associated with psychopathology or impaired cognition (Aragona 2009 **Level II**, n=17, JS 5). Similarly, its adverse effects were assessed in an open-label study following a trial for treating spasticity in 146 patients having MS for a mean duration of 334 d (Serpell 2013 **Level IV**). Adverse effects typically reported as “dizziness”, “fatigue” and “headache” caused treatment withdrawal in 14% of patients and were serious (eg psychosis) in 4.3%. A further 9% of these patients withdrew due to lack of efficacy.

There is widespread concern about chronic exposure to cannabis and the development of psychosis in susceptible individuals. Whilst a causal link is yet to be established, one meta-analysis concluded that there is a dose-response relationship between the level of cannabis use and the risk for psychosis (Marconi 2016 **Level III-3** [PRISMA], 10 studies, n=66,816). The risk for schizophrenia and other psychosis-related symptoms is highest in the heaviest cannabis users vs non-users (OR 3.90; 95%CI 2.84 to 5.34). Others have argued that there is little evidence that, at a population level, cannabis use is a primary contributing factor in the development of psychiatric illness (Hamilton 2014 **Level III-3**; Gage 2013 **NR**; Macleod 2010 **NR**).

Rapidly absorbed cannabis (eg by smoking) produces a tachycardia by a beta-adrenergic mechanism (Beaconsfield 1972 **NR**). A detailed literature review identifies an increased risk of acute coronary syndrome and chronic cardiovascular disease associated with cannabis use

through other mechanisms postulated as vascular inflammation, platelet activation and carboxyhaemoglobin formation (Richards 2019 **Level IV SR** [PRISMA], 85 studies, n=541,518). However, in patients surviving acute myocardial infarction there was no statistically significant association between cannabis use and mortality (Frost 2013 **Level IV**, n=519). There are emerging concerns regarding severe pulmonary toxicity related to "vaping", with unclear trigger factors but many reports involve cannabinoids (Schier 2019 **GL**). Overall, cardiovascular and pulmonary effects of cannabinoids need to be considered (Pacher 2018 **NR**).

Acute cannabis intake impairs driving, but the increase in accident risk is of low to medium magnitude (increase in accident risk pooled OR 1.28; 95%CI 1.16 to 1.40, in culpable accident risk pooled OR 1.42; 95%CI 1.11 to 1.75) (Rogeberg 2019 **Level III-3 SR**, 13 studies [culpability], n unspecified).

After trauma, marijuana use, in particular chronic use, leads to higher pain scores and higher opioid requirements (Salottolo 2018 **Level III-2**, n=261).

Epidemiological evidence of harms is typically derived from "recreational" users where the "cannabis" is defined neither chemically nor posologically and its relevance to the medical use, particularly of pharmaceutical grade cannabis, in supervised patients, is questionable.

4.11.4 | General considerations

It should be noted that all clinical studies to date have various design limitations, most involving small numbers of patients and most using only nonselective highly lipophilic cannabinoids, often of unknown composition. It should also be noted that several RCTs with negative results are yet to be published. The possible benefits from more selective agonists have yet to be investigated in the clinical setting, along with more innovative or reliable modes of administration.

Many leading stakeholder institutions world-wide, which hold either scientific, best practice or regulatory interests in the use of pharmacological agents for the treatment of pain, express a universal concern for the proliferation of cannabis related products for the indications of acute or chronic pain (FPMANZCA 2019b **GL**). This concern is largely underpinned by the current lack of quality and robust evidence for its efficacy and concerns over significant adverse effects both in the short and long terms. These same institutions welcome further dialogue within the framework of well-designed clinical studies to better determine usefulness of cannabinoids and their side-effect profile.

KEY MESSAGES

1. Adverse effects including dizziness, cognitive changes and psychiatric symptoms (eg psychosis) may limit the usefulness of cannabinoids in pain treatment (**S**) (**Level I** [Cochrane Review]).
2. Current evidence does not support the use of cannabinoids in acute pain management (**S**) (**Level I** [PRISMA]).
3. Smoking cannabis has short-term efficacy in treating neuropathic pain in patients with HIV/AIDS, although potential study bias means that this is not recommended as routine treatment (**Q**) (**Level I** [PRISMA]).
4. Cannabinoids appear to be mildly effective when used in the treatment of pain and spasticity associated with multiple sclerosis and HIV (**W**) (**Level III-2 SR** [PRISMA]).
5. Smoked cannabis increases the risk of acute coronary syndrome and chronic cardiovascular disease (**N**) (**Level IV SR**)

4.12 | Corticosteroids

4.12.1 | Systemic corticosteroids

Surgical tissue trauma leads to the conversion of arachidonic acid to prostaglandins and leukotrienes. NSAIDs inhibit the formation of prostaglandins, whereas corticosteroids also inhibit the production of leukotrienes and cytokines (Royse 2017 **NR**; Gilron 2004 **NR**). The anti-inflammatory effects of corticosteroids account for some, but not all, of the antinociceptive effects of corticosteroids seen in clinical practice. It is likely that the analgesic actions of systemically administered corticosteroids are attributable predominantly to rapid-onset nongenomic mechanisms. However, the well-documented anti-inflammatory actions may contribute to a more delayed analgesic effect and may be due to genomic effects (Rijsdijk 2014 **NR**; Lowenberg 2008 **NR**).

4.12.1.1 | Efficacy

Perioperative administration of corticosteroids reduces the severity of postoperative pain and decreases analgesic requirements as discussed below. However, corticosteroids are not only administered in the perioperative setting for their analgesic effects but also for other reasons. These include (but are not limited to) a reduction of PONV (De Oliveira 2013b **Level I** [PRISMA], 60 RCTs, n=6,696), decreased swelling in dental and maxillofacial surgery (Dan 2010 **Level I**, 12 RCTs, n=574) and an improvement in quality of recovery and decreased postoperative fatigue (Yue 2017 **Level I**, 11 RCTs, n=774; Murphy 2014 **Level II**, n=200, JS 5; Murphy 2011a **Level II**, n=120, JS 5; Murphy 2011b **Level II**, n=117, JS 5) with facilitation of earlier hospital discharge (Murphy 2011a **Level II**, n=120, JS 5).

Corticosteroids have also been shown to have antihyperalgesic effects in animals and humans (Romundstad 2007 **NR**; Brandsborg 2007 **NR**). In experimental burn injury pain, both methylprednisolone and ketorolac reduced secondary hyperalgesia and increased pain pressure tolerance threshold vs placebo, although the increase in pain pressure tolerance threshold was greater with ketorolac (Romundstad 2007 **Level II EH**, n=12, JS 4). In surgical patients, preoperative administration of methylprednisolone resulted in significantly less hyperalgesia compared with parecoxib and placebo but there was no reduction in persistent spontaneous or evoked pain (Romundstad 2006 **Level II**, n=204, JS 4).

Dexamethasone administration to surgical patients decreases postoperative pain scores, opioid consumption, time to first analgesia, requirements for rescue analgesia and PACU LOS (Waldron 2013 **Level I** [PRISMA], 45 RCTs, n=5,796). However, the differences are small and, while statistically significant, unlikely to confer clinically relevant analgesic benefit (eg 13% reduction in postoperative opioid consumption equals 3 mg morphine equivalent over the first 24 h). Preoperative dexamethasone administration is superior to later administration. When steroid doses were classified into three levels, an optimal dose of 0.1 to 0.2 mg/kg dexamethasone was identified (De Oliveira 2011 **Level I** [PRISMA], 24 RCTs, n=2,751); however, a subsequent metaregression did not identify any dose-response relationship for an opioid-sparing effect (Waldron 2013 **Level I** [PRISMA], 45 RCTs, n=5,796).

Systemic dexamethasone improves quality of analgesia after spinal anaesthesia, with reduced 24 h morphine consumption (6 RCTs, n=326) and prolonged time to first analgesia request (Heesen 2019 **Level I** [PRISMA], 17 RCTs, n=1,133). Systemic and caudal dexamethasone doubles to triples the duration of analgesia from caudal blockade after paediatric surgery to a similar extent (Chong 2018 **Level I** [PRISMA], 14 RCTs, n=1,315).

Orthopaedic surgery

After THA and TKA, glucocorticoids in a dose greater than 0.1 mg/kg dexamethasone equivalent seem to be required to achieve reduction of PONV and pain severity within the first 24 h only (Yue 2017 **Level I**, 11 RCTs, n=774); in addition, systemic steroids are associated with faster functional rehabilitation and greater inflammation control. This is supported by another parallel meta-analysis of elective primary THA with perioperative glucocorticoid administration (dexamethasone 8 to 40 mg, methylprednisolone 125 mg or hydrocortisone 200 mg) (Li 2017c **Level I**, 6 RCTs, n=449).

In patients undergoing elective TKA, perioperative dexamethasone administration decreases postoperative pain scores at 12, 24, and 48 h, and decreases opioid consumption up to 12 h only (Zhou 2018 **Level I**, 6 RCTs, n=576). Similar effects are achieved with dexamethasone in THA (Fan 2018 **Level I** [PRISMA] 3 RCTs, n=207).

High-dose methylprednisolone (dexamethasone equivalent >10 mg), but not low-dose systemic perioperative corticosteroid administration improves analgesia in patients undergoing elective knee or hip surgery (Lunn 2013 **Level I** [PRISMA], 17 RCTs, n=1,081). After orthopaedic surgery, there was no difference in the analgesic effect of IV methylprednisolone 125 mg vs IV ketorolac 30 mg, with both being better than placebo; IV methylprednisolone led to greater opioid-sparing but there was no difference in the incidence of adverse effects (Romundstad 2004 **Level II**, n=75, JS 5).

Tonsillectomy

Dexamethasone in doses >10 mg over 24 h given to adults undergoing tonsillectomy appears to decrease postoperative pain, an effect further improved by repeated administration in the postoperative period (Diakos 2011 **Level I**, 7 RCTs, n=580). This has been confirmed by a subsequent meta-analysis, which shows pain reduction by 23% at 4 h (MD -1.4/10; 95% CI -1.6 to -1.2) (Tolska 2019 **Level I [**PRISMA], 10 RCTs [dexamethasone], n=590) (6 RCTs overlap).

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

Thyroidectomy

Dexamethasone in adults undergoing thyroidectomy reduces postoperative pain scores and analgesic requirements (Chen 2012 **Level I** [PRISMA], 5 RCTs, n=497) and the need for rescue analgesia (Zou 2014 **Level I**, 13 RCTs, n=2,180). Only higher dose dexamethasone (8 to 10 mg) appeared to confer this analgesic benefit.

Maxillofacial surgery

Similarly, after maxillofacial surgery, the perioperative administration of corticosteroids (dexamethasone equivalent >5 mg) results in significant analgesic effects vs placebo in addition to decreased swelling (Dan 2010 **Level I**, 12 RCTs, n=574).

In rhinoplasty surgery, the combination of dexamethasone/pregabalin showed significant analgesic benefits up to 24 h (Demirhan 2013 **Level II**, n=60, JS 3).

Other surgery

In lumbar disc surgery, 16 mg dexamethasone administered orally preoperatively was associated with a reduction on pain with mobilisation in the first 24 h postoperatively (Nielsen 2015b **Level II**, n=160, JS 5).

After mixed ambulatory surgery, ketorolac provided better pain relief than either dexamethasone or betamethasone in the immediate postoperative period but there were no differences in pain relief or analgesic use in the 4 to 72 h period after surgery (Thagaard 2007 **Level II**, n=179, JS 5).

A combination of dexamethasone/gabapentin provided better pain relief and led to less PONV than either medicine given alone after varicocoele surgery; both the combination and the individual medicines were more effective than placebo (Koç 2007 **Level II**, n=80, JS 5). In contrast, there was no difference in pain scores or PCA-morphine requirements during the first 24 h postoperatively in patients given pregabalin, dexamethasone/pregabalin or placebo after hysterectomy (Mathiesen 2009 **Level II**, n=116, JS 5).

Nonetheless, not all of the procedure-specific trials demonstrate benefit. Dexamethasone (0.1 mg/kg) did not decrease the severity of pain nor opioid consumption up to 72 h in patients undergoing thoracotomy (Joung 2018 **Level II**, n=40, JS 4). Likewise, in patients undergoing elective bowel surgery, dexamethasone 8 mg did not improve the quality of recovery, fatigue nor pain severity at 120 h postoperatively (Collaborators 2017 **Level II**, n=1,350, JS 5). When added to a multimodal analgesic combination including intrathecal morphine for Caesarean section under spinal anaesthesia, dexamethasone 8 mg did not decrease opioid consumption up to 24 h postoperatively (Ituk 2018 **Level II**, n=52, JS 4).

After breast augmentation, IV methylprednisolone 125 mg and IV parecoxib 40 mg provided comparable analgesia; however, PONV and fatigue scores were lower in the patients given methylprednisolone (Romundstad 2006 **Level II**, n=204, JS 4). In cardiac surgery, 250 mg methylprednisolone at induction and repeated immediately prior to cardiopulmonary bypass did not reduce the incidence of delirium nor improve the quality of recovery (Royse 2017 **Level II**, n=555, JS 5). Oral prednisolone (50 mg) preoperatively did not improve pain, fatigue, nausea or vomiting in patients undergoing laparoscopic cholecystectomy vs placebo (Bisgaard 2008 **Level II**, n=200, JS 3). In total abdominal hysterectomy, 125 mg of methylprednisolone did not confer analgesic benefit (Aabakke 2014 **Level II**, n=49, JS 4).

Sore throat

Corticosteroids administered in a single dose (most commonly 10 mg dexamethasone orally) provide pain relief for sore throat including pharyngitis more effectively and faster than placebo (Sadeghirad 2017 **Level I**, 10 RCTs, n=1,426).

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

Acute gout

In acute gout, corticosteroids provide similar analgesic effects to non-corticosteroid treatments (Liu 2017b **Level I** [PRISMA], 7 RCTs, n=929).

4.12.1.2 | Adverse effects

The principal safety concerns of perioperative corticosteroid administration relate to the development of hyperglycaemia, increased infection and bleeding risk and the risk of recurrence of malignancy (Ali Khan 2013 **NR**; Yee 2013a **NR**; Turan 2011 **NR**; Ho 2011 **NR**).

Two meta-analyses have examined these safety issues with similar conclusions, although with significant methodological differences and including all corticosteroids (Toner 2017 **Level I**,

11 RCTs [hyperglycaemia], n=685; Polderman 2018 **Level I** [Cochrane], 38 RCTs, n=4,931) (17 RCTs overlap). However, the RCTs summarised in these meta-analyses are essentially efficacy studies of the antiemetic and anti-inflammatory effects of dexamethasone. Few trials have examined long-term effects or patient outcomes and those that have, were not adequately powered to do so. In consequence, a large RCT (PADDI) has completed recruitment, the results of which will address many of the safety issues relating to the administration of intraoperative dexamethasone (Corcoran 2019 **Trial Protocol**, n=8,880).

Hyperglycaemia

In non-cardiac surgical patients, glucocorticoids increase blood glucose concentrations (WMD 1.1mmol/L; 95%CI 0.6 to 1.6) up to 12 h postoperatively (Toner 2017 **Level I**, 11 RCTs [hyperglycaemia], n=685). When only trials which excluded patients with diabetes were examined, the observed increase in blood glucose is smaller (WMD 0.7 mmol/L). These findings are confirmed by the subsequent meta-analysis of dexamethasone only, which finds a similar increase in non-diabetic patients (10 RCTs, n=595) and a more pronounced increase (1.8 mmol/L) (2 RCTs, n=74) in diabetic patients (Polderman 2018 **Level I** [Cochrane], 38 RCTs, n=4,931).

A large dose of dexamethasone (1 mg/kg at induction) in cardiac surgery patients not excluding diabetic patients resulted in a higher maximum postoperative blood-glucose concentration (MD 0.9 mmol/L) vs placebo (Dieleman 2012 **Level II**, n=4,494, JS 5). As all patients received glucose-lowering therapy in the ICU postoperatively, the dexamethasone effect may have been mitigated.

Infection risk

The administration of dexamethasone to patients undergoing surgery is not associated with an increase in the risk of any infection (OR 1.01; 95%CI 0.80 to 1.27) (Polderman 2018 **Level I** [Cochrane] (27 RCTs [infection], n=4,931]). This is also shown for all glucocorticoids (OR 0.9; 95%CI, 0.6 to 1.3) (Toner 2017 (**Level I** [PRISMA], 18 RCTs [infection], n=2,138).There is also no increase in impaired wound healing or anastomotic leakage.

In cardiac surgery, a single intraoperative high dose of dexamethasone (1 mg/kg) did not significantly increase the incidence of postoperative wound infection; there was actually a reduction in total infection complications, due mainly to a reduction in pneumonia (Dieleman 2012 **Level II**, n=4,494, JS 5).

Bleeding risk

Perioperative glucocorticoids do not increase the risk of postoperative haemorrhage in non-cardiac surgery (OR, 1.4; CI, 0.7 to 2.7) (Toner 2017 (**Level I** [PRISMA], 18 RCTs [bleeding], n=2,138).

Specifically, in paediatric tonsillectomy dexamethasone does not increase the overall bleeding risk; however, its use increases the need for operative intervention for bleeding (Plante 2012 **Level I**, 29 RCTs, n=2,674).

See paediatric section 10.4.10.3 for details of corticosteroid effects on bleeding risk.

Malignancy recurrence

There are limited and contradictory results on recurrence of malignancy; after colorectal surgery there was an increase in one small RCT (Singh 2014 **Level II**, n=43, JS 4), while a propensity-matched study failed to confirm such an association in ovarian cancer (De Oliveira 2014b **Level III-2**, n=260).

KEY MESSAGES

1. Mild increase in blood glucose concentration follows perioperative administration of dexamethasone (**S**) (**Level I** [Cochrane Review]) and all corticosteroids (**S**) (**Level I** [PRISMA), particularly in patients with diabetes mellitus.
2. Perioperative administration of dexamethasone (**N**) (**Level I** [Cochrane Review]) and all corticosteroids (**N**) (**Level I** [PRISMA]) does not increase the risk of infection.
3. Perioperative administration of dexamethasone reduces postoperative pain and opioid requirements to a limited extent but also reduces nausea and vomiting, fatigue, and improves the quality of recovery compared with placebo (**U**) (**Level I** [PRISMA]).
4. Preoperative dexamethasone appears to be more effective than intraoperative or postoperative administration (**U**) (**Level I** [PRISMA]).
5. Perioperative glucocorticoids do not increase the risk of impaired wound healing, anastomotic leakage or postoperative haemorrhage (**N**) (**Level I** [PRISMA]).
6. A single dose of corticosteroids provides more effective and faster relief of pain from sore throat than placebo (**N**) (**Level I**) and decreases incidence and severity of sore throat after extubation when administered at induction (**N**) (**Level I** [PRISMA]).
7. Systemic dexamethasone reduces pain intensity and opioid requirements after spinal anaesthesia (**N**) (**Level I** [PRISMA].

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

☑ As all safety data on the risks of using corticosteroids in surgical populations are based on analysis of efficacy trials only, the safety remains to be evaluated (**N**).

4.12.2 | Regional corticosteroids

4.12.2.1 | Neuraxial

Caudal and IV dexamethasone doubles to triples the duration of analgesia from caudal blockade after paediatric surgery to a similar extent (Chong 2018 **Level I** [PRISMA], 14 RCTs, n=1,315).

Dexamethasone when added to bupivacaine/fentanyl solution in epidural analgesia prolonged duration of analgesia in abdominal or thoracic surgery (372 min ± 58.1 vs 234.6 min ± 24.3) and decreased opioid requirements in the first 24 h (Naghipour 2013 **Level II**, n=72, JS 5). In patients having lower abdominal surgery, single-dose epidural bupivacaine/dexamethasone had similar prolongation of time to first analgesia, opioid-sparing and antiemetic effects as bupivacaine/fentanyl when compared with epidural bupivacaine alone (Khafagy 2010 **Level II**, n=90, JS 5). Preoperative single-dose epidural administration of dexamethasone, with or without bupivacaine, reduced postoperative pain and morphine consumption following laparoscopic cholecystectomy (Thomas 2006 **Level II**, n=94, JS 5). Epidural dexamethasone/ropivacaine reduced postoperative pain in patients undergoing gastrectomy under epidural analgesia vs ropivacaine alone in a dose-dependent way with 10 mg superior to 5 mg (Hong 2017 **Level II**, n=120, JS 5). Use of epidural methylprednisolone resulted in no difference in morphine requirements or pain scores following thoracotomy vs epidural saline (Blanloeil 2001 **Level II**, n=24, JS 4).

Epidural corticosteroids (triamcinolone, methylprednisolone or dexamethasone) applied by the surgeons intraoperatively for microdiscectomy or laminectomy reduce pain at 24 h and 1 mth postoperatively as well as opioid requirements and hospital LOS vs placebo (Wilson-Smith 2018 **Level I** [PRISMA], 17 RCTs, n=1,727; Arirachakaran 2018 **Level I** [PRISMA], 12 RCTs, n=1,006) (10 RCTs overlap). There is no difference in complications; a meta-analysis looking specifically for complications found no significant difference in overall complications (RR 1.94; 95%CI 0.72 to 5.26) nor infectious complications (RR 4.58; 95%CI 0.75 to 27.95) (Akinduro 2015 **Level III-2 SR**, 16 RCTs & 1 study, n=1,933).

Lumbar epidural steroid injections (ESI) for acute sciatica provide small but significant short-term relief (≤3 mth) from acute radicular pain (MD -6.2/100; 95%CI -3.0 to -9.4) and reduce disability but do not provide significant longer-term benefits beyond this time (Pinto 2012 **Level I,** 23 RCTs, n=2,334). Results specifically for transforaminal ESI vs saline or local anaesthetic are similar, with modest but significant pain reduction at 3 mth (MD−0.97/10; 95% CI −1.42 to −0.51) but no benefit on disability or need for later surgery (Bhatia 2016 **Level I** [PRISMA] 8 RCTs, n=771) (4 RCTs overlap).

Several meta-analyses overlapping for multiple studies with each other and the above have analysed specific questions. ESI is superior to saline (6 RCTs) with regard to improved function and pain control and superior to local anaesthetic with regard to improved pain control (2 RCTs), but these findings are only maintained at 1 mth with no significant long-term advantage (Lee 2018a **Level I**, 14 RCTS, n unspecified). Fluoroscopically guided lumbar ESI provide significant short-term improvement of radicular pain caused by lumbar disc herniation and stenosis, but not for axial back pain, based on low-quality evidence (Sharma 2017 **Level IV SR**, 41 studies, n unspecified). Non-image guided ESI provide inferior short-term improvement based on low-quality evidence and should only be performed if image-guidance is not available (Vorobeychik 2016 **Level IV SR**, 39 studies, n unspecified). Transforaminal ESI compared to interlaminar ones result in better short-term pain control (2 to 4 wk) based on weak evidence with no other significant benefits (Lee 2018c **Level III-2 SR**, 10 RCTs & 2 studies, n unspecified). There is no significant difference between transforaminal and caudal ESI based on very weak evidence (Lee 2018b **Level III-2 SR**, 4 RCTs & 2 studies, n unspecified). Preganglionic (supraneural, retrodiscal) ESI increases the chance of effectiveness vs postganglionic injection (Pairuchvej 2018 **Level III-2 SR**, 3 RCTs & 1 study, n=412). Particulate steroids compared to non-particulate ones result in statistically significant, but clinically questionable improved pain control (MD -0.53/10; 95%CI -0.14 to -0.92) (Makkar 2016 **Level III-2 SR**, 4 RCTs & 3 studies, n=4,398). For fluoroscopically guided cervical transforaminal epidural steroid injections the response rate for <50% pain reduction is 48% (95%CI 34 to 61%) at 1 mth and 55% (95%CI 45 to 64%) at 3 mth, based on very low-quality studies with no control group comparison (Conger 2020 **Level IV SR** [PRISMA], 17 studies, n unspecified).

The FDA issued a warning in April 2014 that injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse effects, including loss of vision, stroke, paralysis and death (FDA 2014a **GL**). These concerns have been subsequently addressed in a number of consensus statements by multiple organisations (Rathmell 2015 **GL**; Kennedy 2015 **GL**). Recommendations are in particular addressing image-guidance and use of particulate vs. non-particulate steroids and have led to subsequent discussions in the literature.

Furthermore, repeat ESI (mean 1 to 14.7 injections with cumulative methyl-prednisolone equivalent doses of 80 to 8,130 mg) are associated with reduced bone mineral density and increased risk of vertebral fractures (Kerezoudis 2018 **Level IV SR**, 8 studies, n=7,233).

4.12.2.2 | Perineural sites

When compared with local anaesthetic alone, the addition of dexamethasone to local anaesthetic prolongs the duration of sensory block of peripheral nerve block techniques (MD 6.70 h; 95%CI 5.54 to 7.85), and reduces postoperative pain intensity at 12 h (MD -2.08/10; 95%CI -2.63 to -1.53) and 24 h (MD -1.63/10; 95%CI -2.34 to -0.93) (Pehora 2017 **Level I** [Cochrane], 35 RCTs, n=2,702). Similar findings re analgesia are reported in another meta-analysis, which also finds a decrease in PONV (RR 0.36; 95%CI 0.19 to 0.70) (Huynh 2015 **Level I** [PRISMA], 12 RCTs, n=1,054) (9 RCTs overlap). Specifically in brachial plexus block, there were similar findings, with low quality evidence of a ceiling effect of dexamethasone at 4 mg (Kirkham 2018 **Level I** [PRISMA], 33 RCTs, n=2,138) (23 RCTs overlap with Pehora 2017). The effect on duration of sensory block is more pronounced with bupivacaine (MD 4.0 h; 95%CI 2.8 to 5.2) (4 RCTs, n=429) than with ropivacaine (MD 2.0 h; 95%CI -0.5 to 4.5 h) (5 RCTs, n=357) (Baeriswyl 2017 **Level I** [PRISMA], 11 RCTs, n=914) (10 RCTs overlap with Pehora 2017).

IV dexamethasone vs placebo (8 RCTs, n=499) increases the duration of sensory block (MD 6.21 h; 95%CI 3.53 to 8.88) and reduces postoperative pain intensity at 12 h (MD -1.24/10; 95%CI -2.44 to -0.04) and 24 h (MD -1.26/10; 95% CI -2.23 to -0.29) as well as postoperative opioid consumption to 24 h (MD -6.58 mg; 95% CI -10.56 to -2.60) (Pehora 2017 **Level I** [Cochrane], 35 RCTs, n=2,702).

Perineural vs IV dexamethasone (9 RCTs, n=720) increases the duration of sensory block (MD 3.14 h; 95%CI 1.68 to 4.59), but improves analgesia only in a clinically insignificant way and has no opioid-sparing effect (Pehora 2017 **Level I** [Cochrane], 35 RCTs, n=2,702). However, a subsequent meta-analysis using the Hartung-Knapp-Sidik-Jonkman (HKSJ) methodology, which the authors claim to provide a more conservative estimate of effect, could not even confirm the extended duration of sensory block with perineural vs IV dexamethasone (Hussain 2018 **Level I**, 14 RCTs, n=1,007) (9 RCTs overlap).

Adding dexamethasone perineurally as an adjunct to saphenous nerve block increased the duration of analgesia vs placebo (Bjorn 2017 **Level II**, n=40, JS 5). However, time to first rescue analgesia was similar with dexamethasone perineurally for an ankle block vs IV administration (Marty 2018 **Level II,** n=100, JS 5). Dexamethasone/bupivacaine versus IV dexamethasone for sciatic and ankle blocks improved pain scores at 24 h in the sciatic group only, but conferred no other analgesic benefits in either group (Fredrickson 2013 **Level II**, n=126, JS 5).

Perineural dexamethasone for TAPB prolongs sensory block duration (MD 2.98 h; 95%CI 2.19 to 3.78) and reduces pain scores at 2, 6 and 12 h postoperatively (Chen 2018b **Level I** [PRISMA] 9 RCTs, n=575). It also reduces systemic analgesic consumption (SMD -1.29; 95%CI -1.88 to -0.70) and the incidence of PONV (OR 0.28; 95%CI 0.16 to 0.49) on POD 1.

Dexamethasone/bupivacaine vs bupivacaine alone for thoracic paravertebral block improved analgesia and duration of analgesia in patients undergoing nephrectomy (Tomar 2017 **Level II**, n=60, JS 4).

Further addition of dexamethasone to local anaesthetics for scalp nerve blocks in the setting of perioperative systemic dexamethasone therapy did not prolong duration of the block (Jose 2017 **Level II**, n=90, JS 5).

Although perineural dexamethasone has been shown to prolong sensory and motor block of perineural local anaesthetics, there is little safety data to support its use. Animal data to date are reassuring, with dexamethasone not increasing ropivacaine-induced sensory nerve toxicity at clinically relevant concentrations (Williams 2011 **BS**) and dexamethasone attenuating bupivacaine-induced neuronal injury (Ma 2010 **BS**). In a meta-analysis, although underpowered for complications, there is no difference in complications or nerve injury (10 RCTs, n=763) (Hussain 2018 **Level I**, 14 RCTs, n=1,007). However, given the lack of human safety data, the practice of

perineural dexamethasone administration needs to be further evaluated (Rahangdale 2014 **NR**). Furthermore, mixtures of ropivacaine and nonparticulate dexamethasone sodium phosphate demonstrated a pH-dependent crystallisation and the use of such combinations may be not advisable (Watkins 2015 **BS**).

4.12.2.3 | Peripheral sites

Periarticular injection of combinations of local anaesthetic, opioid and anti-inflammatory agents including steroids have been studied (LIA), however the range of mixtures makes determination of the effect of individual components difficult. In patients having simultaneous bilateral knee joint arthroplasties, bupivacaine/fentanyl/methylprednisolone were infiltrated by the surgeon around one knee but not the other (Mullaji 2010 **Level II**, n=40, JS 4). Pain scores on the infiltrated side were significantly lower and the joint had greater active flexion up to 4 wk and superior quadriceps recovery up to 2 wk after surgery when vs the noninfiltrated knee. Periarticular injection of a mixture of bupivacaine/morphine/adrenaline/clonidine showed a reduced hospital LOS by 24 h without any significant effect on pain relief, motion or function following TKA, when methylprednisolone was added (Christensen 2009 **Level II**, n=76, JS 4). In comparing ropivacaine/adrenaline in three groups with no added steroid, 40 mg and 80 mg triamcinolone, the addition of corticosteroid to periarticular injection of local anaesthetic did not improve pain relief or range of movement outcomes for up to 12 wk of follow-up (Chia 2013 **Level II**, n=126, JS 5).

Intra-articular (IA) corticosteroid injections would be expected to have a direct analgesic effect in inflammatory arthropathies. Following knee joint arthroscopy, IA steroids were more effective than placebo in reducing pain, analgesic consumption and duration of immobilisation either alone (Wang 1998 **Level II**, n=60, JS 4) or in conjunction with opioids (Kizilkaya 2005 **Level II**, n=72, JS 4; Kizilkaya 2004 **Level II**, n=60, JS 2) and/or local anaesthetics (Moeen 2017, **Level II,** n= 60, JS 5; Rasmussen 2002 **Level II**, n=60, JS 3). Dexamethasone on its own was less effective than pethidine or fentanyl (Saryazdi 2006 **Level II**, n=48, JS 3). A single IA injection of methylprednisolone one wk before TKA did not reduce acute postoperative pain (Luna 2017 **Level II,** n=48, JS 4). There may be a higher risk of septic arthritis with IA steroids (Armstrong 1992 **Level IV**, n=4,256).

Subacromial injections of corticosteroids have been shown to be effective in treating rotator cuff tendonitis for up to 9 mth vs placebo (NNT 3.3; 95%CI 1.8 to 7.7) and are superior to oral NSAIDs (NNT 2.5; 95%CI 1 to 9) (Arroll 2005 **Level I** [QUOROM], 7 RCTs, n=347). In patients with tendonitis of the shoulder or elbow, steroid injections show similar benefits to NSAIDs for early (up to 1 wk) pain relief (Gaujoux-Viala 2009 **Level I**, 20 RCTs, n=1,731).

In patients having hand surgery, IVRA using a combination of lidocaine/dexamethasone resulted in lower pain scores and lower analgesic requirements for 24 h vs lidocaine alone or lidocaine IVRA with dexamethasone in the nonoperative arm (Bigat 2006 **Level II**, n=75, JS 2). The addition of dexamethasone to lidocaine/ketorolac IVRA for hand surgery improved intraoperative tourniquet tolerance and postoperative analgesia vs lidocaine IVRA alone (Jankovic 2008 **Level II**, n=45, JS 3).

KEY MESSAGES

1. For brachial plexus blocks, addition of dexamethasone to local anaesthetic prolongs the duration of sensory and motor block and improves postoperative analgesia with only very limited benefits over systemic administration (**S**) (**Level I** [Cochrane Review]).
2. For transverse abdominis plane blocks, addition of dexamethasone to local anaesthetics prolongs the duration of sensory block, improves postoperative analgesia and PONV with no comparison to systemic administration (**N**) (**Level I** [PRISMA]).
3. After spinal surgery, epidural steroid application intraoperatively by the surgeon provides analgesic benefit up to 24 hours and reduces length of stay (**N**) (**Level I** [PRISMA]).
4. For acute radicular pain, lumbar epidural corticosteroid administration is effective for short-term relief (**S**) (**Level I** [PRISMA]).
5. Subacromial injections of corticosteroids are superior to oral NSAIDs in treating rotator cuff tendonitis (**U**) (**Level I** [QUOROM])
6. For peripheral nerve blocks, addition of dexamethasone to local anaesthetics prolongs the duration of sensory block and improves postoperative analgesia with only limited benefits over systemic administration (**N**) (**Level II**).
7. For epidural analgesia, addition of dexamethasone improves postoperative analgesia and reduces opioid requirements (**N**) (**Level II**).
8. Addition of dexamethasone to intravenous regional anaesthesia with lidoocaine improves analgesia for up to 24 hours (**U**) (**Level II**).
9. Addition of corticosteroid to periarticular injection of local anaesthetic does not improve pain relief or range of movement following total knee arthroplasty (**U**) (**Level II**).
10. Following knee joint arthroscopy, intra-articular steroids in combination with either local anaesthetic or opioids reduce pain, analgesic consumption and duration of immobilisation (**U**) (**Level II**).
12. There is a risk of septic arthritis with intra-articular steroids (**U**) (**Level IV**).

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

☑ Concerns have been raised regarding the safety of epidural steroids (**U**); these include epidural steroid injections being associated with osteoporosis (**N**).

☑ There is little data in humans regarding the neurotoxicity of perineural corticosteroids (**N**).

4.13 | Other regional analgesic medicines

4.13.1 | Midazolam

Preservative-free midazolam has been proposed as a spinal analgesic due to its action on $GABA_A$ receptors. Robust safety data for the use of intrathecal (IT) midazolam in humans is lacking (Yaksh 2017 **NR**), consequently midazolam is currently not licenced for IT use. Several studies in animal models have raised concern about IT midazolam toxicity (Williams 2011 **BS**; Lavand'homme 2006 **NR**; Yaksh 2004 **NR**; Erdine 1999 **BS**; Malinovsky 1991 **NR**). However, cumulative experience with IT midazolam in human trials confirms beneficial analgesic activity with no demonstrable irreversible side effects in comparison to placebo (Ho 2008 **Level I**, 13 RCTs, n=672; Yaksh 2017 **NR**; Staikou 2014 **NR**). There is insufficient long-term data to unequivocally exclude long-term neurological complications, although none have yet been reported.

IT midazolam added to IT local anaesthetic in perioperative and peripartum patients in comparison with IT local anaesthetic alone shows a reduced incidence of nausea and vomiting and delayed time to request for rescue analgesia (WMD 99 min; 95%CI 76 to 121), but did not affect the duration of motor block (Ho 2008 **Level I**, 13 RCTs, n=672). Multiple subsequent RCTs have confirmed these findings as well as earlier onset and better quality of analgesia for addition of IT midazolam to IT local anaesthetics vs IT local anaesthetic alone (Abdollahpour 2015 **Level II**, n=75, JS 4; Selvaraj 2015 **Level II**, n=100, JS 3; Chattopadhyay 2013 **Level II**, n=90, JS 5; Shadangi 2011 **Level II**, n=100, JS 4), compared to addition of IT dexmedetomidine (Shukla 2016 **Level II**, n=80, JS 3; Samantaray 2015 **Level II**, n=60, JS 4) or IT fentanyl (Codero 2016 **Level II**, n=40, JS 3; Safari 2012 **Level II**, n=90, JS 3) and also when added to IT fentanyl (Gupta 2015 **Level II,** 75 patients, JS 4) or IT sufentanil (Salimi 2014 **Level II**, n=80, JS2). In addition, IT midazolam decreased the incidence of transient neurologic symptoms with IT lidocaine (Selvaraj 2015 **Level II**, n=100, JS 3). Overall, an optimum dose of IT midazolam has not been clearly determined; doses less than 1 mg probably have no effect on prolongation of spinal blockade or analgesia, and the commonly effective doses administered in clinical trials range between 1 to 2 mg (Staikou 2014 **NR**). On the basis of the above meta-analyses, reviews and trials, IT midazolam may cause mild, but not excessive sedation, no additional cardio-respiratory adverse effects or urinary retention.

Specific to the obstetric population, IT midazolam does not seem have any deleterious effect on infants' Apgar scores (Abdollahpour 2015 **Level II**, n=75, JS 4). IT midazolam (1 mg) as a part of combined spinal epidural technique in pre-eclamptic parturients undergoing elective Caesarean section is inferior to IT preservative free magnesium sulphate (50 mg) with regard to prolongation of analgesia (Paleti 2018 **Level II**, n=50, JS 4; Sapna 2013 **Level III-2**, n=124).

A single preoperative epidural dose of midazolam combined with ketamine in patients having a gastrectomy improved analgesia and prolonged the time to rescue analgesia vs epidural ketamine or placebo, with no significant adverse effects (Wang 2006 **Level II**, n=44, JS 4). Midazolam added to bupivacaine for epidural infusion improved analgesia but increased sedation (Nishiyama 2002 **Level II**, n=100, JS 1).

Midazolam has been added to caudal epidural analgesia in paediatric surgery although age-related toxicity issues have not been addressed. In combination with bupivacaine it prolongs postoperative analgesia (Kumar 2005 **Level II**, n=80, JS 5; Ansermino 2003 **Level I**, 2 RCTs [midazolam], n=60). In infants having hernia repairs, neither midazolam nor fentanyl added to bupivacaine for caudal anaesthesia improved postoperative analgesia or recovery (Baris 2003 **Level II**, n=75, JS 4).

4.13.2 | Neostigmine

Neostigmine acts as a spinal analgesic by potentiation of muscarinic cholinergic activity. In a literature review of animal and human studies, there was no evidence of neurotoxicity with spinal neostigmine (Hodgson 1999 **NR**).

4.13.2.1 | Neuraxial

Adding neostigmine to local anaesthetics (bupivacaine or ropivacaine) plus/minus opioid for neuraxial administration in labour analgesia and postoperative analgesia after Caesarean section permits reduction of local anaesthetic doses (MD -4.08 mg/h; 95% CI -6.7 to -1.5) (Cossu 2015 **Level I**, 16 RCTs, n= 1,186). Only IT neostigmine (5 RCTs), but not epidural neostigmine (11 RCTs), increases risk of nausea (OR 9; 95%CI 4.7 to 17.1). Neuraxial neostigmine reduces risk of pruritus (OR 0.4; 95%CI 0.2 to 0.7) (6 RCTs), but does not increase hypotension, sedation or affect fetal outcome.

4.13.2.2 | Intrathecal

IT neostigmine for perioperative and peripartum analgesia prolongs the time to first analgesia request and results in a slight improvement in pain scores and a reduced need for rescue medication, however, it increases nausea and vomiting (OR 5.0; 95%CI 3.4 to 7.3), bradycardia requiring atropine (OR 2.7; 95%CI 1.4 to 5.4) and anxiety, agitation and restlessness (OR 10.3; 95%CI 3.7 to 28.9) (Ho 2005 **Level I**, 19 RCTs, n=1,019) (4 RCTs overlap with Cossu 2015). The authors conclude that the significant adverse effects outweighed any clinical benefit, a conclusion supported by another systematic review, where a lack of a clear dose-response is also identified (Habib 2006 **Level I,** 17 RCTs [IT neostigmine], n unspecified) (15 RCTs overlap).

Subsequent RCTs not included in these meta-analyses support their findings in principle. In patients having various types of surgery under spinal anaesthesia, IT neostigmine prolonged time to first analgesic request (Kayalha 2015 **Level II** n=68, JS 4; Akinwale 2012 **Level II**, n=60, JS 4) and/or effective postoperative analgesia (Kumari Vasantha 2018 **Level II** n=100, JS 4) and/or reduced analgesic consumption (Jain 2012 **Level II**, n=45, JS 4).

In patients having spinal anaesthesia, a comparison of IT clonidine (75 mcg) to IT neostigmine (50 mcg) found the clonidine group to have a longer time to first analgesic request (MD 62 min) but more hypotension during surgery (Yoganarasimha 2014 **Level II**, n=50, JS 3). Both, IT clonidine (30 mcg) and IT neostigmine (75 mcg) increased the duration spinal analgesia, but neostigmine caused more nausea and vomiting (Bhar 2016 **Level II**, n=150, JS 4). In patients undergoing orthopaedic surgery under spinal anaesthesia, IT dexmedetomidine (5 mcg) is superior to IT neostigmine (50 mcg) due to faster onset of anaesthesia, better intra- and postoperative analgesia, and prolonged duration of motor and sensory blockade without significant increases in adverse effects (Singh 2017 **Level II** n=75, JS 4). After elective gynaecological surgery under spinal anaesthesia, IT neostigmine extended postoperative analgesia more than IT magnesium (Joshi-Khadke 2015 **Level II**, n=75, JS 4). After surgery for tibial fracture under spinal anaesthesia, IT neostigmine 150 mcg vs IT fentanyl 25 mcg and IT magnesium 50 mg increased the incidence of hypotension, bradycardia, and nausea and vomiting, and failed to prolong duration of analgesia (Mokaram Dori 2016 **Level II**, n=210, JS 4).

Adverse events of IT neostigmine seem to be dose-dependent. In patients undergoing lower abdominal and lower limb surgery, the administration of IT neostigmine 150 mcg vs IT neostigmine 50 mcg as an adjuvant to bupivacaine 12.5 mg caused more nausea and vomiting (Pandey 2016 **Level II**, n=75, JS 4). IT neostigmine 75 mcg caused less nausea and vomiting than IT neostigmine 150 mcg when added to spinal anaesthesia for Caesarean section (Hye 2010 **Level II**,

n=90, JS 4). Very low-dose IT neostigmine 1 mcg increased the duration of analgesia and decreased the analgesic consumption over 24 h postoperatively in patients undergoing total knee replacement with no increase in the incidence of adverse effects including nausea or vomiting. (Jain 2012 **Level II**, n=45, JS 4).

4.13.2.3 | Epidural

Epidural neostigmine in the general surgical and obstetric populations improves postoperative analgesia in most studies without increasing the incidence of adverse effects (Habib 2006 **Level I**, 7 RCTs [epidural neostigmine], n unspecified). Epidural neostigmine combined with an opioid reduces epidural opioid requirements but may not decrease opioid-related adverse effects vs the opioid alone (Walker 2002 **Level I**, 6 RCTs [neostigmine], n=370).

See Section 10.6.3.1 for use of neostigmine in paediatric caudal epidural analgesia.

4.13.2.4 | Other

Intra-articular administration of neostigmine produces a useful analgesic effect in the postoperative period and is not associated with an increase in the incidence of adverse effects (Habib 2006 **Level I**, 4 RCTs [intra-articular neostigmine], n unspecified).

Studies investigating the efficacy of adding neostigmine to the local anaesthetics used for brachial plexus block and IVRA report conflicting results (Habib 2006 **Level I,** 4 RCTs [perineural neostigmine], n unspecified).

4.13.3 | Botulinum toxin A

Botulinum toxin (botox) A is an exotoxin produced from clostridium botulinum (Sandrini 2017 **NR**; Shilpa 2014 **NR**). Following direct IM injection, botulinum toxin A irreversibly binds to the acetylcholine receptor inducing chemical denervation with resultant dose-dependent muscular paralysis. The extent and duration of paralysis depends on the dose administered. Systemic weakness may follow high cumulative doses. Reinnervation occurs over weeks to months. Botulinum toxin A does not interfere with acute pain perception, nor does it cause local anaesthesia. The use of botulinum toxin in the treatment of chronic painful conditions is beyond the scope of this section.

In treating pain and related muscle spasm in a range of conditions, botulinum toxin A is effective in reducing limb spasm (Son 2019 **Level I**, 27 RCTs, n=2,793; Dong 2017 **Level I**, 22 RCTs, n=1,804), but evidence relating to spasticity-related pain remains uncertain (Baker 2013 **Level I**, 10 RCTs [in pain], n=971). In a range of neuropathic pain conditions (eg trigeminal neuralgia), Botulinum toxin A reduces pain at 4 wk (MD -1.6/10; 95%CI -3.2 to -0.1), 12 wk (MD -1.5/10; 95%CI -2.1 to -0.9) and 24 wk (MD -1.6/10; 95%CI -2.8 to -0.4) (Meng 2018 **Level I**, 12 RCTs, n=495).

In subacute and chronic neck disorders with or without associated cervicogenic headache, IM botulinum toxin A injections provide no clear benefit (Langevin 2011 **Level I** [Cochrane], 9 RCTs, n=503). There is insufficient evidence for the use botulinum toxin A for the treatment of rare head and neck pain syndromes (cluster headache, chronic paroxysmal hemicrania, trigeminal neuralgia) with varying results from only a few small sized trials (cervicogenic headache, chronic neck pain, temporomandibular disorders) (Sycha 2004 **Level I**, 15 RCTs, n=721).

KEY MESSAGES

1. Intrathecal midazolam combined with a local anaesthetic improves and prolongs analgesia and reduces postoperative nausea and vomiting (**U**) (**Level I**).
2. Intrathecal neostigmine improves perioperative and peripartum analgesia in combination with other intrathecal medications (**S**) (**Level I**) but is associated with dose-dependent significant adverse effects, in particular nausea and vomiting (**Q**) (**Level I**).
3. Epidural neostigmine combined with local anaesthetics improves postoperative and peripartum analgesia without increasing the incidence of adverse effects (**U**) (**Level I**).
4. Epidural neostigmine combined with an opioid reduces the dose of epidural opioid that is required for analgesia (**U**) (**Level I**).

4.14 | Complementary and alternative medicine

Complementary and alternative medicine (CAM) is defined as healthcare practices outside the conventional dominant "orthodox" health system of Western industrialised society (Belgrade 2008 **NR**). The boundary between CAM and conventional medicine overlaps and changes with time. In some cultures, these therapies may be considered conventional mainstream practices.

CAM may be classified into two groups; on the one hand are natural products, including but not limited to herbs, vitamins, minerals and probiotics, and on the other are mind and body practices such as yoga, meditation, massage, acupuncture, tai chi, qi gong, chiropractic and osteopathic manipulation, hypnotherapy and others (NCCIH 2018 **GL**). Ayurvedic medicine, traditional Chinese medicine, homeopathy and naturopathy are considered CAM. CAM approaches are usually termed "alternative" when used in place of conventional medical treatments and "complementary" when used together. This section covers the use of natural products administered as analgesic medicines for treatment of acute pain only; good data on their use in this indication are limited.

4.14.1 | Vitamins

Several mechanisms have been described to explain the analgesic effect of Vitamin C (Carr 2017 **NR**).

Vitamin C reduces acute postoperative pain (Chaitanya 2018 **Level IV SR** [PRISMA], 4 RCTs & 3 studies, n=12,395) and has moderate evidence for a reduction of postoperative morphine consumption (Chen 2016 **Level I** [PRISMA], 7 RCTs [postoperative], n=854). In subsequent RCTs, oral Vitamin C (1 g/d) decreased postoperative pain score and rescue analgesia requirements after foot and ankle surgery (Jain 2019 **Level II**, n=60, JS 5) and after major abdominal surgery vs placebo; here Vitamin C (2 g) was comparable to melatonin (6 mg) (Lafli Tunay 2020 **Level II**, n=165, JS 5). In acute herpes zoster, concomitant Vitamin C infusion (5 g) did not improve pain relief (Kim 2016 **Level II**, n=87, JS 2).

Vitamin B complex (comprising of thiamine [B1], riboflavin [B2], pyridoxine [B6] and nicotinamide) reduced pain intensity and analgesic consumption after Caesarean section when combined with gabapentin vs gabapentin alone (Khezri 2017 **Level II**, n=128, JS 4). Vitamin B complex (thiamine, pyridoxine and hydroxo- or cyanocobalamin) when combined with ketorolac 15 mg was as effective as ketorolac 30 mg monotherapy after Caesarean section (Beltran-Montoya 2012 **Level II**, n=100, JS 3) or more effective when combined with diclofenac 50 mg in acute lumbago relief than diclofenac monotherapy (Mibielli 2009 **Level II**, n=372, JS 5). A combination therapy of diclofenac/vitamin B complex TPC (thiamine, pyridoxine, and cyanocobalamin) provides greater analgesia vs diclofenac monotherapy in acute low back pain (OR 2.23; 95%CI 1.59 to 3.13) (Calderon-Ospina 2020 **Level I**, 4 RCTs, n=1,108). In patients with acute ophthalmic zoster, Vitamin B 12 1,000 mcg/lidocaine 20 mg SC daily for 12 d into the regions of the affected innervations of V1 achieved better pain relief vs controls (IM vitamin B 12, local lidocaine) (Xu 2016a **Level II**, n=98, JS 3; Xu 2016b **Level II**, n=204, JS 3).

4.14.2 | Herbal Medicines

A meta-analysis on oral homeopathic St John's wort *(Hypericum perforatum)* showed no significant benefit on dental pain; the meta-analysis was limited by marked heterogeneity and poor study quality (Raak 2012 **Level I** [QUOROM], 4 studies, n=325). A subsequent review on topical application of *Hypericum perforatum* found studies on improved pain relief for acute otitis media, herpes skin lesions and wound pain after Caesarean section and suggests that this may be due to its anti-inflammatory effects (Galeotti 2017 **NR**). Oral *Hypericum perforatum* affects the

metabolism of oxycodone through induction of cytochrome P450 3A (CYP3A) and leads to a significant reduction of plasma concentration and half-life reducing efficacy (Nieminen 2010 **Level II**, n=12, JS 3).

Homeopathic preparations of *Arnica montana* (containing sesquiterpenes) in acute postoperative pain have shown variable results. A systematic review and other studies concluded that homeopathic arnica vs placebo is not effective for pain relief after orthopaedic surgery (Roberts 2012 **Level I** [PRISMA], 3 studies (arnica), n=181), hallux valgus surgery (Karow 2008 **Level II**, n=88, JS 4) and abdominal hysterectomy (Hart 1997 **Level II**, n=93, JS 5). In contrast, some other studies have reported that homeopathic arnica provides a significant reduction in pain after tonsillectomy (Robertson 2007 **Level II**, n=190, JS 5), although a large number of patients in this study were lost to follow-up, while another reported greater reduction in pain in the arnica group after varicose vein surgery (Wolf 2003 **Level II**, n=60, JS 5). A subsequent review (covering many of the studies above) concluded that arnica in homeopathic dilutions has high tolerability and may have effects in treating inflammation (Iannitti 2016 **NR**). The authors argue that variations in formulation affects the quantity of active sesquiterpenes and hence result in variable clinical effects. Traumeel S (an over-the-counter homeopathic highly diluted preparation of extracts from a combination of plants [including arnica] and minerals) was also ineffective following foot surgery (Singer 2010 **Level II**, n=80, JS 4).

A systematic review of the efficacy and safety of Damask rose *(Rosa damascena Mill*) suggests safe use with some pain relief in acute settings (3 RCTs) (Nayebi 2017 **Level I**, 12 RCTs, n=748). Although most of the studies compared topical or inhalational (aromatherapy) applications, one study used oral extract and found that pain relief after Caesarean section was greater than in the placebo group. The group also experienced a longer delay before requesting rescue analgesia, while total analgesic consumption was lower (Gharabaghi 2011 **Level II**, n=92, JS 3).

Zingiberaceae include turmeric (*Curcuma longa*), ginger (*Zingiber officinale*), Javanese ginger (*Curcuma zanthorrhiza*) and galangal (*Alpinia galanga*). Curcumin (diferuloyl methane) is the principal curcuminoid of Indian spice turmeric, while the anti-inflammatory components of ginger are gingerol and zingerone. Extracts of Zingiberaceae reduce pain intensity in a mix of acute and chronic pain states (SMD -0.67; 95%CI -1.13 to -0.21) (Lakhan 2015 **Level I** [PRISMA], 8 RCTs, n=734). Curcuminoids are effective in reducing pain vs a pooled control group of placebo or NSAID (SMD -0.57; 95%CI -1.11 to -0.03), but not vs either placebo or NSAID in a mix of acute and chronic pain states (Sahebkar 2016 **Level I** [PRISMA], 8 RCTs, n=606) (2 RCTs overlap). The effect was greater when a bioavailability enhancer such as piperine was administered (SMD -0.98; 95%CI -1.81 to -0.15); however, only three RCTs in the review evaluated the effectiveness of curcuminoids in acute pain and were not separately analysed. A combination nutritional supplement containing *Boswellia serrata* (30% boswellic acid) and *Curcuma longa* (95% curcuminoids) in patients after arthroscopic supraspinatus tendon repair found that the compound lowered pain and tramadol rescue requirements only in the first postoperative wk vs placebo (Merolla 2015 **Level II**, n=104, JS 3). A subsequent RCT found ginger powder 500 mg as effective as ibuprofen 400 mg and superior to placebo with regard to pain relief and rescue analgesic requirements POD 1 in patients after wisdom tooth extraction (Rayati 2017 **Level II**, n=67, JS 4).

There is weak evidence for a reduction of rescue analgesia requirements (RR 0.5; 95%CI 0.1 to 2.1) with use of Damask rose (*Rosa damascena*) and ginger vs placebo after laparoscopic and obstetric/gynaecological surgery (Arruda 2019 **Level III-1 SR** [PRISMA], 10 RCTs & 1 study, n=693).

A transdermal preparation of Fenugreek seeds 10% (*Trigonella foenum-graecum L*.) applied topically for open hernioplasty reduced pain intensity and rescue analgesics consumption when vs placebo patch and in the first 6 h vs diclofenac patch (Ansari 2019 **Level II**, n=90, JS 4).

Saffron (*Crocus sativus*) 250 mg as a syrup taken together orally with date-juice vs saffron with artificial sugar and placebo reduced pain intensity and anxiety during labour in primiparous women (Mohammadierad 2018 **Level II**, n=96, JS 5).

Herbal medicines (White willow bark [*Salix alba*] and Devil's claw [*Harpagophytum procumbens*]) for non-specific low-back pain (a mix of acute, subacute and chronic back pain) result in short-term improvement vs placebo (Gagnier 2016 **Level I** [Cochrane], 14 RCTs, n=2,050). The review also reported on the effectiveness of several topical preparations of herbal plaster and ointment-based applications including Cayenne (*Capsicum frutescens*), Comfrey root extract (*Symphytum officinale*) and Brazilian arnica (*Solidago chilensis*). However, the quality of evidence was poor. Side effects were usually mild and transient.

Herbal and dietary supplement combinations are commonly prescribed in CAM treatment. A study using a mixture of homoeopathic preparations (arnica, *Bryonia alba, Hypericum perforatum, Ruta graveolens*) did not show any benefit in postoperative pain relief and morphine consumption after knee ligament reconstruction surgery (Paris 2008a **Level II**, n=158, JS 4). There is also no clear evidence that the combination of oral arnica with *Hypericum perforatum* is effective in pain relief after dental procedures (Galeotti 2017 **NR**). Another herbal combination consisting of anise (*Pimpinella anisum*), celery (*Apium graveolens*) and saffron (*Crocus sativus*) (referred to as PAC), when compared to mefenamic acid, was shown to have greater pain reduction and faster onset in patients with post-partum pain in a single-blind study (Simbar 2015 **Level II**, n=108, JS 2).

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

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

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

For dysmenorrhoea, a Cochrane review investigated twelve different herbal medicines German chamomile (*Matricaria chamomilla, M recutita, Chamomilla recutita*), cinnamon (*Cinnamomum zeylanicum, C. verum*), Damask rose (*Rosa damascena*), dill (*Anethum graveolens*), fennel (*Foeniculum vulgare*), fenugreek (*Trigonella foenum-graecum*), ginger (*Zingiber officinale*), guava (*Psidium guajava*), rhubarb (*Rheum emodi*), uzara (*Xysmalobium undulatum*), valerian (*Valeriana officinalis*), and zataria (*Zataria multiflora*) and five non-herbal supplements (fish oil, melatonin, vitamins B1 and E, and zinc sulphate) in a variety of formulations and doses (Pattanittum 2016 **Level I** [Cochrane], 27 RCTs, n=3,101). Very limited evidence of effectiveness versus placebo or no treatment was found for fenugreek (1 RCT, n=101), fish oil (1 RCT, n=120), fish oil plus vitamin B1 (1 RCT, n=120), ginger (4 RCTs, n=335), valerian (1 RCT, n=100), vitamin B1 alone (1 RCT, n=120), zataria (1 RCT, n=99), and zinc sulphate (1 RCT, n=99). Very limited evidence was found that chamomile was more effective than NSAIDs (1 RCT, n=160), while no difference versus NSAIDs was found for dill (1 RCT, n=47), fennel (1 RCT, n=59), guava (1 RCT, n=155), rhubarb (1 RCT, n=45), valerian (1 RCT, n=99) and Damask rose (1 RCT, n=92). Comparisons between CAM for dysmenorrhoea showed that Vitamin B1 may be more effective than fish oil (1 RCT, n=120). Subsequent systematic reviews emphasise again the limited quality of the evidence, the high risk of bias and the difficulties to draw definitive conclusions on efficacy. One systematic review analysed results for fennel (*Foeniculum vulgare*) (4 RCTs, n=295), chamomile (*Matricaria chamomilla)* (3 RCTs, n=220) and zataria (*Zataria multiflora*) (3 RCTs, n=302) (Sharghi 2019 **Level I**, 17 RCTs, n unspecified). Another identified only one RCT with low risk of bias to be considered supportive evidence for use of Damask rose (*Rosa damascena*) (Pellow 2018 **Level I** [PRISMA], 22 RCTs, n unspecified).

4.14.3 | Aromatherapy

Aromatherapy describes the inhalation (or sometimes administration to the skin) of essential oils as part of herbal medicine, possibly affecting emotions through the neuroendocrine and autonomic nervous system.

Aromatherapy (oil inhalation and oil massage) reduces pain of dysmenorrhoea vs no treatment or placebo treatment; however, there is a high risk of bias weakening these results (Lee 2018d **Level III-1 SR**, 19 studies, n=1,787; Song 2018 **Level III-3 SR** [PRISMA], 9 RCTs & 12 studies, n unspecified) (13 studies overlap).

There is no sufficient evidence to support the use of aroma therapy for the treatment of postoperative pain (Dimitriou 2017 **Level I**, 9 RCTs, n=644).

Aroma therapy may reduce pain, anxiety and improve sleep quality in burns patients, but the low quality of trials with regard to randomisation and bias does not permit a conclusion (Choi 2018 **Level I** [PRISMA], 4 RCTs, n=248). The addition of aroma therapy (lavender) to standard treatment of renal colic with parenteral diclofenac improved pain scores at 30 min, but only in female patients (Irmak Sapmaz 2015 **Level II**, n=100, JS 0).

4.14.4 | Melatonin

An experimental study on volunteers observed a dose dependent effect on pain threshold and pain tolerance after sublingual melatonin (0.15mg/kg or 0.25mg/kg) vs placebo (Stefani 2013 **Level II EH**, n=61, JS 5). Two preoperative melatonin doses (5 mg) led to lower pain and anxiety scores in the first 24 h (NNT 2.20 and 2.53) and reduced IV PCA morphine usage after abdominal hysterectomy (Caumo 2007 **Level II**, n=35, JS 5). Melatonin (6 mg) reduced pain and patient-controlled morphine consumption and supplementary doses of diclofenac in patients after major abdominal surgery (Lafli Tunay 2020 **Level II**, n=165, JS 5). Melatonin was also found to reduce pain during blood taking in children (Marseglia 2015 **Level II**, n=60, JS 5).

4.14.5 | Honey

Oral administration of honey has been associated with improved pain relief (3 RCTs, n=201) and reduced need for analgesic intake after tonsillectomy vs placebo, especially in the early postoperative period based on RCTs of poor methodological quality (Lal 2017 **Level I** [PRISMA], 8 RCTs, n unspecified; Hwang 2016 **Level I**, 4 RCTs, n=264) (all 4 RCTs overlap). An RCT not included in the meta-analyses found that onset to pain relief was faster, pain severity was lower and the need for rescue analgesia was less in the honey group than in the control group (Mohebbi 2014 **Level II**, n=80, JS 2).

KEY MESSAGES

1. White willow bark (*Salix alba*) and devil's claw (*Harpagophytum procumbens*) are effective in treating acute episodes of low-back pain (**U**) (**Level I** [Cochrane Review])
2. A variety of complementary medicines may show efficacy in prevention and treatment of primary dysmenorrhoea based on very limited evidence (**W**) (**Level I** [Cochrane Review]), including aromatherapy (**N**) (**Level III-1 SR**).
3. Curcuminoids and extracts of Zingiberaceae may reduce pain intensity in acute and chronic pain states compared to placebo (**N**) (**Level I** [PRISMA]).
4. Oral administration of honey versus control reduces postoperative pain and analgesic use after tonsillectomy (**N**) (**Level I** [PRISMA]).
5. Vitamin C reduces postoperative opioid requirements (**N**) (**Level I** [PRISMA] and postoperative pain compared to placebo (**N**) (**Level IV SR** [PRISMA]).
6. Aromatherapy (**N**) (**Level I**), homeopathic preparations of arnica (*Arnica montana*) (**U**) (**Level I** [PRISMA]) and St John's wort (*Hypericum perforatum*) are not effective in treating acute postoperative pain (**U**) (**Level I** [QUOROM]).
7. St John's wort (*Hypericum perforatum*) induces metabolism of oxycodone reducing its plasma concentrations and efficacy (**U**) (**Level II**).

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

☑ There is some evidence that some complementary and alternative medicines may be effective in some acute pain states. Adverse effects and interactions with medications have been described with complementary and alternative medicines and must be considered before their use (**U**).

☑ The evidence on complementary and alternative medicines is characterised by small sample sizes and study designs prone to bias and caution is urged in interpreting results. Additionally, the safety and potential drug interactions of many complementary and alternative medicines have not been adequately assessed **(N).**

References

Aabakke AJ, Holst LB, Jorgensen JC et al (2014) The effect of a preoperative single-dose methylprednisolone on postoperative pain after abdominal hysterectomy: a randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol* **180**: 83–88.

AAGBI (2010) *Management of Severe Local Anaesthetic Toxicity.* https://anaesthetists.org/Home/Resources-publications/Guidelines/Management-of-severe-local-anaesthetic-toxicity Accessed 10 February 2020

Abd El-Rahman AM & El Sherif FA (2018a) Efficacy of Postoperative Analgesia of Local Ketamine Wound Instillation Following Total Thyroidectomy: A Randomized, Double-blind, Controlled Clinical Trial. *Clin J Pain* **34**(1): 53-58.

Abd El-Rahman AM, Mohamed AA, Mohamed SA et al (2018b) Effect of Intrathecally Administered Ketamine, Morphine, and Their Combination Added to Bupivacaine in Patients Undergoing Major Abdominal Cancer Surgery a Randomized, Double-Blind Study. *Pain Med* **19**(3): 561-68.

Abd-Elsalam KA, Fares KM, Mohamed MA et al (2017) Efficacy of Magnesium Sulfate Added to Local Anesthetic in a Transversus Abdominis Plane Block for Analgesia Following Total Abdominal Hysterectomy: A Randomized Trial. *Pain Physician* **20**(7): 641-47.

Abdallah FW, Abrishami A & Brull R (2013) The facilitatory effects of intravenous dexmedetomidine on the duration of spinal anesthesia: a systematic review and meta-analysis. *Anesth Analg* **117**(1): 271-8.

Abdel-Ghaffar HS, Mohamed SA & Fares KM (2016) Combined Intrathecal Morphine and Dexmedetomidine for Postoperative Analgesia in Patients Undergoing Major Abdominal Cancer Surgery. *Pain Med* **17**(11): 2109-18.

Abdollahpour A, Azadi R, Bandari R et al (2015) Effects of Adding Midazolam and Sufentanil to Intrathecal Bupivacaine on Analgesia Quality and Postoperative Complications in Elective Cesarean Section. *Anesth Pain Med* **5**(4): e23565.

Abeyaratne C, Lalic S, Bell JS et al (2018) Spontaneously reported adverse drug events related to tapentadol and oxycodone/naloxone in Australia. *Ther Adv Drug Saf* **9**(4): 197-205.

Abrahams MS, Panzer O, Atchabahian A et al (2008) Case report: limitation of local anesthetic spread during ultrasound-guided interscalene block. Description of an anatomic variant with clinical correlation. *Reg Anesth Pain Med* **33**(4): 357–59.

Abrams GD, Chang W & Dragoo JL (2017) In Vitro Chondrotoxicity of Nonsteroidal Anti-inflammatory Drugs and Opioid Medications. *Am J Sports Med* **45**(14): 3345-50.

Abul-Husn N, Sutuk M, Milne B et al (2007) Augmentation of spinal morphine analgesia and inhibition of tolerance by low doses of mu and delta-opioid receptor anatagonists. *Br J Pharmacol* **151**: 877–87.

ACMT (2016) ACMT Position Statement: The Use of Methadone as an Analgesic. *J Med Toxicol* **12**(2): 213-5.

Affas F (2016) Local infiltration analgesia in knee and hip arthroplasty efficacy and safety. *Scand J Pain* **13**: 59-66.

Affas F, Eksborg S, Wretenberg P et al (2014) Plasma concentration of ketorolac after local infiltration analgesia in hip arthroplasty. *Acta Anaesthesiol Scand* **58**(9): 1140-5.

Afolayan JM, Olajumoke TO, Amadasun FE et al (2014) Intrathecal tramadol versus intrathecal fentanyl for visceral pain control during bupivacaine subarachnoid block for open appendicectomy. *Niger J Clin Pract* **17**(3): 324–30.

Afshar K, Jafari S, Marks AJ et al (2015) Nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioids for acute renal colic. *Cochrane Database Syst Rev*(6): CD006027.

Ahmedzai SH & Boland J (2006) Constipation in people prescribed opioids. *BMJ Clin Evid* **12**: 2407.

Aiyer R, Barkin RL & Bhatia A (2017) Treatment of Neuropathic Pain with Venlafaxine: A Systematic Review. *Pain Med* **18**(10): 1999-2012.

Aiyer R, Mehta N, Gungor S et al (2018) A Systematic Review of NMDA Receptor Antagonists for Treatment of Neuropathic Pain in Clinical Practice. *Clin J Pain* **34**(5): 450-67.

Akinduro OO, Miller BA, Haussen DC et al (2015) Complications of intraoperative epidural steroid use in lumbar discectomy: a systematic review and meta-analysis. *Neurosurg Focus* **39**(4): E12.

Akinwale MO, Sotunmbi PT & Akinyemi OA (2012) Analgesic effect of intrathecal neostigmine combined with bupivacaine and fentanyl. *Afr J Med Med Sci* **41**(2): 231–37.

Akural E, Jarvimaki V, Alaniska K et al (2016) Peripheral morphine reduces acute pain in inflamed tissue after third molar extraction: A double-blind, randomized, active-controlled clinical trial. *Scand J Pain* **11**: 59-64.

Al-Metwalli RR, Mowafi HA, Ismail SA et al (2008) Effect of intra-articular dexmedetomidine on postoperative analgesia after arthroscopic knee surgery. *Br J Anaesth* **101**(3): 395–99.

Al-Sukhun J, Koivusalo A, Tornwall J et al (2006) COX-2 inhibitors and early failure of free vascular flaps. *N Engl J Med* **355**(5): 528–29.

Albrecht E, Kirkham KR, Liu SS et al (2013) Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. *Anaesthesia* **68**(1): 79–90.

Albrecht E, Vorobeichik L, Jacot-Guillarmod A et al (2019) Dexamethasone Is Superior to Dexmedetomidine as a Perineural Adjunct for Supraclavicular Brachial Plexus Block: Systematic Review and Indirect Meta-analysis. *Anesth Analg* **128**(3): 543-54.

Ali Khan S, McDonagh DL & Gan TJ (2013) Wound complications with dexamethasone for postoperative nausea and vomiting prophylaxis: a moot point? *Anesth Analg* **116**(5): 966–68.
Alinejad S, Kazemi T, Zamani N et al (2015) A systematic review of the cardiotoxicity of methadone. *EXCLI J* **14**: 577-600.
Allegaert K, Mian P, Lapillonne A et al (2019) Maternal paracetamol intake and fetal ductus arteriosus constriction or closure: a case series analysis. *Br J Clin Pharmacol* **85**(1): 245-51.
Allen TK, Mishriky BM, Klinger RY et al (2018) The impact of neuraxial clonidine on postoperative analgesia and perioperative adverse effects in women having elective Caesarean section-a systematic review and meta-analysis. *Br J Anaesth* **120**(2): 228-40.
Alviar MJ, Hale T & Dungca M (2016) Pharmacologic interventions for treating phantom limb pain. *Cochrane Database Syst Rev* **10**: CD006380.
Aly M, Ibrahim A, Farrag W et al (2018) Pruritus after intrathecal morphine for cesarean delivery: incidence, severity and its relation to serum serotonin level. *Int J Obstet Anesth* **35**: 52-56.
Amos RJ, Amess JA, Hinds CJ et al (1982) Incidence and pathogenesis of acute megaloblastic bone-marrow change in patients receiving intensive care. *Lancet* **2**(8303): 835–38.
Amr YM & Yousef AA (2010) Evaluation of efficacy of the perioperative administration of Venlafaxine or gabapentin on acute and chronic postmastectomy pain. *Clin J Pain* **26**(5): 381–85.
Andersen JH, Jaeger P, Grevstad U et al (2019) Systemic dexmedetomidine is not as efficient as perineural dexmedetomidine in prolonging an ulnar nerve block. *Reg Anesth Pain Med*(Epub ahead of print).
Andersen JH, Jaeger P, Sonne TL et al (2017) Clonidine used as a perineural adjuvant to ropivacaine, does not prolong the duration of sensory block when controlling for systemic effects: A paired, blinded, randomized trial in healthy volunteers. *PLoS One* **12**(9): e0181351.
Andersen LO & Kehlet H (2014a) Analgesic efficacy of local infiltration analgesia in hip and knee arthroplasty: a systematic review. *Br J Anaesth* **113**(3): 360–74.
Andersen LP, Werner MU, Rosenberg J et al (2014b) Analgesic treatment in laparoscopic gastric bypass surgery: a systematic review of randomized trials. *Obes Surg* **24**(3): 462-70.
Anglin R, Yuan Y, Moayyedi P et al (2014) Risk of upper gastrointestinal bleeding with selective serotonin reuptake inhibitors with or without concurrent nonsteroidal anti-inflammatory use: a systematic review and meta-analysis. *Am J Gastroenterol* **109**(6): 811–19.
Angst MS (2015) Intraoperative Use of Remifentanil for TIVA: Postoperative Pain, Acute Tolerance, and Opioid-Induced Hyperalgesia. *J Cardiothorac Vasc Anesth* **29 Suppl 1**: S16-22.
Angst MS & Clark JD (2006) Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* **104**(3): 570–87.
Ansari M, Sadeghi P, Mahdavi H et al (2019) Fenugreek dermal patch, a new natural topical antinociceptive medication for relieving the postherniotomy pain, a double-blind placebo controlled trial. *J Complement Integr Med* **16**(3).
Ansermino M, Basu R, Vandebeek C et al (2003) Nonopioid additives to local anaesthetics for caudal blockade in children: a systematic review. *Paediatr Anaesth* **13**(7): 561–73.
Aouad MT, Siddik-Sayyid SM, Taha SK et al (2007) Haloperidol vs. ondansetron for the prevention of postoperative nausea and vomiting following gynaecological surgery. *Eur J Anaesthesiol* **24**(2): 171–78.
Apfel CC, Heidrich FM, Jukar-Rao S et al (2012) Evidence-based analysis of risk factors for postoperative nausea and vomiting. *Br J Anaesth* **109**(5): 742–53.
Apfel CC, Turan A, Souza K et al (2013) Intravenous acetaminophen reduces postoperative nausea and vomiting: a systematic review and meta-analysis. *Pain* **154**(5): 677–89.
Apfel CC, Zhang K, George E et al (2010) Transdermal scopolamine for the prevention of postoperative nausea and vomiting: a systematic review and meta-analysis. *Clin Ther* **32**(12): 1987–2002.
Arfe A, Scotti L, Varas-Lorenzo C et al (2016) Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. *Bmj* **354**: i4857.
Arirachakaran A, Siripaiboonkij M, Pairuchvej S et al (2018) Comparative outcomes of epidural steroids versus placebo after lumbar discectomy in lumbar disc herniation: a systematic review and meta-analysis of randomized controlled trials. *Eur J Orthop Surg Traumatol* **28**(8): 1589-99.
Armellin G, Nardacchione R & Ori C (2008) Intra-articular sufentanil in multimodal analgesic management after outpatient arthroscopic anterior cruciate ligament reconstruction: a prospective, randomized, double-blinded study. *Arthroscopy* **24**(8): 909–13.
Armingeat T, Brondino R, Pham T et al (2006) Intravenous pamidronate for pain relief in recent osteoporotic vertebral compression fracture: a randomized double-blind controlled study. *Osteoporos Int* **17**(11): 1659–65.
Armstrong RW, Bolding F & Joseph R (1992) Septic arthritis following arthroscopy: clinical syndromes and analysis of risk factors. *Arthroscopy* **8**(2): 213-23.
Armstrong S & Fernando R (2016) Side Effects and Efficacy of Neuraxial Opioids in Pregnant Patients at Delivery: A Comprehensive Review. *Drug Saf* **39**(5): 381-99.
Arout CA, Edens E, Petrakis IL et al (2015) Targeting Opioid-Induced Hyperalgesia in Clinical Treatment: Neurobiological Considerations. *CNS Drugs* **29**(6): 465-86.

Arroll B & Goodyear-Smith F (2005) Corticosteroid injections for painful shoulder: a meta-analysis. *Br J Gen Pract* **55**(512): 224–28.
Arruda APN, Zhang Y, Gomaa H et al (2019) Herbal medications for anxiety, depression, pain, nausea and vomiting related to preoperative surgical patients: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open* **9**(5): e023729.
Aryana P, Rajaei S, Bagheri A et al (2014) Acute effect of intravenous administration of magnesium sulfate on serum levels of interleukin-6 and tumor necrosis factor-alpha in patients undergoing elective coronary bypass graft with cardiopulmonary bypass. *Anesth Pain Med* **4**(3): e16316.
ASA (2016) Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration: An Updated Report by the American Society of Anesthesiologists Task Force on Neuraxial Opioids and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology* **124**(3): 535-52.
Assouline RB, Tramèr RM, Kreienbühl RL et al (2016) Benefit and harm of adding ketamine to an opioid in a patient-controlled analgesia device for the control of postoperative pain: systematic review and meta-analyses of randomized controlled trials with trial sequential analyses. *PAIN* **157**(12): 2854-64.
Atalan N, Efe Sevim M, Akgun S et al (2013) Morphine is a reasonable alternative to haloperidol in the treatment of postoperative hyperactive-type delirium after cardiac surgery. *J Cardiothorac Vasc Anesth* **27**(5): 933–38.
Athanasos P, Ling W, Bochner F et al (2019) Buprenorphine Maintenance Subjects Are Hyperalgesic and Have No Antinociceptive Response to a Very High Morphine Dose. *Pain Med* **20**(1): 119-28.
Atkinson Rallis L, Drover D, Clavijo C et al (2011) Prior epidural lidocaine alters the pharmacokinetics and drug effeects of extended-release epidural morphine (Depodur) after cesarian delivery. *Anesth Analg* **113**(2): 251–58.
Atsuta J, Inoue S, Tanaka Y et al (2017) Fosaprepitant versus droperidol for prevention of PONV in craniotomy: a randomized double-blind study. *J Anesth* **31**(1): 82-88.
Aubrun F, Mazoit JX & Riou B (2012) Postoperative intravenous morphine titration. *Br J Anaesth* **108**(2): 193–201.
Auriel E, Regev K & Korczyn AD (2014) Nonsteroidal anti-inflammatory drugs exposure and the central nervous system. *Handb Clin Neurol* **119**: 577–84.
Aviram J & Samuelly-Leichtag G (2017) Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Pain Physician* **20**(6): E755-E96.
Azari P, Lindsay DR, Briones D et al (2012) Efficacy and safety of ketamine in patients with complex regional pain syndrome: a systematic review. *CNS Drugs* **26**(3): 215–28.
Azimaraghi O, Marashi SM, Khazaei N et al (2015) The Effect of Adding Sufentanil to 0.5% Hyperbaric Bupivacaine on Duration of Brachial Plexus Blockade in Chronic Opium Abusers: a Randomized Clinical Trial. *Anesth Pain Med* **5**(3): e21960.
Baaklini LG, Arruda GV & Sakata RK (2017) Assessment of the Analgesic Effect of Magnesium and Morphine in Combination in Patients With Cancer Pain: A Comparative Randomized Double-Blind Study. *Am J Hosp Palliat Care* **34**(4): 353-57.
Babl F, Barnett P, Palmer G et al (2007) A pilot study of inhaled methoxyflurane for procedural analgesia in children. *Paediatr Anaesth* **17**(2): 148–53.
Babl FE, Jamison SR, Spicer M et al (2006) Inhaled methoxyflurane as a prehospital analgesic in children. *Emerg Med Australas* **18**(4): 404–10.
Badner NH, Drader K, Freeman D et al (1998) The use of intraoperative nitrous oxide leads to postoperative increases in plasma homocysteine. *Anesth Analg* **87**(3): 711–13.
Badner NH, Freeman D & Spence JD (2001) Preoperative oral B vitamins prevent nitrous oxide-induced postoperative plasma homocysteine increases. *Anesth Analg* **93**(6): 1507–10.
Baeriswyl M, Kirkham KR, Jacot-Guillarmod A et al (2017) Efficacy of perineural vs systemic dexamethasone to prolong analgesia after peripheral nerve block: a systematic review and meta-analysis. *Br J Anaesth* **119**(2): 183-91.
Bailard NS, Ortiz J & Flores RA (2014) Additives to local anesthetics for peripheral nerve blocks: Evidence, limitations, and recommendations. *Am J Health Syst Pharm* **71**(5): 373–85.
Bailey E, Worthington HV, van Wijk A et al (2013) Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth. *Cochrane Database Syst Rev* **12**(12): CD004624.
Bailey M, Corcoran T, Schug S et al (2018) Perioperative lidocaine infusions for the prevention of chronic postsurgical pain: a systematic review and meta-analysis of efficacy and safety. *Pain* **159**(9): 1696-704.
Baker JA & Pereira G (2013) The efficacy of Botulinum Toxin A for spasticity and pain in adults: a systematic review and meta-analysis using the Grades of Recommendation, Assessment, Development and Evaluation approach. *Clin Rehabil* **27**(12): 1084–96.
Bakhshayesh B, Seyed Saadat SM, Rezania K et al (2013) A randomized open-label study of sodium valproate vs sumatriptan and metoclopramide for prolonged migraine headache. *Am J Emerg Med* **31**(3): 540–44.
Ball AJ, Din S, Donnelly M et al (2015) A randomized controlled trial comparing continuous and as-required nitrous oxide use during screening colonoscopy. *Eur J Gastroenterol Hepatol* **27**(3): 271-8.
Bally M, Dendukuri N, Rich B et al (2017) Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *Bmj* **357**: j1909.

Bandolier (2004) *NSAIDs, coxibs, smoking and bone.* http://www.bandolier.org.uk/booth/painpag/wisdom/NSB.pdf Accessed 7 February 2020

Banzi R, Cusi C, Randazzo C et al (2015) Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention of tension-type headache in adults. *Cochrane Database Syst Rev*(5): Cd011681.

Bao YJ, Hou W, Kong XY et al (2016) Hydromorphone for cancer pain. *Cochrane Database Syst Rev* **10**: CD011108.

Baptista JF, Gomez RS, Paulo DN et al (2014) Epidural anesthesia with ropivacaine with or without clonidine and postoperative pain in hemorrhoidectomies. *Acta Cir Bras* **29**(3): 201–08.

Bardsley H, Gristwood R, Baker H et al (1998) A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol* **46**(3): 245–49.

Baris S, Karakaya D, Kelsaka E et al (2003) Comparison of fentanyl-bupivacaine or midazolam-bupivacaine mixtures with plain bupivacaine for caudal anaesthesia in children. *Paediatr Anaesth* **13**(2): 126–31.

Barkin RL, Barkin SJ & Barkin DS (2006) Propoxyphene (dextropropoxyphene): a critical review of a weak opioid analgesic that should remain in antiquity. *Am J Ther* **13**(6): 534–42.

Barletta JF (2012) Clinical and economic burden of opioid use for postsurgical pain: focus on ventilatory impairment and ileus. *Pharmacotherapy* **32**(9 Suppl): 12S–8S.

Barletta JF, Asgeirsson T & Senagore AJ (2011) Influence of intravenous opioid dose on postoperative ileus. *Ann Pharmacother* **45**(7-8): 916–23.

Barnung SK, Treschow M & Borgbjerg FM (1997) Respiratory depression following oral tramadol in a patient with impaired renal function. *Pain* **71**(1): 111–12.

Barreveld A, Witte J, Chahal H et al (2013a) Preventive analgesia by local anesthetics: the reduction of postoperative pain by peripheral nerve blocks and intravenous drugs. *Anesth Analg* **116**(5): 1141–61.

Barreveld AM, Correll DJ, Liu X et al (2013b) Ketamine decreases postoperative pain scores in patients taking opioids for chronic pain: results of a prospective, randomized, double-blind study. *Pain Med* **14**(6): 925–34.

Barrington MJ & Kluger R (2013) Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. *Reg Anesth Pain Med* **38**(4): 289–97.

Barrons RW & Woods JA (2017) Low-Dose Naloxone for Prophylaxis of Postoperative Nausea and Vomiting: A Systematic Review and Meta-analysis. *Pharmacotherapy* **37**(5): 546-54.

Bassiony MM, Abdelghani M, Salah El-Deen GM et al (2018) Opioid Use Disorders Attributed to Tramadol Among Egyptian University Students. *J Addict Med* **12**(2): 150-55.

Bauchat JR, McCarthy R, Fitzgerald P et al (2017) Transcutaneous Carbon Dioxide Measurements in Women Receiving Intrathecal Morphine for Cesarean Delivery: A Prospective Observational Study. *Anesth Analg* **124**(3): 872-78.

Beaconsfield P, Ginsburg J & Rainsbury R (1972) Marihuana smoking. Cardiovascular effects in man and possible mechanisms. *N Engl J Med* **287**(5): 209–12.

Belgrade MJ & Schamber CD (2008) Evaluation of complementary and alternative therapies. In: *Clinical Pain Management: Chronic Pain* 2nd edn. Wilson PR, Watson, P.J., Haythornwaite, J.A., Jensen, T.S. (eds). London, Hodder Arnold. 304.

Bell RF (2012) Ketamine for chronic noncancer pain: concerns regarding toxicity. *Curr Opin Support Palliat Care* **6**(2): 183–87.

Bell RF, Eccleston C & Kalso EA (2017) Ketamine as an adjuvant to opioids for cancer pain. *Cochrane Database Syst Rev* **6**: CD003351.

Bell S, Rennie T, Marwick CA et al (2018) Effects of peri-operative nonsteroidal anti-inflammatory drugs on post-operative kidney function for adults with normal kidney function. *Cochrane Database Syst Rev* **11**: Cd011274.

Beltran-Montoya JJ, Herrerias-Canedo T, Arzola-Paniagua A et al (2012) A randomized, clinical trial of ketorolac tromethamine vs ketorolac trometamine plus complex B vitamins for cesarean delivery analgesia. *Saudi J Anaesth* **6**(3): 207–12.

Ben Abraham R, Marouani N & Weinbroum AA (2003) Dextromethorphan mitigates phantom pain in cancer amputees. *Ann Surg Oncol* **10**(3): 268-74.

Benner KW & Durham SH (2011) Meperidine restriction in a pediatric hospital. *J Pediatr Pharmacol Ther* **16**(3): 185–90.

Benzon HT, Liu SS & Buvanendran A (2016) Evolving Definitions and Pharmacologic Management of Complex Regional Pain Syndrome. *Anesth Analg* **122**(3): 601-4.

Berger AS & Goldschneider KR (2019) The Role of Neuraxial Opioids in Pediatric Practice. *Clin J Pain* **35**(6): 497-500.

Bernards CM (2004) Recent insights into the pharmacokinetics of spinal opioids and the relevance to opioid selection. *Curr Opin Anaesthesiol* **17**(5): 441–47.

Bernards CM, Shen DD, Sterling ES et al (2003) Epidural, cerebrospinal fluid, and plasma pharmacokinetics of epidural opioids (part 1): differences among opioids. *Anesthesiology* **99**(2): 455–65.

Bhala N, Emberson J, Merhi A et al (2013) Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* **382**(9894): 769–79.

Bhar D, RoyBasunia S, Das A et al (2016) A comparison between intrathecal clonidine and neostigmine as an adjuvant to bupivacaine in the subarachnoid block for elective abdominal hysterectomy operations: A prospective, double-blind and randomized controlled study. *Saudi J Anaesth* **10**(2): 121-6.
Bhatia A, Flamer D, Shah PS et al (2016) Transforaminal Epidural Steroid Injections for Treating Lumbosacral Radicular Pain from Herniated Intervertebral Discs: A Systematic Review and Meta-Analysis. *Anesth Analg* **122**(3): 857-70.
Bhattacharjee D, Doleman B, Lund J et al (2019) Mirtazapine for Postoperative Nausea and Vomiting: Systematic Review, Meta-analysis, and Trial Sequential Analysis. *J Perianesth Nurs* **34**(4): 680-90.
Bigat Z, Boztug N, Hadimioglu N et al (2006) Does dexamethasone improve the quality of intravenous regional anesthesia and analgesia? A randomized, controlled clinical study. *Anesth Analg* **102**(2): 605–09.
Binning AR, Przesmycki K, Sowinski P et al (2011) A randomised controlled trial on the efficacy and side-effect profile (nausea/vomiting/sedation) of morphine-6-glucuronide versus morphine for post-operative pain relief after major abdominal surgery. *Eur J Pain* **15**(4): 402–08.
Biondi DM, Xiang J, Etropolski M et al (2014) Evaluation of blood pressure and heart rate in patients with hypertension who received tapentadol extended release for chronic pain: a post hoc, pooled data analysis. *Clin Drug Investig* **34**(8): 565–76.
Birse F, Derry S & Moore RA (2012) Phenytoin for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* **5**: CD009485.
Bisgaard T, Schulze S, Christian Hjortso N et al (2008) Randomized clinical trial comparing oral prednisone (50 mg) with placebo before laparoscopic cholecystectomy. *Surg Endosc* **22**(2): 566-72.
Bjarnason I, Scarpignato C, Holmgren E et al (2018) Mechanisms of Damage to the Gastrointestinal Tract From Nonsteroidal Anti-Inflammatory Drugs. *Gastroenterology* **154**(3): 500-14.
Bjorn S, Linde F, Nielsen KK et al (2017) Effect of Perineural Dexamethasone on the Duration of Single Injection Saphenous Nerve Block for Analgesia After Major Ankle Surgery: A Randomized, Controlled Study. *Reg Anesth Pain Med* **42**(2): 210-16.
Blackler RW, Gemici B, Manko A et al (2014) NSAID-gastroenteropathy: new aspects of pathogenesis and prevention. *Curr Opin Pharmacol* **19C**: 11–16.
Blanda M, Rench T, Gerson LW et al (2001) Intranasal lidocaine for the treatment of migraine headache: a randomized, controlled trial. *Acad Emerg Med* **8**(4): 337–42.
Blanloeil Y, Bizouarn P, Le Teurnier Y et al (2001) Postoperative analgesia by epidural methylprednisolone after posterolateral thoracotomy. *Br J Anaesth* **87**(4): 635–38.
Blaudszun G, Lysakowski C, Elia N et al (2012) Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* **116**(6): 1312–22.
Blieden M, Paramore LC, Shah D et al (2014) A perspective on the epidemiology of acetaminophen exposure and toxicity in the United States. *Expert Rev Clin Pharmacol* **7**(3): 341–48.
Bodley PO, Mirza V, Spears JR et al (1966) Obstetric analgesia with methoxyflurane. A clinical trial. *Anaesthesia* **21**(4): 457–63.
Bonnet U & Scherbaum N (2017) How addictive are gabapentin and pregabalin? A systematic review. *Eur Neuropsychopharmacol* **27**(12): 1185-215.
Boom M, Niesters M, Sarton E et al (2012) Non-analgesic effects of opioids: opioid-induced respiratory depression. *Curr Pharm Des* **18**(37): 5994–6004.
Borgelt LM, Franson KL, Nussbaum AM et al (2013) The pharmacologic and clinical effects of medical cannabis. *Pharmacotherapy* **33**(2): 195–209.
Borghi B, Facchini F, Agnoletti V et al (2006) Pain relief and motor function during continuous interscalene analgesia after open shoulder surgery: a prospective, randomized, double-blind comparison between levobupivacaine 0.25%, and ropivacaine 0.25% or 0.4%. *Eur J Anaesthesiol* **23**(12): 1005–09.
Bornemann-Cimenti H, Dorn C & Rumpold-Seitlinger G (2017) Early Onset and Treatment of Phantom Limb Pain Following Surgical Amputation. *Pain Med* **18**(12): 2510-12.
Bostrom E, Hammarlund-Udenaes M & Simonsson US (2008) Blood-brain barrier transport helps to explain discrepancies in in vivo potency between oxycodone and morphine. *Anesthesiology* **108**(3): 495–505.
Botting RM (2006) Inhibitors of cyclooxygenases: mechanisms, selectivity and uses. *J Physiol Pharmacol* **57 Suppl 5**: 113–24.
Bowsher D (1997) The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage* **13**(6): 327–31.
Brandsborg B, Nikolajsen L, Hansen CT et al (2007) Risk factors for chronic pain after hysterectomy: a nationwide questionnaire and database study. *Anesthesiology* **106**(5): 1003–12.
Bravo L, Mico JA & Berrocoso E (2017) Discovery and development of tramadol for the treatment of pain. *Expert Opin Drug Discov* **12**(12): 1281-91.
Bredlau AL, Thakur R, Korones DN et al (2013) Ketamine for pain in adults and children with cancer: a systematic review and synthesis of the literature. *Pain Med* **14**(10): 1505–17.

Brinck EC, Tiippana E, Heesen M et al (2018) Perioperative intravenous ketamine for acute postoperative pain in adults. *Cochrane Database Syst Rev* **12**: CD012033.
Brodner G, Buerkle H, Van Aken H et al (2007) Postoperative analgesia after knee surgery: a comparison of three different concentrations of ropivacaine for continuous femoral nerve blockade. *Anesth Analg* **105**(1): 256–62.
Brotzman EA, Sandoval LF & Crane J (2018) Use of Nitrous Oxide in Dermatology: A Systematic Review. *Dermatol Surg* **44**(5): 661-69.
Brouquet A, Cudennec T, Benoist S et al (2010) Impaired mobility, ASA status and administration of tramadol are risk factors for postoperative delirium in patients aged 75 years or more after major abdominal surgery. *Ann Surg* **251**(4): 759–65.
Brubaker L, Kendall L & Reina E (2016) Multimodal analgesia: A systematic review of local NSAIDs for non-ophthalmologic postoperative pain management. *Int J Surg* **32**: 158-66.
Bryson GL, Thompson C, Gagne S et al (2007) The addition of adrenaline to thoracic epidural meperidine does not improve analgesia following thoracotomy. *Can J Anaesth* **54**(11): 882–90.
Buckley NA & Faunce TA (2013) Trials and tribulations in the removal of dextropropoxyphene from the Australian Register of Therapeutic Goods. *Med J Aust* **199**(4): 257–60.
Buhre W, Disma N, Hendrickx J et al (2019) European Society of Anaesthesiology Task Force on Nitrous Oxide: a narrative review of its role in clinical practice. *Br J Anaesth* **122**(5): 587-604.
Bujak-Gizycka B, Kacka K, Suski M et al (2012) Beneficial effect of amantadine on postoperative pain reduction and consumption of morphine in patients subjected to elective spine surgery. *Pain Med* **13**(3): 459–65.
Bujedo B (2014) Spinal opioid bioavailability in postoperative pain. *Pain Pract* **14**(4): 350–64.
Buntine P, Thom O, Babl F et al (2007) Prehospital analgesia in adults using inhaled methoxyflurane. *Emerg Med Australas* **19**(6): 509–14.
Burns JW, Hodsman NB, McLintock TT et al (1989) The influence of patient characteristics on the requirements for postoperative analgesia. A reassessment using patient-controlled analgesia. *Anaesthesia* **44**(1): 2–6.
Buttner M, Walder B, von Elm E et al (2004) Is low-dose haloperidol a useful antiemetic?: A meta-analysis of published and unpublished randomized trials. *Anesthesiology* **101**(6): 1454–63.
Buvanendran A & Kroin JS (2009) Multimodal analgesia for controlling acute postoperative pain. *Curr Opin Anaesthesiol* **22**(5): 588–93.
Calderon-Ospina CA, Nava-Mesa MO & Arbelaez Ariza CE (2020) Effect of Combined Diclofenac and B Vitamins (Thiamine, Pyridoxine, and Cyanocobalamin) for Low Back Pain Management: Systematic Review and Meta-analysis. *Pain Med* **21**(4): 766-81.
Campbell G, Hall WD, Peacock A et al (2018) Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. *Lancet Public Health* **3**(7): e341-e50.
Campesi I, Fois M & Franconi F (2012) Sex and gender aspects in anesthetics and pain medication. *Handb Exp Pharmacol*(214): 265–78.
Cann C, Curran J, Milner T et al (2002) Unwanted effects of morphine-6-glucoronide and morphine. *Anaesthesia* **57**(12): 1200–03.
Caparrotta TM, Antoine DJ & Dear JW (2018) Are some people at increased risk of paracetamol-induced liver injury? A critical review of the literature. *Eur J Clin Pharmacol* **74**(2): 147-60.
Capogna G, Celleno D, Fusco P et al (1999) Relative potencies of bupivacaine and ropivacaine for analgesia in labour. *Br J Anaesth* **82**(3): 371–73.
Carlisle JB (2012) A meta-analysis of prevention of postoperative nausea and vomiting: randomised controlled trials by Fujii et al. compared with other authors. *Anaesthesia* **67**(10): 1076–90.
Carlisle JB & Stevenson CA (2006) Drugs for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev* **3**: CD004125.
Carmel R (2000) Current concepts in cobalamin deficiency. *Annu Rev Med* **51**: 357–75.
Carr AC & McCall C (2017) The role of vitamin C in the treatment of pain: new insights. *J Transl Med* **15**(1): 77.
Carvalho B (2012) Intrathecal fentanyl added to bupivacaine and morphine for cesarean delivery may induce a subtle acute opioid tolerance. *Int J Obstet Anesth* **21**: 29–34.
Carvalho B, Riley E, Cohen SE et al (2005) Single-dose, sustained-release epidural morphine in the management of postoperative pain after elective cesarean delivery: results of a multicenter randomized controlled study. *Anesth Analg* **100**(4): 1150–58.
Carvalho B, Roland LM, Chu LF et al (2007) Single-dose, extended-release epidural morphine (DepoDur) compared to conventional epidural morphine for post-cesarean pain. *Anesth Analg* **105**(1): 176–83.
Carvalho F & Tenorio S (2013) Comparative study between doses of intrathecal morphine for analgesia after caesarian. *Braz J Anesthesiol* **63**(6): 492–99.
Casati A, Borghi B, Fanelli G et al (2002) A double-blinded, randomized comparison of either 0.5% levobupivacaine or 0.5% ropivacaine for sciatic nerve block. *Anesth Analg* **94**(4): 987–90.
Casati A, Borghi B, Fanelli G et al (2003a) Interscalene brachial plexus anesthesia and analgesia for open shoulder surgery: a randomized, double-blinded comparison between levobupivacaine and ropivacaine. *Anesth Analg* **96**(1): 253–59.

Casati A, Santorsola R, Aldegheri G et al (2003b) Intraoperative epidural anesthesia and postoperative analgesia with levobupivacaine for major orthopedic surgery: a double-blind, randomized comparison of racemic bupivacaine and ropivacaine. *J Clin Anesth* **15**(2): 126–31.
Casati A, Vinciguerra F, Cappelleri G et al (2004) Levobupivacaine 0.2% or 0.125% for continuous sciatic nerve block: a prospective, randomized, double-blind comparison with 0.2% ropivacaine. *Anesth Analg* **99**(3): 919–23.
Casati A, Vinciguerra F, Scarioni M et al (2003c) Lidocaine versus ropivacaine for continuous interscalene brachial plexus block after open shoulder surgery. *Acta Anaesthesiol Scand* **47**(3): 355–60.
Cashman JN & Dolin SJ (2004) Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data. *Br J Anaesth* **93**(2): 212-23.
Castera L, Negre I, Samii K et al (2001) Patient-administered nitrous oxide/oxygen inhalation provides safe and effective analgesia for percutaneous liver biopsy: a randomized placebo-controlled trial. *Am J Gastroenterol* **96**(5): 1553–57.
Catley DM, Thornton C, Jordan C et al (1985) Pronounced, episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern and analgesic regimen. *Anesthesiology* **63**(1): 20–28.
Caumo W, Torres F, Moreira NL, Jr. et al (2007) The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. *Anesth Analg* **105**(5): 1263–71.
Cavalcante AN, Sprung J, Schroeder DR et al (2017) Multimodal Analgesic Therapy With Gabapentin and Its Association With Postoperative Respiratory Depression. *Anesth Analg* **125**(1): 141-46.
Cave G, Harvey M, Willers J et al (2014) LIPAEMIC report: results of clinical use of intravenous lipid emulsion in drug toxicity reported to an online lipid registry. *J Med Toxicol* **10**(2): 133–42.
Cazarim GDS, Vercosa N, Carneiro L et al (2018) A 50-50% mixture of nitrous oxide-oxygen in transrectal ultrasound-guided prostate biopsy: A randomized and prospective clinical trial. *PLoS One* **13**(4): e0195574.
Ceelie I, James LP, Gijsen V et al (2011) Acute liver failure after recommended doses of acetaminophen in patients with myopathies. *Crit Care Med* **39**(4): 678–82.
Cepeda MS, Carr DB, Miranda N et al (2005) Comparison of morphine, ketorolac, and their combination for postoperative pain: results from a large, randomized, double-blind trial. *Anesthesiology* **103**(6): 1225–32.
Cepeda MS, Fife D, Ma Q et al (2013a) Comparison of the risks of opioid abuse or dependence between tapentadol and oxycodone: results from a cohort study. *J Pain* **14**(10): 1227–41.
Cepeda MS, Fife D, Vo L et al (2013b) Comparison of opioid doctor shopping for tapentadol and oxycodone: a cohort study. *J Pain* **14**(2): 158–64.
Cepeda MS, Tzortzopoulou A, Thackrey M et al (2010) Adjusting the pH of lidocaine for reducing pain on injection. *Cochrane Database Syst Rev*(12): CD006581.
Cepeda MS, Uribe C, Betancourt J et al (1997) Pain relief after knee arthroscopy: intra-articular morphine, intra-articular bupivacaine, or subcutaneous morphine? *Reg Anesth* **22**(3): 233-8.
Cerchietti LC, Navigante AH, Bonomi MR et al (2002) Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. *Cancer* **95**(10): 2230–36.
Cerchietti LC, Navigante AH, Korte MW et al (2003) Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: a pilot study. *Pain* **105**(1-2): 265–73.
Chaitanya NC, Muthukrishnan A, Krishnaprasad CMS et al (2018) An Insight and Update on the Analgesic Properties of Vitamin C. *J Pharm Bioallied Sci* **10**(3): 119-25.
Chakraborty S, Chakrabarti J, Mandal MC et al (2010) Effect of clonidine as adjuvant in bupivacaine-induced supraclavicular brachial plexus block: A randomized controlled trial. *Indian J Pharmacol* **42**(2): 74–77.
Chalkiadis GA, Abdullah F, Bjorksten AR et al (2013) Absorption characteristics of epidural levobupivacaine with adrenaline and clonidine in children. *Paediatr Anaesth* **23**(1): 58–67.
Challapalli V, Tremont-Lukats IW, McNicol ED et al (2005) Systemic administration of local anesthetic agents to relieve neuropathic pain. *Cochrane Database Syst Rev* **4**: CD003345.
Chan AK, Cheung CW & Chong YK (2010a) Alpha-2 agonists in acute pain management. *Expert Opin Pharmacother* **11**(17): 2849–68.
Chan DK & Parikh SR (2014) Perioperative ketorolac increases post-tonsillectomy hemorrhage in adults but not children. *Laryngoscope* **124**(8): 1789–93.
Chan FK, Lanas A, Scheiman J et al (2010b) Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *Lancet* **376**(9736): 173–79.
Chan FKL, Ching JYL, Tse YK et al (2017) Gastrointestinal safety of celecoxib versus naproxen in patients with cardiothrombotic diseases and arthritis after upper gastrointestinal bleeding (CONCERN): an industry-independent, double-blind, double-dummy, randomised trial. *Lancet* **389**(10087): 2375-82.
Chan MT, Choi KC, Gin T et al (2006) The additive interactions between ondansetron and droperidol for preventing postoperative nausea and vomiting. *Anesth Analg* **103**(5): 1155–62.
Chan MT, Peyton PJ, Myles PS et al (2016) Chronic postsurgical pain in the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA)-II trial. *Br J Anaesth* **117**(6): 801-11.
Chan MT, Wan AC, Gin T et al (2011) Chronic postsurgical pain after nitrous oxide anesthesia. *Pain* **152**(11): 2514–20.
Chang G, Chen L & Mao J (2007) Opioid tolerance and hyperalgesia. *Med Clin North Am* **91**(2): 199–211.

Chang SH, Maney KM, Phillips JP et al (2010) A comparison of the respiratory effects of oxycodone versus morphine: a randomised, double-blind, placebo-controlled investigation. *Anaesthesia* **65**(10): 1007–12.
Chang YC, Liu CL, Liu TP et al (2017) Effect of Perioperative Intravenous Lidocaine Infusion on Acute and Chronic Pain after Breast Surgery: A Meta-Analysis of Randomized Controlled Trials. *Pain Pract* **17**(3): 336-43.
Channell JS & Schug S (2018) Toxicity of tapentadol: a systematic review. *Pain Manag* **8**(5): 327-39.
Chaparro LE, Smith SA, Moore RA et al (2013) Pharmacotherapy for the prevention of chronic pain after surgery in adults. *Cochrane Database Syst Rev* **7**: CD008307.
Chaplan SR, Duncan SR, Brodsky JB et al (1992) Morphine and hydromorphone epidural analgesia. A prospective, randomized comparison. *Anesthesiology* **77**(6): 1090–94.
Chapman SJ, Garner JJ, Drake TM et al (2019) Systematic Review and Meta-analysis of Nonsteroidal Anti-inflammatory Drugs to Improve GI Recovery After Colorectal Surgery. *Dis Colon Rectum* **62**(2): 248-56.
Chattopadhyay A, Maitra S, Sen S et al (2013) A study to compare the analgesic efficacy of intrathecal bupivacaine alone with intrathecal bupivacaine midazolam combination in patients undergoing elective infraumbilical surgery. *Anesthesiol Res Pract* **2013**: 567134.
Chazalon P, Tourtier JP, Villevielle T et al (2003) Ropivacaine-induced cardiac arrest after peripheral nerve block: successful resuscitation. *Anesthesiology* **99**(6): 1449–51.
Chen C & Tao R (2018a) The Impact of Magnesium Sulfate on Pain Control After Laparoscopic Cholecystectomy: A Meta-Analysis of Randomized Controlled Studies. *Surg Laparosc Endosc Percutan Tech* **28**(6): 349-53.
Chen CC, Siddiqui FJ, Chen TL et al (2012) Dexamethasone for prevention of postoperative nausea and vomiting in patients undergoing thyroidectomy: meta-analysis of randomized controlled trials. *World J Surg* **36**(1): 61–68.
Chen Q, An R, Zhou J et al (2018b) Clinical analgesic efficacy of dexamethasone as a local anesthetic adjuvant for transversus abdominis plane (TAP) block: A meta-analysis. *PLoS One* **13**(6): e0198923.
Chen S, Roffey DM, Dion CA et al (2016) Effect of Perioperative Vitamin C Supplementation on Postoperative Pain and the Incidence of Chronic Regional Pain Syndrome: A Systematic Review and Meta-Analysis. *Clin J Pain* **32**(2): 179-85.
Cheng CR, Su TH, Hung YC et al (2002) A comparative study of the safety and efficacy of 0.5% levobupivacaine and 0.5% bupivacaine for epidural anesthesia in subjects undergoing elective caesarean section. *Acta Anaesthesiol Sin* **40**(1): 13–20.
Cheng HF & Harris RC (2004) Cyclooxygenases, the kidney, and hypertension. *Hypertension* **43**(3): 525–30.
Cheng HM, Park JH & Hernstadt D (2013) Subacute combined degeneration of the spinal cord following recreational nitrous oxide use. *BMJ Case Rep* **2013**.
Chevreau M, Romand X, Gaudin P et al (2017) Bisphosphonates for treatment of Complex Regional Pain Syndrome type 1: A systematic literature review and meta-analysis of randomized controlled trials versus placebo. *Joint Bone Spine* **84**(4): 393-99.
Chia SK, Wernecke GC, Harris IA et al (2013) Peri-articular steroid injection in total knee arthroplasty: a prospective, double blinded, randomized controlled trial. *J Arthroplasty* **28**(4): 620–23.
Chiang TT, Hung CT, Wang WM et al (2013) Recreational nitrous oxide abuse-induced vitamin B12 deficiency in a patient presenting with hyperpigmentation of the skin. *Case Rep Dermatol* **5**(2): 186–91.
Chiew AL, Gluud C, Brok J et al (2018) Interventions for paracetamol (acetaminophen) overdose. *Cochrane Database Syst Rev* **2**: CD003328.
Chiew AL, Reith D, Pomerleau A et al (2020) Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. *Med J Aust* **212**(4): 175-83.
Chiu HY, Yeh TH, Huang YC et al (2016) Effects of Intravenous and Oral Magnesium on Reducing Migraine: A Meta-analysis of Randomized Controlled Trials. *Pain Physician* **19**(1): E97-112.
Cho HK, Park IJ, Yoon HY et al (2018) Efficacy of Adjuvant Magnesium for Posttonsillectomy Morbidity in Children: A Meta-analysis. *Otolaryngol Head Neck Surg* **158**(1): 27-35.
Choi J, Lee JA, Alimoradi Z et al (2018) Aromatherapy for the relief of symptoms in burn patients: A systematic review of randomized controlled trials. *Burns* **44**(6): 1395-402.
Chong C, Schug SA, Page-Sharp M et al (2009) Development of a sublingual/oral formulation of ketamine for use in neuropathic pain: preliminary findings from a three-way randomized, crossover study. *Clin Drug Investig* **29**(5): 317–24.
Chong MA, Szoke DJ, Berbenetz NM et al (2018) Dexamethasone as an Adjuvant for Caudal Blockade in Pediatric Surgical Patients: A Systematic Review and Meta-analysis. *Anesth Analg* **127**(2): 520-28.
Chou D, Abalos E, Gyte GM et al (2013) Paracetamol/acetaminophen (single administration) for perineal pain in the early postpartum period. *Cochrane Database Syst Rev* **1**: CD008407.
Chou R, Gordon DB, de Leon-Casasola OA et al (2016) Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain* **17**(2): 131-57.

Chou R, Weimer MB & Dana T (2014) Methadone overdose and cardiac arrhythmia potential: findings from a review of the evidence for an American Pain Society and College on Problems of Drug Dependence clinical practice guideline. *J Pain* **15**(4): 338–65.
Christensen B, Guttormsen AB, Schneede J et al (1994) Preoperative methionine loading enhances restoration of the cobalamin-dependent enzyme methionine synthase after nitrous oxide anesthesia. *Anesthesiology* **80**(5): 1046–56.
Christensen CP, Jacobs CA & Jennings HR (2009) Effect of periarticular corticosteroid injections during total knee arthroplasty. A double-blind randomized trial. *J Bone Joint Surg Am* **91**(11): 2550–55.
Christoph T, Schroder W, Tallarida RJ et al (2013) Spinal-supraspinal and intrinsic mu-opioid receptor agonist-norepinephrine reuptake inhibitor (MOR-NRI) synergy of tapentadol in diabetic heat hyperalgesia in mice. *J Pharmacol Exp Ther* **347**(3): 794-801.
Chu LF, Angst MS & Clark D (2008) Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clin J Pain* **24**(6): 479–96.
Chu LF, Cun T, Ngai LK et al (2012) Modulation of remifentanil-induced postinfusion hyperalgesia by the beta-blocker propranolol in humans. *Pain* **153**(5): 974–81.
Chung JW, Zeng Y & Wong TK (2013) Drug therapy for the treatment of chronic nonspecific low back pain: systematic review and meta-analysis. *Pain Physician* **16**(6): E685–704.
Cialkowska-Rysz A & Dzierzanowski T (2019) Topical morphine for treatment of cancer-related painful mucosal and cutaneous lesions: a double-blind, placebo-controlled cross-over clinical trial. *Arch Med Sci* **15**(1): 146-51.
Clarke H, Page GM, McCartney CJ et al (2015) Pregabalin reduces postoperative opioid consumption and pain for 1 week after hospital discharge, but does not affect function at 6 weeks or 3 months after total hip arthroplasty. *Br J Anaesth* **115**(6): 903-11.
Clattenburg EJ, Hailozian C, Haro D et al (2018) Slow Infusion of Low-dose Ketamine Reduces Bothersome Side Effects Compared to Intravenous Push: A Double-blind, Double-dummy, Randomized Controlled Trial. *Acad Emerg Med* **25**(9): 1048-52.
Clements JA, Nimmo WS & Grant IS (1982) Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. *J Pharm Sci* **71**(5): 539–42.
Clerc S, Vuilleumier H, Frascarolo P et al (2005) Is the effect of inguinal field block with 0.5% bupivacaine on postoperative pain after hernia repair enhanced by addition of ketorolac or S(+) ketamine? *Clin J Pain* **21**(1): 101–05.
Codero F, Vitalis M & Thikra S (2016) A randomised controlled trial comparing the effect of adjuvant intrathecal 2 mg midazolam to 20 micrograms fentanyl on postoperative pain for patients undergoing lower limb orthopaedic surgery under spinal anaesthesia. *Afr Health Sci* **16**(1): 282-91.
Coffey F, Wright J, Hartshorn S et al (2014) STOP!: a randomised, double-blind, placebo-controlled study of the efficacy and safety of methoxyflurane for the treatment of acute pain. *Emerg Med J* **31**(8): 613-8.
Cohen M, Zuk J, McKay N et al (2017) Intrathecal Morphine Versus Extended-Release Epidural Morphine for Postoperative Pain Control in Pediatric Patients Undergoing Posterior Spinal Fusion. *Anesth Analg* **124**(6): 2030-37.
Cohen SP, Bhatia A, Buvanendran A et al (2018) Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med* **43**(5): 521-46.
Cole PJ, Craske DA & Wheatley RG (2000) Efficacy and respiratory effects of low-dose spinal morphine for postoperative analgesia following knee arthroplasty. *Br J Anaesth* **85**(2): 233–37.
Collaborators DT & West Midlands Research C (2017) Dexamethasone versus standard treatment for postoperative nausea and vomiting in gastrointestinal surgery: randomised controlled trial (DREAMS Trial). *BMJ* **357**: j1455.
Colli A, Conte D, Valle SD et al (2012) Meta-analysis: nonsteroidal anti-inflammatory drugs in biliary colic. *Aliment Pharmacol Ther* **35**(12): 1370–78.
Collins SL, Edwards JE, Moore RA et al (2000) Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. *Cochrane Database Syst Rev* **2**: CD001440.
Colucci SV, Perrino PJ, Shram M et al (2014) Abuse potential of intravenous oxycodone/naloxone solution in nondependent recreational drug users. *Clin Drug Investig* **34**(6): 421–29.
Coluzzi F & Mattia C (2005) Oxycodone. Pharmacological profile and clinical data in chronic pain management. *Minerva Anestesiol* **71**(7-8): 451–60.
Colvin LA, Bull F & Hales TG (2019) Perioperative opioid analgesia-when is enough too much? A review of opioid-induced tolerance and hyperalgesia. *Lancet* **393**(10180): 1558-68.
Comelon M, Raeder J, Stubhaug A et al (2016) Gradual withdrawal of remifentanil infusion may prevent opioid-induced hyperalgesia. *Br J Anaesth* **116**(4): 524-30.
Comelon M, Wisloeff-Aase K, Raeder J et al (2013) A comparison of oxycodone prolonged-release vs. oxycodone + naloxone prolonged-release after laparoscopic hysterectomy. *Acta Anaesthesiol Scand* **57**(4): 509–17.
Compton P, Charuvastra VC & Ling W (2001) Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. *Drug Alcohol Depend* **63**(2): 139–46.

Compton PA, Ling W & Torrington MA (2008) Lack of effect of chronic dextromethorphan on experimental pain tolerance in methadone-maintained patients. *Addict Biol* **13**(3-4): 393–402.
Conger A, Cushman DM, Speckman RA et al (2020) The Effectiveness of Fluoroscopically Guided Cervical Transforaminal Epidural Steroid Injection for the Treatment of Radicular Pain; a Systematic Review and Meta-analysis. *Pain Med* **21**(1): 41-54.
Connelly NR, Freiman JP, Lucas T et al (2011) Addition of epinephrine to epidural bupivacaine infusions following initiation of labor analgesia with epidural fentanyl. *J Clin Anesth* **23**(4): 265–69.
Constantinescu DS, Campbell MP, Moatshe G et al (2019) Effects of Perioperative Nonsteroidal Anti-inflammatory Drug Administration on Soft Tissue Healing: A Systematic Review of Clinical Outcomes After Sports Medicine Orthopaedic Surgery Procedures. *Orthop J Sports Med* **7**(4): 2325967119838873.
Cooper D, Lindsay S & Ryall D, et al (1997) Does intrathecal fentanyl produce acute cross tolerance to iv morphine. *Br J Anaesth* **78**(3): 311–13.
Cooper TE, Chen J, Wiffen PJ et al (2017) Morphine for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* **5**: CD011669.
Coplan PM, Sessler NE, Harikrishnan V et al (2017) Comparison of abuse, suspected suicidal intent, and fatalities related to the 7-day buprenorphine transdermal patch versus other opioid analgesics in the National Poison Data System. *Postgrad Med* **129**(1): 55-61.
Corcoran TB, Myles PS, Forbes AB et al (2019) The perioperative administration of dexamethasone and infection (PADDI) trial protocol: rationale and design of a pragmatic multicentre non-inferiority study. *BMJ Open* **9**(9): e030402.
Cording M, Derry S, Phillips T et al (2015) Milnacipran for pain in fibromyalgia in adults. *Cochrane Database Syst Rev*(10): CD008244.
Corral-Gudino L, Tan AJ, Del Pino-Montes J et al (2017) Bisphosphonates for Paget's disease of bone in adults. *Cochrane Database Syst Rev* **12**: CD004956.
Coulbault L, Beaussier M, Verstuyft C et al (2006) Environmental and genetic factors associated with morphine response in the postoperative period. *Clin Pharmacol Ther* **79**(4): 316–24.
Cousins MJ & Mather LE (1984) Intrathecal and epidural administration of opioids. *Anesthesiology* **61**(3): 276–310.
Covino BG & Wildsmith JA (1998) Clinical pharmacology of local anaesthetic agents. In: *Neural Blockade* 3rd edn. Cousins MJ and Bridenbaugh P (eds). Philadelphia, Lippincott-Raven.
Crespo S, Dangelser G & Haller G (2017) Intrathecal clonidine as an adjuvant for neuraxial anaesthesia during caesarean delivery: a systematic review and meta-analysis of randomised trials. *Int J Obstet Anesth* **32**: 64-76.
Crews JC, Hord AH, Denson DD et al (1999) A comparison of the analgesic efficacy of 0.25% levobupivacaine combined with 0.005% morphine, 0.25% levobupivacaine alone, or 0.005% morphine alone for the management of postoperative pain in patients undergoing major abdominal surgery. *Anesth Analg* **89**(6): 1504–09.
Crews KR, Gaedigk A, Dunnenberger HM et al (2014) Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther* **95**(4): 376–82.
Cruciani RA (2008) Methadone: to ECG or not to ECG...That is still the question. *J Pain Symptom Manage* **36**(5): 545–52.
Culebras X, Savoldelli GL, Van Gessel E et al (2007) Low-dose sufentanil does not potentiate intrathecal morphine for perioperative analgesia after major colorectal surgery. *Can J Anaesth* **54**(10): 811–17.
Curatolo M, Petersen-Felix S, Scaramozzino P et al (1998) Epidural fentanyl, adrenaline and clonidine as adjuvants to local anaesthetics for surgical analgesia: meta-analyses of analgesia and side-effects. *Acta Anaesthesiol Scand* **42**(8): 910-20.
Curtis E, Fuggle N, Shaw S et al (2019) Safety of Cyclooxygenase-2 Inhibitors in Osteoarthritis: Outcomes of a Systematic Review and Meta-Analysis. *Drugs Aging* **36**(Suppl 1): 25-44.
Czock D, Keller F, Rasche FM et al (2005) Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet* **44**(1): 61–98.
Dahan A, Kest B, Waxman AR et al (2008a) Sex-specific responses to opiates: animal and human studies. *Anesth Analg* **107**(1): 83–95.
Dahan A, van Dorp E, Smith T et al (2008b) Morphine-6-glucuronide (M6G) for postoperative pain relief. *Eur J Pain* **12**(4): 403–11.
Dahan A, Yassen A, Bijl H et al (2005) Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth* **94**(6): 825–34.
Dahan A, Yassen A, Romberg R et al (2006) Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth* **96**(5): 627–32.
Dahl JB, Jeppesen IS, Jorgensen H et al (1999) Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. *Anesthesiology* **91**(6): 1919–27.
Dale O, Somogyi AA, Li Y et al (2012) Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. *Anesth Analg* **115**(4): 934–43.
Dan AE, Thygesen TH & Pinholt EM (2010) Corticosteroid administration in oral and orthognathic surgery: a systematic review of the literature and meta-analysis. *J Oral Maxillofac Surg* **68**(9): 2207–20.

Dart RC & Bailey E (2007) Does therapeutic use of acetaminophen cause acute liver failure? *Pharmacotherapy* **27**(9): 1219–30.
Dart RC, Cicero TJ, Surratt HL et al (2012) Assessment of the abuse of tapentadol immediate release: the first 24 months. *J Opioid Manag* **8**(6): 395–402.
Dart RC, Green JL, Kuffner EK et al (2010) The effects of paracetamol (acetaminophen) on hepatic tests in patients who chronically abuse alcohol - a randomized study. *Aliment Pharmacol Ther* **32**(3): 478–86.
Dart RC, Surratt HL, Le Lait MC et al (2016) Diversion and Illicit Sale of Extended Release Tapentadol in the United States. *Pain Med* **17**(8): 1490-6.
Davies G, Kingswood C & Street M (1996) Pharmacokinetics of opioids in renal dysfunction. *Clin Pharmacokinet* **31**(6): 410–22.
Davis MP (2012) Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. *J Support Oncol* **10**(6): 209-19.
Dayan AD (2016) Analgesic use of inhaled methoxyflurane: Evaluation of its potential nephrotoxicity. *Hum Exp Toxicol* **35**(1): 91-100.
De Gregori S, De Gregori M, Ranzani GN et al (2012) Morphine metabolism, transport and brain disposition. *Metab Brain Dis* **27**(1): 1–5.
de Leon-Casasola OA & Lema MJ (1996) Postoperative epidural opioid analgesia: what are the choices? *Anesth Analg* **83**(4): 867–75.
de Lima J, Beggs S & Howard R (2000) Neural toxicity of ketamine and other NMDA antagonists. *Pain* **88**(3): 311–12.
de Looze F, Russo M, Bloch M et al (2016) Efficacy of flurbiprofen 8.75 mg spray in patients with sore throat due to an upper respiratory tract infection: A randomised controlled trial. *Eur J Gen Pract* **22**(2): 111-8.
De Oliveira GS, Bialek J, Fitzgerald P et al (2013a) Systemic magnesium to improve quality of post-surgical recovery in outpatient segmental mastectomy: a randomized, double-blind, placebo-controlled trial. *Magnes Res* **26**(4): 156–64.
De Oliveira GS, Jr., Almeida MD, Benzon HT et al (2011) Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology* **115**(3): 575–88.
de Oliveira GS, Jr., Balliu B, Nader A et al (2012a) Dose-ranging effects of intrathecal epinephrine on anesthesia/analgesia: a meta-analysis and metaregression of randomized controlled trials. *Reg Anesth Pain Med* **37**(4): 423–32.
De Oliveira GS, Jr., Castro-Alves LJ, Ahmad S et al (2013b) Dexamethasone to prevent postoperative nausea and vomiting: an updated meta-analysis of randomized controlled trials. *Anesth Analg* **116**(1): 58–74.
De Oliveira GS, Jr., Castro-Alves LJ, Chang R et al (2012b) Systemic metoclopramide to prevent postoperative nausea and vomiting: a meta-analysis without Fujii's studies. *Br J Anaesth* **109**(5): 688–97.
De Oliveira GS, Jr., Castro-Alves LJ, Khan JH et al (2013c) Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology* **119**(1): 178–90.
De Oliveira GS, Jr., Duncan K, Fitzgerald P et al (2014a) Systemic lidocaine to improve quality of recovery after laparoscopic bariatric surgery: a randomized double-blinded placebo-controlled trial. *Obes Surg* **24**(2): 212-8.
De Oliveira GS, Jr., McCarthy R, Turan A et al (2014b) Is dexamethasone associated with recurrence of ovarian cancer? *Anesth Analg* **118**(6): 1213–18.
Deljou A, Hedrick SJ, Portner ER et al (2018) Pattern of perioperative gabapentinoid use and risk for postoperative naloxone administration. *Br J Anaesth* **120**(4): 798-806.
Demirhan A, Tekelioglu UY, Akkaya A et al (2013) Effect of pregabalin and dexamethasone addition to multimodal analgesia on postoperative analgesia following rhinoplasty surgery. *Aesthetic Plast Surg* **37**(6): 1100–06.
Dernedde M, Stadler M, Bardiau F et al (2006) Low vs. high concentration of levobupivacaine for post-operative epidural analgesia: influence of mode of delivery. *Acta Anaesthesiol Scand* **50**(5): 613–21.
Derry S, Bell RF, Straube S et al (2019) Pregabalin for neuropathic pain in adults. *Cochrane Database Syst Rev* **1**: Cd007076.
Derry S, Cording M, Wiffen PJ et al (2016a) Pregabalin for pain in fibromyalgia in adults. *Cochrane Database Syst Rev* **9**: CD011790.
Derry S & Moore RA (2013a) Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* **4**(4): CD008040.
Derry S, Moore RA, Gaskell H et al (2015a) Topical NSAIDs for acute musculoskeletal pain in adults. *Cochrane Database Syst Rev*(6): CD007402.
Derry S, Phillips T, Moore RA et al (2015b) Milnacipran for neuropathic pain in adults. *Cochrane Database Syst Rev*(7): CD011789.
Derry S, Rabbie R & Moore RA (2013b) Diclofenac with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* **4**(4): CD008783.
Derry S, Stannard C, Cole P et al (2016b) Fentanyl for neuropathic pain in adults. *Cochrane Database Syst Rev* **10**: CD011605.
Desmedt C, Demicheli R, Fornili M et al (2018) Potential Benefit of Intra-operative Administration of Ketorolac on Breast Cancer Recurrence According to the Patient's Body Mass Index. *J Natl Cancer Inst* **110**(10): 1115-22.

Desmeules JA, Piguet V, Collart L et al (1996) Contribution of monoaminergic modulation to the analgesic effect of tramadol. *Br J Clin Pharmacol* **41**(1): 7–12.
Devabhakthuni S (2013) Efficacy and safety of remifentanil as an alternative labor analgesic. *Clin Med Insights Womens Health* **6**: 37–49.
Devinsky O, Cilio MR, Cross H et al (2014) Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* **55**(6): 791–802.
Dhatariya K (2013) II. Does dexamethasone-induced hyperglycaemia contribute to postoperative morbidity and mortality? *Br J Anaesth* **110**(5): 674–75.
Diakos EA, Gallos ID, El-Shunnar S et al (2011) Dexamethasone reduces pain, vomiting and overall complications following tonsillectomy in adults: a systematic review and meta-analysis of randomised controlled trials. *Clin Otolaryngol* **36**(6): 531–42.
Dib RA, Chinzon D, Fontes LH et al (2014) Ulcer and bleeding complications and their relationship with dyspeptic symptoms in NSAIDs users: a transversal multicenter study. *Scand J Gastroenterol* **49**(7): 785–89.
Dieleman JM, Nierich AP, Rosseel PM et al (2012) Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. *JAMA* **308**(17): 1761–67.
Diercks GR, Comins J, Bennett K et al (2019) Comparison of Ibuprofen vs Acetaminophen and Severe Bleeding Risk After Pediatric Tonsillectomy: A Noninferiority Randomized Clinical Trial. *JAMA Otolaryngol Head Neck Surg* **145**(6): 494-500.
Dimitriou V, Mavridou P, Manataki A et al (2017) The Use of Aromatherapy for Postoperative Pain Management: A Systematic Review of Randomized Controlled Trials. *Journal of PeriAnesthesia Nursing* **32**(6): 530-41.
Ding X, Jin S, Niu X et al (2014) Morphine with adjuvant ketamine versus higher dose of morphine alone for acute pain: a meta-analysis. *Int J Clin Exp Med* **7**(9): 2504–10.
do Vale AH, Videira RL, Gomez DS et al (2016) Effect of nitrous oxide on fentanyl consumption in burned patients undergoing dressing change. *Braz J Anesthesiol* **66**(1): 7-11.
Doleman B, Heinink TP, Read DJ et al (2015a) A systematic review and meta-regression analysis of prophylactic gabapentin for postoperative pain. *Anaesthesia* **70**(10): 1186-204.
Doleman B, Read D, Lund JN et al (2015b) Preventive Acetaminophen Reduces Postoperative Opioid Consumption, Vomiting, and Pain Scores After Surgery: Systematic Review and Meta-Analysis. *Reg Anesth Pain Med* **40**(6): 706-12.
Dolin SJ & Cashman JN (2005) Tolerability of acute postoperative pain management: nausea, vomiting, sedation, pruritus, and urinary retention. Evidence from published data. *Br J Anaesth* **95**(5): 584–91.
Dolin SJ, Cashman JN & Bland JM (2002) Effectiveness of acute postoperative pain management: I. Evidence from published data. *Br J Anaesth* **89**(3): 409–23.
Dong T, Liu M & Lv K (2017) Inhaled nitrous oxide can reduce the pain perception in post Caldwell-Luc operation patients-a randomised trial. *Sci Rep* **7**(1): 17760.
Duan P, Liu Y & Li J (2017) The comparative efficacy and safety of topical non-steroidal anti-inflammatory drugs for the treatment of anterior chamber inflammation after cataract surgery: a systematic review and network meta-analysis. *Graefes Arch Clin Exp Ophthalmol* **255**(4): 639-49.
Ducasse JL, Siksik G, Durand-Bechu M et al (2013) Nitrous oxide for early analgesia in the emergency setting: a randomized, double-blind multicenter prehospital trial. *Acad Emerg Med* **20**(2): 178–84.
Duehmke RM, Derry S, Wiffen PJ et al (2017) Tramadol for neuropathic pain in adults. *Cochrane Database Syst Rev* **6**: CD003726.
Dunn LK, Yerra S, Fang S et al (2018) Safety profile of intraoperative methadone for analgesia after major spine surgery: An observational study of 1,478 patients. *J Opioid Manag* **14**(2): 83-87.
Echevarria G, Elgueta F, Fierro C et al (2011) Nitrous oxide (N(2)O) reduces postoperative opioid-induced hyperalgesia after remifentanil-propofol anaesthesia in humans. *Br J Anaesth* **107**(6): 959–65.
Edwards RR, Wasan AD, Michna E et al (2011) Elevated pain sensitivity in chronic pain patients at risk for opioid misuse. *J Pain* **12**(9): 953–63.
Ehret GB, Daali Y, Chabert J et al (2013) Influence of CYP2D6 activity on pre-emptive analgesia by the N-methyl-D-aspartate antagonist dextromethorphan in a randomized controlled trial of acute pain. *Pain Physician* **16**(1): 45–56.
Ehrlich AT & Darcq E (2019) Recommending buprenorphine for pain management. *Pain Manag* **9**(1): 13-16.
Eichenberger U, Neff F, Sveticic G et al (2008) Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg* **106**(4): 1265–73.
Eipe N, Penning J, Yazdi F et al (2015) Perioperative use of pregabalin for acute pain-a systematic review and meta-analysis. *Pain* **156**(7): 1284-300.
Eisenberg E, Ogintz M & Almog S (2014) The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: a phase 1a study. *J Pain Palliat Care Pharmacother* **28**(3): 216–25.

Eisenberg E, Pud D, Koltun L et al (2007) Effect of early administration of the N-methyl-d-aspartate receptor antagonist amantadine on the development of postmastectomy pain syndrome: a prospective pilot study. *J Pain* **8**(3): 223–29.

El-Boghdadly K, Brull R, Sehmbi H et al (2017) Perineural Dexmedetomidine Is More Effective Than Clonidine When Added to Local Anesthetic for Supraclavicular Brachial Plexus Block: A Systematic Review and Meta-analysis. *Anesth Analg* **124**(6): 2008-20.

Elia N, Culebras X, Mazza C et al (2008) Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. *Reg Anesth Pain Med* **33**(2): 159–67.

Elia N, Lysakowski C & Tramer MR (2005) Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology* **103**(6): 1296–304.

EMA (2013) *Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation.* http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001829.jsp&mid=WC0b01ac058004d5c1 Accessed 15 February 2020

Emanuelsson BM, Zaric D, Nydahl PA et al (1995) Pharmacokinetics of ropivacaine and bupivacaine during 21 hours of continuous epidural infusion in healthy male volunteers. *Anesth Analg* **81**(6): 1163–68.

Endo N, Fujino K, Doi T et al (2017) Effect of elcatonin versus nonsteroidal anti-inflammatory medications for acute back pain in patients with osteoporotic vertebral fracture: a multiclinic randomized controlled trial. *J Bone Miner Metab* **35**(4): 375-84.

Engelman E & Marsala C (2013) Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis. *Br J Anaesth* **110**(1): 21–27.

Enthoven WT, Roelofs PD, Deyo RA et al (2016) Non-steroidal anti-inflammatory drugs for chronic low back pain. *Cochrane Database Syst Rev* **2**: Cd012087.

Erdine S, Yucel A, Ozyalcin S et al (1999) Neurotoxicity of midazolam in the rabbit. *Pain* **80**(1-2): 419-23.

Esmaoglu A, Mizrak A, Akin A et al (2005) Addition of dexmedetomidine to lidocaine for intravenous regional anaesthesia. *Eur J Anaesthesiol* **22**(6): 447–51.

Etminan M, Sadatsafavi M, Jafari S et al (2009) Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. *Chest* **136**(5): 1316–23.

Evoy KE, Morrison MD & Saklad SR (2017) Abuse and Misuse of Pregabalin and Gabapentin. *Drugs* **77**(4): 403-26.

Eyler EC (2013) Chronic and acute pain and pain management for patients in methadone maintenance treatment. *Am J Addict* **22**(1): 75–83.

Ezri T, Lurie S, Stein A et al (2002) Postoperative nausea and vomiting: comparison of the effect of postoperative meperidine or morphine in gynecologic surgery patients. *J Clin Anesth* **14**(4): 262-6.

Fabritius ML, Geisler A, Petersen PL et al (2016) Gabapentin for post-operative pain management - a systematic review with meta-analyses and trial sequential analyses. *Acta Anaesthesiol Scand* **60**(9): 1188-208.

Fabritius ML, Strom C, Koyuncu S et al (2017) Benefit and harm of pregabalin in acute pain treatment: a systematic review with meta-analyses and trial sequential analyses. *Br J Anaesth* **119**(4): 775-91.

Fan G, Wang B, Liu C et al (2017) Prenatal paracetamol use and asthma in childhood: A systematic review and meta-analysis. *Allergol Immunopathol (Madr)* **45**(6): 528-33.

Fan Y, Ji M, Zang L et al (2011) Comparison of epidural tramadol-ropivacaine and fentanyl-ropivacaine for labor analgesia: a prospective randomized study. *Ups J Med Sci* **116**(4): 252-7.

Fan ZR, Ma J, Ma XL et al (2018) The efficacy of dexamethasone on pain and recovery after total hip arthroplasty: A systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* **97**(13): e0100.

Fanoe S, Jensen GB, Sjogren P et al (2009) Oxycodone is associated with dose-dependent QTc prolongation in patients and low-affinity inhibiting of hERG activity in vitro. *Br J Clin Pharmacol* **67**(2): 172–79.

Farmery AD & Wilson-MacDonald J (2009) The analgesic effect of epidural clonidine after spinal surgery: a randomized placebo-controlled trial. *Anesth Analg* **108**(2): 631–34.

Farzanegan B, Zangi M, Saeedi K et al (2018) Effect of Adding Magnesium Sulphate to Epidural Bupivacaine and Morphine on Post-Thoracotomy Pain Management: A Randomized, Double-Blind, Clinical Trial. *Basic Clin Pharmacol Toxicol* **123**(5): 602-06.

Farzi F, Mirmansouri A & Kambiz F, et al (2014) Addition of intrathecal fentanyl or meperidine to lidocaine and epinephrine for spinal anesthesia in elective cesarian delivery. *Anesth Pain Med* **4**(1): e14081.

Fassoulaki A, Patris K, Sarantopoulos C et al (2002) The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. *Anesth Analg* **95**(4): 985–91.

Faura CC, Collins SL, Moore RA et al (1998) Systematic review of factors affecting the ratios of morphine and its major metabolites. *Pain* **74**(1): 43–53.

FDA (2005) Determination that Penthrane (methoxyflurane) inhalational liquid, 99.9 percent, was withdrawn from sale for reasons of safety or effectiveness. *Federal Register* **70**(171): 53019.

FDA (2006) *Concomitant Use of Ibuprofen and Aspirin: Potential for Attenuation of the Anti- Platelet Effect of Aspirin.* https://www.fda.gov/media/76636/download Accessed 13 May 2020

FDA (2007) *Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).* https://www.fda.gov/media/73092/download Accessed 13 May 2020
FDA (2013) *Safety review update of codeine use in children; new Boxed Warning and contraindication on use after tonsillectomy and/or adenoidectomy* https://www.fda.gov/media/85072/download Accessed 20 February 2020
FDA (2014a) *Epidural corticosteroid injection: Drug Safety Communication - risk of rare but serious neurologic problems.* http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm394530.htm Accessed 12 October 2015
FDA (2014b) *Questions and answers: changes to the indicated population for miacalcin (calcitonin-salmon).* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm388641.htm Accessed 28 February 2020
Fedosov SN, Brito A, Miller JW et al (2015) Combined indicator of vitamin B12 status: modification for missing biomarkers and folate status and recommendations for revised cut-points. *Clin Chem Lab Med* **53**(8): 1215-25.
Felden L, Walter C, Harder S et al (2011) Comparative clinical effects of hydromorphone and morphine: a meta-analysis. *Br J Anaesth* **107**(3): 319–28.
Felder L, Saccone G, Scuotto S et al (2019) Perioperative gabapentin and post cesarean pain control: A systematic review and meta-analysis of randomized controlled trials. *Eur J Obstet Gynecol Reprod Biol* **233**: 98-106.
Felice K & Schumann H (2008) Intravenous lipid emulsion for local anesthetic toxicity: a review of the literature. *J Med Toxicol* **4**(3): 184–91.
Feng X, Tian M, Zhang W et al (2018) Gastrointestinal safety of etoricoxib in osteoarthritis and rheumatoid arthritis: A meta-analysis. *PLoS One* **13**(1): e0190798.
Fettiplace MR, Akpa BS, Ripper R et al (2014) Resuscitation with lipid emulsion: dose-dependent recovery from cardiac pharmacotoxicity requires a cardiotonic effect. *Anesthesiology* **120**(4): 915–25.
Fettiplace MR & Weinberg G (2018) The Mechanisms Underlying Lipid Resuscitation Therapy. *Reg Anesth Pain Med* **43**(2): 138-49.
Finnerup NB, Attal N, Haroutounian S et al (2015) Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* **14**(2): 162–73.
Firn S (1972) Methoxyflurane analgesia for burns dressings and other painful ward procedures in children. *Br J Anaesth* **44**(5): 517–22.
Flamiatos JF, Beer TM, Graff JN et al (2017) Cyclooxygenase-2 (COX-2) inhibition for prostate cancer chemoprevention: double-blind randomised study of pre-prostatectomy celecoxib or placebo. *BJU Int* **119**(5): 709-16.
Fletcher D & Martinez V (2014) Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth* **112**(6): 991–1004.
Flory JH, Wiesenthal AC, Thaler HT et al (2016) Methadone Use and the Risk of Hypoglycemia for Inpatients With Cancer Pain. *J Pain Symptom Manage* **51**(1): 79-87 e1.
Ford SR, Swanevelder CS & Mills PM (2012) Extended-release epidural morphine (DepoDur) as analgesia for rib fractures. *Br J Anaesth* **108**(5): 883–84.
Forget P, Bentin C, Machiels JP et al (2014) Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery. *Br J Anaesth* **113 Suppl 1**: i82–87.
Forget P, Borovac JA, Thackeray EM et al (2019) Transient neurological symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics in adult surgical patients: a network meta-analysis. *Cochrane Database Syst Rev* **12**: CD003006.
Forget P, Machiels JP, Coulie PG et al (2013) Neutrophil:lymphocyte ratio and intraoperative use of ketorolac or diclofenac are prognostic factors in different cohorts of patients undergoing breast, lung, and kidney cancer surgery. *Ann Surg Oncol* **20 Suppl 3**: S650–60.
Forster JG, Lumme HM, Palkama VJ et al (2008) Epinephrine 4 microg/mL added to a low-dose mixture of ropivacaine and fentanyl for lumbar epidural analgesia after total knee arthroplasty. *Anesth Analg* **106**(1): 301–04.
Forster JG, Niemi TT, Aromaa U et al (2003) Epinephrine added to a lumbar epidural infusion of a small-dose ropivacaine-fentanyl mixture after arterial bypass surgery of the lower extremities. *Acta Anaesthesiol Scand* **47**(9): 1106–13.
Fournier JP, Sommet A, Durrieu G et al (2014) Drug interactions between antihypertensive drugs and non-steroidal anti-inflammatory agents: a descriptive study using the French Pharmacovigilance database. *Fundam Clin Pharmacol* **28**(2): 230–35.
Fournier R, Faust A, Chassot O et al (2012) Perineural clonidine does not prolong levobupivacaine 0.5% after sciatic nerve block using the Labat approach in foot and ankle surgery. *Reg Anesth Pain Med* **37**(5): 521–24.
Fox C, Richardson K, Maidment ID et al (2011) Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. *J Am Geriatr Soc* **59**(8): 1477–83.
Foxall G, McCahon R, Lamb J et al (2007) Levobupivacaine-induced seizures and cardiovascular collapse treated with Intralipid. *Anaesthesia* **62**(5): 516–18.
Foye PM, Shupper P & Wendel I (2014) Coccyx fractures treated with intranasal calcitonin. *Pain Physician* **17**(2): E229–33.
FPMANZCA (2019a) *Opioid Calculator.* http://www.opioidcalculator.com.au Accessed 25 January 2020

FPMANZCA (2019b) *Statement on "Medicinal Cannabis" with particular reference to its use in the management of patients with chronic non-cancer pain.* http://fpm.anzca.edu.au/documents/pm10-2018.pdf Accessed 19 September 2019
FPMANZCA (2020) *Proposal for practice guideline*
Low dose ketamine infusion in the management of chronic non-cancer pain. Accessed 10 April 2020
Frampton JE (2016) Sublingual Sufentanil: A Review in Acute Postoperative Pain. *Drugs* **76**(6): 719-29.
Fransen M, Anderson C, Douglas J et al (2006) Safety and efficacy of routine postoperative ibuprofen for pain and disability related to ectopic bone formation after hip replacement surgery (HIPAID): randomised controlled trial. *BMJ* **333**(7567): 519.
Fredheim OM, Moksnes K, Borchgrevink PC et al (2008) Clinical pharmacology of methadone for pain. *Acta Anaesthesiol Scand* **52**(7): 879–89.
Fredrickson MJ, Danesh-Clough TK & White R (2013) Adjuvant dexamethasone for bupivacaine sciatic and ankle blocks: results from 2 randomized placebo-controlled trials. *Reg Anesth Pain Med* **38**(4): 300–07.
Freo U, Romualdi P & Kress HG (2019) Tapentadol for neuropathic pain: a review of clinical studies. *J Pain Res* **12**: 1537-51.
Friedrichsdorf SJ, Nugent AP & Strobl AQ (2013) Codeine-associated pediatric deaths despite using recommended dosing guidelines: three case reports. *J Opioid Manag* **9**(2): 151–55.
Furberg CD, Psaty BM & FitzGerald GA (2005) Parecoxib, valdecoxib, and cardiovascular risk. *Circulation* **111**(3): 249.
Fuseini AG, Afizu A, Yakubu YH et al (2019) Facilitators to the continuous abuse of tramadol among the youth: A qualitative study in Northern Ghana. *Nurs Open* **6**(4): 1388-98.
Gage SH, Zammit S & Hickman M (2013) Stronger evidence is needed before accepting that cannabis plays an important role in the aetiology of schizophrenia in the population. *F1000 Med Rep* **5**: 2.
Gagliese L, Gauthier LR, Macpherson AK et al (2008) Correlates of postoperative pain and intravenous patient-controlled analgesia use in younger and older surgical patients. *Pain Med* **9**(3): 299–314.
Gagliese L, Jackson M, Ritvo P et al (2000) Age is not an impediment to effective use of patient-controlled analgesia by surgical patients. *Anesthesiology* **93**(3): 601–10.
Gagnier JJ, Oltean H, van Tulder MW et al (2016) Herbal Medicine for Low Back Pain: A Cochrane Review. *Spine (Phila Pa 1976)* **41**(2): 116-33.
Gajraj NM & Joshi GP (2005) Role of cyclooxygenase-2 inhibitors in postoperative pain management. *Anesthesiol Clin North America* **23**(1): 49–72.
Galeotti N (2017) Hypericum perforatum (St John's wort) beyond depression: A therapeutic perspective for pain conditions. *J Ethnopharmacol* **200**: 136-46.
Galgon RE, Strube P, Heier J et al (2015) Magnesium sulfate with lidocaine for preventing propofol injection pain: a randomized, double-blind, placebo-controlled trial. *J Anesth* **29**(2): 206-11.
Gallagher HC, Gallagher RM, Butler M et al (2015) Venlafaxine for neuropathic pain in adults. *Cochrane Database Syst Rev* **2017 (6)** (8): CD011091.
Gambling D, Hughes T, Martin G et al (2005) A comparison of Depodur, a novel, single-dose extended-release epidural morphine, with standard epidural morphine for pain relief after lower abdominal surgery. *Anesth Analg* **100**(4): 1065–74.
Gambling DR, Hughes TL & Manvelian GZ (2009) Extended-release epidural morphine (DepoDur) following epidural bupivacaine in patients undergoing lower abdominal surgery: a randomized controlled pharmacokinetic study. *Reg Anesth Pain Med* **34**(4): 316–25.
Gammaitoni AR, Fine P, Alvarez N et al (2003) Clinical application of opioid equianalgesic data. *Clin J Pain* **19**(5): 286–97.
Gan TJ, Diemunsch P, Habib AS et al (2014) Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* **118**(1): 85–113.
Gan TJ, Robinson SB, Oderda GM et al (2015) Impact of postsurgical opioid use and ileus on economic outcomes in gastrointestinal surgeries. *Curr Med Res Opin* **31**(4): 677-86.
Ganesh A & Maxwell LG (2007) Pathophysiology and management of opioid-induced pruritus. *Drugs* **67**(16): 2323–33.
Garcia-Henares JF, Moral-Munoz JA, Salazar A et al (2018) Effects of Ketamine on Postoperative Pain After Remifentanil-Based Anesthesia for Major and Minor Surgery in Adults: A Systematic Review and Meta-Analysis. *Front Pharmacol* **9**: 921.
Gaskell AL, Jephcott CG, Smithells JR et al (2016a) Self-administered methoxyflurane for procedural analgesia: experience in a tertiary Australasian centre. *Anaesthesia* **71**(4): 417-23.
Gaskell H, Derry S, Stannard C et al (2016b) Oxycodone for neuropathic pain in adults. *Cochrane Database Syst Rev* **7**: CD010692.
Gasse C, Derby L, Vasilakis-Scaramozza C et al (2000) Incidence of first-time idiopathic seizures in users of tramadol. *Pharmacotherapy* **20**(6): 629–34.
Gaujoux-Viala C, Dougados M & Gossec L (2009) Efficacy and safety of steroid injections for shoulder and elbow tendonitis: a meta-analysis of randomised controlled trials. *Ann Rheum Dis* **68**(12): 1843–49.

Gehling M & Tryba M (2009) Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. *Anaesthesia* **64**(6): 643–51.
George E, Hornuss C & Apfel CC (2010) Neurokinin-1 and novel serotonin antagonists for postoperative and postdischarge nausea and vomiting. *Curr Opin Anaesthesiol* **23**(6): 714–21.
Gerhardt RT, King KM & Wiegert RS (2001) Inhaled nitrous oxide versus placebo as an analgesic and anxiolytic adjunct to peripheral intravenous cannulation. *Am J Emerg Med* **19**(6): 492-4.
Gerstenfeld LC & Einhorn TA (2004) COX inhibitors and their effects on bone healing. *Expert Opin Drug Saf* **3**(2): 131–36.
Gewandter JS, Mohile SG, Heckler CE et al (2014) A phase III randomized, placebo-controlled study of topical amitriptyline and ketamine for chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study of 462 cancer survivors. *Support Care Cancer* **22**(7): 1807–14.
Ghanem CI, Perez MJ, Manautou JE et al (2016) Acetaminophen from liver to brain: New insights into drug pharmacological action and toxicity. *Pharmacol Res* **109**: 119-31.
Gharabaghi PM, Tabatabei F & Sedigheh AF (2011) Evaluation of the effect of preemptive administration of Rosa damascene extract on post-operative pain in elective caesarean sections. *African Journal of Pharmacy and Pharmacology* **5**(15): 1950-5.
Gharaei B, Jafari A, Aghamohammadi H et al (2013) Opioid-sparing effect of preemptive bolus low-dose ketamine for moderate sedation in opioid abusers undergoing extracorporeal shock wave lithotripsy: a randomized clinical trial. *Anesth Analg* **116**(1): 75–80.
Ghate G, Clark E & Vaillancourt C (2018) Systematic review of the use of low-dose ketamine for analgesia in the emergency department. *CJEM* **20**(1): 36-45.
Ghobrial GM, Dalyai R, Flanders AE et al (2012) Nitrous oxide myelopathy posing as spinal cord injury. *J Neurosurg Spine* **16**(5): 489–91.
Gill D, Derry S, Wiffen PJ et al (2011) Valproic acid and sodium valproate for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* **10**: CD009183.
Gilron I (2004) Corticosteroids in postoperative pain management: future research directions for a multifaceted therapy. *Acta Anaesthesiol Scand* **48**(10): 1221–22.
Ginosar Y, Riley ET & Angst MS (2003) The site of action of epidural fentanyl in humans: the difference between infusion and bolus administration. *Anesth Analg* **97**(5): 1428–38.
Ginosar Y, Riley ET & Angst MS (2013) Analgesic and sympatholytic effects of low-dose intrathecal clonidine compared with bupivacaine: a dose-response study in female volunteers. *Br J Anaesth* **111**(2): 256–63.
Girgin NK, Gurbet A, Turker G et al (2008) Intrathecal morphine in anesthesia for cesarean delivery: dose-response relationship for combinations of low-dose intrathecal morphine and spinal bupivacaine. *J Clin Anesth* **20**(3): 180–85.
Gitman M & Barrington MJ (2018) Local Anesthetic Systemic Toxicity: A Review of Recent Case Reports and Registries. *Reg Anesth Pain Med* **43**(2): 124-30.
Glassou EN, Kristensen N, Moller BK et al (2019) Impact of preadmission anti-inflammatory drug use on the risk of RBC transfusion in elderly hip fracture patients: a Danish nationwide cohort study, 2005-2016. *Transfusion* **59**(3): 935-44.
Gobble RM, Hoang HL, Kachniarz B et al (2014) Ketorolac does not increase perioperative bleeding: a meta-analysis of randomized controlled trials. *Plast Reconstr Surg* **133**(3): 741–55.
Goldstein JL, Kivitz AJ, Verburg KM et al (2003) A comparison of the upper gastrointestinal mucosal effects of valdecoxib, naproxen and placebo in healthy elderly subjects. *Aliment Pharmacol Ther* **18**(1): 125–32.
Gomes LM, Garcia JB, Ribamar JS, Jr. et al (2011) Neurotoxicity of subarachnoid preservative-free S(+)-ketamine in dogs. *Pain Physician* **14**(1): 83–90.
Gomes T, Juurlink DN, Antoniou T et al (2017) Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. *PLoS Med* **14**(10): e1002396.
Gonda X (2012) Basic pharmacology of NMDA receptors. *Curr Pharm Des* **18**(12): 1558–67.
Gonul O, Satilmis T, Ciftci A et al (2015) Comparison of the Effects of Topical Ketamine and Tramadol on Postoperative Pain After Mandibular Molar Extraction. *J Oral Maxillofac Surg* **73**(11): 2103-7.
Gopalakrishnan V, Nagori SA, Roy Chowdhury SK et al (2018) The use of intra-articular analgesics to improve outcomes after temporomandibular joint arthrocentesis: a review. *Oral Maxillofac Surg* **22**(4): 357-64.
Gordh TE, Stubhaug A, Jensen TS et al (2008) Gabapentin in traumatic nerve injury pain: a randomized, double-blind, placebo-controlled, cross-over, multi-center study. *Pain* **138**(2): 255–66.
Gottschalk A, Schroeder F, Ufer M et al (2001) Amantadine, a N-methyl-D-aspartate receptor antagonist, does not enhance postoperative analgesia in women undergoing abdominal hysterectomy. *Anesth Analg* **93**(1): 192–96.
Gourlay DL & Heit HA (2008) Pain and addiction: managing risk through comprehensive care. *J Addict Dis* **27**(3): 23–30.
Gowing L, Farrell MF, Ali R et al (2014) Alpha2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev* **3**(3): CD002024.
Grace D & Fee JP (1996) A comparison of intrathecal morphine-6-glucuronide and intrathecal morphine sulfate as analgesics for total hip replacement. *Anesth Analg* **83**(5): 1055–59.

Graham GG, Davies MJ, Day RO et al (2013a) The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology* **21**(3): 201–32.
Graham T, Grocott P & Probst S, et al. (2013b) How are topical opioids used to manage painful cutaneous lesions in palliative care? A critical review. *Pain* **154**: 1920–23.
Grant MC, Betz M, Hulse M et al (2016a) The Effect of Preoperative Pregabalin on Postoperative Nausea and Vomiting: A Meta-analysis. *Anesth Analg* **123**(5): 1100-07.
Grant MC, Lee H, Page AJ et al (2016b) The Effect of Preoperative Gabapentin on Postoperative Nausea and Vomiting: A Meta-Analysis. *Anesth Analg* **122**(4): 976-85.
Grape S, Schug SA, Lauer S et al (2010) Formulations of fentanyl for the management of pain. *Drugs* **70**(1): 57–72.
Grape S, Usmanova I, Kirkham KR et al (2018) Intravenous dexamethasone for prophylaxis of postoperative nausea and vomiting after administration of long-acting neuraxial opioids: a systematic review and meta-analysis. *Anaesthesia* **73**(4): 480-89.
Grecu L, Bittner EA, Kher J et al (2008) Haloperidol plus ondansetron versus ondansetron alone for prophylaxis of postoperative nausea and vomiting. *Anesth Analg* **106**(5): 1410–13.
Green JL, Heard KJ, Reynolds KM et al (2013) Oral and intravenous acetylcysteine for treatment of acetaminophen toxicity: a systematic review and meta-analysis. *West J Emerg Med* **14**(3): 218–26.
Green RJ, Chambers J, Thomas PW et al (2007) Comparison of the relative analgesic efficacies of epidural or intramuscular diamorphine following total knee arthroplasty. *Eur J Anaesthesiol* **24**(11): 951–57.
Greer KC, Terkawi AS, Tsang S et al (2017) The Effect of Ondansetron on Acute Opioid Tolerance in Patients Receiving Intrathecal Opioids Prior to Cesarean Delivery. *Reg Anesth Pain Med* **42**(5): 669-73.
Gressler LE, Hammond DA & Painter JT (2017) Serotonin Syndrome in Tapentadol Literature: Systematic Review of Original Research. *J Pain Palliat Care Pharmacother* **31**(3-4): 228-36.
Grimsby GM, Andrews PE, Castle EP et al (2014) Long-term renal function after donor nephrectomy: secondary follow-up analysis of the randomized trial of ketorolac vs placebo. *Urology* **84**(1): 78–81.
Grindlay J & Babl FE (2009) Review article: efficacy and safety of methoxyflurane analgesia in the emergency department and prehospital setting. *Emerg Med Australas* **21**(1): 4–11.
Groban L & Dolinski SY (2001) Differences in cardiac toxicity among ropivacaine, levobupivacaine, bupivacaine, and lidocaine. *Tech Reg Anesth Pain Manage* **5**(2): 48–55.
Grummet J, Huang S, Konstantatos A et al (2012) The 'green whistle': a novel method of analgesia for transrectal prostate biopsy. *BJU Int* **110 Suppl 4**: 85–88.
Gudgin EJ, Besser MW & Craig JI (2008) Entonox as a sedative for bone marrow aspiration and biopsy. *Int J Lab Hematol* **30**(1): 65–67.
Guetti C, Angeletti C, Marinangeli F et al (2011) Transdermal buprenorphine for central neuropathic pain: clinical reports. *Pain Pract* **11**(5): 446–52.
Guindon J & Hohmann AG (2011) The endocannabinoid system and cancer: therapeutic implication. *Br J Pharmacol* **163**(7): 1447–63.
Gunter BR, Butler KA, Wallace RL et al (2017) Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: a meta-analysis. *J Clin Pharm Ther* **42**(1): 27-38.
Gupta A, Kamat H & Kharod U (2015) Efficacy of intrathecal midazolam in potentiating the analgesic effect of intrathecal fentanyl in patients undergoing lower limb surgery. *Anesth Essays Res* **9**(3): 379-83.
Gupta K, Nagappa M, Prasad A et al (2018a) Risk factors for opioid-induced respiratory depression in surgical patients: a systematic review and meta-analyses. *BMJ Open* **8**(12): e024086.
Gupta K, Prasad A, Nagappa M et al (2018b) Risk factors for opioid-induced respiratory depression and failure to rescue: a review. *Curr Opin Anaesthesiol* **31**(1): 110-19.
Gupta M, Shailaja S & Hegde KS (2014) Comparison of intrathecal dexmedetomidine with buprenorphine as adjuvant to bupivacaine in spinal asnaesthesia. *J Clin Diagn Res* **8**(2): 114–17.
Gurbet A, Turker G, Girgin NK et al (2008) Combination of ultra-low dose bupivacaine and fentanyl for spinal anaesthesia in out-patient anorectal surgery. *J Int Med Res* **36**(5): 964–70.
Habib AS & Gan TJ (2006) Use of neostigmine in the management of acute postoperative pain and labour pain: a review. *CNS Drugs* **20**(10): 821–39.
Habib AS & Gan TJ (2008a) Haloperidol for postoperative nausea and vomiting: are we reinventing the wheel? *Anesth Analg* **106**(5): 1343–45.
Habib AS & Gan TJ (2008b) Pro: The Food and Drug Administration Black box warning on droperidol is not justified. *Anesth Analg* **106**(5): 1414–17.
Habibollahi P, Garjani A, Shams Vahdati S et al (2019) Severe complications of tramadol overdose in Iran. *Epidemiol Health* **41**: e2019026.
Hakim SM, Latif FS & Anis SG (2012) Comparison between lumbar and thoracic epidural morphine for severe isolated blunt chest wall trauma: a randomized open-label trial. *J Anesth* **26**(6): 836–44.
Halloran K & Barash PG (2010) Inside the black box: current policies and concerns with the United States Food and Drug Administration's highest drug safety warning system. *Curr Opin Anaesthesiol* **23**(3): 423–27.

Hamilton I, Lloyd C, Hewitt C et al (2014) Effect of reclassification of cannabis on hospital admissions for cannabis psychosis: a time series analysis. *Int J Drug Policy* **25**(1): 151–56.
Hamilton TW, Strickland LH & Pandit HG (2016) A Meta-Analysis on the Use of Gabapentinoids for the Treatment of Acute Postoperative Pain Following Total Knee Arthroplasty. *J Bone Joint Surg Am* **98**(16): 1340-50.
Hammonds B, Sidebotham DA & Anderson BJ (2003) Aspects of tramadol and ondansetron interactions. *Acute Pain* **5**(1): 31–34.
Hammoud HA, Aymard G, Lechat P et al (2011) Relationships between plasma concentrations of morphine, morphine-3-glucuronide, morphine-6-glucuronide, and intravenous morphine titration outcomes in the postoperative period. *Fundam Clin Pharmacol* **25**(4): 518–27.
Han C, Kuang MJ, Ma JX et al (2017a) The Efficacy of Preoperative Gabapentin in Spinal Surgery: A Meta-Analysis of Randomized Controlled Trials. *Pain Physician* **20**(7): 649-61.
Han C, Kuang MJ, Ma JX et al (2017b) Is pregabalin effective and safe in total knee arthroplasty? A PRISMA-compliant meta-analysis of randomized-controlled trials. *Medicine (Baltimore)* **96**(26): e6947.
Han C, Li XD, Jiang HQ et al (2016) The use of gabapentin in the management of postoperative pain after total hip arthroplasty: a meta-analysis of randomised controlled trials. *J Orthop Surg Res* **11**(1): 79.
Han SS, Do SH, Kim TH et al (2015) Stepwise tapering of remifentanil at the end of surgery decreased postoperative pain and the need of rescue analgesics after thyroidectomy. *BMC Anesthesiol* **15**: 46.
Hanna MH, Elliott KM & Fung M (2005) Randomized, double-blind study of the analgesic efficacy of morphine-6-glucuronide versus morphine sulfate for postoperative pain in major surgery. *Anesthesiology* **102**(4): 815–21.
Hans G (2007) Buprenorphine--a review of its role in neuropathic pain. *J Opioid Manag* **3**(4): 195–206.
Harding TA & Gibson JA (2000) The use of inhaled nitrous oxide for flexible sigmoidoscopy: a placebo-controlled trial. *Endoscopy* **32**(6): 457–60.
Hardy J, Quinn S, Fazekas B et al (2012) Randomized, double-blind, placebo-controlled study to assess the efficacy and toxicity of subcutaneous ketamine in the management of cancer pain. *J Clin Oncol* **30**(29): 3611–17.
Harris SI, Kuss M, Hubbard RC et al (2001) Upper gastrointestinal safety evaluation of parecoxib sodium, a new parenteral cyclooxygenase-2-specific inhibitor, compared with ketorolac, naproxen, and placebo. *Clin Ther* **23**(9): 1422–28.
Hart O, Mullee MA, Lewith G et al (1997) Double-blind, placebo-controlled, randomized clinical trial of homoeopathic arnica C30 for pain and infection after total abdominal hysterectomy. *J R Soc Med* **90**(2): 73–78.
Hartrick CT (2010) Tapentadol immediate-release for acute pain. *Expert Rev Neurother* **10**(6): 861-9.
Hassanian-Moghaddam H, Farajidana H, Sarjami S et al (2013) Tramadol-induced apnea. *Am J Emerg Med* **31**(1): 26–31.
Hauser W, Petzke F & Fitzcharles MA (2018) Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management - An overview of systematic reviews. *Eur J Pain* **22**(3): 455-70.
Hauser W, Welsch P, Klose P et al (2019) Efficacy, tolerability and safety of cannabis-based medicines for cancer pain : A systematic review with meta-analysis of randomised controlled trials. *Schmerz* **33**(5): 424-36.
Hauser W, Wolfe F, Tolle T et al (2012) The role of antidepressants in the management of fibromyalgia syndrome: a systematic review and meta-analysis. *CNS Drugs* **26**(4): 297–307.
Hazekamp A, Ruhaak R, Zuurman L et al (2006) Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol. *J Pharm Sci* **95**(6): 1308–17.
Health Canada (2006) *Notice to hospitals: Health Canada issued important safety information on Anzemet (dolasetron mesylate): new contraindications.* https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2006/14390a-eng.php Accessed 15 February 2020
Hearn L, Derry S & Moore RA (2012) Lacosamide for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* **2**: CD009318.
Hearn L, Derry S, Phillips T et al (2014) Imipramine for neuropathic pain in adults. *Cochrane Database Syst Rev* **5**: CD010769.
Heesen M, Bohmer J, Brinck EC et al (2015) Intravenous ketamine during spinal and general anaesthesia for caesarean section: systematic review and meta-analysis. *Acta Anaesthesiol Scand* **59**(4): 414-26.
Heesen M, Rijs K, Hilber N et al (2019) Effect of intravenous dexamethasone on postoperative pain after spinal anaesthesia - a systematic review with meta-analysis and trial sequential analysis. *Anaesthesia* **74**(8): 1047-56.
Hegi TR, Bombeli T, Seifert B et al (2004) Effect of rofecoxib on platelet aggregation and blood loss in gynaecological and breast surgery compared with diclofenac. *Br J Anaesth* **92**(4): 523–31.
Heid F, Muller N, Piepho T et al (2008) Postoperative analgesic efficacy of peripheral levobupivacaine and ropivacaine: a prospective, randomized double-blind trial in patients after total knee arthroplasty. *Anesth Analg* **106**(5): 1559–61.
Hein A, Gillis-Haegerstrand C & Jakobsson JG (2017) Neuraxial opioids as analgesia in labour, caesarean section and hysterectomy: A questionnaire survey in Sweden. *F1000Res* **6**: 133.
Hein A, Rosblad P & Gillis-Haegerstrand Cea (2012) Low dose intrathecal morphine effects on post-hysterectomy pain: a randomised placebo-controlled study. *Acta Anaesthesiol Scand* **56**: 102–09.

Heo BH, Lee HJ, Lee HG et al (2016) Femoral nerve block for patient undergoing total knee arthroplasty: Prospective, randomized, double-blinded study evaluating analgesic effect of perineural fentanyl additive to local anesthetics. *Medicine (Baltimore)* **95**(36): e4771.
Herrick IA, Ganapathy S, Komar W et al (1996) Postoperative cognitive impairment in the elderly. Choice of patient-controlled analgesia opioid. *Anaesthesia* **51**(4): 356–60.
Higgins C, Smith BH & Matthews K (2019) Evidence of opioid-induced hyperalgesia in clinical populations after chronic opioid exposure: a systematic review and meta-analysis. *Br J Anaesth* **122**(6): e114-e26.
Hill MN (2014) Clearing the smoke: what do we know about adolescent cannabis use and schizophrenia? *J Psychiatry Neurosci* **39**(2): 75–77.
Hines S, Steels E, Chang A et al (2018) Aromatherapy for treatment of postoperative nausea and vomiting. *Cochrane Database Syst Rev* **3**: CD007598.
Ho CM, Wu HL, Ho ST et al (2011) Dexamethasone prevents postoperative nausea and vomiting: benefit versus risk. *Acta Anaesthesiol Taiwan* **49**(3): 100–04.
Ho KM & Ismail H (2008) Use of intrathecal midazolam to improve perioperative analgesia: a meta-analysis. *Anaesth Intensive Care* **36**(3): 365–73.
Ho KM, Ismail H, Lee KC et al (2005) Use of intrathecal neostigmine as an adjunct to other spinal medications in perioperative and peripartum analgesia: a meta-analysis. *Anaesth Intensive Care* **33**(1): 41–53.
Ho KY, Tay W, Yeo MC et al (2010) Duloxetine reduces morphine requirements after knee replacement surgery. *Br J Anaesth* **105**(3): 371-6.
Hocking G, Visser EJ & Schug SA (2007) Ketamine: does life begin at 40? *Pain: Clinical Updates (IASP)* **15**(3): 1–6.
Hodgson PS, Neal JM, Pollock JE et al (1999) The neurotoxicity of drugs given intrathecally (spinal). *Anesth Analg* **88**(4): 797–809.
Hogan ME, vanderVaart S, Perampaladas K et al (2011) Systematic review and meta-analysis of the effect of warming local anesthetics on injection pain. *Ann Emerg Med* **58**(1): 86–98 e1.
Hollmann MW & Durieux ME (2000) Local anesthetics and the inflammatory response: a new therapeutic indication? *Anesthesiology* **93**(3): 858-75.
Holmquist GL (2009) Opioid metabolism and effects of cytochrome P450. *Pain Med* **10**(S1): S20–29.
Holyoak R, Vlok R, Melhuish T et al (2019) Buprenorphine in acute pain: a partial agonist or not? *Br J Anaesth* **123**(4): e484-e85.
Hong JM, Kim KH, Lee HJ et al (2017) Epidural Dexamethasone Influences Postoperative Analgesia after Major Abdominal Surgery. *Pain Physician* **20**(4): 261-69.
Horbach SJ, Lopes RD, da CGJC et al (2011) Naproxen as prophylaxis against atrial fibrillation after cardiac surgery: the NAFARM randomized trial. *Am J Med* **124**(11): 1036–42.
Horlocker T, Burton A & Connis R, et al (2009) Practice guidelines for the prevention, detection and management of respiratory depression associated with neuroaxial opioid administration. *Anesthesiology* **110**: 218–30.
Horn CC, Wallisch WJ, Homanics GE et al (2014) Pathophysiological and neurochemical mechanisms of postoperative nausea and vomiting. *Eur J Pharmacol* **722**: 55–66.
Hossain SM, Hussain SM & Ekram AR (2016) Duloxetine in Painful Diabetic Neuropathy: A Systematic Review. *Clin J Pain* **32**(11): 1005-10.
Hovaguimian F, Lysakowski C, Elia N et al (2013) Effect of intraoperative high inspired oxygen fraction on surgical site infection, postoperative nausea and vomiting, and pulmonary function: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* **119**(2): 303–16.
Hu J, Huang D, Li M et al (2018a) Effects of a single dose of preoperative pregabalin and gabapentin for acute postoperative pain: a network meta-analysis of randomized controlled trials. *J Pain Res* **11**: 2633-43.
Hu J, Li P & Zhang T (2018b) Rhubarb combined with trypsin inhibitor for severe acute pancreatitis: A systematic review and meta-analysis. *Phytother Res* **32**(8): 1450-58.
Hu MH, Huang GS, Wu CT et al (2014) Nitrous oxide myelopathy in a pediatric patient. *Pediatr Emerg Care* **30**(4): 266–67.
Huang S, Hu H, Cai YH et al (2019) Effect of parecoxib in the treatment of postoperative cognitive dysfunction: A systematic review and meta-analysis. *Medicine (Baltimore)* **98**(1): e13812.
Huang S, Pepdjonovic L, Konstantatos A et al (2016) Penthrox alone versus Penthrox plus periprostatic infiltration of local analgesia for analgesia in transrectal ultrasound-guided prostate biopsy. *ANZ J Surg* **86**(3): 139-42.
Huang Y, Tang SR & Young CJ (2018) Nonsteroidal anti-inflammatory drugs and anastomotic dehiscence after colorectal surgery: a meta-analysis. *ANZ J Surg* **88**(10): 959-65.
Huang YS, Lin LC, Huh BK et al (2007) Epidural clonidine for postoperative pain after total knee arthroplasty: a dose-response study. *Anesth Analg* **104**(5): 1230–35.
Hubler M, Gabler R, Ehm B et al (2010) Successful resuscitation following ropivacaine-induced systemic toxicity in a neonate. *Anaesthesia* **65**(11): 1137–40.
Hubler M, Litz RJ, Sengebusch KH et al (2001) A comparison of five solutions of local anaesthetics and/or sufentanil for continuous, postoperative epidural analgesia after major urological surgery. *Eur J Anaesthesiol* **18**(7): 450–57.

Hudcova J, McNicol E, Quah C et al (2006) Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. *Cochrane Database Syst Rev* **4**: CD003348.
Hudson M, Baron M, Rahme E et al (2005) Ibuprofen may abrogate the benefits of aspirin when used for secondary prevention of myocardial infarction. *J Rheumatol* **32**(8): 1589–93.
Huestis MA (2007) Human cannabinoid pharmacokinetics. *Chem Biodivers* **4**(8): 1770–804.
Huet O, Eyrolle LJ, Mazoit JX et al (2003) Cardiac arrest after injection of ropivacaine for posterior lumbar plexus blockade. *Anesthesiology* **99**(6): 1451–53.
Hughes GJ, Patel PN & Saxena N (2011) Effect of acetaminophen on international normalized ratio in patients receiving warfarin therapy. *Pharmacotherapy* **31**(6): 591–97.
Huhn AS, Berry MS & Dunn KE (2018) Systematic review of sex-based differences in opioid-based effects. *Int Rev Psychiatry* **30**(5): 107-16.
Huhn AS, Strain EC, Bigelow GE et al (2019) Analgesic Effects of Hydromorphone versus Buprenorphine in Buprenorphine-maintained Individuals. *Anesthesiology* **130**(1): 131-41.
Humble SR (2011) Calcitonin for acute neuropathic pain associated with spinal cord injury. *Anaesth Intensive Care* **39**(4): 682–86.
Hurley RW & Adams MC (2008) Sex, gender, and pain: an overview of a complex field. *Anesth Analg* **107**(1): 309–17.
Hussain N, Grzywacz VP, Ferreri CA et al (2017) Investigating the Efficacy of Dexmedetomidine as an Adjuvant to Local Anesthesia in Brachial Plexus Block: A Systematic Review and Meta-Analysis of 18 Randomized Controlled Trials. *Reg Anesth Pain Med* **42**(2): 184-96.
Hussain N, Van den Langenbergh T, Sermer C et al (2018) Equivalent analgesic effectiveness between perineural and intravenous dexamethasone as adjuvants for peripheral nerve blockade: a systematic review and meta-analysis. *Can J Anaesth* **65**(2): 194-206.
Huxtable CA, Roberts LJ, Somogyi AA et al (2011) Acute pain management in opioid-tolerant patients: a growing challenge. *Anaesth Intensive Care* **39**(5): 804–23.
Huynh TM, Marret E & Bonnet F (2015) Combination of dexamethasone and local anaesthetic solution in peripheral nerve blocks: A meta-analysis of randomised controlled trials. *Eur J Anaesthesiol* **32**(11): 751-8.
Hwang JY, Na HS, Jeon YT et al (2010) I.V. infusion of magnesium sulphate during spinal anaesthesia improves postoperative analgesia. *Br J Anaesth* **104**(1): 89–93.
Hwang SH, Song JN, Jeong YM et al (2016) The efficacy of honey for ameliorating pain after tonsillectomy: a meta-analysis. *Eur Arch Otorhinolaryngol* **273**(4): 811-8.
Hye MA, Masud KM, Banik D et al (2010) Intrathecal neostigmine for postoperatrive analgesia in caesarean section. *Mymensingh Med J* **19**(4): 586–93.
Iannitti T, Morales-Medina JC, Bellavite P et al (2016) Effectiveness and Safety of Arnica montana in Post-Surgical Setting, Pain and Inflammation. *Am J Ther* **23**(1): e184-97.
Idowu A, Aremu AO, Olumide A et al (2018) Substance abuse among students in selected secondary schools of an urban community of Oyo-state, South West Nigeria: implication for policy action. *Afr Health Sci* **18**(3): 776-85.
Iijima T, Ishiyama T, Kashimoto S et al (2007) A comparison of three different concentrations of ropivacaine with fentanyl for patient-controlled epidural analgesia. *Anesth Analg* **105**(2): 507–11.
Ilfeld BM, Le LT, Ramjohn J et al (2009) The effects of local anesthetic concentration and dose on continuous infraclavicular nerve blocks: a multicenter, randomized, observer-masked, controlled study. *Anesth Analg* **108**(1): 345–50.
Ilfeld BM, Loland VJ, Gerancher JC et al (2008) The effects of varying local anesthetic concentration and volume on continuous popliteal sciatic nerve blocks: a dual-center, randomized, controlled study. *Anesth Analg* **107**(2): 701–07.
Imani F, Entezary S, Razi M et al (2015) The effect of intra-articular meperidine and bupivacaine 0.5% on postoperative pain of arthroscopic knee surgery; a randomized double blind clinical trial. *Anesth Pain Med* **5**(1): e27470.
Irmak Sapmaz H, Uysal M, Tas U et al (2015) The Effect of Lavender Oil in Patients with Renal Colic: A Prospective Controlled Study Using Objective and Subjective Outcome Measurements. *J Altern Complement Med* **21**(10): 617-22.
Isik C, Demirhan A, Yetis T et al (2015) Efficacy of intraarticular application of ketamine or ketamine-levobupivacaine combination on post-operative pain after arthroscopic meniscectomy. *Knee Surg Sports Traumatol Arthrosc* **23**(9): 2721-6.
Ituk U & Thenuwara K (2018) The effect of a single intraoperative dose of intravenous dexamethasone 8mg on post-cesarean delivery analgesia: a randomized controlled trial. *Int J Obstet Anesth* **35**: 57-63.
Ivie CS, Viscomi CM, Adams DC et al (2011) Clonidine as an adjunct to intravenous regional anesthesia: A randomized, double-blind, placebo-controlled dose ranging study. *J Anaesthesiol Clin Pharmacol* **27**(3): 323–27.
Jabbour HJ, Naccache NM, Jawish RJ et al (2014) Ketamine and magnesium association reduces morphine consumption after scoliosis surgery: prospective randomised double-blind study. *Acta Anaesthesiol Scand* **58**(5): 572–79.
Jackson JL, Mancuso JM, Nickoloff S et al (2017) Tricyclic and Tetracyclic Antidepressants for the Prevention of Frequent Episodic or Chronic Tension-Type Headache in Adults: A Systematic Review and Meta-Analysis. *J Gen Intern Med* **32**(12): 1351-58.

Jackson JL, Shimeall W, Sessums L et al (2010) Tricyclic antidepressants and headaches: systematic review and meta-analysis. *BMJ* **341**: c5222.
Jacobs IG (2010) Health effects of patients given methoxyflurane in the pre-hospital setting: a data linkage study. *Open Emerg Med J* **3**: 7–13.
Jaeger H & Maier C (1992) Calcitonin in phantom limb pain: a double-blind study. *Pain* **48**(1): 21–27.
Jaffe RA & Rowe MA (1996) A comparison of the local anesthetic effects of meperidine, fentanyl, and sufentanil on dorsal root axons. *Anesth Analg* **83**(4): 776–81.
Jain A, Jain K & Bhardawaj N (2012) Analgesic efficacy of low-dose intrathecal neostigmine in combination with fentanyl and bupivacaine for total knee replacement surgery. *J Anaesthesiol Clin Pharmacol* **28**(4): 486–90.
Jain SK, Dar MY, Kumar S et al (2019) Role of anti-oxidant (vitamin-C) in post-operative pain relief in foot and ankle trauma surgery: A prospective randomized trial. *Foot Ankle Surg* **25**(4): 542-45.
Jalota L, Kalira V, George E et al (2011) Prevention of pain on injection of propofol: systematic review and meta-analysis. *BMJ* **342**: d1110.
Jankovic RJ, Visnjic MM, Milic DJ et al (2008) Does the addition of ketorolac and dexamethasone to lidocaine intravenous regional anesthesia improve postoperative analgesia and tourniquet tolerance for ambulatory hand surgery? *Minerva Anestesiol* **74**(10): 521–27.
Jannetto PJ, Helander A, Garg U et al (2019) The Fentanyl Epidemic and Evolution of Fentanyl Analogs in the United States and the European Union. *Clin Chem* **65**(2): 242-53.
Jannuzzi RG (2016) Nalbuphine for Treatment of Opioid-induced Pruritus: A Systematic Review of Literature. *Clin J Pain* **32**(1): 87-93.
Jasani NB, O'Conner RE & Bouzoukis JK (1994) Comparison of hydromorphone and meperidine for ureteral colic. *Acad Emerg Med* **1**(6): 539–43.
Jayaram P, Kennedy DJ, Yeh P et al (2019) Chondrotoxic Effects of Local Anesthetics on Human Knee Articular Cartilage: A Systematic Review. *PM R* **11**(4): 379-400.
Jebali C, Kahloul M, Hassine N et al (2018) Magnesium Sulfate as Adjuvant in Prehospital Femoral Nerve Block for a Patient with Diaphysial Femoral Fracture: A Randomized Controlled Trial. *Pain Res Manag* **2018**: 2926404.
Jendoubi A, Naceur IB, Bouzouita A et al (2017) A comparison between intravenous lidocaine and ketamine on acute and chronic pain after open nephrectomy: A prospective, double-blind, randomized, placebo-controlled study. *Saudi J Anaesth* **11**(2): 177-84.
Jennings PA, Cameron P & Bernard S (2011) Ketamine as an analgesic in the pre-hospital setting: a systematic review. *Acta Anaesthesiol Scand* **55**(6): 638–43.
Jephcott C, Grummet J, Nguyen N et al (2018) A review of the safety and efficacy of inhaled methoxyflurane as an analgesic for outpatient procedures. *Br J Anaesth* **120**(5): 1040-48.
Jewer JK, Wong MJ, Bird SJ et al (2019) Supplemental perioperative intravenous crystalloids for postoperative nausea and vomiting. *Cochrane Database Syst Rev* **3**: CD012212.
Jick H, Derby LE, Vasilakis C et al (1998) The risk of seizures associated with tramadol. *Pharmacotherapy* **18**(3): 607–11.
Jo HR, Chae YK, Kim YH et al (2011) Remifentanil-induced pronociceptive effect and its prevention with pregabalin. *Korean J Anesthesiol* **60**(3): 198–204.
Johns RA, Hanousek J & Montgomery JE (2006) A comparison of cyclizine and granisetron alone and in combination for the prevention of postoperative nausea and vomiting. *Anaesthesia* **61**(11): 1053–57.
Johnson CB & Steele-Moses SK (2011) The use of continuous femoral nerve blocks versus extended release epidural morphine: a study comparing outcomes in total knee arthroplasty procedures. *Orthop Nurs* **30**(1): 44–53.
Johnson WL & Pugh MA (2016) Prolongation of Subarachnoid Block With Concomitant Use of Intravenous Dexmedetomidine: An Evidence-based Review. *AANA J* **84**(4): 271-8.
Jones HE, Finnegan LP & Kaltenbach K (2012) Methadone and buprenorphine for the management of opioid dependence in pregnancy. *Drugs* **72**(6): 747–57.
Jones JG, Sapsford DJ & Wheatley RG (1990) Postoperative hypoxaemia: mechanisms and time course. *Anaesthesia* **45**(7): 566–73.
Jonkman K, Dahan A, van de Donk T et al (2017) Ketamine for pain. *F1000Res* **6**.
Joo DT (2007) Mechanisms of opioid tolerance: merging evidence and therapeutic implications. *Can J Anaesth* **54**(12): 969–76.
Jorgensen H, Fomsgaard JS, Dirks J et al (2000) Effect of continuous epidural 0.2% ropivacaine vs 0.2% bupivacaine on postoperative pain, motor block and gastrointestinal function after abdominal hysterectomy. *Br J Anaesth* **84**(2): 144–50.
Jose R, Chakravarthy K, Nair S et al (2017) A Randomized Controlled Trial Studying the Role of Dexamethasone in Scalp Nerve Blocks for Supratentorial Craniotomy. *J Neurosurg Anesthesiol* **29**(2): 150-56.
Joseph C, Gaillat F, Duponq R et al (2012) Is there any benefit to adding intravenous ketamine to patient-controlled epidural analgesia after thoracic surgery? A randomized double-blind study. *Eur J Cardiothorac Surg* **42**(4): e58–65.

Joshi-Khadke S, Khadke VV, Patel SJ et al (2015) Efficacy of spinal additives neostigmine and magnesium sulfate on characteristics of subarachnoid block, hemodynamic stability and postoperative pain relief: A randomized clinical trial. *Anesth Essays Res* **9**(1): 63-71.

Joung KW, Kim HR, Kim WJ et al (2018) Preoperative dexamethasone for acute post-thoracotomy analgesia: a randomized, double-blind, placebo-controlled study. *BMC Anesthesiol* **18**(1): 135.

Juhlin T, Bjorkman S & Hoglund P (2005) Cyclooxygenase inhibition causes marked impairment of renal function in elderly subjects treated with diuretics and ACE-inhibitors. *Eur J Heart Fail* **7**(6): 1049–56.

Jung HS, Seo KH, Kang JH et al (2018) Optimal dose of perineural dexmedetomidine for interscalene brachial plexus block to control postoperative pain in patients undergoing arthroscopic shoulder surgery: A prospective, double-blind, randomized controlled study. *Medicine (Baltimore)* **97**(16): e0440.

Jungquist CR, Quinlan-Colwell A, Vallerand A et al (2020) American Society for Pain Management Nursing Guidelines on Monitoring for Opioid-Induced Advancing Sedation and Respiratory Depression: Revisions. *Pain Manag Nurs* **21**(1): 7-25.

Jungquist CR, Smith K, Nicely KL et al (2017) Monitoring Hospitalized Adult Patients for Opioid-Induced Sedation and Respiratory Depression. *Am J Nurs* **117**(3 Suppl 1): S27-S35.

Justo D, Gal-Oz A, Paran Y et al (2006) Methadone-associated Torsades de Pointes (polymorphic ventricular tachycardia) in opioid-dependent patients. *Addiction* **101**(9): 1333–38.

Kahraman F & Eroglu A (2014) The effect of intravenous magnesium sulfate infusion on sensory spinal block and postoperative pain score in abdominal hysterectomy. *Biomed Res Int* **2014**: 236024.

Kalsi SS, Wood DM & Dargan PI (2011) The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. *Emerg Health Threats J* **4**: 7107.

Kalso E, Tramer MR, McQuay HJ et al (1998) Systemic local-anaesthetic-type drugs in chronic pain: a systematic review. *Eur J Pain* **2**(1): 3-14.

Kam PCA & So A (2009) COX-3: uncertainties and controversies. *Curr Anaesth Crit Care* **20**: 50–53.

Kang R, Jeong JS, Yoo JC et al (2018a) Effective Dose of Intravenous Dexmedetomidine to Prolong the Analgesic Duration of Interscalene Brachial Plexus Block: A Single-Center, Prospective, Double-Blind, Randomized Controlled Trial. *Reg Anesth Pain Med* **43**(5): 488-95.

Kang Z, Xie W, Xie W et al (2018b) Comparison of neurotoxicity of dexmedetomidine as an adjuvant in brachial plexus block in rats of different age. *Neurotoxicol Teratol* **69**: 21-26.

Kapur BM, Hutson JR, Chibber T et al (2011) Methadone: a review of drug-drug and pathophysiological interactions. *Crit Rev Clin Lab Sci* **48**(4): 171–95.

Karaman S, Kocabas S, Uyar M et al (2006) The effects of sufentanil or morphine added to hyperbaric bupivacaine in spinal anaesthesia for caesarean section. *Eur J Anaesthesiol* **23**(4): 285–91.

Karlow N, Schlaepfer CH, Stoll CRT et al (2018) A Systematic Review and Meta-analysis of Ketamine as an Alternative to Opioids for Acute Pain in the Emergency Department. *Acad Emerg Med* **25**(10): 1086-97.

Karow JH, Abt HP, Frohling M et al (2008) Efficacy of Arnica montana D4 for healing of wounds after Hallux valgus surgery compared to diclofenac. *J Altern Complement Med* **14**(1): 17–25.

Karschner EL, Darwin WD, Goodwin RS et al (2011a) Plasma cannabinoid pharmacokinetics following controlled oral delta9-tetrahydrocannabinol and oromucosal cannabis extract administration. *Clin Chem* **57**(1): 66–75.

Karschner EL, Darwin WD, McMahon RP et al (2011b) Subjective and physiological effects after controlled Sativex and oral THC administration. *Clin Pharmacol Ther* **89**(3): 400–07.

Kashefi P, Montazeri K, Honarmand A et al (2008) Adding magnesium to lidocaine for intravenous regional anesthesia. *J Res Med Sci* **13**(3): 108–14.

Kathirvel S, Sadhasivam S, Saxena A et al (2000) Effects of intrathecal ketamine added to bupivacaine for spinal anaesthesia. *Anaesthesia* **55**(9): 899–904.

Katz NP, Paillard FC & Edwards RR (2015) Review of the performance of quantitative sensory testing methods to detect hyperalgesia in chronic pain patients on long-term opioids. *Anesthesiology* **122**(3): 677–85.

Kaur P, Kundra TS & Sood D (2017) Comparative efficacy of clonidine versus magnesium sulfate as an adjunct to lignocaine in intravenous regional anesthesia for postoperative analgesia: A prospective, randomized, double-blind study. *J Anaesthesiol Clin Pharmacol* **33**(3): 387-90.

Kaya FN, Yavascaoglu B, Turker G et al (2010) Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. *Can J Anaesth* **57**(1): 39–45.

Kayalha H, Mousavi Z, Sadat Barikani A et al (2015) The Effects of Intrathecal Neostigmine Added to Bupivacaine on Postoperative Analgesic Requirement in Patients Undergoing Lower Limb Orthopedic Surgery. *Middle East J Anaesthesiol* **23**(2): 199-204.

Kehlet H (1997) Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* **78**(5): 606–17.

Keller GA, Villa Etchegoyen C, Fernandez N et al (2018) Dextrophropoxyphene effects on QTc-interval prolongation: Frequency and characteristics in relation to plasma levels. *J Opioid Manag* **14**(5): 335-44.

Kelly LE, Rieder M, van den Anker J et al (2012) More codeine fatalities after tonsillectomy in North American children. *Pediatrics* **129**(5): e1343–47.

Kendall J, Maconochie I, Wong IC et al (2015) A novel multipatient intranasal diamorphine spray for use in acute pain in children: pharmacovigilance data from an observational study. *Emerg Med J* **32**(4): 269–73.
Kendall MC, Castro Alves LJ & De Oliveira G, Jr. (2018) Liposome Bupivacaine Compared to Plain Local Anesthetics to Reduce Postsurgical Pain: An Updated Meta-Analysis of Randomized Controlled Trials. *Pain Res Treat* **2018**: 5710169.
Kennedy DJ, Levin J, Rosenquist R et al (2015) Epidural Steroid Injections are Safe and Effective: Multisociety Letter in Support of the Safety and Effectiveness of Epidural Steroid Injections. *Pain Med* **16**(5): 833-8.
Kerezoudis P, Rinaldo L, Alvi MA et al (2018) The Effect of Epidural Steroid Injections on Bone Mineral Density and Vertebral Fracture Risk: A Systematic Review and Critical Appraisal of Current Literature. *Pain Med* **19**(3): 569-79.
Kerrick JM, Fine PG, Lipman AG et al (1993) Low-dose amitriptyline as an adjunct to opioids for postoperative orthopedic pain: a placebo-controlled trial. *Pain* **52**(3): 325–30.
Kessler ER, Shah M, Gruschkus SK et al (2013) Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes. *Pharmacotherapy* **33**(4): 383–91.
Khafagy HF, Refaat AI, El-Sabae HH et al (2010) Efficacy of epidural dexamethasone versus fentanyl on postoperative analgesia. *J Anesth* **24**(4): 531–36.
Khan JS, Margarido C, Devereaux PJ et al (2016) Preoperative celecoxib in noncardiac surgery: A systematic review and meta-analysis of randomised controlled trials. *Eur J Anaesthesiol* **33**(3): 204-14.
Khezri MB, Nasseh N & Soltanian G (2017) The comparative preemptive analgesic efficacy of addition of vitamin B complex to gabapentin versus gabapentin alone in women undergoing cesarean section under spinal anesthesia: A prospective randomized double-blind study. *Medicine (Baltimore)* **96**(15): e6545.
Khoo LP & Corbett AR (2006) Successful resuscitation of an ASA 3 patient following ropivacaine-induced cardiac arrest. *Anaesth Intensive Care* **34**(6): 804–07.
Kiasari AZ, Firouzian A, Baradari AG et al (2014) The Effect of Vitamin B12 Infusion on Prevention of Nitrous Oxide-induced Homocysteine Increase: A Double-blind Randomized Controlled Trial. *Oman Med J* **29**(3): 194-7.
Kidd S, Brennan S, Stephen R et al (2009) Comparison of morphine concentration-time profiles following intravenous and intranasal diamorphine in children. *Arch Dis Child* **94**(12): 974–78.
Kilbas Z, Mentes MO, Harlak A et al (2015) Efficacy of wound infiltration with lornoxicam for postoperative analgesia following thyroidectomy: a prospective, randomized, double-blind study. *Turk J Med Sci* **45**(3): 700-5.
Kim EG, Park HJ, Kang H et al (2014a) Antiemetic effect of propofol administered at the end of surgery in laparoscopic assisted vaginal hysterectomy. *Korean J Anesthesiol* **66**(3): 210–15.
Kim MS, Kim DJ, Na CH et al (2016) A Study of Intravenous Administration of Vitamin C in the Treatment of Acute Herpetic Pain and Postherpetic Neuralgia. *Ann Dermatol* **28**(6): 677-83.
Kim SH, Kim DH, Kim E et al (2018) Does perioperative intravenous dextrose reduce postoperative nausea and vomiting? A systematic review and meta-analysis. *Ther Clin Risk Manag* **14**: 2003-11.
Kim SH, Stoicea N, Soghomonyan S et al (2014b) Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: systematic review. *Front Pharmacol* **5**: 108.
Kimura S & Haji A (2014) Pharmacological strategy for overcoming opioid-induced ventilatory disturbances. *Eur J Pharmacol* **725**: 87–90.
Kimura Y, Kamada Y, Kimura A et al (2007) Ropivacaine-induced toxicity with overdose suspected after axillary brachial plexus block. *J Anesth* **21**(3): 413–16.
King MR, Ladha KS, Gelineau AM et al (2016) Perioperative Dextromethorphan as an Adjunct for Postoperative Pain: A Meta-analysis of Randomized Controlled Trials. *Anesthesiology* **124**(3): 696-705.
Kinney MA, Mantilla CB, Carns PE et al (2012) Preoperative gabapentin for acute post-thoracotomy analgesia: a randomized, double-blinded, active placebo-controlled study. *Pain Pract* **12**(3): 175–83.
Kinnunen M, Piirainen P, Kokki H et al (2019) Updated Clinical Pharmacokinetics and Pharmacodynamics of Oxycodone. *Clin Pharmacokinet* **58**(6): 705-25.
Kirchheiner J, Schmidt H, Tzvetkov M et al (2007) Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J* **7**(4): 257–65.
Kirkham KR, Jacot-Guillarmod A & Albrecht E (2018) Optimal Dose of Perineural Dexamethasone to Prolong Analgesia After Brachial Plexus Blockade: A Systematic Review and Meta-analysis. *Anesth Analg* **126**(1): 270-79.
Kizilcik N, Ozler T, Menda F et al (2017) The effects of intra-articular levobupivacain versus levobupivacain plus magnesium sulfate on postoperative analgesia in patients undergoing arthroscopic meniscectomy: A prospective randomized controlled study. *Acta Orthop Traumatol Turc* **51**(2): 104-09.
Kizilkaya M, Yildirim OS, Dogan N et al (2004) Analgesic effects of intraarticular sufentanil and sufentanil plus methylprednisolone after arthroscopic knee surgery. *Anesth Analg* **98**(4): 1062–65.
Kizilkaya M, Yildirim OS, Ezirmik N et al (2005) Comparisons of analgesic effects of different doses of morphine and morphine plus methylprednisolone after knee surgery. *Eur J Anaesthesiol* **22**(8): 603–08.
Kjellberg F & Tramer MR (2001) Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. *Eur J Anaesthesiol* **18**(6): 346–57.

Klatt E, Zumbrunn T, Bandschapp O et al (2015) Intra- and postoperative intravenous ketamine does not prevent chronic pain: A systematic review and meta-analysis. *Scand J Pain* **7**(1): 42-54.
Klein JA & Jeske DR (2016) Estimated Maximal Safe Dosages of Tumescent Lidocaine. *Anesth Analg* **122**(5): 1350-9.
Klein M, Krarup PM, Kongsbak MB et al (2012) Effect of postoperative diclofenac on anastomotic healing, skin wounds and subcutaneous collagen accumulation: a randomized, blinded, placebo-controlled, experimental study. *Eur Surg Res* **48**(2): 73-8.
Klein SM, Pierce T, Rubin Y et al (2003) Successful resuscitation after ropivacaine-induced ventricular fibrillation. *Anesth Analg* **97**(3): 901–03.
Klepstad P, Dale O, Kaasa S et al (2003) Influences on serum concentrations of morphine, M6G and M3G during routine clinical drug monitoring: a prospective survey in 300 adult cancer patients. *Acta Anaesthesiol Scand* **47**(6): 725–31.
Klimas R & Mikus G (2014) Morphine-6-glucuronide is responsible for the analgesic effect after morphine administration: a quantitative review of morphine, morphine-6-glucuronide, and morphine-3-glucuronide. *Br J Anaesth* **113**(6): 935–44.
Klinge SA & Sawyer GA (2013) Effectiveness and safety of topical versus oral nonsteroidal anti-inflammatory drugs: a comprehensive review. *Phys Sportsmed* **41**(2): 64–74.
Klivinyi C & Bornemann-Cimenti H (2018) Pain medication and long QT syndrome. *Korean J Pain* **31**(1): 3-9.
Klomp T, van Poppel M, Jones L et al (2012) Inhaled analgesia for pain management in labour. *Cochrane Database Syst Rev* **9**(9): CD009351.
Kluger MT, Owen H, Watson D et al (1992) Oxyhaemoglobin saturation following elective abdominal surgery in patients receiving continuous intravenous infusion or intramuscular morphine analgesia. *Anaesthesia* **47**(3): 256–60.
Knopp-Sihota JA, Newburn-Cook CV, Homik J et al (2012) Calcitonin for treating acute and chronic pain of recent and remote osteoporotic vertebral compression fractures: a systematic review and meta-analysis. *Osteoporos Int* **23**(1): 17–38.
Knudsen K, Beckman Suurkula M, Blomberg S et al (1997) Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* **78**(5): 507–14.
Koç S, Memis D & Sut N (2007) The preoperative use of gabapentin, dexamethasone, and their combination in varicocele surgery: a randomized controlled trial. *Anesth Analg* **105**(4): 1137–42.
Koh IJ, Kim MS, Sohn S et al (2019) Duloxetine Reduces Pain and Improves Quality of Recovery Following Total Knee Arthroplasty in Centrally Sensitized Patients: A Prospective, Randomized Controlled Study. *J Bone Joint Surg Am* **101**(1): 64-73.
Kokki H, Kokki M & Sjovall S (2012) Oxycodone for the treatment of postoperative pain. *Expert Opin Pharmacother* **13**(7): 1045–58.
Kokki M, Pesonen M, Vehvilainen P et al (2016) Cytotoxicity of Oxycodone and Morphine in Human Neuroblastoma and Mouse Motoneuronal Cells: A Comparative Approach. *Drugs R D* **16**(2): 155-63.
Kol IO, Ozturk H, Kaygusuz K et al (2009) Addition of dexmedetomidine or lornoxicam to prilocaine in intravenous regional anaesthesia for hand or forearm surgery: a randomized controlled study. *Clin Drug Investig* **29**(2): 121–29.
Konakci S, Adanir T, Yilmaz G et al (2008) The efficacy and neurotoxicity of dexmedetomidine administered via the epidural route. *Eur J Anaesthesiol* **25**(5): 403–09.
Kongsgaard UE & Werner MU (2016) Tachyphylaxis to local anaesthetics. What is the clinical evidence? A systematic review. *Acta Anaesthesiol Scand* **60**(1): 6-14.
Kontinen V & Breivik H (2019) The Yaksh-model of intrathecal opioid-studies: still exciting four decades later. *Scand J Pain* **19**(1): 3-4.
Kopka A, Wallace E, Reilly G et al (2007) Observational study of perioperative PtcCO2 and SpO2 in non-ventilated patients receiving epidural infusion or patient-controlled analgesia using a single earlobe monitor (TOSCA). *Br J Anaesth* **99**(4): 567–71.
Koppert W, Ihmsen H, Korber N et al (2005) Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. *Pain* **118**(1-2): 15–22.
Kosel J, Bobik P & Tomczyk M (2016) Buprenorphine--the unique opioid adjuvant in regional anesthesia. *Expert Rev Clin Pharmacol* **9**(3): 375-83.
Kovac AL (2006) Meta-analysis of the use of rescue antiemetics following PONV prophylactic failure with 5-HT3 antagonist/dexamethasone versus single-agent therapies. *Ann Pharmacother* **40**(5): 873–87.
Kowalski ML, Agache I, Bavbek S et al (2019) Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)-a EAACI position paper. *Allergy* **74**(1): 28-39.
Kraft M, Maclaren R, Du W et al (2010) Alvimopan (entereg) for the management of postoperative ileus in patients undergoing bowel resection. *P T* **35**(1): 44–49.
Kramer BK, Kammerl MC & Komhoff M (2004) Renal cyclooxygenase-2 (COX-2). Physiological, pathophysiological, and clinical implications. *Kidney Blood Press Res* **27**(1): 43–62.
Kranke P, Jokinen J, Pace NL et al (2015) Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. *Cochrane Database Syst Rev*(7): CD009642.

Kress HG (2009) Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. *Eur J Pain* **13**(3): 219–30.
Kreutzwiser D & Tawfic QA (2019) Expanding Role of NMDA Receptor Antagonists in the Management of Pain. *CNS Drugs* **33**(4): 347-74.
Krijthe BP, Heeringa J, Hofman A et al (2014) Non-steroidal anti-inflammatory drugs and the risk of atrial fibrillation: a population-based follow-up study. *BMJ Open* **4**(4): e004059.
Krishna S, Hughes LF & Lin SY (2003) Postoperative hemorrhage with nonsteroidal anti-inflammatory drug use after tonsillectomy: a meta-analysis. *Arch Otolaryngol Head Neck Surg* **129**(10): 1086–89.
Kuczynska K, Grzonkowski P, Kacprzak L et al (2018) Abuse of fentanyl: An emerging problem to face. *Forensic Sci Int* **289**: 207-14.
Kuijpers T, van Middelkoop M, Rubinstein SM et al (2011) A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. *Eur Spine J* **20**(1): 40–50.
Kuip EJ, Zandvliet ML, Koolen SL et al (2017) A review of factors explaining variability in fentanyl pharmacokinetics; focus on implications for cancer patients. *Br J Clin Pharmacol* **83**(2): 294-313.
Kuivalainen AM, Ebeling F, Poikonen E et al (2015) Nitrous oxide analgesia for bone marrow aspiration and biopsy - A randomized, controlled and patient blinded study. *Scand J Pain* **7**(1): 28-34.
Kumar A & Kale TP (2015) A Comparative Study between the Effect of Combined Local Anesthetic and Low-dose Ketamine with Local Anesthetic on Postoperative Complications after Impacted Third Molar Surgery. *J Contemp Dent Pract* **16**(12): 957.
Kumar A, Sharma D & Datta B (2012) Addition of ketamine or dexmedetomidine to lignocaine in intravenous regional anesthesia: A randomized controlled study. *J Anaesthesiol Clin Pharmacol* **28**(4): 501–04.
Kumar A, Srivastava U, Saxena S et al (2007) Comparison of intrathecal morphine and pethidine for post caesarean analgesia and side effects. *J Anaesthesiol Clin Pharmacol* **23**(1): 35–39.
Kumar M, Dayal N, Rautela RS et al (2013) Effect of intravenous magnesium sulphate on postoperative pain following spinal anesthesia. A randomized double blind controlled study. *Middle East J Anaesthesiol* **22**(3): 251–56.
Kumar P, Rudra A, Pan AK et al (2005) Caudal additives in pediatrics: a comparison among midazolam, ketamine, and neostigmine coadministered with bupivacaine. *Anesth Analg* **101**(1): 69–73.
Kumari R, Kumar A, Kumar S et al (2017) Intravenous dexmedetomidine as an adjunct to subarachnoid block: A simple effective method of better perioperative efficacy. *J Anaesthesiol Clin Pharmacol* **33**(2): 203-08.
Kumari Vasantha NS & Madhusudhana R (2018) Intrathecal Bupivacaine with Neostigmine and Bupivacaine with Normal Saline for Postoperative Analgesia: A Cost-effective Additive. *Anesth Essays Res* **12**(2): 328-32.
Kuo CP, Jao SW, Chen KM et al (2006) Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J Anaesth* **97**(5): 640–46.
Kuo HW, Tsai SS, Tiao MM et al (2010) Analgesic use and the risk for progression of chronic kidney disease. *Pharmacoepidemiol Drug Saf* **19**(7): 745–51.
Kuriyama A & Maeda H (2019) Preoperative intravenous dexamethasone prevents tracheal intubation-related sore throat in adult surgical patients: a systematic review and meta-analysis. *Can J Anaesth* **66**(5): 562-75.
Kurmis AP, Kurmis TP, O'Brien JX et al (2012) The effect of nonsteroidal anti-inflammatory drug administration on acute phase fracture-healing: a review. *J Bone Joint Surg Am* **94**(9): 815–23.
Kuusniemi K, Zollner J, Sjovall S et al (2012) Prolonged-release oxycodone/naloxone in postoperative pain management: from a randomized clinical trial to usual clinical practice. *J Int Med Res* **40**(5): 1775–93.
Lacassie HJ & Columb MO (2003) The relative motor blocking potencies of bupivacaine and levobupivacaine in labor. *Anesth Analg* **97**(5): 1509–13.
Lafli Tunay D, Turkeun Ilginel M, Unlugenc H et al (2020) Comparison of the effects of preoperative melatonin or vitamin C administration on postoperative analgesia. *Bosn J Basic Med Sci* **20**(1): 117-24.
Lakhan SE, Ford CT & Tepper D (2015) Zingiberaceae extracts for pain: a systematic review and meta-analysis. *Nutr J* **14**: 50.
Lal A, Chohan K, Chohan A et al (2017) Role of honey after tonsillectomy: a systematic review and meta-analysis of randomised controlled trials. *Clin Otolaryngol* **42**(3): 651-60.
Lalovic B, Kharasch E, Hoffer C et al (2006) Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. *Clin Pharmacol Ther* **79**(5): 461–79.
Lam T, Nagappa M, Wong J et al (2017) Continuous Pulse Oximetry and Capnography Monitoring for Postoperative Respiratory Depression and Adverse Events: A Systematic Review and Meta-analysis. *Anesth Analg* **125**(6): 2019-29.
Lambert DG, Bird MF & Rowbotham DJ (2015) Cebranopadol: a first in-class example of a nociceptin/orphanin FQ receptor and opioid receptor agonist. *Br J Anaesth* **114**(3): 364-6.
Lamminsalo M, Piirainen P, Kokki H et al (2019) Population pharmacokinetics of oxycodone in plasma and cerebrospinal fluid after epidural and intravenous administration. *Expert Opin Drug Deliv* **16**(6): 649-56.

Lanas A, Serrano P, Bajador E et al (2003) Risk of upper gastrointestinal bleeding associated with non-aspirin cardiovascular drugs, analgesics and nonsteroidal anti-inflammatory drugs. *Eur J Gastroenterol Hepatol* **15**(2): 173–78.

Langevin P, Peloso PM, Lowcock J et al (2011) Botulinum toxin for subacute/chronic neck pain. *Cochrane Database Syst Rev* **7**: CD008626.

Laroche M, Cantogrel S, Jamard B et al (2006) Comparison of the analgesic efficacy of pamidronate and synthetic human calcitonin in osteoporotic vertebral fractures: a double-blind controlled study. *Clin Rheumatol* **25**(5): 683–86.

Latta KS, Ginsberg B & Barkin RL (2002) Meperidine: a critical review. *Am J Ther* **9**(1): 53–68.

Laugesen S, Enggaard TP, Pedersen RS et al (2005) Paroxetine, a cytochrome P450 2D6 inhibitor, diminishes the stereoselective O-demethylation and reduces the hypoalgesic effect of tramadol. *Clin Pharmacol Ther* **77**(4): 312–23.

Lavand'homme P (2006) Lessons from spinal midazolam: When misuse of messages from preclinical models exposes patients to unnecessary risks. *Reg Anesth Pain Med* **31**(6): 489-91.

Lavand'homme P, Roelants F & Waterloos H, et al (2008) An evaluation of the post-operative antihyperalgesic and analgesic effects of intrathecal clonidine administered during elective caesarian delivery. *Anesth Analg* **107**(3): 948–55.

Lavernia CJ, Contreras JS, Villa JM et al (2014) Celecoxib and heterotopic bone formation after total hip arthroplasty. *J Arthroplasty* **29**(2): 390–92.

Lavonas EJ, Reynolds KM & Dart RC (2010) Therapeutic acetaminophen is not associated with liver injury in children: a systematic review. *Pediatrics* **126**(6): e1430–44.

Le LT, Loland VJ, Mariano ER et al (2008) Effects of local anesthetic concentration and dose on continuous interscalene nerve blocks: a dual-center, randomized, observer-masked, controlled study. *Reg Anesth Pain Med* **33**(6): 518–25.

Lee A, Chan SK & Fan LT (2015a) Stimulation of the wrist acupuncture point PC6 for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev*(11): CD003281.

Lee C, Lee HW & Kim JN (2013a) Effect of oral pregabalin on opioid-induced hyperalgesia in patients undergoing laparo-endoscopic single-site urologic surgery. *Korean J Anesthesiol* **64**(1): 19–24.

Lee CR, McTavish D & Sorkin EM (1993) Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs* **46**(2): 313–40.

Lee CT, Chang SS, Kamat AM et al (2014a) Alvimopan accelerates gastrointestinal recovery after radical cystectomy: a multicenter randomized placebo-controlled trial. *Eur Urol* **66**(2): 265–72.

Lee CW & Ho IK (2013b) Sex differences in opioid analgesia and addiction: interactions among opioid receptors and estrogen receptors. *Mol Pain* **9**: 45.

Lee IO, Kim WK, Kong MH et al (2002) No enhancement of sensory and motor blockade by ketamine added to ropivacaine interscalene brachial plexus blockade. *Acta Anaesthesiol Scand* **46**(7): 821–26.

Lee JH, Kim DH, Kim DH et al (2018a) Comparison of Clinical Efficacy of Epidural Injection With or Without Steroid in Lumbosacral Disc Herniation: A Systematic Review and Meta-analysis. *Pain Physician* **21**(5): 449-68.

Lee JH, Shin KH, Bahk SJ et al (2018b) Comparison of clinical efficacy of transforaminal and caudal epidural steroid injection in lumbar and lumbosacral disc herniation: A systematic review and meta-analysis. *Spine J* **18**(12): 2343-53.

Lee JH, Shin KH, Park SJ et al (2018c) Comparison of Clinical Efficacy Between Transforaminal and Interlaminar Epidural Injections in Lumbosacral Disc Herniation: A Systematic Review and Meta-Analysis. *Pain Physician* **21**(5): 433-48.

Lee LA, Caplan RA, Stephens LS et al (2015b) Postoperative opioid-induced respiratory depression: a closed claims analysis. *Anesthesiology* **122**(3): 659-65.

Lee M, Silverman SM, Hansen H et al (2011) A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* **14**(2): 145–61.

Lee MS, Lee HW, Khalil M et al (2018d) Aromatherapy for Managing Pain in Primary Dysmenorrhea: A Systematic Review of Randomized Placebo-Controlled Trials. *J Clin Med* **7**(11).

Lee Y, Wang PK, Lai HY et al (2007) Haloperidol is as effective as ondansetron for preventing postoperative nausea and vomiting. *Can J Anaesth* **54**(5): 349–54.

Lee YH & Song GG (2016) Comparative efficacy and tolerability of duloxetine, pregabalin, and milnacipran for the treatment of fibromyalgia: a Bayesian network meta-analysis of randomized controlled trials. *Rheumatol Int* **36**(5): 663-72.

Lee YK, Ko JS, Rhim HY et al (2014b) Acute postoperative pain relief with immediate-release tapentadol: randomized, double-blind, placebo-controlled study conducted in South Korea. *Curr Med Res Opin* **30**(12): 2561–70.

Leppert W (2010) Dihydrocodeine as an opioid analgesic for the treatment of moderate to severe chronic pain. *Curr Drug Metab* **11**(6): 494–506.

Levine JD, Gordon NC, Smith R et al (1986) Desipramine enhances opiate postoperative analgesia. *Pain* **27**(1): 45–49.

Lewis SR, Nicholson A, Cardwell ME et al (2013) Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. *Cochrane Database Syst Rev* **7**: CD003591.

Li A, Wei Z, Liu Y et al (2017a) Ropivacaine versus levobupivacaine in peripheral nerve block: A PRISMA-compliant meta-analysis of randomized controlled trials. *Medicine (Baltimore)* **96**(14): e6551.
Li F, Ma J, Kuang M et al (2017b) The efficacy of pregabalin for the management of postoperative pain in primary total knee and hip arthroplasty: a meta-analysis. *J Orthop Surg Res* **12**(1): 49.
Li L & Vlisides PE (2016a) Ketamine: 50 Years of Modulating the Mind. *Front Hum Neurosci* **10**: 612.
Li M, Jin S, Zhao X et al (2016b) Does Magnesium Sulfate as an Adjuvant of Local Anesthetics Facilitate Better Effect of Perineural Nerve Blocks?: A Meta-analysis of Randomized Controlled Trials. *Clin J Pain* **32**(12): 1053-61.
Li Wan Po A & Zhang WY (1997) Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *BMJ* **315**(7122): 1565–71.
Li X, Sun Z, Han C et al (2017c) A systematic review and meta-analysis of intravenous glucocorticoids for acute pain following total hip arthroplasty. *Medicine (Baltimore)* **96**(19): e6872.
Li XD, Han C & Yu WL (2017d) Is gabapentin effective and safe in open hysterectomy? A PRISMA compliant meta-analysis of randomized controlled trials. *J Clin Anesth* **41**: 76-83.
Licina L, Hamsher C, Lautenschager K et al (2013) Buprenorphine/naloxone therapy for opioid refractory neuropathic pain following traumatic amputation: a case series. *Mil Med* **178**(7): e858–61.
Likis FE, Andrews JC, Collins MR et al (2014) Nitrous oxide for the management of labor pain: a systematic review. *Anesth Analg* **118**(1): 153-67.
Lim AW & Schug SA (2001) Tramadol versus morphine as oral step-down analgesia after postoperative epidural analgesia. *Reg Anesth Pain Med* **26**: S133.
Lin J, Zhang L & Yang H (2013) Perioperative administration of selective cyclooxygenase-2 inhibitors for postoperative pain management in patients after total knee arthroplasty. *J Arthroplasty* **28**(2): 207–13 e2.
Lin RJ, Chen HF, Chang YC et al (2011) Subacute combined degeneration caused by nitrous oxide intoxication: case reports. *Acta Neurol Taiwan* **20**(2): 129-37.
Linde M, Mulleners WM, Chronicle EP et al (2013) Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults. [Review]. *Cochrane Database Syst Rev* **1**(6): Cd010608.
Lindegaard C, Gleerup K & Thomsen M (2010) Anti-inflammatory effects of intra-articular adminsitration of morphine in horses with experimentally induced synovitis. *Am J Vet Res* **71**(1): 69–75.
Lirk P, Picardi S & Hollmann MW (2014) Local anaesthetics: 10 essentials. *Eur J Anaesthesiol* **31**(11): 575-85.
Litz RJ, Popp M, Stehr SN et al (2006) Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. *Anaesthesia* **61**(8): 800–01.
Litz RJ, Roessel T, Heller AR et al (2008) Reversal of central nervous system and cardiac toxicity after local anesthetic intoxication by lipid emulsion injection. *Anesth Analg* **106**(5): 1575–77.
Liu L, Li C, Huang Y et al (2019) Nonsteroidal Anti-inflammatory Drugs for Endoscopic Retrograde Cholangiopancreatography Postoperative Pancreatitis Prevention: a Systematic Review and Meta-analysis. *J Gastrointest Surg* **23**(10): 1991-2001.
Liu M, Zhang H, Du BX et al (2015) Neurokinin-1 receptor antagonists in preventing postoperative nausea and vomiting: a systematic review and meta-analysis. *Medicine (Baltimore)* **94**(19): e762.
Liu Q, Gao LL, Dai YL et al (2018) Nitrous oxide/oxygen mixture for analgesia in adult cancer patients with breakthrough pain: A randomized, double-blind controlled trial. *Eur J Pain* **22**(3): 492-500.
Liu S, Carpenter RL, Mulroy MF et al (1995) Intravenous versus epidural administration of hydromorphone. Effects on analgesia and recovery after radical retropubic prostatectomy. *Anesthesiology* **82**(3): 682–88.
Liu SQ, Chen X, Yu CC et al (2017a) Comparison of periarticular anesthesia with liposomal bupivacaine with femoral nerve block for pain control after total knee arthroplasty: A PRISMA-compliant meta-analysis. *Medicine (Baltimore)* **96**(13): e6462.
Liu SS, Bae JJ, Bieltz M et al (2012) Association of perioperative use of nonsteroidal anti-inflammatory drugs with postoperative myocardial infarction after total joint replacement. *Reg Anesth Pain Med* **37**(1): 45–50.
Liu X, Sun D, Ma X et al (2017b) Benefit-risk of corticosteroids in acute gout patients: An updated meta-analysis and economic evaluation. *Steroids* **128**: 89-94.
Liu X, Zhao X, Lou J et al (2013) Parecoxib added to ropivacaine prolongs duration of axillary brachial plexus blockade and relieves postoperative pain. *Clin Orthop Relat Res* **471**(2): 562–68.
Liu Y, Lin D, Wu B et al (2016) Ketamine abuse potential and use disorder. *Brain Research Bulletin* **126**(Pt 1): 68-73.
Loftus RW, Yeager MP, Clark JA et al (2010) Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology* **113**(3): 639–46.
Loix S, De Kock M & Henin P (2011) The anti-inflammatory effects of ketamine: state of the art. *Acta Anaesthesiol Belg* **62**(1): 47–58.
Lopez-Olivo MA, Shah NA, Pratt G et al (2012) Bisphosphonates in the treatment of patients with lung cancer and metastatic bone disease: a systematic review and meta-analysis. *Support Care Cancer* **20**(11): 2985–98.
Lotsch J (2005) Opioid metabolites. *J Pain Symptom Manage* **29**(5 Suppl): S10–24.
Lotsch J, Rohrbacher M, Schmidt H et al (2009) Can extremely low or high morphine formation from codeine be predicted prior to therapy initiation? *Pain* **144**(1-2): 119–24.

Lotsch J, Walter C, Parnham MJ et al (2013) Pharmacokinetics of non-intravenous formulations of fentanyl. *Clin Pharmacokinet* **52**(1): 23–36.
Low Y, Clarke CF & Huh BK (2012) Opioid-induced hyperalgesia: a review of epidemiology, mechanisms and management. *Singapore Med J* **53**(5): 357–60.
Lowenberg M, Stahn C, Hommes DW et al (2008) Novel insights into mechanisms of glucocorticoid action and the development of new glucocorticoid receptor ligands. *Steroids* **73**(9-10): 1025–29.
Lowenstein O, Leyendecker P, Lux EA et al (2010) Efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. *BMC Clin Pharmacol* **10**: 12.
Loy BM, Britt RB & Brown JN (2016) Memantine for the Treatment of Phantom Limb Pain: A Systematic Review. *J Pain Palliat Care Pharmacother* **30**(4): 276-83.
Lu Y, Li Y, Li FL et al (2015) Do Different Cyclooxygenase Inhibitors Impair Rotator Cuff Healing in a Rabbit Model? *Chin Med J (Engl)* **128**(17): 2354-9.
Ludwin DB & Shafer SL (2008) Con: The black box warning on droperidol should not be removed (but should be clarified!). *Anesth Analg* **106**(5): 1418–20.
Lugo RA, Satterfield KL & Kern SE (2005) Pharmacokinetics of methadone. *J Pain Palliat Care Pharmacother* **19**(4): 13–24.
Luna IE, Kehlet H, Jensen CM et al (2017) The Effect of Preoperative Intra-Articular Methylprednisolone on Pain After TKA: A Randomized Double-Blinded Placebo Controlled Trial in Patients With High-Pain Knee Osteoarthritis and Sensitization. *J Pain* **18**(12): 1476-87.
Lunn MP, Hughes RA & Wiffen PJ (2014) Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev* **1**: CD007115.
Lunn TH, Andersen LO, Kristensen BB et al (2013) Effect of high-dose preoperative methylprednisolone on recovery after total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. *Br J Anaesth* **110**(1): 66–73.
Lunn TH, Frokjaer VG, Hansen TB et al (2015) Analgesic effect of perioperative escitalopram in high pain catastrophizing patients after total knee arthroplasty: A randomized, double-blind, placebo-controlled trial. *Anesthesiology* **122**(4): 884-94.
Lyndon A, Audrey S, Wells C et al (2017) Risk to heroin users of polydrug use of pregabalin or gabapentin. *Addiction* **112**(9): 1580-89.
Lyons G, Columb M, Wilson RC et al (1998) Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine. *Br J Anaesth* **81**(6): 899–901.
Lyons PJ, Rivosecchi RM, Nery JP et al (2015) Fentanyl-induced hyperalgesia in acute pain management. *J Pain Palliat Care Pharmacother* **29**(2): 153-60.
Ma H, Liu Y, Huang L et al (2016a) The Adverse Events of Oxycodone in Cancer-Related Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Medicine (Baltimore)* **95**(15): e3341.
Ma J, Zhang W & Yao S (2016b) Liposomal bupivacaine infiltration versus femoral nerve block for pain control in total knee arthroplasty: A systematic review and meta-analysis. *Int J Surg* **36**(Pt A): 44-55.
Ma W, Bai W, Lin C et al (2010) Effects of Sanyinjiao (SP6) with electroacupuncture on labour pain in women during labour. *Complement Ther Med* **19**(Suppl 1): S13–18.
MacDonald TM, Hawkey CJ, Ford I et al (2017) Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT). *Eur Heart J* **38**(23): 1843-50.
MacDonald TM & Wei L (2003) Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* **361**(9357): 573–74.
Macherey S, Monsef I, Jahn F et al (2017) Bisphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev* **12**: CD006250.
Macias A, Monedero P, Adame M et al (2002) A randomized, double-blinded comparison of thoracic epidural ropivacaine, ropivacaine/fentanyl, or bupivacaine/fentanyl for postthoracotomy analgesia. *Anesth Analg* **95**(5): 1344–50.
Macintyre PE & Coldrey J (2008a) Patient-controlled analgesia. In: *Clinical Pain Management: Acute Pain* 2nd edn. Macintyre PE, Walker SM and Rowbotham DJ (eds). London, Hodder Arnold.
Macintyre PE & Huxtable CA (2017) Buprenorphine for the management of acute pain. *Anaesth Intensive Care* **45**(2): 143-46.
Macintyre PE & Jarvis DA (1996) Age is the best predictor of postoperative morphine requirements. *Pain* **64**(2): 357–64.
Macintyre PE, Loadsman JA & Scott DA (2011) Opioids, ventilation and acute pain management. *Anaesth Intensive Care* **39**(4): 545-58.
Macintyre PE & Schug SA (2015) *Acute Pain Management: A Practical Guide*. Boca Raton, CRC Press.
Macintyre PE & Upton R (2008b) Acute pain management in the elderly patient. In: *Clinical Pain Management: Acute Pain* 2nd edn. Macintyre PE, Walker SM and Rowbotham DJ (eds). London, Hodder Arnold.
Mackie K (2006) Cannabinoid receptors as therapeutic targets. *Annu Rev Pharmacol Toxicol* **46**: 101–22.
Macleod J & Hickman M (2010) How ideology shapes the evidence and the policy: what do we know about cannabis use and what should we do? *Addiction* **105**(8): 1326–30.

Madadi P, Ross CJ, Hayden MR et al (2009) Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther* **85**(1): 31–35.
Madadi P, Shirazi F, Walter FG et al (2008) Establishing causality of CNS depression in breastfed infants following maternal codeine use. *Paediatr Drugs* **10**(6): 399–404.
Mahendru V, Tewari A, Katyal S et al (2013) A comparison of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb surgery: A double blind controlled study. *J Anaesthesiol Clin Pharmacol* **29**(4): 496–502.
Maizels M, Scott B, Cohen W et al (1996) Intranasal lidocaine for treatment of migraine: a randomized, double-blind, controlled trial. *JAMA* **276**(4): 319-21.
Makkar JK, Singh PM, Jain D et al (2016) Particulate vs Non-Particulate Steroids for Transforaminal Epidural Steroid Injections: Systematic Review and Meta-analysis of the Current Literature. *Pain Physician* **19**(6): 327-40.
Makunts T, U A, Atayee RS et al (2019) Retrospective analysis reveals significant association of hypoglycemia with tramadol and methadone in contrast to other opioids. *Sci Rep* **9**(1): 12490.
Malinovsky JM, Cozian A, Lepage JY et al (1991) Ketamine and midazolam neurotoxicity in the rabbit. *Anesthesiology* **75**(1): 91-7.
Mancini F, Landolfi C, Muzio M et al (2003) Acetaminophen down-regulates interleukin-1beta-induced nuclear factor-kappaB nuclear translocation in a human astrocytic cell line. *Neurosci Lett* **353**(2): 79–82.
Manuar MB, Majumdar S, Das A et al (2014) Pain relief after arthroscopic knee surgery: a comparison of intra-articular ropivacaine, fentanyl, and dexmedetomidine: a prospective, double-blinded, randomized controlled study. *Saudi J Anaesth* **8**(2): 233–37.
Manzanares J, Julian M & Carrascosa A (2006) Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. *Curr Neuropharmacol* **4**(3): 239–57.
Mao J (2008) Opioid-induced hyperalgesia. *Pain: Clinical Updates (IASP)* **XVI**(2).
Mao J (2015) Clinical Diagnosis of Opioid-Induced Hyperalgesia. *Reg Anesth Pain Med* **40**(6): 663-4.
Marchal JM, Delgado-Martinez AD, Poncela M et al (2003) Does the type of arthroscopic surgery modify the analgesic effect of intraarticular morphine and bupivacaine? A preliminary study. *Clin J Pain* **19**(4): 240–46.
Marconi A, Di Forti M, Lewis CM et al (2016) Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. *Schizophr Bull* **42**(5): 1262-9.
Marjoribanks J, Ayeleke RO, Farquhar C et al (2015) Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database Syst Rev*(7): Cd001751.
Markham A & Faulds D (1996) Ropivacaine. A review of its pharmacology and therapeutic use in regional anaesthesia. *Drugs* **52**(3): 429–49.
Marret E, Kurdi O, Zufferey P et al (2005) Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. *Anesthesiology* **102**(6): 1249–60.
Marseglia L, Manti S, D'Angelo G et al (2015) Potential Use of Melatonin in Procedural Anxiety and Pain in Children Undergoing Blood Withdrawal. *J Biol Regul Homeost Agents* **29**(2): 509-14.
Marshall MA & Ozorio HP (1972) Analgesia for burns dressing using methoxyflurane. *Br J Anaesth* **44**(1): 80–82.
Marteau D, McDonald R & Patel K (2015) The relative risk of fatal poisoning by methadone or buprenorphine within the wider population of England and Wales. *BMJ Open* **5**(5): e007629.
Martin Arias LH, Martin Gonzalez A, Sanz Fadrique R et al (2019) Gastrointestinal safety of coxibs: systematic review and meta-analysis of observational studies on selective inhibitors of cyclo-oxygenase 2. *Fundam Clin Pharmacol* **33**(2): 134-47.
Martin C, Martin A, Rud C et al (1988) [Comparative study of sodium valproate and ketoprofen in the treatment of postoperative pain]. *Ann Fr Anesth Reanim* **7**(5): 387–92.
Martin E, Narjoz C, Decleves X et al (2019a) Dextromethorphan Analgesia in a Human Experimental Model of Hyperalgesia. *Anesthesiology* **131**(2): 1.
Martin E, Sorel M, Morel V et al (2019b) Dextromethorphan and memantine after ketamine analgesia: a randomized control trial. *Drug Des Devel Ther* **13**: 2677-88.
Martin G, Hartmannsgruber M, Riley E et al (2006) Single-dose extended-release epidural morphine for pain after hip arthroplasty. *J Opioid Manag* **2**(4): 209–18.
Martin WJ, Perez RS, Tuinzing DB et al (2012) Efficacy of antidepressants on orofacial pain: a systematic review. *Int J Oral Maxillofac Surg* **41**(12): 1532–39.
Martinez V, Beloeil H, Marret E et al (2017) Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials. *Br J Anaesth* **118**(1): 22-31.
Martinez V, Guichard L & Fletcher D (2015) Effect of combining tramadol and morphine in adult surgical patients: a systematic review and meta-analysis of randomized trials. *Br J Anaesth* **114**(3): 384-95.
Martinez-Zapata MJ, Roque M, Alonso-Coello P et al (2006) Calcitonin for metastatic bone pain. *Cochrane Database Syst Rev* **3**: CD003223.
Marty P, Rontes O, Chassery C et al (2018) Perineural Versus Systemic Dexamethasone in Front-Foot Surgery Under Ankle Block: A Randomized Double-Blind Study. *Reg Anesth Pain Med* **43**(7): 732-37.

Marwick PC, Levin AI & Coetzee AR (2009) Recurrence of cardiotoxicity after lipid rescue from bupivacaine-induced cardiac arrest. *Anesth Analg* **108**(4): 1344–46.
Marzilawati AR, Ngau YY & Mahadeva S (2012) Low rates of hepatotoxicity among Asian patients with paracetamol overdose: a review of 1024 cases. *BMC Pharmacol Toxicol* **13**(1): 8.
Masic D, Liang E, Long C et al (2018) Intravenous Lidocaine for Acute Pain: A Systematic Review. *Pharmacotherapy* **38**(12): 1250-59.
Mather LE & Chang DH (2001) Cardiotoxicity with modern local anaesthetics: is there a safer choice? *Drugs* **61**(3): 333–42.
Mathews TJ, Churchhouse AM, Housden T et al (2012) Does adding ketamine to morphine patient-controlled analgesia safely improve post-thoracotomy pain? *Interact Cardiovasc Thorac Surg* **14**(2): 194–99.
Mathiesen O, Rasmussen ML, Dierking G et al (2009) Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. *Acta Anaesthesiol Scand* **53**(2): 227–35.
Maund E, McDaid C, Rice S et al (2011) Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. *Br J Anaesth* **106**(3): 292–97.
Mayhood J & Cress K (2015) Effectiveness of ketamine gargle in reducing postoperative sore throat in patients undergoing airway instrumentation: a systematic review. *JBI Database System Rev Implement Rep* **13**(9): 244-78.
Mazloomdoost D, Pauls RN, Hennen EN et al (2017) Liposomal bupivacaine decreases pain following retropubic sling placement: a randomized placebo-controlled trial. *Am J Obstet Gynecol* **217**(5): 598 e1-98 e11.
McAlindon TE, Bannuru RR, Sullivan MC et al (2014) OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* **22**(3): 363-88.
McCartney CJ, Duggan E & Apatu E (2007) Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. *Reg Anesth Pain Med* **32**(4): 330–38.
McCormack JG, Kelly KP, Wedgwood J et al (2008) The effects of different analgesic regimens on transcutaneous CO2 after major surgery. *Anaesthesia* **63**(8): 814–21.
McCormick Z, Chang-Chien G, Marshall B et al (2014) Phantom limb pain: a systematic neuroanatomical-based review of pharmacologic treatment. *Pain Med* **15**(2): 292–305.
McCullagh N, Pereira P, Cullen P et al (2012) Randomised trial of magnesium in the treatment of Irukandji syndrome. *Emerg Med Australas* **24**(5): 560–65.
McDowell K & Clements JN (2014) How can NSAIDs harm cardiovascular and renal function? *Jaapa* **27**(4): 12–15.
McGlade DP, Kalpokas MV, Mooney PH et al (1998) A comparison of 0.5% ropivacaine and 0.5% bupivacaine for axillary brachial plexus anaesthesia. *Anaesth Intensive Care* **26**(5): 515–20.
McGuinness SK, Wasiak J, Cleland H et al (2011) A systematic review of ketamine as an analgesic agent in adult burn injuries. *Pain Med* **12**(10): 1551–58.
McKeown A, Seppi V & Hodgson R (2017) Intravenous Magnesium Sulphate for Analgesia after Caesarean Section: A Systematic Review. *Anesthesiol Res Pract* **2017**: 9186374.
McLean S & Twomey F (2015) Methods of Rotation From Another Strong Opioid to Methadone for the Management of Cancer Pain: A Systematic Review of the Available Evidence. *J Pain Symptom Manage* **50**(2): 248-59 e1.
McLeod GA & Burke D (2001) Levobupivacaine. *Anaesthesia* **56**(4): 331–41.
McLeod GA, Munishankar B & Columb MO (2005) Is the clinical efficacy of epidural diamorphine concentration-dependent when used as analgesia for labour? *Br J Anaesth* **94**(2): 229–33.
McNeely JK, Buczulinski B & Rosner DR (2000) Severe neurological impairment in an infant after nitrous oxide anesthesia. *Anesthesiology* **93**(6): 1549–50.
McNicol ED, Boyce D, Schumann R et al (2008) Mu-opioid antagonists for opioid-induced bowel dysfunction. *Cochrane Database Syst Rev* **2**: CD006332.
McNicol ED, Ferguson MC & Schumann R (2017) Methadone for neuropathic pain in adults. *Cochrane Database Syst Rev* **5**: CD012499.
McNicol ED, Schumann R & Haroutounian S (2014) A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. *Acta Anaesthesiol Scand* **58**(10): 1199–213.
McPartland JM, Guy GW & Di Marzo V (2014) Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system. *PLoS One* **9**(3): e89566.
McQuay HJ (1991) Opioid clinical pharmacology and routes of administration. *Br Med Bull* **47**(3): 703–17.
McQuay HJ (2010) More evidence cannabis can help in neuropathic pain. *CMAJ* **182**(14): 1494–95.
Medical Devices International (2009) *Penthrox (methoxyflurane) inhalation product information.* http://www.medicaldev.com/pdf_files/Products_Pain_Relief_Healthcare_Professionals_Medical/Penthrox_Product%20Information%20sheet.pdf Accessed 21 September 2015
Meek IL, Vonkeman HE, Kasemier J et al (2013) Interference of NSAIDs with the thrombocyte inhibitory effect of aspirin: a placebo-controlled, ex vivo, serial placebo-controlled serial crossover study. *Eur J Clin Pharmacol* **69**(3): 365–71.

Memis D, Turan A, Karamanlioglu B et al (2004) Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. *Anesth Analg* **98**(3): 835–40.
Mendola C, Ferrante D, Oldani E et al (2009) Thoracic epidural analgesia in post-thoracotomy patients: comparison of three different concentrations of levobupivacaine and sufentanil. *Br J Anaesth* **102**(3): 418–23.
Meng F, Peng K, Yang JP et al (2018) Botulinum toxin-A for the treatment of neuralgia: a systematic review and meta-analysis. *J Pain Res* **11**: 2343-51.
Meng Z, Yu J, Acuff M et al (2017) Tolerability of Opioid Analgesia for Chronic Pain: A Network Meta-Analysis. *Sci Rep* **7**(1): 1995.
Mercadante S (2017) The role of tapentadol as a strong opioid in cancer pain management: a systematic and critical review. *Curr Med Res Opin* **33**(11): 1965-69.
Mercadante S & Caraceni A (2011) Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review. *Palliat Med* **25**(5): 504–15.
Mercieri M, De Blasi RA, Palmisani S et al (2012) Changes in cerebrospinal fluid magnesium levels in patients undergoing spinal anaesthesia for hip arthroplasty: does intravenous infusion of magnesium sulphate make any difference? A prospective, randomized, controlled study. *Br J Anaesth* **109**(2): 208–15.
Mercieri M, Palmisani S, De Blasi RA et al (2017) Low-dose buprenorphine infusion to prevent postoperative hyperalgesia in patients undergoing major lung surgery and remifentanil infusion: a double-blind, randomized, active-controlled trial. *Br J Anaesth* **119**(4): 792-802.
Merivirta R, Pitkanen M, Alanen J et al (2015) Postoperative pain management with transdermal fentanyl after forefoot surgery: a randomized, placebo-controlled study. *J Pain Res* **8**: 39-45.
Merolla G, Dellabiancia F, Ingardia A et al (2015) Co-analgesic therapy for arthroscopic supraspinatus tendon repair pain using a dietary supplement containing Boswellia serrata and Curcuma longa: a prospective randomized placebo-controlled study. *Musculoskelet Surg* **99 Suppl 1**: S43-52.
Merry AF, Webster CS, Holland RL et al (2004) Clinical tolerability of perioperative tenoxicam in 1001 patients--a prospective, controlled, double-blind, multi-centre study. *Pain* **111**(3): 313–22.
Merson N (2001) A comparison of motor block between ropivacaine and bupivacaine for continuous labor epidural analgesia. *AANA J* **69**(1): 54–58.
Meylan N, Elia N, Lysakowski C et al (2009) Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. *Br J Anaesth* **102**(2): 156–67.
Mhaskar R, Kumar A, Miladinovic B et al (2017) Bisphosphonates in multiple myeloma: an updated network meta-analysis. *Cochrane Database Syst Rev* **12**: CD003188.
Mibielli MA, Geller M, Cohen JC et al (2009) Diclofenac plus B vitamins versus diclofenac monotherapy in lumbago: the DOLOR study. *Curr Med Res Opin* **25**(11): 2589-99.
Michelet D, Andreu-Gallien J, Bensalah T et al (2012) A meta-analysis of the use of nonsteroidal antiinflammatory drugs for pediatric postoperative pain. *Anesth Analg* **114**(2): 393–406.
Mihara T, Tojo K, Uchimoto K et al (2013) Reevaluation of the effectiveness of ramosetron for preventing postoperative nausea and vomiting: a systematic review and meta-analysis. *Anesth Analg* **117**(2): 329–39.
Mildh LH, Leino KA & Kirvela OA (1999) Effects of tramadol and meperidine on respiration, plasma catecholamine concentrations, and hemodynamics. *J Clin Anesth* **11**(4): 310–16.
Miller JL & Hagemann TM (2011) Use of pure opioid antagonists for management of opioid-induced pruritus. *Am J Health Syst Pharm* **68**(15): 1419–25.
Minalyan A, Gabrielyan L, Scott D et al (2017) The Gastric and Intestinal Microbiome: Role of Proton Pump Inhibitors. *Curr Gastroenterol Rep* **19**(8): 42.
Minkowitz HS, Gruschkus SK, Shah M et al (2014a) Adverse drug events among patients receiving postsurgical opioids in a large health system: risk factors and outcomes. *Am J Health Syst Pharm* **71**(18): 1556–65.
Minkowitz HS, Scranton R, Gruschkus SK et al (2014b) Development and validation of a risk score to identify patients at high risk for opioid-related adverse drug events. *J Manag Care Spec Pharm* **20**(9): 948–58.
Minto CF, Schnider TW, Egan TD et al (1997) Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* **86**(1): 10–23.
Mion G & Villevieille T (2013) Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). *CNS Neurosci Ther* **19**(6): 370–80.
Miotto K, Cho AK, Khalil MA et al (2017) Trends in Tramadol: Pharmacology, Metabolism, and Misuse. *Anesth Analg* **124**(1): 44-51.
Mitra S (2008) Opioid-induced hyperalgesia: pathophysiology and clinical implications. *J Opioid Manag* **4**(3): 123–30.
Miyoshi RH & Lackband SG (2001) Systemic opioid analgesics. In: *Bonica's Management of Pain* 3rd edn. Loeser J (eds). Lippincott Williams & Wilkins.
Mizrak A, Gul R, Erkutlu I et al (2010) Premedication with dexmedetomidine alone or together with 0.5% lidocaine for IVRA. *J Surg Res* **164**(2): 242–47.
Modasi A, Pace D, Godwin M et al (2019) NSAID administration post colorectal surgery increases anastomotic leak rate: systematic review/meta-analysis. *Surg Endosc* **33**(3): 879-85.

Moeen SM & Moeen AM (2019) Usage of Intravenous Lidocaine Infusion with Enhanced Recovery Pathway in Patients Scheduled for Open Radical Cystectomy: A Randomized Trial. *Pain Physician* **22**(2): E71-E80.

Moeen SM, Ramadan IK & Elkady HA (2017) Dexamethasone and Dexmedetomidine as an Adjuvant to Intraarticular Bupivacaine for Postoperative Pain Relief in Knee Arthroscopic Surgery: A Randomized Trial. *Pain Physician* **20**(7): 671-80.

Mohamed SA, Sayed DM, El Sherif FA et al (2018) Effect of local wound infiltration with ketamine versus dexmedetomidine on postoperative pain and stress after abdominal hysterectomy, a randomized trial. *Eur J Pain* **22**(5): 951-60.

Mohammadierad R, Mohammad-Alizadeh-Charandabi S, Mirghafourvand M et al (2018) Effect of Saffron with or Without Date Sugar on Intensity of Pain and Anxiety During Labor in Primiparous Females: A Randomized, Controlled Trial. *Iran Red Crescent Med J* **20**(S1): e61289.

Mohebbi S, Nia FH, Kelantari F et al (2014) Efficacy of honey in reduction of post tonsillectomy pain, randomized clinical trial. *Int J Pediatr Otorhinolaryngol* **78**(11): 1886-9.

Moisset X, Sia MA, Pereira B et al (2017) Fixed 50:50 mixture of nitrous oxide and oxygen to reduce lumbar-puncture-induced pain: a randomized controlled trial. *Eur J Neurol* **24**(1): 46-52.

Mokaram Dori M & Foruzin F (2016) The Analgesic Efficacy of Intrathecal Bupivacaine and Fentanyl with Added Neostigmine or Magnesium Sulphate. *Anesth Pain Med* **6**(6): e9651.

Moore RA, Derry S, Aldington D et al (2015a) Amitriptyline for neuropathic pain in adults. *Cochrane Database Syst Rev* **2017 (10) (no pagination)**(7): CD008242.

Moore RA, Derry S, Aldington D et al (2015b) Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. *Cochrane Database Syst Rev*(9): Cd008659.

Morales DR, Lipworth BJ, Guthrie B et al (2013) Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: Meta-analysis of controlled clinical trials. *J Allergy Clin Immunol* **134**(1): 40–45.

Morel V, Joly D, Villatte C et al (2016) Memantine before Mastectomy Prevents Post-Surgery Pain: A Randomized, Blinded Clinical Trial in Surgical Patients. *PLoS One* **11**(4): e0152741.

Morelli KM, Brown LB & Warren GL (2018) Effect of NSAIDs on Recovery From Acute Skeletal Muscle Injury: A Systematic Review and Meta-analysis. *Am J Sports Med* **46**(1): 224-33.

Morgan CJ & Curran HV (2012) Ketamine use: a review. *Addiction* **107**(1): 27–38.

Morgan CJ, Muetzelfeldt L & Curran HV (2010) Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. *Addiction* **105**(1): 121–33.

Morrison AP, Hunter JM, Halpern SH et al (2013) Effect of intrathecal magnesium in the presence or absence of local anaesthetic with and without lipophilic opioids: a systematic review and meta-analysis. *Br J Anaesth* **110**(5): 702–12.

Motov S, Mai M, Pushkar I et al (2017) A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED. *Am J Emerg Med* **35**(8): 1095-100.

Mucke M, Phillips T, Radbruch L et al (2018a) Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* **3**: CD012182.

Mucke M, Weier M, Carter C et al (2018b) Systematic review and meta-analysis of cannabinoids in palliative medicine. *J Cachexia Sarcopenia Muscle* **9**(2): 220-34.

Muderris T, Gul F, Yalciner G et al (2016) Oral Flurbiprofen Spray for Posttonsillectomy Pain. *Otolaryngol Head Neck Surg* **155**(1): 166-72.

Mujtaba S, Romero J & Taub CC (2013) Methadone, QTc prolongation and torsades de pointes: Current concepts, management and a hidden twist in the tale? *J Cardiovasc Dis Res* **4**(4): 229–35.

Muldoon T, Milligan K, Quinn P et al (1998) Comparison between extradural infusion of ropivacaine or bupivacaine for the prevention of postoperative pain after total knee arthroplasty. *Br J Anaesth* **80**(5): 680–81.

Mullaji A, Kanna R, Shetty GM et al (2010) Efficacy of periarticular injection of bupivacaine, fentanyl, and methylprednisolone in total knee arthroplasty:a prospective, randomized trial. *J Arthroplasty* **25**(6): 851–57.

Munsterhjelm E, Niemi TT, Ylikorkala O et al (2006) Influence on platelet aggregation of i.v. parecoxib and acetaminophen in healthy volunteers. *Br J Anaesth* **97**(2): 226–31.

Murmu A, Bhar Kundu S, Pahari A et al (2015) Effect of ondansetron on the analgesic efficacy of tramadol used for postoperative analgesia: a randomised controlled study. *Southern African Journal of Anaesthesia and Analgesia* **21**(5): 135-39.

Murphy DL, Lebin JA, Severtson SG et al (2018) Comparative Rates of Mortality and Serious Adverse Effects Among Commonly Prescribed Opioid Analgesics. *Drug Saf* **41**(8): 787-95.

Murphy GS, Sherwani SS, Szokol JW et al (2011a) Small-dose dexamethasone improves quality of recovery scores after elective cardiac surgery: a randomized, double-blind, placebo-controlled study. *J Cardiothorac Vasc Anesth* **25**(6): 950–60.

Murphy GS, Szokol JW, Avram MJ et al (2014) The effect of single low-dose dexamethasone on blood glucose concentrations in the perioperative period: a randomized, placebo-controlled investigation in gynecologic surgical patients. *Anesth Analg* **118**(6): 1204–12.
Murphy GS, Szokol JW, Greenberg SB et al (2011b) Preoperative dexamethasone enhances quality of recovery after laparoscopic cholecystectomy: effect on in-hospital and postdischarge recovery outcomes. *Anesthesiology* **114**(4): 882–90.
Murphy JD, Paskaradevan J, Eisler LL et al (2013) Analgesic efficacy of continuous intravenous magnesium infusion as an adjuvant to morphine for postoperative analgesia: a systematic review and meta-analysis. *Middle East J Anaesthesiol* **22**(1): 11–20.
Murphy JD, Yan D, Hanna MN et al (2010) Comparison of the postoperative analgesic efficacy of intravenous patient-controlled analgesia with tramadol to intravenous patient-controlled analgesia with opioids. *J Opioid Manag* **6**(2): 141–47.
Murray A & Hagen NA (2005) Hydromorphone. *J Pain Symptom Manage* **29**(5 Suppl): S57-66.
Murray N, Malla U, Vlok R et al (2018) Buprenorphine versus Morphine in Paediatric Acute Pain: A Systematic Review and Meta-Analysis. *Crit Care Res Pract* **2018**: 3792043.
Myers J, Wielage RC, Han B et al (2014) The efficacy of duloxetine, non-steroidal anti-inflammatory drugs, and opioids in osteoarthritis: a systematic literature review and meta-analysis. *BMC Musculoskelet Disord* **15**: 76.
Myles PS, Chan MT, Kaye DM et al (2008) Effect of nitrous oxide anesthesia on plasma homocysteine and endothelial function. *Anesthesiology* **109**(4): 657–63.
Myles PS, Leslie K, Chan MT et al (2014) The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. *Lancet* **384**(9952): 1446–54.
Nagele P, Zeugswetter B, Wiener C et al (2008) Influence of methylenetetrahydrofolate reductase gene polymorphisms on homocysteine concentrations after nitrous oxide anesthesia. *Anesthesiology* **109**(1): 36–43.
Naghipour B, Aghamohamadi D, Azarfarin R et al (2013) Dexamethasone added to bupivacaine prolongs duration of epidural analgesia. *Middle East J Anesthesiol* **22**(1): 53–57.
Nahravani M, Tekye SM, Alipour M et al (2017) Analgesia Following Arthroscopy - a Comparison of Intra-articular Bupivacaine and/or Midazolam and or Fentanyl. *Arch Bone Jt Surg* **5**(1): 28-31.
Nalamachu S, Pergolizzi JV, Raffa RB et al (2014) Drug-drug interaction between NSAIDS and low-dose aspirin: a focus on cardiovascular and GI toxicity. *Expert Opin Drug Saf* **13**(7): 903–17.
Nasir D, Gasanova I, Drummond S et al (2017) Clonidine, but not Dexamethasone, Prolongs Ropivacaine-Induced Supraclavicular Brachial Plexus Nerve Block Duration. *Curr Clin Pharmacol* **12**(2): 92-98.
Nayagam HA, Singh NR & Singh HS (2014) A prospective randomised double blind study of intrathecal fentanyl and dexmedetomidine added to low dose bupivacaine for spinal anesthesia for lower abdominal surgeries. *Indian J Anaesth* **58**(4): 430–35.
Nayebi N, Khalili N, Kamalinejad M et al (2017) A systematic review of the efficacy and safety of Rosa damascena Mill. with an overview on its phytopharmacological properties. *Complement Ther Med* **34**: 129-40.
NCCIH (2018) *Complementary, Alternative, or Integrative Health: What's In a Name?* https://nccih.nih.gov/health/integrative-health Accessed 28 September 2019
Neal JM (2016) Ultrasound-Guided Regional Anesthesia and Patient Safety: Update of an Evidence-Based Analysis. *Reg Anesth Pain Med* **41**(2): 195-204.
Neal JM, Barrington MJ, Fettiplace MR et al (2018) The Third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity: Executive Summary 2017. *Reg Anesth Pain Med* **43**(2): 113-23.
Nee J, Zakari M, Sugarman MA et al (2018) Efficacy of Treatments for Opioid-Induced Constipation: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* **16**(10): 1569-84 e2.
Nelson EM & Philbrick AM (2012) Avoiding serotonin syndrome: the nature of the interaction between tramadol and selective serotonin reuptake inhibitors. *Ann Pharmacother* **46**(12): 1712–16.
Ng KF, Yuen TS & Ng VM (2006) A comparison of postoperative cognitive function and pain relief with fentanyl or tramadol patient-controlled analgesia. *J Clin Anesth* **18**(3): 205–10.
Ngan Kee WD (1998) Epidural pethidine: pharmacology and clinical experience. *Anaesth Intensive Care* **26**(3): 247–55.
Nguyen NQ, Toscano L, Lawrence M et al (2013) Patient-controlled analgesia with inhaled methoxyflurane versus conventional endoscopist-provided sedation for colonoscopy: a randomized multicenter trial. *Gastrointest Endosc* **78**(6): 892–901.
Nicholson AB, Watson GR, Derry S et al (2017) Methadone for cancer pain. *Cochrane Database Syst Rev* **2**: CD003971.
Nielsen BN, Henneberg SW, Schmiegelow K et al (2015a) Peripherally applied opioids for postoperative pain: evidence of an analgesic effect? A systematic review and meta-analysis. *Acta Anaesthesiol Scand* **59**(7): 830-45.
Nielsen RV, Fomsgaard JS, Nikolajsen L et al (2019) Intraoperative S-ketamine for the reduction of opioid consumption and pain one year after spine surgery: A randomized clinical trial of opioid-dependent patients. *Eur J Pain* **23**(3): 455-60.

Nielsen RV, Fomsgaard JS, Siegel H et al (2017) Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial. *Pain* **158**(3): 463-70.

Nielsen RV, Siegel H, Fomsgaard JS et al (2015b) Preoperative dexamethasone reduces acute but not sustained pain after lumbar disk surgery: a randomized, blinded, placebo-controlled trial. *Pain* **156**(12): 2538-44.

Nielsen S, Germanos R, Weier M et al (2018) The Use of Cannabis and Cannabinoids in Treating Symptoms of Multiple Sclerosis: a Systematic Review of Reviews. *Curr Neurol Neurosci Rep* **18**(2): 8.

Niemi G & Breivik H (2002) Epinephrine markedly improves thoracic epidural analgesia produced by a small-dose infusion of ropivacaine, fentanyl, and epinephrine after major thoracic or abdominal surgery: a randomized, double-blinded crossover study with and without epinephrine. *Anesth Analg* **94**(6): 1598–605.

Niemi G & Breivik H (2003) The minimally effective concentration of adrenaline in a low-concentration thoracic epidural analgesic infusion of bupivacaine, fentanyl and adrenaline after major surgery. A randomized, double-blind, dose-finding study. *Acta Anaesthesiol Scand* **47**(4): 439–50.

Niemi G & Breivik H (2013) Thoracic epidural fentanyl has spinal cord analgesic effects. *Acta Anaesthesiol Scand* **57**(9): 1089–91.

Nieminen TH, Hagelberg NM, Saari TI et al (2010) St John's wort greatly reduces the concentrations of oral oxycodone. *Eur J Pain* **14**(8): 854–59.

Niesters M, Dahan A, Kest B et al (2010) Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. *Pain* **151**(1): 61–68.

Niesters M, Martini C & Dahan A (2014a) Ketamine for chronic pain: risks and benefits. *Br J Clin Pharmacol* **77**(2): 357–67.

Niesters M, Proto PL, Aarts L et al (2014b) Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. *Br J Anaesth* **113**(1): 148–56.

Nilsson-Ehle H (1998) Age-related changes in cobalamin (vitamin B12) handling. Implications for therapy. *Drugs Aging* **12**(4): 277–92.

Nimmaanrat S, Jongjidpranitarn M, Prathep S et al (2019) Premedication with oral paracetamol for reduction of propofol injection pain: a randomized placebo-controlled trial. *BMC Anesthesiol* **19**(1): 100.

Nir RR, Nahman-Averbuch H, Moont R et al (2016) Preoperative preemptive drug administration for acute postoperative pain: A systematic review and meta-analysis. *Eur J Pain* **20**(7): 1025-43.

Nishiyama T, Matsukawa T & Hanaoka K (2002) Effects of adding midazolam on the postoperative epidural analgesia with two different doses of bupivacaine. *J Clin Anesth* **14**(2): 92–97.

Nissen SE, Yeomans ND, Solomon DH et al (2016) Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. *N Engl J Med* **375**(26): 2519-29.

Nizam I, Kohan L, Field C et al (2015) Do Nonsteroidal Anti-Inflammatory Drugs Cause Endoprosthetic Loosening? Mid- to Long-Term Follow-Up of 100 Total Hip Arthroplasties after Local NSAID Infiltration. *Biomed Res Int* **2015**: 703071.

NPS MedicineWise (2015) *Safe and appropriate use of paracetamol: closing the consumer knowledge gap.* https://www.nps.org.au/news/safe-and-appropriate-use-of-paracetamol-closing-the-consumer-knowledge-gap Accessed 5 November 2019

NSW TAG (2008) *Paracetamol Use: A Position Statement of the NSW Therapeutic Advisory Group Inc.* http://www.nswtag.org.au/wp-content/uploads/2017/07/paracetamol-use-dec-2008.pdf Accessed 4 November 2019

Nuttall GA, Eckerman KM, Jacob KA et al (2007) Does low-dose droperidol administration increase the risk of drug-induced QT prolongation and torsade de pointes in the general surgical population? *Anesthesiology* **107**(4): 531–36.

O'Connor A, Schug SA & Cardwell H (2000) A comparison of the efficacy and safety of morphine and pethidine as analgesia for suspected renal colic in the emergency setting. *J Accid Emerg Med* **17**(4): 261–64.

O'Leary U, Puglia C, Friehling TD et al (1987) Nitrous oxide anesthesia in patients with ischemic chest discomfort: effect on beta-endorphins. *J Clin Pharmacol* **27**(12): 957–61.

O'Rourke KM, McMaster S & Lust KM (2011) A case of hepatitis attributable to repeated exposure to methoxyflurane during its use for procedural analgesia. *Med J Aust* **194**(8): 423–24.

Obal D, Yang D & Sessler DI (2014) Perioperative doses of ondansetron or dolasetron do not lengthen the QT interval. *Mayo Clin Proc* **89**(1): 69–80.

Oderda GM, Gan TJ, Johnson BH et al (2013) Effect of opioid-related adverse events on outcomes in selected surgical patients. *J Pain Palliat Care Pharmacother* **27**(1): 62–70.

Oderda GM, Said Q, Evans RS et al (2007) Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay. *Ann Pharmacother* **41**(3): 400–06.

Oh JH, Seo HJ, Lee YH et al (2018) Do Selective COX-2 Inhibitors Affect Pain Control and Healing After Arthroscopic Rotator Cuff Repair? A Preliminary Study. *Am J Sports Med* **46**(3): 679-86.

Ohlsson A & Shah PS (2018) Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. *Cochrane Database Syst Rev* **4**: CD010061.

Ohmura S, Kawada M, Ohta T et al (2001) Systemic toxicity and resuscitation in bupivacaine-, levobupivacaine-, or ropivacaine-infused rats. *Anesth Analg* **93**(3): 743–48.
Okamoto Y, Tsuneto S, Tanimukai H et al (2013) Can gradual dose titration of ketamine for management of neuropathic pain prevent psychotomimetic effects in patients with advanced cancer? *Am J Hosp Palliat Care* **30**(5): 450–54.
Olczak B, Kowalski G, Leppert W et al (2017) Analgesic efficacy and safety of epidural oxycodone in patients undergoing total hip arthroplasty: a pilot study. *J Pain Res* **10**: 2303-09.
Oliveri L, Jerzewski K & Kulik A (2014) Black box warning: is ketorolac safe for use after cardiac surgery? *J Cardiothorac Vasc Anesth* **28**(2): 274–79.
Olkkola KT, Kontinen VK, Saari TI et al (2013) Does the pharmacology of oxycodone justify its increasing use as an analgesic? *Trends Pharmacol Sci* **34**(4): 206–14.
Ong CK, Seymour RA, Lirk P et al (2010) Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg* **110**(4): 1170-9.
Oni JK, Pinero JR, Saltzman BM et al (2014) Effect of a selective COX-2 inhibitor, celecoxib, on heterotopic ossification after total hip arthroplasty: a case-controlled study. *Hip Int* **24**(3): 256–62.
Oral EG, Hanci A, Ulufer Sivrikaya G et al (2015) The Analgesic Effects of Morphine and Tramadol Added to Intra-articular Levobupivacaine-Tenoxicam Combination for Arthroscopic Knee Surgery on Postoperative Pain; a Randomized Clinical Trial. *Anesth Pain Med* **5**(3): e24047.
Orhan-Sungur M, Kranke P, Sessler D et al (2008) Does supplemental oxygen reduce postoperative nausea and vomiting? A meta-analysis of randomized controlled trials. *Anesth Analg* **106**(6): 1733–38.
Oscier CD & Milner QJ (2009) Peri-operative use of paracetamol. *Anaesthesia* **64**(1): 65–72.
Othman AH, El-Rahman AM & El Sherif F (2016) Efficacy and Safety of Ketamine Added to Local Anesthetic in Modified Pectoral Block for Management of Postoperative Pain in Patients Undergoing Modified Radical Mastectomy. *Pain Physician* **19**(7): 485-94.
Oussalah A, Julien M, Levy J et al (2019) Global Burden Related to Nitrous Oxide Exposure in Medical and Recreational Settings: A Systematic Review and Individual Patient Data Meta-Analysis. *J Clin Med* **8**(4): 551.
Overdyk F, Dahan A, Roozekrans M et al (2014) Opioid-induced respiratory depression in the acute care setting: a compendium of case reports. *Pain Manag* **4**(4): 317-25.
Overman RA, Borse M & Gourlay ML (2013) Salmon calcitonin use and associated cancer risk. *Ann Pharmacother* **47**(12): 1675–84.
Ozdamar D, Dayioglu H, Anik I et al (2018) Evaluation of the neurotoxicity of intrathecal dexmedetomidine on rat spinal cord (electromicroscopic observations). *Saudi J Anaesth* **12**(1): 10-15.
Pacher P, Steffens S, Hasko G et al (2018) Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nat Rev Cardiol* **15**(3): 151-66.
Packer KJ & Titel JH (1969) Methoxyflurane analgesia for burns dressings: experience with the analgizer. *Br J Anaesth* **41**(12): 1080–85.
Paech MJ, Moore JS & Evans SF (1994) Meperidine for patient-controlled analgesia after cesarean section. Intravenous versus epidural administration. *Anesthesiology* **80**(6): 1268–76.
Paech MJ, Pavy TJ, Orlikowski CE et al (2000) Postoperative intraspinal opioid analgesia after caesarean section; a randomised comparison of subarachnoid morphine and epidural pethidine. *Int J Obstet Anesth* **9**(4): 238–45.
Pairuchvej S, Arirachakaran A, Keorochana G et al (2018) The short and midterm outcomes of lumbar transforaminal epidural injection with preganglionic and postganglionic approach in lumbosacral radiculopathy: a systematic review and meta-analysis. *Neurosurg Rev* **41**(4): 909-16.
Paleti S, Prasad PK & Lakshmi BS (2018) A randomized clinical trial of intrathecal magnesium sulfate versus midazolam with epidural administration of 0.75% ropivacaine for patients with preeclampsia scheduled for elective cesarean section. *J Anaesthesiol Clin Pharmacol* **34**(1): 23-28.
Palmer H, Graham G, Williams K et al (2010) A risk-benefit assessment of paracetamol (acetaminophen) combined with caffeine. *Pain Med* **11**(6): 951–65.
Pan L, Shen Y, Ma T et al (2019) The efficacy of ketamine supplementation on pain management for knee arthroscopy: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)* **98**(27): e16138.
Pandey V, Mohindra BK & Sodhi GS (2016) Comparative evaluation of different doses of intrathecal neostigmine as an adjuvant to bupivacaine for postoperative analgesia. *Anesth Essays Res* **10**(3): 538-45.
Pani PP, Trogu E, Maremmani I et al (2013) QTc interval screening for cardiac risk in methadone treatment of opioid dependence. *Cochrane Database Syst Rev* **6**: CD008939.
Parashchanka A, Schelfout S & Coppens M (2014) Role of novel drugs in sedation outside the operating room: dexmedetomidine, ketamine and remifentanil. *Curr Opin Anaesthesiol* **27**(4): 442-7.
Paris A, Gonnet N, Chaussard C et al (2008a) Effect of homeopathy on analgesic intake following knee ligament reconstruction: a phase III monocentre randomized placebo controlled study. *Br J Clin Pharmacol* **65**(2): 180–87.
Paris A, Horvath R, Basset P et al (2008b) Nitrous oxide-oxygen mixture during care of bedsores and painful ulcers in the elderly: a randomized, crossover, open-label pilot study. *J Pain Symptom Manage* **35**(2): 171–76.

Park JH, Shim JK, Song JW et al (2015) A Randomized, Double-blind, Non-inferiority Trial of Magnesium Sulphate versus Dexamethasone for Prevention of Postoperative Sore Throat after Lumbar Spinal Surgery in the Prone Position. *Int J Med Sci* **12**(10): 797-804.

Pascual-Ramirez J, Gil-Trujillo S & Alcantarilla C (2013) Intrathecal magnesium as analgesic adjuvant for spinal anesthesia: a meta-analysis of randomized trials. *Minerva Anestesiol* **79**(6): 667–78.

Patanwala AE, Martin JR & Erstad BL (2017) Ketamine for Analgosedation in the Intensive Care Unit: A Systematic Review. *J Intensive Care Med* **32**(6): 387-95.

Patel KK, Mejia Munne JC, Gunness VRN et al (2018) Subacute combined degeneration of the spinal cord following nitrous oxide anesthesia: A systematic review of cases. *Clin Neurol Neurosurg* **173**: 163-68.

Pattanittum P, Kunyanone N, Brown J et al (2016) Dietary supplements for dysmenorrhoea. *Cochrane Database Syst Rev* **3**: Cd002124.

Pattanittum P, Turner T, Green S et al (2013) Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults. *Cochrane Database Syst Rev* **5**: CD003686.

Paul S, Bhattacharjee DP, Ghosh S et al (2010) Efficacy of intra-articular dexmedetomidine for postoperative analgesia in arthroscopic knee surgery. *Ceylon Med J* **55**(4): 111–15.

Pehora C, Pearson AM, Kaushal A et al (2017) Dexamethasone as an adjuvant to peripheral nerve block. *Cochrane Database Syst Rev* **11**: Cd011770.

Pellow J & Nienhuis C (2018) Medicinal plants for primary dysmenorrhoea: A systematic review. *Complement Ther Med* **37**: 13-26.

Peltoniemi MA, Hagelberg NM, Olkkola KT et al (2016) Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. *Clin Pharmacokinet* **55**(9): 1059-77.

Pendi A, Field R, Farhan SD et al (2018) Perioperative Ketamine for Analgesia in Spine Surgery: A Meta-analysis of Randomized Controlled Trials. *Spine (Phila Pa 1976)* **43**(5): E299-E307.

Peng K, Chen L, Peng J et al (2015) Effects of calcitonin on lumbar spinal stenosis: a systematic review and meta-analysis. *Int J Clin Exp Med* **8**(2): 2536-44.

Peng YN, Sung FC, Huang ML et al (2018) The use of intravenous magnesium sulfate on postoperative analgesia in orthopedic surgery: A systematic review of randomized controlled trials. *Medicine (Baltimore)* **97**(50): e13583.

Perets I, Walsh JP, Mu BH et al (2018) Intraoperative Infiltration of Liposomal Bupivacaine vs Bupivacaine Hydrochloride for Pain Management in Primary Total Hip Arthroplasty: A Prospective Randomized Trial. *J Arthroplasty* **33**(2): 441-46.

Perez RS, Kwakkel G, Zuurmond WW et al (2001) Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials. *J Pain Symptom Manage* **21**(6): 511–26.

Pergolizzi J, Aloisi AM, Dahan A et al (2010) Current knowledge of buprenorphine and its unique pharmacological profile. *Pain Pract* **10**(5): 428–50.

Pergolizzi Jr JV, LeQuang JA, Taylor Jr R et al (2017) The Introduction of a New Term: Multigesics in PAINWeek Abstract Book 2017. *Postgraduate Medicine* **129**(sup1): 33.

Persson J (2013) Ketamine in pain management. *CNS Neurosci Ther* **19**(6): 396–402.

Pert CB, Kuhar MJ & Snyder SH (1976) Opiate receptor: autoradiographic localization in rat brain. *Proc Natl Acad Sci U S A* **73**(10): 3729–33.

Petrenko AB, Yamakura T, Sakimura K et al (2014) Defining the role of NMDA receptors in anesthesia: are we there yet? *Eur J Pharmacol* **723**: 29–37.

Pham Dang C, Delecrin J, Pereon Y et al (2008) Epidural analgesia after scoliosis surgery: electrophysiologic and clinical assessment of the effects of bupivacaine 0.125% plus morphine versus ropivacaine 0.2% plus morphine. *J Clin Anesth* **20**(1): 17–24.

Pham-Dang C, Beaumont S, Floch H et al (2000) [Acute toxic accident following lumbar plexus block with bupivacaine]. *Ann Fr Anesth Reanim* **19**(5): 356–59.

Philip BK, Reese PR & Burch SP (2002) The economic impact of opioids on postoperative pain management. *J Clin Anesth* **14**(5): 354–64.

Phillips TJ, Cherry CL, Cox S et al (2010) Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. *PLoS One* **5**(12): e14433.

Picard PR, Tramer MR, McQuay HJ et al (1997) Analgesic efficacy of peripheral opioids (all except intra-articular): a qualitative systematic review of randomised controlled trials. *Pain* **72**(3): 309–18.

Pichardo D, Luginbuehl IA, Shakur Y et al (2012) Effect of nitrous oxide exposure during surgery on the homocysteine concentrations of children. *Anesthesiology* **117**(1): 15–21.

Pickering G, Creveaux I, Macian N et al (2020) Paracetamol and Pain Modulation by TRPV1, UGT2B15, SULT1A1 Genotypes: A Randomized Clinical Trial in Healthy Volunteers. *Pain Med* **21**(4): 661-69.

Pickering G, Esteve V, Loriot MA et al (2008) Acetaminophen reinforces descending inhibitory pain pathways. *Clin Pharmacol Ther* **84**(1): 47–51.

Pickering G, Loriot MA, Libert F et al (2006) Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. *Clin Pharmacol Ther* **79**(4): 371–78.

Pickering G & Morel V (2018) Memantine for the treatment of general neuropathic pain: a narrative review. *Fundam Clin Pharmacol* **32**(1): 4-13.
Pickering G, Morel V, Simen E et al (2011) Oral magnesium treatment in patients with neuropathic pain: a randomized clinical trial. *Magnes Res* **24**(2): 28–35.
Piirainen P, Kokki H, Hautajarvi H et al (2018) The analgesic efficacy and pharmacokinetics of epidural oxycodone after gynaecological laparotomy: a randomized, double-blind, double-dummy comparison with intravenous administration. *Br J Clin Pharmacol* **84**(9): 2088-96.
Pilotto A, Franceschi M, Leandro G et al (2003) The risk of upper gastrointestinal bleeding in elderly users of aspirin and other non-steroidal anti-inflammatory drugs: the role of gastroprotective drugs. *Aging Clin Exp Res* **15**(6): 494–99.
Ping Y, Ye Q, Wang W et al (2017) Dexmedetomidine as an adjuvant to local anesthetics in brachial plexus blocks: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)* **96**(4): e5846.
Pinto RZ, Maher CG, Ferreira ML et al (2012) Epidural corticosteroid injections in the management of sciatica: a systematic review and meta-analysis. *Ann Intern Med* **157**(12): 865–77.
Pitimana-aree S, Visalyaputra S, Komoltri C et al (2005) An economic evaluation of bupivacaine plus fentanyl versus ropivacaine alone for patient-controlled epidural analgesia after total-knee replacement procedure: a double-blinded randomized study. *Reg Anesth Pain Med* **30**(5): 446–51.
Plante J, Turgeon AF, Zarychanski R et al (2012) Effect of systemic steroids on post-tonsillectomy bleeding and reinterventions: systematic review and meta-analysis of randomised controlled trials. *BMJ* **345**: e5389.
Polderman JA, Farhang-Razi V, Van Dieren S et al (2018) Adverse side effects of dexamethasone in surgical patients. *Cochrane Database Syst Rev* **8**: CD011940.
Polley LS, Columb MO, Naughton NN et al (1999) Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: implications for therapeutic indexes. *Anesthesiology* **90**(4): 944–50.
Polley LS, Columb MO, Naughton NN et al (2003) Relative analgesic potencies of levobupivacaine and ropivacaine for epidural analgesia in labor. *Anesthesiology* **99**(6): 1354–58.
Polzin A, Zeus T, Schror K et al (2013) Dipyrone (metamizole) can nullify the antiplatelet effect of aspirin in patients with coronary artery disease. *J Am Coll Cardiol* **62**(18): 1725–26.
Popping D, Elia N, Wenk M et al (2013) Combination of a reduced dose of an intrathecal local anesthetic with a small dose of an opioid: a meta-analysis of randomised trials. *Pain* **154**: 1383–90.
Popping DM, Elia N, Marret E et al (2009) Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials. *Anesthesiology* **111**(2): 406–15.
Popping DM, Elia N, Marret E et al (2012) Opioids added to local anesthetics for single-shot intrathecal anesthesia in patients undergoing minor surgery: a meta-analysis of randomized trials. *Pain* **153**(4): 784–93.
Porta-Sales J, Garzon-Rodriguez C, Llorens-Torrome S et al (2017) Evidence on the analgesic role of bisphosphonates and denosumab in the treatment of pain due to bone metastases: A systematic review within the European Association for Palliative Care guidelines project. *Palliat Med* **31**(1): 5-25.
Porter KM, Dayan AD, Dickerson S et al (2018a) The role of inhaled methoxyflurane in acute pain management. *Open Access Emerg Med* **10**: 149-64.
Porter KM, Siddiqui MK, Sharma I et al (2018b) Management of trauma pain in the emergency setting: low-dose methoxyflurane or nitrous oxide? A systematic review and indirect treatment comparison. *J Pain Res* **11**: 11-21.
Queensland Health (2014) *Safe paracetamol use.* https://www.health.qld.gov.au/__data/assets/pdf_file/0030/147666/qh-gdl-415.pdf Accessed 4 November 2019
Quigley C (2002) Hydromorphone for acute and chronic pain. *Cochrane Database Syst Rev* **1**: CD003447.
Quigley C (2004) Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev* **3**: CD004847.
Quiralte J, Delgado J, Saenz de San Pedro B et al (2004) Safety of the new selective cyclooxygenase type 2 inhibitors rofecoxib and celecoxib in patients with anaphylactoid reactions to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* **93**(4): 360–64.
Raak C, Bussing A, Gassmann G et al (2012) A systematic review and meta-analysis on the use of Hypericum perforatum (St. John's Wort) for pain conditions in dental practice. *Homeopathy* **101**(4): 204–10.
Rabbie R, Derry S & Moore RA (2013) Ibuprofen with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* **4**(4): CD008039.
Racine M, Tousignant-Laflamme Y, Kloda LA et al (2012a) A systematic literature review of 10 years of research on sex/gender and experimental pain perception - part 1: are there really differences between women and men? *Pain* **153**(3): 602–18.
Racine M, Tousignant-Laflamme Y, Kloda LA et al (2012b) A systematic literature review of 10 years of research on sex/gender and pain perception - part 2: do biopsychosocial factors alter pain sensitivity differently in women and men? *Pain* **153**(3): 619–35.
Racoosin JA, Roberson DW, Pacanowski MA et al (2013) New evidence about an old drug--risk with codeine after adenotonsillectomy. *N Engl J Med* **368**(23): 2155–57.
Radbruch L, Glaeske G, Grond S et al (2013) Topical review on the abuse and misuse potential of tramadol and tilidine in Germany. *Subst Abus* **34**(3): 313-20.

Radbruch L, Grond S & Lehmann KA (1996) A risk-benefit assessment of tramadol in the management of pain. *Drug Saf* **15**(1): 8–29.

Radkova E, Burova N, Bychkova V et al (2017) Efficacy of flurbiprofen 8.75 mg delivered as a spray or lozenge in patients with sore throat due to upper respiratory tract infection: a randomized, non-inferiority trial in the Russian Federation. *J Pain Res* **10**: 1591-600.

Raff M, Belbachir A, El-Tallawy S et al (2019) Intravenous Oxycodone Versus Other Intravenous Strong Opioids for Acute Postoperative Pain Control: A Systematic Review of Randomized Controlled Trials. *Pain Ther* **8**(1): 19-39.

Raffa RB (2014a) On subclasses of opioid analgesics. *Curr Med Res Opin* **30**(12): 2579-84.

Raffa RB, Buschmann H, Christoph T et al (2012) Mechanistic and functional differentiation of tapentadol and tramadol. *Expert Opin Pharmacother* **13**(10): 1437–49.

Raffa RB, Elling C & Tzschentke TM (2018) Does 'Strong Analgesic' Equal 'Strong Opioid'? Tapentadol and the Concept of 'mu-Load'. *Adv Ther* **35**(10): 1471-84.

Raffa RB, Friderichs E, Reimann W et al (1992) Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther* **260**(1): 275–85.

Raffa RB, Haidery M, Huang HM et al (2014b) The clinical analgesic efficacy of buprenorphine. *J Clin Pharm Ther* **39**(6): 577-83.

Rahangdale R, Kendall MC, McCarthy RJ et al (2014) The effects of perineural versus intravenous dexamethasone on sciatic nerve blockade outcomes: a randomized, double-blind, placebo-controlled study. *Anesth Analg* **118**(5): 1113–19.

Rahimzadeh P, Faiz SHR, Imani F et al (2018) Comparative addition of dexmedetomidine and fentanyl to intrathecal bupivacaine in orthopedic procedure in lower limbs. *BMC Anesthesiol* **18**(1): 62.

Rai AS, Khan JS, Dhaliwal J et al (2017) Preoperative pregabalin or gabapentin for acute and chronic postoperative pain among patients undergoing breast cancer surgery: A systematic review and meta-analysis of randomized controlled trials. *J Plast Reconstr Aesthet Surg* **70**(10): 1317-28.

Rakhman E, Shmain D, White I et al (2011) Repeated and escalating preoperative subanesthetic doses of ketamine for postoperative pain control in patients undergoing tumor resection: a randomized, placebo-controlled, double-blind trial. *Clin Ther* **33**(7): 863–73.

Ramachandran SK, Haider N, Saran KA et al (2011) Life-threatening critical respiratory events: a retrospective study of postoperative patients found unresponsive during analgesic therapy. *J Clin Anesth* **23**(3): 207-13.

Ramirez L, Cros J, Marin B et al (2015) Analgesic interaction between ondansetron and acetaminophen after tonsillectomy in children: the Paratron randomized, controlled trial. *Eur J Pain* **19**(5): 661-8.

Ramsay DS, Leroux BG, Rothen M et al (2005) Nitrous oxide analgesia in humans: acute and chronic tolerance. *Pain* **114**(1-2): 19–28.

Rapp SE, Egan KJ, Ross BK et al (1996) A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* **82**(5): 1043–48.

Rasmussen S, Lorentzen JS, Larsen AS et al (2002) Combined intra-articular glucocorticoid, bupivacaine and morphine reduces pain and convalescence after diagnostic knee arthroscopy. *Acta Orthop Scand* **73**(2): 175–78.

Rathbone J, Franklin R, Gibbs C et al (2017) Review article: Role of magnesium sulphate in the management of Irukandji syndrome: A systematic review. Melbourne, Wiley Publishing Asia Pty Ltd. **29:** 9-17.

Rathmell JP, Benzon HT, Dreyfuss P et al (2015) Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. *Anesthesiology* **122**(5): 974-84.

Ravn P, Frederiksen R, Skovsen AP et al (2012) Prediction of pain sensitivity in healthy volunteers. *J Pain Res* **5**: 313–26.

Ravn P, Secher EL, Skram U et al (2013) Morphine- and buprenorphine-induced analgesia and antihyperalgesia in a human inflammatory pain model: a double-blind, randomized, placebo-controlled, five-arm crossover study. *J Pain Res* **6**: 23-38.

Rayati F, Hajmanouchehri F & Najafi E (2017) Comparison of anti-inflammatory and analgesic effects of Ginger powder and Ibuprofen in postsurgical pain model: A randomized, double-blind, case-control clinical trial. *Dent Res J (Isfahan)* **14**(1): 1-7.

Razavi BM & Fazly Bazzaz BS (2019) A review and new insights to antimicrobial action of local anesthetics. *Eur J Clin Microbiol Infect Dis* **38**(6): 991-1002.

RCA (1998) *Guidelines for the Use of Nonsteroidal Antiinflammatory Drugs in the Perioperative Period.* London, Royal College of Anaesthetists.

Ready LB, Oden R, Chadwick HS et al (1988) Development of an anesthesiology-based postoperative pain management service. *Anesthesiology* **68**(1): 100–06.

Reed GW, Abdallah MS, Shao M et al (2018) Effect of Aspirin Coadministration on the Safety of Celecoxib, Naproxen, or Ibuprofen. *J Am Coll Cardiol* **71**(16): 1741-51.

Ren H, Lin D, Mou Z et al (2013) The adverse effect of selective cyclooxygenase-2 inhibitor on random skin flap survival in rats. *PLoS One* **8**(12): e82802.

Rennick A, Atkinson T, Cimino NM et al (2016) Variability in Opioid Equivalence Calculations. *Pain Med* **17**(5): 892-98.

Reuben SS & Duprat KM (1996) Comparison of wound infiltration with ketorolac versus intravenous regional anesthesia with ketorolac for postoperative analgesia following ambulatory hand surgery. *Reg Anesth* **21**(6): 565–68.
Reuben SS, Steinberg RB, Kreitzer JM et al (1995) Intravenous regional anesthesia using lidocaine and ketorolac. *Anesth Analg* **81**(1): 110–13.
Rheinboldt M, Harper D, Parrish D et al (2014) Nitrous oxide induced myeloneuropathy: a case report. *Emerg Radiol* **21**(1): 85–88.
Richards BL, Whittle SL & Buchbinder R (2011) Antidepressants for pain management in rheumatoid arthritis. *Cochrane Database Syst Rev* **11**: CD008920.
Richards JR, Bing ML, Moulin AK et al (2019) Cannabis use and acute coronary syndrome. *Clin Toxicol (Phila)* **57**(10): 831-41.
Richards S, Torre L & Lawther B (2017) Buprenorphine-related complications in elderly hospitalised patients: a case series. *Anaesth Intensive Care* **45**(2): 256-61.
Richardson MD, Palmeri NO, Williams SA et al (2016) Routine perioperative ketorolac administration is not associated with hemorrhage in pediatric neurosurgery patients. *J Neurosurg Pediatr* **17**(1): 107-15.
Riemsma R, Forbes C, Harker J et al (2011) Systematic review of tapentadol in chronic severe pain. *Curr Med Res Opin* **27**(10): 1907–30.
Riggin L, Ramakrishna J, Sommer DD et al (2013) A 2013 updated systematic review & meta-analysis of 36 randomized controlled trials; no apparent effects of non steroidal anti-inflammatory agents on the risk of bleeding after tonsillectomy. *Clin Otolaryngol* **38**(2): 115–29.
Rigler ML, Drasner K, Krejcie TC et al (1991) Cauda equina syndrome after continuous spinal anesthesia. *Anesth Analg* **72**(3): 275–81.
Rijsdijk M, van Wijck AJ, Kalkman CJ et al (2014) The effects of glucocorticoids on neuropathic pain: a review with emphasis on intrathecal methylprednisolone acetate delivery. *Anesth Analg* **118**(5): 1097-112.
Rivosecchi RM, Rice MJ, Smithburger PL et al (2014) An evidence based systematic review of remifentanil associated opioid-induced hyperalgesia. *Expert Opin Drug Saf* **13**(5): 587–603.
Roberts GW, Bekker TB, Carlsen HH et al (2005) Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. *Anesth Analg* **101**(5): 1343–48.
Roberts M, Brodribb W & Mitchell G (2012) Reducing the pain: a systematic review of postdischarge analgesia following elective orthopedic surgery. *Pain Med* **13**(5): 711–27.
Robertson A, Suryanarayanan R & Banerjee A (2007) Homeopathic Arnica montana for post-tonsillectomy analgesia: a randomised placebo control trial. *Homeopathy* **96**(1): 17–21.
Robinson SL, Rowbotham DJ & Smith G (1991) Morphine compared with diamorphine. A comparison of dose requirements and side-effects after hip surgery. *Anaesthesia* **46**(7): 538–40.
Robson P (2011) Abuse potential and psychoactive effects of delta-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. *Expert Opin Drug Saf* **10**(5): 675–85.
Rochford M, Kiernan TJ & Aziz A (2007) Dolasetron overdose resulting in prolonged QTc interval and severe hypotension: a case report and literature review. *Emerg Med J* **24**(7): 515–17.
Rock EM, Kopstick RL, Limebeer CL et al (2013) Tetrahydrocannabinolic acid reduces nausea-induced conditioned gaping in rats and vomiting in Suncus murinus. *Br J Pharmacol* **170**(3): 641–48.
Rodda LN, Pilgrim JL, Di Rago M et al (2017) A Cluster of Fentanyl-Laced Heroin Deaths in 2015 in Melbourne, Australia. *J Anal Toxicol* **41**(4): 318-24.
Roelofs P, Deyo RA, Koes BW et al (2008) Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane Database Syst Rev* **1**: CD000396.
Rogeberg O (2019) A meta-analysis of the crash risk of cannabis-positive drivers in culpability studies-Avoiding interpretational bias. *Accid Anal Prev* **123**: 69-78.
Rolan P, Lim S, Sunderland V et al (2014) The absolute bioavailability of racemic ketamine from a novel sublingual formulation. *Br J Clin Pharmacol* **77**(6): 1011–16.
Romberg R, Olofsen E, Sarton E et al (2003) Pharmacodynamic effect of morphine-6-glucuronide versus morphine on hypoxic and hypercapnic breathing in healthy volunteers. *Anesthesiology* **99**(4): 788–98.
Romberg R, van Dorp E, Hollander J et al (2007) A randomized, double-blind, placebo-controlled pilot study of IV morphine-6-glucuronide for postoperative pain relief after knee replacement surgery. *Clin J Pain* **23**(3): 197–203.
Romsing J, Moiniche S, Ostergaard D et al (2000) Local infiltration with NSAIDs for postoperative analgesia: evidence for a peripheral analgesic action. *Acta Anaesthesiol Scand* **44**(6): 672–83.
Romundstad L, Breivik H, Niemi G et al (2004) Methylprednisolone intravenously 1 day after surgery has sustained analgesic and opioid-sparing effects. *Acta Anaesthesiol Scand* **48**(10): 1223–31.
Romundstad L, Breivik H, Roald H et al (2006) Methylprednisolone reduces pain, emesis, and fatigue after breast augmentation surgery: a single-dose, randomized, parallel-group study with methylprednisolone 125 mg, parecoxib 40 mg, and placebo. *Anesth Analg* **102**(2): 418–25.
Romundstad L & Stubhaug A (2007) Glucocorticoids for acute and persistent postoperative neuropathic pain: what is the evidence? *Anesthesiology* **107**(3): 371–73.

Rosenblatt MA, Abel M, Fischer GW et al (2006) Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. *Anesthesiology* **105**(1): 217–18.
Rosener M & Dichgans J (1996) Severe combined degeneration of the spinal cord after nitrous oxide anaesthesia in a vegetarian. *J Neurol Neurosurg Psychiatry* **60**(3): 354.
Rosow CE, Gomery P, Chen TY et al (2007) Reversal of opioid-induced bladder dysfunction by intravenous naloxone and methylnaltrexone. *Clin Pharmacol Ther* **82**(1): 48–53.
Rosow CE, Haspel KL, Smith SE et al (2008) Haloperidol versus ondansetron for prophylaxis of postoperative nausea and vomiting. *Anesth Analg* **106**(5): 1407–09.
Rosseland LA, Stubhaug A, Sandberg L et al (2003) Intra-articular (IA) catheter administration of postoperative analgesics. A new trial design allows evaluation of baseline pain, demonstrates large variation in need of analgesics, and finds no analgesic effect of IA ketamine compared with IA saline. *Pain* **104**(1–2): 25–34.
Royse CE, Royse AG & Deelen DA (2005) An audit of morphine versus fentanyl as an adjunct to ropivacaine 0.2% for high thoracic epidural analgesia. *Anaesth Intensive Care* **33**(5): 639–44.
Royse CF, Saager L, Whitlock R et al (2017) Impact of Methylprednisolone on Postoperative Quality of Recovery and Delirium in the Steroids in Cardiac Surgery Trial: A Randomized, Double-blind, Placebo-controlled Substudy. *Anesthesiology* **126**(2): 223-33.
Rudroju N, Bansal D, Talakokkula ST et al (2013) Comparative efficacy and safety of six antidepressants and anticonvulsants in painful diabetic neuropathy: a network meta-analysis. *Pain Physician* **16**(6): E705–14.
Rumack B, Heard K, Green J et al (2012) Effect of therapeutic doses of acetaminophen (up to 4 g/day) on serum alanine aminotransferase levels in subjects consuming ethanol: systematic review and meta-analysis of randomized controlled trials. *Pharmacotherapy* **32**(9): 784–91.
Rusch D, Arndt C, Martin H et al (2007) The addition of dexamethasone to dolasetron or haloperidol for treatment of established postoperative nausea and vomiting. *Anaesthesia* **62**(8): 810–17.
Russo EB (2011) Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol* **163**(7): 1344–64.
Russo M, Bloch M, de Looze F et al (2013) Flurbiprofen microgranules for relief of sore throat: a randomised, double-blind trial. *Br J Gen Pract* **63**(607): e149–55.
Ryan NM & Isbister GK (2015) Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. *Clin Toxicol (Phila)* **53**(6): 545-50.
Ryan T, Hodge A, Holyoak R et al (2019) Tramadol as an adjunct to intra-articular local anaesthetic infiltration in knee arthroscopy: a systematic review and meta-analysis. *ANZ J Surg* **89**(7-8): 827-32.
Saarto T & Wiffen P (2007) Antidepressants for neuropathic pain. *Cochrane Database Syst Rev* **4**: CD005454.
Sachan P, Kumar N & Sharma J (2014) Intrathecal clonidine with hyperbaric bupivacaine administered as a mixture and sequentially in caesarean section: A randomised controlled study. *Indian J Anaesth* **58**(3): 287–92.
Sadeghirad B, Siemieniuk RAC, Brignardello-Petersen R et al (2017) Corticosteroids for treatment of sore throat: systematic review and meta-analysis of randomised trials. *BMJ* **358**: j3887.
Sadurni M, Beltra de Heredia S & Dursteler C, et al (2013) Epidural vs intravenous fentnayl during colorectal surgery using a double-blind, double-dummy design. *Acta Anaesthesiol Scand* **57**(9): 1103–10.
Safari F, Dabbagh A & Sharifnia M (2012) The effect of adjuvant midazolam compared with fentanyl on the duration of spinal anesthesia with 0.5% bupivacaine in opium abusers. *Korean J Anesthesiol* **63**(6): 521-6.
Sahebkar A & Henrotin Y (2016) Analgesic Efficacy and Safety of Curcuminoids in Clinical Practice: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Pain Med* **17**(6): 1192-202.
Sahin F, Yilmaz F, Kotevoglu N et al (2006) Efficacy of salmon calcitonin in complex regional pain syndrome (type 1) in addition to physical therapy. *Clin Rheumatol* **25**(2): 143–48.
Sakaguchi Y, Sakura S, Shinzawa M et al (2000) Does adrenaline improve epidural bupivacaine and fentanyl analgesia after abdominal surgery? *Anaesth Intensive Care* **28**(5): 522–26.
Saliba SW, Marcotegui AR, Fortwangler E et al (2017) AM404, paracetamol metabolite, prevents prostaglandin synthesis in activated microglia by inhibiting COX activity. *J Neuroinflammation* **14**(1): 246.
Salimi A, Nejad RA, Safari F et al (2014) Reduction in labor pain by intrathecal midazolam as an adjunct to sufentanil. *Korean J Anesthesiol* **66**(3): 204–09.
Salm-Reifferscheidt L (2018) Tramadol: Africa's opioid crisis. *Lancet* **391**(10134): 1982-83.
Salottolo K, Peck L, Tanner Ii A et al (2018) The grass is not always greener: a multi-institutional pilot study of marijuana use and acute pain management following traumatic injury. *Patient Saf Surg* **12**: 16.
Saltan P, Gutierrez M & Carvalho B (2011) Neuroaxial morphine and respiratory depression: finding the right balance. *Drugs* **71**(14): 1807–19.
Samantaray A, Hemanth N, Gunnampati K et al (2015) Comparison of the effects of adding dexmedetomidine versus midazolam to intrathecal bupivacaine on postoperative analgesia. *Pain Physician* **18**(1): 71-7.
Samer CF, Daali Y, Wagner M et al (2010a) The effects of CYP2D6 and CYP3A activities on the pharmacokinetics of immediate release oxycodone. *Br J Pharmacol* **160**(4): 907–18.
Samer CF, Daali Y, Wagner M et al (2010b) Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety. *Br J Pharmacol* **160**(4): 919–30.

Sanchez Munoz MC, De Kock M & Forget P (2017) What is the place of clonidine in anesthesia? Systematic review and meta-analyses of randomized controlled trials. *J Clin Anesth* **38**: 140-53.
Sanders RD, Weimann J & Maze M (2008) Biologic effects of nitrous oxide: a mechanistic and toxicologic review. *Anesthesiology* **109**(4): 707–22.
Sandrini G, De Icco R, Tassorelli C et al (2017) Botulinum neurotoxin type A for the treatment of pain: not just in migraine and trigeminal neuralgia. *J Headache Pain* **18**(1): 38.
Sanel S, Arpaz O, Unay K et al (2016) Comparison of intra-articular bupivacaine-morphine with bupivacaine-tenoxicam combinations on post-operative analgesia in patients with arthroscopic meniscectomy: a prospective, randomised study. *Int Orthop* **40**(3): 601-5.
Sanli M, Gulhas N, Bilen BT et al (2016) The effect of addition of ketamine to lidocaine on postoperative pain in rhinoplasties. *Turk J Med Sci* **46**(3): 789-94.
Sapna S, Abhijit SN & Gopal TVS (2013) Clinical effects of intrathecal midazolam versus intrathecal magnesium sulfate as adjunctsto hyperbaric bupivacaine: A comparative study. *Indian J Pain* **27**(3): 175-81.
Saragiotto BT, Machado GC, Ferreira ML et al (2016) Paracetamol for low back pain. *Cochrane Database Syst Rev*(6): CD012230.
Sarvizadeh M, Hemati S, Meidani M et al (2015) Morphine mouthwash for the management of oral mucositis in patients with head and neck cancer. *Adv Biomed Res* **4**: 44.
Saryazdi H, Kashefi P, Heydari M et al (2006) Analgesic effects of intra-articular fentanyl, pethidine and dexamethasone after knee arthroscopic surgery. *J Res Med Sci* **11**(3): 156–59.
Satsumae T, Yamaguchi H, Inomata S et al (2013) Magnesium sulfate attenuates tourniquet pain in healthy volunteers. *J Anesth* **27**(2): 231–35.
Saxena A, Balaramnavar VM, Hohlfeld T et al (2013) Drug/drug interaction of common NSAIDs with antiplatelet effect of aspirin in human platelets. *Eur J Pharmacol* **721**(1-3): 215–24.
Sayin P, Dobrucali H, Turk HS et al (2015) Effects of intra-articular levobupivacaine, fentanyl-levobupivacaine and tramadol-levobupivacaine for postoperative pain in arthroscopic knee surgery. *Acta Orthop Traumatol Turc* **49**(3): 267-73.
Schack A, Fransgaard T, Klein MF et al (2019) Perioperative Use of Nonsteroidal Anti-inflammatory Drugs Decreases the Risk of Recurrence of Cancer After Colorectal Resection: A Cohort Study Based on Prospective Data. *Ann Surg Oncol* **26**(12): 3826-37.
Schaub I, Lysakowski C, Elia N et al (2012) Low-dose droperidol (</=1 mg or </=15 mug kg-1) for the prevention of postoperative nausea and vomiting in adults: quantitative systematic review of randomised controlled trials. *Eur J Anaesthesiol* **29**(6): 286–94.
Schell RM, Brauer FS, Cole DJ et al (1991) Persistent sacral nerve root deficits after continuous spinal anaesthesia. *Can J Anaesth* **38**(7): 908–11.
Schenk BE, Kuipers EJ, Klinkenberg-Knol EC et al (1999) Atrophic gastritis during long-term omeprazole therapy affects serum vitamin B12 levels. *Aliment Pharmacol Ther* **13**(10): 1343–46.
Schiene K, De Vry J & Tzschentke TM (2011) Antinociceptive and antihyperalgesic effects of tapentadol in animal models of inflammatory pain. *J Pharmacol Exp Ther* **339**(2): 537–44.
Schier JG, Meiman JG, Layden J et al (2019) Severe Pulmonary Disease Associated with Electronic-Cigarette-Product Use - Interim Guidance. *MMWR Morb Mortal Wkly Rep* **68**(36): 787-90.
Schilling RF (1986) Is nitrous oxide a dangerous anesthetic for vitamin B12-deficient subjects? *JAMA* **255**(12): 1605–06.
Schjerning O, Rosenzweig M, Pottegård A et al (2016) Abuse Potential of Pregabalin. *CNS Drugs* **30**(1): 9-25.
Schleiffarth JR, Bayon R, Chang KE et al (2014) Ketorolac after free tissue transfer: a comparative effectiveness study. *Ann Otol Rhinol Laryngol* **123**(6): 446–49.
Schmidt-Hansen M, Bennett MI, Arnold S et al (2018) Efficacy, tolerability and acceptability of oxycodone for cancer-related pain in adults: an updated Cochrane systematic review. *BMJ Support Palliat Care* **8**(2): 117-28.
Schnabel A, Eberhart LH, Muellenbach R et al (2010) Efficacy of perphenazine to prevent postoperative nausea and vomiting: a quantitative systematic review. *Eur J Anaesthesiol* **27**(12): 1044–51.
Schnabel A, Poepping DM, Kranke P et al (2011) Efficacy and adverse effects of ketamine as an additive for paediatric caudal anaesthesia: a quantitative systematic review of randomized controlled trials. *Br J Anaesth* **107**(4): 601–11.
Schnabel A, Reichl SU, Weibel S et al (2018) Efficacy and safety of dexmedetomidine in peripheral nerve blocks: A meta-analysis and trial sequential analysis. *Eur J Anaesthesiol* **35**(10): 745-58.
Schnabel A, Reichl SU, Zahn PK et al (2017) Efficacy and safety of buprenorphine in peripheral nerve blocks: A meta-analysis of randomised controlled trials. *Eur J Anaesthesiol* **34**(9): 576-86.
Schroer WC, Diesfeld PJ, LeMarr AR et al (2011) Benefits of prolonged postoperative cyclooxygenase-2 inhibitor administration on total knee arthroplasty recovery: a double-blind, placebo-controlled study. *J Arthroplasty* **26**(6 Suppl): 2–7.
Schubart CD, Sommer IE, van Gastel WA et al (2011) Cannabis with high cannabidiol content is associated with fewer psychotic experiences. *Schizophr Res* **130**(1–3): 216–21.
Schug SA (2001) Correction factor for comparisons between levobupivacaine and racemic bupivacaine. *Reg Anesth Pain Med* **26**(1): 91.

Schug SA (2019) The atypical opioids buprenorphine, tramadol and tapentadol. *Medicine Today* **20**(1): 31-36.
Schug SA, Parsons B, Li C et al (2017) The safety profile of parecoxib for the treatment of postoperative pain: a pooled analysis of 28 randomized, double-blind, placebo-controlled clinical trials and a review of over 10 years of postauthorization data. *J Pain Res* **10**: 2451-59.
Schug SA, Scott DA, Payne J et al (1996) Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery. *Br J Anaesth* **76**(4): 487-91.
Schwenk ES, Viscusi ER, Buvanendran A et al (2018) Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med* **43**(5): 456-66.
Scott DA, Beilby DS & McClymont C (1995a) Postoperative analgesia using epidural infusions of fentanyl with bupivacaine. A prospective analysis of 1,014 patients. *Anesthesiology* **83**(4): 727–37.
Scott DA, Blake D, Buckland M et al (1999) A comparison of epidural ropivacaine infusion alone and in combination with 1, 2, and 4 microg/mL fentanyl for seventy-two hours of postoperative analgesia after major abdominal surgery. *Anesth Analg* **88**(4): 857-64.
Scott DA, Chamley DM, Mooney PH et al (1995b) Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery--a dose finding study. *Anesth Analg* **81**(5): 982-6.
Scott DA, Emanuelsson BM, Mooney PH et al (1997) Pharmacokinetics and efficacy of long-term epidural ropivacaine infusion for postoperative analgesia. *Anesth Analg* **85**(6): 1322–30.
Scott DB, Lee A, Fagan D et al (1989) Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg* **69**(5): 563–69.
Scott JC & Stanski DR (1987) Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* **240**(1): 159–66.
Scott WW, Levy M, Rickert KL et al (2014) Assessment of common nonsteroidal anti-inflammatory medications by whole blood aggregometry: a clinical evaluation for the perioperative setting. *World Neurosurg* **82**(5): e633-8.
Seervi SN, Singariya G, Kamal M et al (2019) Effect of addition of buprenorphine or dexamethasone to levobupivacaine on postoperative analgesia in ultrasound guided transversus abdominis plane block in patients undergoing unilateral inguinal hernia repair: a prospective randomized double blind controlled trial. *Korean J Anesthesiol* **72**(3): 245-52.
Selden T, Ahlner J, Druid H et al (2012) Toxicological and pathological findings in a series of buprenorphine related deaths. Possible risk factors for fatal outcome. *Forensic Sci Int* **220**(1-3): 284–90.
Selvaraj V & Ray T (2015) Midazolam as an adjuvant to intrathecal lignocaine: A prospective randomized control study. *Saudi J Anaesth* **9**(4): 393-6.
Senard M, Deflandre EP, Ledoux D et al (2010) Effect of celecoxib combined with thoracic epidural analgesia on pain after thoracotomy. *Br J Anaesth* **105**(2): 196–200.
Senard M, Joris JL, Ledoux D et al (2002) A comparison of 0.1% and 0.2% ropivacaine and bupivacaine combined with morphine for postoperative patient-controlled epidural analgesia after major abdominal surgery. *Anesth Analg* **95**(2): 444–49.
Shadangi BK, Garg R, Pandey R et al (2011) Effects of intrathecal midazolam in spinal anaesthesia: a prospective randomised case control study. *Singapore Med J* **52**(6): 432–35.
Shadnia S, Brent J, Mousavi-Fatemi K et al (2012) Recurrent seizures in tramadol intoxication: implications for therapy based on 100 patients. *Basic Clin Pharmacol Toxicol* **111**(2): 133–36.
Shafi S, Collinsworth AW, Copeland LA et al (2018) Association of Opioid-Related Adverse Drug Events With Clinical and Cost Outcomes Among Surgical Patients in a Large Integrated Health Care Delivery System. *JAMA Surg* **153**(8): 757-63.
Shaibani AI, Pope LE, Thisted R et al (2012) Efficacy and safety of dextromethorphan/quinidine at two dosage levels for diabetic neuropathic pain: a double-blind, placebo-controlled, multicenter study. *Pain Med* **13**(2): 243–54.
Shapiro A, Zohar E, Zaslansky R et al (2005) The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. *J Clin Anesth* **17**(7): 537–42.
Sharawi N, Carvalho B, Habib AS et al (2018) A Systematic Review Evaluating Neuraxial Morphine and Diamorphine-Associated Respiratory Depression After Cesarean Delivery. *Anesth Analg* **127**(6): 1385-95.
Sharghi M, Mansurkhani SM, Larky DA et al (2019) An update and systematic review on the treatment of primary dysmenorrhea. *JBRA Assist Reprod* **23**(1): 51-57.
Sharma AK, Vorobeychik Y, Wasserman R et al (2017) The Effectiveness and Risks of Fluoroscopically Guided Lumbar Interlaminar Epidural Steroid Injections: A Systematic Review with Comprehensive Analysis of the Published Data. *Pain Med* **18**(2): 239-51.
Shaw AD & Morgan M (1998) Nitrous oxide: time to stop laughing? *Anaesthesia* **53**(3): 213–15.
Shen YD, Chen CY, Wu CH et al (2014) Dexamethasone, ondansetron, and their combination and postoperative nausea and vomiting in children undergoing strabismus surgery: a meta-analysis of randomized controlled trials. *Paediatr Anaesth* **24**(5): 490–98.

Sherif AA & Elsersy HE (2017) The impact of dexmedetomidine or xylocaine continuous infusion on opioid consumption and recovery after laparoscopic sleeve gastrectomy. *Minerva Anestesiol* **83**(12): 1274-82.
Sheyklo SG, Hajebrahimi S, Moosavi A et al (2017) Effect of Entonox for pain management in labor: A systematic review and meta-analysis of randomized controlled trials. *Electron Physician* **9**(12): 6002-09.
Shilpa PS, Kaul R, Sultana N et al (2014) Botulinum toxin: The Midas touch. *J Nat Sci Biol Med* **5**(1): 8-14.
Shin HW, Ju BJ, Jang YK et al (2017) Effect of tramadol as an adjuvant to local anesthetics for brachial plexus block: A systematic review and meta-analysis. *PLoS One* **12**(9): e0184649.
Shukla U, Prabhakar T, Malhotra K et al (2016) Dexmedetomidine versus midazolam as adjuvants to intrathecal bupivacaine: A clinical comparison. *J Anaesthesiol Clin Pharmacol* **32**(2): 214-9.
Sieber FE, Mears S, Lee H et al (2011) Postoperative opioid consumption and its relationship to cognitive function in older adults with hip fracture. *J Am Geriatr Soc* **59**(12): 2256–62.
Silva LOJ, Scherber K, Cabrera D et al (2018) Safety and Efficacy of Intravenous Lidocaine for Pain Management in the Emergency Department: A Systematic Review. *Ann Emerg Med* **72**(2): 135-44 e3.
Silvasti M, Svartling N, Pitkanen M et al (2000) Comparison of intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction. *Eur J Anaesthesiol* **17**(7): 448–55.
Silverman ME, Shih RD & Allegra J (2004) Morphine induces less nausea than meperidine when administered parenterally. *J Emerg Med* **27**(3): 241–43.
Simbar M, Shadipour M, Salamzadeh J et al (2015) The combination of "Pimpinella anisum, Apium graveolens and Crocus sativus (PAC)" is more effective than "mefenamic acid" on postpartum after-pain. *Journal of Herbal Medicine* **5**(1): 20-25.
Simmons DL, Botting RM & Hla T (2004) Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. *Pharmacol Rev* **56**(3): 387–437.
Simopoulos TT, Smith HS, Peeters-Asdourian C et al (2002) Use of meperidine in patient-controlled analgesia and the development of a normeperidine toxic reaction. *Arch Surg* **137**(1): 84–88.
Singer SR, Amit-Kohn M, Weiss S et al (2010) Traumeel S for pain relief following hallux valgus surgery: a randomized controlled trial. *BMC Clin Pharmacol* **10**: 9.
Singh AK, Kumar A, Kumar A et al (2017) A Comparison of Intrathecal Dexmedetomidine and Neostigmine as Adjuvant to Ropivacaine for Lower Limb Surgeries: A Double-blind Randomized Controlled Study. *Anesth Essays Res* **11**(4): 987-92.
Singh NP, Makkar JK, Wourms V et al (2019) Role of topical magnesium in post-operative sore throat: A systematic review and meta-analysis of randomised controlled trials. *Indian J Anaesth* **63**(7): 520-29.
Singh PM, Borle A, Gouda D et al (2016a) Efficacy of palonosetron in postoperative nausea and vomiting (PONV)-a meta-analysis. *J Clin Anesth* **34**: 459-82.
Singh PP, Lemanu DP, Taylor MH et al (2014) Association between preoperative glucocorticoids and long-term survival and cancer recurrence after colectomy: follow-up analysis of a previous randomized controlled trial. *Br J Anaesth* **113 Suppl 1**: i68–i73.
Singh RH, Thaxton L, Carr S et al (2016b) A randomized controlled trial of nitrous oxide for intrauterine device insertion in nulliparous women. *Int J Gynaecol Obstet* **135**(2): 145-48.
Singh S & Aggarwal A (2010) A randomized controlled double-blinded prospective study of the efficacy of clonidine added to bupivacaine as compared with bupivacaine alone used in supraclavicular brachial plexus block for upper limb surgeries. *Indian J Anaesth* **54**(6): 552–57.
Sinha AC, Singh PM, Williams NW et al (2014) Aprepitant's prophylactic efficacy in decreasing postoperative nausea and vomiting in morbidly obese patients undergoing bariatric surgery. *Obes Surg* **24**(2): 225–31.
Sitsen E, van Poorten F, van Alphen W et al (2007) Postoperative epidural analgesia after total knee arthroplasty with sufentanil 1 microg/ml combined with ropivacaine 0.2%, ropivacaine 0.125%, or levobupivacaine 0.125%: a randomized, double-blind comparison. *Reg Anesth Pain Med* **32**(6): 475–80.
Skolnik A & Gan TJ (2014) New formulations of bupivacaine for the treatment of postoperative pain: liposomal bupivacaine and SABER-Bupivacaine. *Expert Opin Pharmacother* **15**(11): 1535–42.
Sleigh J, Harvey M, Voss L et al (2014) Ketamine – More mechanisms of action than just NMDA blockade. *Trends Anaesth Crit Care* **4**(2–3): 76–81.
Smith MT (2000) Neuroexcitatory effects of morphine and hydromorphone: evidence implicating the 3-glucuronide metabolites. *Clin Exp Pharmacol Physiol* **27**(7): 524–28.
Smith SR, Deshpande BR, Collins JE et al (2016) Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic analytic review. *Osteoarthritis Cartilage* **24**(6): 962-72.
Smith TW, Binning AR & Dahan A (2009) Efficacy and safety of morphine-6-glucuronide (M6G) for postoperative pain relief: a randomized, double-blind study. *Eur J Pain* **13**(3): 293–99.
Snedecor SJ, Sudharshan L, Cappelleri JC et al (2014) Systematic review and meta-analysis of pharmacological therapies for pain associated with postherpetic neuralgia and less common neuropathic conditions. *Int J Clin Pract* **68**(7): 900–18.
Sng BL, Kwok SC, Mathur D et al (2016) Comparison of epidural oxycodone and epidural morphine for post-caesarean section analgesia: A randomised controlled trial. *Indian J Anaesth* **60**(3): 187-93.

Snijdelaar DG, Koren G & Katz J (2004) Effects of perioperative oral amantadine on postoperative pain and morphine consumption in patients after radical prostatectomy: results of a preliminary study. *Anesthesiology* **100**(1): 134–41.

Solomon DH, Rassen JA, Glynn RJ et al (2010) The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med* **170**(22): 1968–76.

Solomon SD, Wittes J, Finn PV et al (2008) Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis. *Circulation* **117**(16): 2104–13.

Soltesz EG, van Pelt F & Byrne JG (2003) Emergent cardiopulmonary bypass for bupivacaine cardiotoxicity. *J Cardiothorac Vasc Anesth* **17**(3): 357–58.

Somogyi AA, Barratt DT & Coller JK (2007) Pharmacogenetics of opioids. *Clin Pharmacol Ther* **81**(3): 429–44.

Song JA, Lee MK, Min E et al (2018) Effects of aromatherapy on dysmenorrhea: A systematic review and meta-analysis. *Int J Nurs Stud* **84**: 1-11.

Spruyt O, Westerman D, Milner A et al (2014) A randomised, double-blind, placebo-controlled study to assess the safety and efficacy of methoxyflurane for procedural pain of a bone marrow biopsy. *BMJ Support Palliat Care* **4**(4): 342–48.

Srebro D, Vuckovic S, Milovanovic A et al (2016) Magnesium in pain research: state of the art. *Curr Med Chem*(Epub ahead of print).

Sridharan K & Sivaramakrishnan G (2018) Drugs for Treating Opioid-Induced Constipation: A Mixed Treatment Comparison Network Meta-analysis of Randomized Controlled Clinical Trials. *J Pain Symptom Manage* **55**(2): 468-79 e1.

Stahn C & Buttgereit F (2008) Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol* **4**(10): 525–33.

Staiger TO, Gaster B, Sullivan MD et al (2003) Systematic review of antidepressants in the treatment of chronic low back pain. *Spine* **28**(22): 2540–45.

Staikou C & Paraskeva A (2014) The effects of intrathecal and systemic adjuvants on subarachnoid block. *Minerva Anestesiol* **80**(1): 96–112.

Stamer UM, Lehnen K, Hothker F et al (2003) Impact of CYP2D6 genotype on postoperative tramadol analgesia. *Pain* **105**(1-2): 231–38.

Stamer UM & Stuber F (2007a) Genetic factors in pain and its treatment. *Curr Opin Anaesthesiol* **20**(5): 478–84.

Stamer UM & Stuber F (2007b) The pharmacogenetics of analgesia. *Expert Opin Pharmacother* **8**(14): 2235–45.

Stamer UM, Stuber F, Muders T et al (2008) Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. *Anesth Analg* **107**(3): 926–29.

Stannard C, Gaskell H, Derry S et al (2016) Hydromorphone for neuropathic pain in adults. *Cochrane Database Syst Rev*(5): CD011604.

Stefani LC, Muller S, Torres IL et al (2013) A Phase II, Randomized, Double-Blind, Placebo Controlled, Dose-Response Trial of the Melatonin Effect on the Pain Threshold of Healthy Subjects. *PLoS One* **8**(10): e74107.

Stein C (2013) Targeting pain and inflammation by peripherally acting opioids. *Front Pharmacol* **4**: 123.

Stein C & Machelska H (2011) Modulation of peripheral sensory neurons by the immune system: implications for pain therapy. *Pharmacol Rev* **63**(4): 860-81.

Steinberg RB, Reuben SS & Gardner G (1998) The dose-response relationship of ketorolac as a component of intravenous regional anesthesia with lidocaine. *Anesth Analg* **86**(4): 791–93.

Steinbrook RA, Garfield F, Batista SH et al (2013) Caffeine for the prevention of postoperative nausea and vomiting. *J Anaesthesiol Clin Pharmacol* **29**(4): 526–29.

Stellato C (2004) Post-transcriptional and nongenomic effects of glucocorticoids. *Proc Am Thorac Soc* **1**(3): 255–63.

Stephens G, Derry S & Moore RA (2016) Paracetamol (acetaminophen) for acute treatment of episodic tension-type headache in adults. *Cochrane Database Syst Rev*(6): CD011889.

Stevens AJ & Higgins MD (2017) A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain. *Acta Anaesthesiol Scand* **61**(3): 268-80.

Stevens AJ, Woodman RJ & Owen H (2015) The effect of ondansetron on the efficacy of postoperative tramadol: a systematic review and meta-analysis of a drug interaction. *Anaesthesia* **70**(2): 209-18.

Stewart J, Kellett N & Castro D (2003) The central nervous system and cardiovascular effects of levobupivacaine and ropivacaine in healthy volunteers. *Anesth Analg* **97**(2): 412–16.

Stockings E, Campbell G, Hall WD et al (2018) Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain* **159**(10): 1932-54.

Stollenwerk A, Sohns M, Heisig F et al (2018) Review of Post-Marketing Safety Data on Tapentadol, a Centrally Acting Analgesic. *Adv Ther* **35**(1): 12-30.

Stoltz RR, Harris SI, Kuss ME et al (2002) Upper GI mucosal effects of parecoxib sodium in healthy elderly subjects. *Am J Gastroenterol* **97**(1): 65–71.

Strang J, Knight A, Baillie S et al (2018) Norbuprenorphine and respiratory depression: Exploratory analyses with new lyophilized buprenorphine and sublingual buprenorphine. *Int J Clin Pharmacol Ther* **56**(2): 81-85.

Straube S, Derry S, Moore RA et al (2010) Single dose oral gabapentin for established acute postoperative pain in adults. *Cochrane Database Syst Rev* **5**: CD008183.
Strom BL, Berlin JA, Kinman JL et al (1996) Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study. *JAMA* **275**(5): 376–82.
Subedi A, Biswas B & Tripathi M, et al (2013) Analgesic effects of intrathecal tramadol in patients undergoing caesarian section: a randomised,double-blind study. *Int J Obstet Anesth* **22**(4): 316–21.
Subramaniam K, Akhouri V, Glazer PA et al (2011) Intra- and postoperative very low dose intravenous ketamine infusion does not increase pain relief after major spine surgery in patients with preoperative narcotic analgesic intake. *Pain Med* **12**(8): 1276–83.
Subramaniam K, Subramaniam B & Steinbrook RA (2004) Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Anesth Analg* **99**(2): 482–95.
Subramanya V, Kapinigowda ST, Math AT et al (2017) Dexmedetomidine as an Adjuvant for Intravenous Regional Anesthesia in Upper Limb Surgeries. *Anesth Essays Res* **11**(3): 661-64.
Sumida S, Lesley MR, Hanna MN et al (2009) Meta-analysis of the effect of extended-release epidural morphine versus intravenous patient-controlled analgesia on respiratory depression. *J Opioid Manag* **5**(5): 301–05.
Sun J, Feng X, Zhu Q et al (2017a) Analgesic effect of perineural magnesium sulphate for sciatic nerve block for diabetic toe amputation: A randomized trial. *PLoS One* **12**(5): e0176589.
Sun Q, Liu S, Wu H et al (2019) Dexmedetomidine as an Adjuvant to Local Anesthetics in Transversus Abdominis Plane Block: A Systematic Review and Meta-analysis. *Clin J Pain* **35**(4): 375-84.
Sun R, Zhao W, Hao Q et al (2014) Intra-articular clonidine for post-operative analgesia following arthroscopic knee surgery: a systematic review and meta-analysis. *Knee Surg Sports Traumatol Arthrosc* **22**(9): 2076-84.
Sun S, Wang J, Bao N et al (2017b) Comparison of dexmedetomidine and fentanyl as local anesthetic adjuvants in spinal anesthesia: a systematic review and meta-analysis of randomized controlled trials. *Drug Des Devel Ther* **11**: 3413-24.
Sun Y & Liu Y (2016) Efficacy of preemptive gabapentin for laparoscopic cholecystectomy: A meta-analysis of randomized controlled trials. *Internat J Clin Experi Med* **9**(8): 15157-66.
Suzuki M, Haraguti S, Sugimoto K et al (2006) Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology* **105**(1): 111–19.
Swart LM, van der Zanden V, Spies PE et al (2017) The Comparative Risk of Delirium with Different Opioids: A Systematic Review. *Drugs Aging* **34**(6): 437-43.
Tabrizian P, Giacca M, Prigoff J et al (2019) Renal Safety of Intravenous Ketorolac Use After Donor Nephrectomy. *Prog Transplant* **29**(3): 283-86.
Takahashi K, Patel AK, Nagai S et al (2017) Perioperative Ketorolac Use: A Potential Risk Factor for Renal Dysfunction After Live-Donor Nephrectomy. *Ann Transplant* **22**: 563-69.
Takeda S, Misawa K, Yamamoto I et al (2008) Cannabidiolic acid as a selective cyclooxygenase-2 inhibitory component in cannabis. *Drug Metab Dispos* **36**(9): 1917–21.
Tan HP & Conroy T (2018) The Effectiveness of Intravenous Oxycodone in the Treatment of Acute Postoperative Pain: A Systematic Review. *J Perianesth Nurs* **33**(6): 865-79.
Tan PH, Cheng JT, Kuo CH et al (2007) Preincisional subcutaneous infiltration of ketamine suppresses postoperative pain after circumcision surgery. *Clin J Pain* **23**(3): 214–18.
Tanen DA, Miller S, French T et al (2003) Intravenous sodium valproate versus prochlorperazine for the emergency department treatment of acute migraine headaches: a prospective, randomized, double-blind trial. *Ann Emerg Med* **41**(6): 847–53.
Tang DH & Malone DC (2012) A network meta-analysis on the efficacy of serotonin type 3 receptor antagonists used in adults during the first 24 hours for postoperative nausea and vomiting prophylaxis. *Clin Ther* **34**(2): 282–94.
Tang Q, Li X, Yu L et al (2016) Preoperative ropivacaine with or without tramadol for femoral nerve block in total knee arthroplasty. *J Orthop Surg (Hong Kong)* **24**(2): 183-7.
Targownik LE, Metge CJ, Leung S et al (2008) The relative efficacies of gastroprotective strategies in chronic users of nonsteroidal anti-inflammatory drugs. *Gastroenterology* **134**(4): 937–44.
Tarkkila P, Tuominen M & Lindgren L (1997) Comparison of respiratory effects of tramadol and oxycodone. *J Clin Anesth* **9**(7): 582–85.
Tarkkila P, Tuominen M & Lindgren L (1998) Comparison of respiratory effects of tramadol and pethidine. *Eur J Anaesthesiol* **15**(1): 64–68.
Tawfic QA (2013) A review of the use of ketamine in pain management. *J Opioid Manag* **9**(5): 379–88.
Taylor S, Kirton OC, Staff I et al (2005) Postoperative day one: a high risk period for respiratory events. *Am J Surg* **190**(5): 752-6.
Teasell RW, Mehta S, Aubut JA et al (2010) A systematic review of pharmacologic treatments of pain after spinal cord injury. *Arch Phys Med Rehabil* **91**(5): 816–31.
Teerawattananon C, Tantayakom P, Suwanawiboon B et al (2017) Risk of perioperative bleeding related to highly selective cyclooxygenase-2 inhibitors: A systematic review and meta-analysis. *Semin Arthritis Rheum* **46**(4): 520-28.

Thagaard KS, Jensen HH & Raeder J (2007) Analgesic and antiemetic effect of ketorolac vs. betamethasone or dexamethasone after ambulatory surgery. *Acta Anaesthesiol Scand* **51**(3): 271–77.

Than NN, Soe HHK, Palaniappan SK et al (2019) Magnesium for treating sickle cell disease. *Cochrane Database Syst Rev* **9**: CD011358.

Thevenin A, Beloeil H, Blanie A et al (2008) The limited efficacy of tramadol in postoperative patients: a study of ED80 using the continual reassessment method. *Anesth Analg* **106**(2): 622–27.

Thiels CA, Habermann EB, Hooten WM et al (2019) Chronic use of tramadol after acute pain episode: cohort study. *BMJ* **365**: l1849.

Thomas S & Beevi S (2006) Epidural dexamethasone reduces postoperative pain and analgesic requirements. *Can J Anaesth* **53**(9): 899–905.

Thompson T, Whiter F, Gallop K et al (2019) NMDA receptor antagonists and pain relief: A meta-analysis of experimental trials. *Neurology* **92**(14): e1652-e62.

Tiippana EM, Hamunen K, Kontinen VK et al (2007) Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg* **104**(6): 1545–56.

Titirungruang C, Seresirikachorn K, Kasemsuwan P et al (2019) The use of steroids to reduce complications after tonsillectomy: a systematic review and meta-analysis of randomized controlled studies. *Eur Arch Otorhinolaryngol* **276**(2): 585-604.

Tolska HK, Hamunen K, Takala A et al (2019) Systematic review of analgesics and dexamethasone for post-tonsillectomy pain in adults. *Br J Anaesth* **123**(2): e397-e411.

Tomar GS, Ganguly S & Cherian G (2017) Effect of Perineural Dexamethasone With Bupivacaine in Single Space Paravertebral Block for Postoperative Analgesia in Elective Nephrectomy Cases: A Double-Blind Placebo-Controlled Trial. *Am J Ther* **24**(6): e713-e17.

Tompkins DA, Smith MT, Mintzer MZ et al (2014) A double blind, within subject comparison of spontaneous opioid withdrawal from buprenorphine versus morphine. *J Pharmacol Exp Ther* **348**(2): 217-26.

Toner AJ, Ganeshanathan V, Chan MT et al (2017) Safety of Perioperative Glucocorticoids in Elective Noncardiac Surgery: A Systematic Review and Meta-analysis. *Anesthesiology* **126**(2): 234-48.

Tong YC, Kaye AD & Urman RD (2014) Liposomal bupivacaine and clinical outcomes. *Best Pract Res Clin Anaesthesiol* **28**(1): 15-27.

Toomath RJ & Morrison RB (1987) Renal failure following methoxyflurane analgesia. *N Z Med J* **100**(836): 707–08.

Toth B, Lantos T, Hegyi P et al (2018) Ginger (Zingiber officinale): An alternative for the prevention of postoperative nausea and vomiting. A meta-analysis. *Phytomedicine* **50**: 8-18.

Toyoda T, Terao Y, Oji M et al (2013) The interaction of antiemetic dose of droperidol with propofol on QT interval during anesthetic induction. *J Anesth* **27**(6): 885–89.

Tran KM, Ganley TJ, Wells L et al (2005) Intraarticular bupivacaine-clonidine-morphine versus femoral-sciatic nerve block in pediatric patients undergoing anterior cruciate ligament reconstruction. *Anesth Analg* **101**(5): 1304–10.

Treillet E, Laurent S & Hadjiat Y (2018) Practical management of opioid rotation and equianalgesia. *J Pain Res* **11**: 2587-601.

Trelle S, Reichenbach S, Wandel S et al (2011) Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* **342**: c7086.

Treman J & Bonica J (2001) Spinal mechanisms and their mechanisms. In: *Bonica's Management of Pain* 3rd edn. Loesser J (eds). Philadelphia USA, Lippincott Williams and Wilkins. 101.

Tremont-Lukats IW, Challapalli V, McNicol ED et al (2005) Systemic administration of local anesthetics to relieve neuropathic pain: a systematic review and meta-analysis. *Anesth Analg* **101**(6): 1738–49.

Tricco AC, Soobiah C, Blondal E et al (2015a) Comparative efficacy of serotonin (5-HT3) receptor antagonists in patients undergoing surgery: a systematic review and network meta-analysis. *BMC Med* **13**: 136.

Tricco AC, Soobiah C, Blondal E et al (2015b) Comparative safety of serotonin (5-HT3) receptor antagonists in patients undergoing surgery: a systematic review and network meta-analysis. *BMC Med* **13**: 142.

Tsaousi GG, Pourzitaki C, Aloisio S et al (2018) Dexmedetomidine as a sedative and analgesic adjuvant in spine surgery: a systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Pharmacol* **74**(11): 1377-89.

Tschopp C, Tramer MR, Schneider A et al (2018) Benefit and Harm of Adding Epinephrine to a Local Anesthetic for Neuraxial and Locoregional Anesthesia: A Meta-analysis of Randomized Controlled Trials With Trial Sequential Analyses. *Anesth Analg* **127**(1): 228-39.

Tseng WC, Lin WL, Lai HC et al (2019) Fentanyl-based intravenous patient-controlled analgesia with low dose of ketamine is not inferior to thoracic epidural analgesia for acute post-thoracotomy pain following video-assisted thoracic surgery: A randomized controlled study. *Medicine (Baltimore)* **98**(28): e16403.

Tsujimoto S, Mokuda S, Matoba K et al (2018) The prevalence of endoscopic gastric mucosal damage in patients with rheumatoid arthritis. *PLoS One* **13**(7): e0200023.

Tsutaoka BT, Ho RY, Fung SM et al (2015) Comparative Toxicity of Tapentadol and Tramadol Utilizing Data Reported to the National Poison Data System. *Ann Pharmacother* **49**(12): 1311-6.

Tsutsumi YM, Kakuta N, Soga T et al (2014) The effects of intravenous fosaprepitant and ondansetron for the prevention of postoperative nausea and vomiting in neurosurgery patients: a prospective, randomized, double-blinded study. *Biomed Res Int* **2014**: 307025.
Turan A, Babazade R, Kurz A et al (2016) Clonidine Does Not Reduce Pain or Opioid Consumption After Noncardiac Surgery. *Anesth Analg* **123**(3): 749-57.
Turan A, Kaya G, Karamanlioglu B et al (2006) Effect of oral gabapentin on postoperative epidural analgesia. *Br J Anaesth* **96**(2): 242–46.
Turan A, Memis D, Karamanlioglu B et al (2005) Intravenous regional anesthesia using lidocaine and magnesium. *Anesth Analg* **100**(4): 1189–92.
Turan A & Sessler DI (2011) Steroids to ameliorate postoperative pain. *Anesthesiology* **115**(3): 457–59.
Turek T & Wigton A (2012) Calcitonin for phantom limb pain in a pregnant woman. *Am J Health Syst Pharm* **69**(24): 2149–52.
Turker G, Goren S, Bayram S et al (2005) Comparison of lumbar epidural tramadol and lumbar epidural morphine for pain relief after thoracotomy: a repeated-dose study. *J Cardiothorac Vasc Anesth* **19**(4): 468-74.
Turtle EJ, Dear JW & Webb DJ (2013) A systematic review of the effect of paracetamol on blood pressure in hypertensive and non-hypertensive subjects. *Br J Clin Pharmacol* **75**(6): 1396–405.
Tzortzopoulou A, McNicol ED, Cepeda MS et al (2011) Single dose intravenous propacetamol or intravenous paracetamol for postoperative pain. *Cochrane Database Syst Rev* **10**: CD007126.
Tzschentke TM, Christoph T & Kogel BY (2014) The mu-opioid receptor agonist/noradrenaline reuptake inhibition (MOR-NRI) concept in analgesia: the case of tapentadol. *CNS Drugs* **28**(4): 319–29.
Unlugenc H, Ozalevli M, Gunes Y et al (2006) A double-blind comparison of intrathecal S(+) ketamine and fentanyl combined with bupivacaine 0.5% for Caesarean delivery. *Eur J Anaesthesiol* **23**(12): 1018–24.
Urban MK, Ya Deau JT, Wukovits B et al (2008) Ketamine as an adjunct to postoperative pain management in opioid tolerant patients after spinal fusions: a prospective randomized trial. *HSS J* **4**(1): 62–65.
Urman RD, Seger DL, Fiskio JM et al (2019) The Burden of Opioid-Related Adverse Drug Events on Hospitalized Previously Opioid-Free Surgical Patients. *J Patient Saf*(epub ahead of print).
Urquhart DM, Hoving JL, Assendelft WW et al (2008) Antidepressants for non-specific low back pain. *Cochrane Database Syst Rev* **1**: CD001703.
Uusalo P, Jatinvuori H, Loyttyniemi E et al (2019) Intranasal Low-Dose Dexmedetomidine Reduces Postoperative Opioid Requirement in Patients Undergoing Hip Arthroplasty Under General Anesthesia. *J Arthroplasty* **34**(4): 686-92 e2.
van Beek R, Zonneveldt HJ, van der Ploeg T et al (2017) In patients undergoing fast track total knee arthroplasty, addition of buprenorphine to a femoral nerve block has no clinical advantage: A prospective, double-blinded, randomized, placebo controlled trial. *Medicine (Baltimore)* **96**(27): e7393.
van den Bekerom MP, Sjer A, Somford MP et al (2015) Non-steroidal anti-inflammatory drugs (NSAIDs) for treating acute ankle sprains in adults: benefits outweigh adverse events. *Knee Surg Sports Traumatol Arthrosc* **23**(8): 2390–99.
van der Schier R, Roozekrans M, van Velzen M et al (2014) Opioid-induced respiratory depression: reversal by non-opioid drugs. *F1000Prime Rep* **6**: 79.
van der Schrier R, Jonkman K, van Velzen M et al (2017) An experimental study comparing the respiratory effects of tapentadol and oxycodone in healthy volunteers. *Br J Anaesth* **119**(6): 1169-77.
van der Wal SE, van den Heuvel SA, Radema SA et al (2016) The in vitro mechanisms and in vivo efficacy of intravenous lidocaine on the neuroinflammatory response in acute and chronic pain. *Eur J Pain* **20**(5): 655-74.
van Dorp E, Yassen A, Sarton E et al (2006a) Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology* **105**(1): 51–57.
van Dorp EL, Romberg R, Sarton E et al (2006b) Morphine-6-glucuronide: morphine's successor for postoperative pain relief? *Anesth Analg* **102**(6): 1789–97.
Van Elstraete A, Sitbon P & Trabold F, et al (2005) A single dose of intrathecal morphine in rats induces long-lasting hyperalgesia: the protective effect of prior administration of ketamine. *Anesth Analg* **101**(6): 1750–56.
Van Elstraete AC, Sitbon P, Benhamou D et al (2011) The median effective dose of ketamine and gabapentin in opioid-induced hyperalgesia in rats: an isobolographic analysis of their interaction. *Anesth Analg* **113**(3): 634–40.
van Niel JC, Schneider J & Tzschentke TM (2016) Efficacy of Full micro-Opioid Receptor Agonists is not Impaired by Concomitant Buprenorphine or Mixed Opioid Agonists/Antagonists - Preclinical and Clinical Evidence. *Drug Res (Stuttg)* **66**(11): 562-70.
Vayne-Bossert P, Escher M & de Vautibault C, et al (2010) Effect of topical morphine (mouthwash) on oral pain due to chemotherapy-and/or-radiotherapy-induced mucositis: a randomised double-blinded study. *J Palliat Med* **13**(2): 125–28.
Vaysbrot EE, Osani MC, Musetti MC et al (2018) Are bisphosphonates efficacious in knee osteoarthritis? A meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage* **26**(2): 154-64.
Verlinde M, Hollmann MW, Stevens MF et al (2016) Local Anesthetic-Induced Neurotoxicity. *Int J Mol Sci* **17**(3): 339.
Vernassiere C, Cornet C, Trechot P et al (2005) Study to determine the efficacy of topical morphine on painful chronic skin ulcers. *J Wound Care* **14**(6): 289–93.

Veronese N, Stubbs B, Maggi S et al (2017) Low-Dose Aspirin Use and Cognitive Function in Older Age: A Systematic Review and Meta-analysis. *J Am Geriatr Soc* **65**(8): 1763-68.
Vila H, Jr., Smith RA, Augustyniak MJ et al (2005) The efficacy and safety of pain management before and after implementation of hospital-wide pain management standards: is patient safety compromised by treatment based solely on numerical pain ratings? *Anesth Analg* **101**(2): 474–80.
Vineyard JC, Toohey JS, Neidre A et al (2014) Evaluation of a single-dose, extended-release epidural morphine formulation for pain control after lumbar spine surgery. *J Surg Orthop Adv* **23**(1): 9–12.
Vinik AI, Shapiro DY, Rauschkolb C et al (2014) A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. *Diabetes Care* **37**(8): 2302–09.
Viscomi CM, Friend A, Parker C et al (2009) Ketamine as an adjuvant in lidocaine intravenous regional anesthesia: a randomized, double-blind, systemic control trial. *Reg Anesth Pain Med* **34**(2): 130–33.
Viscusi E, Gambling D, Hughes T et al (2009) Pharmacokinetics of extended-release epidural morphine sulphate: pooled analysis of six clinical studies. *Am J Health Syst Pharm* **66**: 1020–30.
Viscusi ER, Kopacz D, Hartrick C et al (2006) Single-dose extended-release epidural morphine for pain following hip arthroplasty. *Am J Ther* **13**(5): 423–31.
Viscusi ER, Martin G, Hartrick CT et al (2005) Forty-eight hours of postoperative pain relief after total hip arthroplasty with a novel, extended-release epidural morphine formulation. *Anesthesiology* **102**(5): 1014–22.
Viscusi ER, Sinatra R, Onel E et al (2014) The safety of liposome bupivacaine, a novel local analgesic formulation. *Clin J Pain* **30**(2): 102–10.
Visser E (2005) A review of calcitonin and its use in the treatment of acute pain. *Acute Pain* **7**(4): 143–48.
Vlok R, An GH, Binks M et al (2019) Sublingual buprenorphine versus intravenous or intramuscular morphine in acute pain: A systematic review and meta-analysis of randomized control trials. *Am J Emerg Med* **37**(3): 381-86.
Vorobeichik L, Brull R & Abdallah FW (2017) Evidence basis for using perineural dexmedetomidine to enhance the quality of brachial plexus nerve blocks: a systematic review and meta-analysis of randomized controlled trials. *Br J Anaesth* **118**(2): 167-81.
Vorobeychik Y, Sharma A, Smith CC et al (2016) The Effectiveness and Risks of Non-Image-Guided Lumbar Interlaminar Epidural Steroid Injections: A Systematic Review with Comprehensive Analysis of the Published Data. *Pain Med* **17**(12): 2185-202.
Vosburg SK, Severtson SG, Dart RC et al (2018) Assessment of Tapentadol API Abuse Liability With the Researched Abuse, Diversion and Addiction-Related Surveillance System. *J Pain* **19**(4): 439-53.
Voscopoulos CJ, MacNabb CM, Freeman J et al (2014) Continuous noninvasive respiratory volume monitoring for the identification of patients at risk for opioid-induced respiratory depression and obstructive breathing patterns. *J Trauma Acute Care Surg* **77**(3 Suppl 2): S208–15.
Wakai A, Lawrenson JG, Lawrenson AL et al (2017) Topical non-steroidal anti-inflammatory drugs for analgesia in traumatic corneal abrasions. *Cochrane Database Syst Rev* **5**: CD009781.
Walczyk H, Liu CH, Alafris A et al (2016) Probable Tapentadol-Associated Serotonin Syndrome After Overdose. *Hosp Pharm* **51**(4): 320-7.
Waldron NH, Jones CA, Gan TJ et al (2013) Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. *Br J Anaesth* **110**(2): 191–200.
Walitt B, Klose P, Fitzcharles MA et al (2016) Cannabinoids for fibromyalgia. *Cochrane Database Syst Rev* **7**: CD011694.
Walitt B, Urrutia G, Nishishinya MB et al (2015) Selective serotonin reuptake inhibitors for fibromyalgia syndrome. *Cochrane Database Syst Rev* **2015 (6)** (6): CD011735.
Walker C & Biasucci LM (2018) Cardiovascular safety of non-steroidal anti-inflammatory drugs revisited. *Postgrad Med* **130**(1): 55-71.
Walker NJ, Jones VM, Kratky L et al (2019) Hematoma Risks of Nonsteroidal Anti-inflammatory Drugs Used in Plastic Surgery Procedures: A Systematic Review and Meta-analysis. *Ann Plast Surg* **82**(6S Suppl 5): S437-S45.
Walker SM, Goudas LC, Cousins MJ et al (2002) Combination spinal analgesic chemotherapy: a systematic review. *Anesth Analg* **95**(3): 674–715.
Wallace MS, Barger D & Schulteis G (2002) The effect of chronic oral desipramine on capsaicin-induced allodynia and hyperalgesia: a double-blinded, placebo-controlled, crossover study. *Anesth Analg* **95**(4): 973–78.
Wallenborn J, Gelbrich G, Bulst D et al (2006) Prevention of postoperative nausea and vomiting by metoclopramide combined with dexamethasone: randomised double blind multicentre trial. *BMJ* **333**(7563): 324.
Walter JH (2011) Vitamin B12 deficiency and phenylketonuria. *Mol Genet Metab* **104 Suppl**: S52–54.
Wang HL, Zhang GY, Dai WX et al (2019) Dose-dependent neurotoxicity caused by the addition of perineural dexmedetomidine to ropivacaine for continuous femoral nerve block in rabbits. *J Int Med Res* **47**(6): 2562-70.
Wang JJ, Ho ST, Lee SC et al (1998) Intraarticular triamcinolone acetonide for pain control after arthroscopic knee surgery. *Anesth Analg* **87**(5): 1113–16.
Wang JK, Nauss LA & Thomas JE (1979) Pain relief by intrathecally applied morphine in man. *Anesthesiology* **50**(2): 149–51.

Wang K, Wang LJ, Yang TJ et al (2018a) Dexmedetomidine combined with local anesthetics in thoracic paravertebral block: A systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* **97**(46): e13164.
Wang L, Johnston B, Kaushal A et al (2016a) Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials. *Can J Anaesth* **63**(3): 311-25.
Wang PK, Tsay PJ, Huang CC et al (2012) Comparison of dexamethasone with ondansetron or haloperidol for prevention of patient-controlled analgesia-related postoperative nausea and vomiting: a randomized clinical trial. *World J Surg* **36**(4): 775–81.
Wang SC, Pan PT, Chiu HY et al (2017a) Neuraxial magnesium sulfate improves postoperative analgesia in Cesarean section delivery women: A meta-analysis of randomized controlled trials. *Asian J Anesthesiol* **55**(3): 56-67.
Wang T, Ma J, Wang R et al (2018b) Poly-Drug Use of Prescription Medicine among People with Opioid Use Disorder in China: A Systematic Review and Meta-Analysis. *Subst Use Misuse* **53**(7): 1117-27.
Wang TF, Liu YH, Chu CC et al (2008) Low-dose haloperidol prevents post-operative nausea and vomiting after ambulatory laparoscopic surgery. *Acta Anaesthesiol Scand* **52**(2): 280–84.
Wang W, Sun Y & Zhang D (2016b) Association Between Non-Steroidal Anti-Inflammatory Drug Use and Cognitive Decline: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Drugs Aging* **33**(7): 501-9.
Wang W, Zhou L & Sun L (2017b) Ondansetron for neuraxial morphine-induced pruritus: A meta-analysis of randomized controlled trials. *J Clin Pharm Ther* **42**(4): 383-93.
Wang X, Ding X, Tong Y et al (2014) Ketamine does not increase intracranial pressure compared with opioids: meta-analysis of randomized controlled trials. *J Anesth* **28**(6): 821–27.
Wang X, Liu N, Chen J et al (2018c) Effect of Intravenous Dexmedetomidine During General Anesthesia on Acute Postoperative Pain in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clin J Pain* **34**(12): 1180-91.
Wang X, Xie H & Wang G (2006) Improved postoperative analgesia with coadministration of preoperative epidural ketamine and midazolam. *J Clin Anesth* **18**(8): 563–69.
Wang Y, Zhang FC & Wang YJ (2015a) The efficacy and safety of non-steroidal anti-inflammatory drugs in preventing the recurrence of colorectal adenoma: a meta-analysis and systematic review of randomized trials. *Colorectal Dis* **17**(3): 188-96.
Wang ZY, Shi SY, Li SJ et al (2015b) Efficacy and Safety of Duloxetine on Osteoarthritis Knee Pain: A Meta-Analysis of Randomized Controlled Trials. *Pain Med* **16**(7): 1373-85.
Ward VD & Mc Crory CR (2014) An assessment of intrathecal catheters in the perioperative period: an analysis of 84 cases. *Ir J Med Sci* **183**(2): 293-6.
Warren JA, Thoma RB, Georgescu A et al (2008) Intravenous lipid infusion in the successful resuscitation of local anesthetic-induced cardiovascular collapse after supraclavicular brachial plexus block. *Anesth Analg* **106**(5): 1578–80.
Warren PM, Taylor JH, Nicholson KE et al (2000) Influence of tramadol on the ventilatory response to hypoxia in humans. *Br J Anaesth* **85**(2): 211–16.
Wasiak J, Mahar P, McGuinness SK et al (2012) Intravenous lidocaine for the treatment of background or procedural burn pain. *Cochrane Database Syst Rev* **6**: CD005622.
Wasiak J, Spinks A, Costello V et al (2011) Adjuvant use of intravenous lidocaine for procedural burn pain relief: a randomized double-blind, placebo-controlled, cross-over trial. *Burns* **37**(6): 951–57.
Watkins TW, Dupre S & Coucher JR (2015) Ropivacaine and dexamethasone: a potentially dangerous combination for therapeutic pain injections. *J Med Imaging Radiat Oncol* **59**(5): 571–77.
Wax MK, Reh DD & Levack MM (2007) Effect of celecoxib on fasciocutaneous flap survival and revascularization. *Arch Facial Plast Surg* **9**(2): 120–24.
Weber L, Yeomans DC & Tzabazis A (2017) Opioid-induced hyperalgesia in clinical anesthesia practice: what has remained from theoretical concepts and experimental studies? *Curr Opin Anaesthesiol* **30**(4): 458-65.
Webster LR & Fine PG (2012) Review and critique of opioid rotation practices and associated risks of toxicity. *Pain Med* **13**(4): 562–70.
Wedam EF, Bigelow GE, Johnson RE et al (2007) QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Arch Intern Med* **167**(22): 2469–75.
Wee MY, Tuckey JP, Thomas PW et al (2014) A comparison of intramuscular diamorphine and intramuscular pethidine for labour analgesia: a two-centre randomised blinded controlled trial. *BJOG* **121**(4): 447–56.
Wehrfritz A, Schaefer S, Troester A et al (2016) A randomized phase I trial evaluating the effects of inhaled 50-50% N2 O-O2 on remifentanil-induced hyperalgesia and allodynia in human volunteers. *Eur J Pain* **20**(9): 1467-77.
Weibel S, Jelting Y, Pace NL et al (2018) Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. *Cochrane Database Syst Rev* **6**: CD009642.
Weimann J (2003) Toxicity of nitrous oxide. *Best Pract Res Clin Anaesthesiol* **17**(1): 47–61.
Weinberg G, Ripper R, Feinstein DL et al (2003) Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. *Reg Anesth Pain Med* **28**(3): 198–202.

Weinberg GL, Palmer JW, VadeBoncouer TR et al (2000) Bupivacaine inhibits acylcarnitine exchange in cardiac mitochondria. *Anesthesiology* **92**(2): 523–28.
Weinberg GL, VadeBoncouer T, Ramaraju GA et al (1998) Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology* **88**(4): 1071–75.
Weinberg L, Rachbuch C, Ting S et al (2016) A randomised controlled trial of peri-operative lidocaine infusions for open radical prostatectomy. *Anaesthesia* **71**(4): 405-10.
Weingarten TN, Herasevich V, McGlinch MC et al (2015) Predictors of Delayed Postoperative Respiratory Depression Assessed from Naloxone Administration. *Anesth Analg* **121**(2): 422-9.
Weiss E, Jolly C, Dumoulin JL et al (2014) Convulsions in 2 patients after bilateral ultrasound-guided transversus abdominis plane blocks for cesarean analgesia. *Reg Anesth Pain Med* **39**(3): 248–51.
Weiss NS (2016) Use of acetaminophen in relation to the occurrence of cancer: a review of epidemiologic studies. *Cancer Causes Control* **27**(12): 1411-18.
Welchman S, Cochrane S, Minto G et al (2010) Systematic review: the use of nitrous oxide gas for lower gastrointestinal endoscopy. *Aliment Pharmacol Ther* **32**(3): 324–33.
Welling A (2007) A randomised controlled trial to test the analgesic efficacy of topical morphine on minor superficial and partial thickness burns in accident and emergency departments. *Emerg Med J* **24**(6): 408-12.
Wells C & Adcock L (2018) *Methoxyflurane for Acute Pain in the Emergency Department: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines*. Ottawa (ON), Canadian Agency for Drugs and Technologies in Health.
Wells G, Chernoff J, Gilligan JP et al (2016) Does salmon calcitonin cause cancer? A review and meta-analysis. *Osteoporos Int* **27**(1): 13-9.
Welsch P, Uceyler N, Klose P et al (2018) Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database Syst Rev* **2**: CD010292.
Werdehausen R, Braun S, Hermanns H et al (2011) The influence of adjuvants used in regional anesthesia on lidocaine-induced neurotoxicity in vitro. *Reg Anesth Pain Med* **36**(5): 436–43.
Wertli MM, Kessels AG, Perez RS et al (2014) Rational pain management in complex regional pain syndrome 1 (CRPS 1)--a network meta-analysis. *Pain Med* **15**(9): 1575-89.
Weschules DJ & Bain KT (2008a) A systematic review of opioid conversion ratios used with methadone for the treatment of pain. *Pain Med* **9**(5): 595–612.
Weschules DJ, Bain KT & Richeimer S (2008b) Actual and potential drug interactions associated with methadone. *Pain Med* **9**(3): 315–44.
Wheatley BM, Nappo KE, Christensen DL et al (2019) Effect of NSAIDs on Bone Healing Rates: A Meta-analysis. *J Am Acad Orthop Surg* **27**(7): e330-e36.
Wheatley RG, Schug SA & Watson D (2001) Safety and efficacy of postoperative epidural analgesia. *Br J Anaesth* **87**(1): 47-61.
Wheatley RG, Somerville ID, Sapsford DJ et al (1990) Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia. *Br J Anaesth* **64**(3): 267–75.
White LD, Hodge A, Vlok R et al (2018) Efficacy and adverse effects of buprenorphine in acute pain management: systematic review and meta-analysis of randomised controlled trials. *Br J Anaesth* **120**(4): 668-78.
White PF, Song D, Abrao J et al (2005) Effect of low-dose droperidol on the QT interval during and after general anesthesia: a placebo-controlled study. *Anesthesiology* **102**(6): 1101–05.
WHO (2012) *WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses*. Geneva, World Health Organisation.
WHO (2018) *Critical Review Report: Tramadol.* https://www.who.int/medicines/access/controlled-substances/Tramadol.pdf?ua=1 Accessed 25 January 2020
Wiffen PJ, Derry S, Bell RF et al (2017a) Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* **6**: CD007938.
Wiffen PJ, Derry S & Moore RA (2013a) Lamotrigine for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* **12**: CD006044.
Wiffen PJ, Derry S & Moore RA (2017b) Tramadol with or without paracetamol (acetaminophen) for cancer pain. *Cochrane Database Syst Rev* **5**: CD012508.
Wiffen PJ, Derry S, Moore RA et al (2013b) Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. *Cochrane Database Syst Rev* **11**: CD010567.
Wiffen PJ, Derry S, Moore RA et al (2014) Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* **4**(4): CD005451.
Wiffen PJ, Derry S, Moore RA et al (2015) Buprenorphine for neuropathic pain in adults. *Cochrane Database Syst Rev*(9): CD011603.
Wiffen PJ, Wee B & Moore RA (2016) Oral morphine for cancer pain. *Cochrane Database Syst Rev* **4**: CD003868.
Wilder-Smith CH & Bettiga A (1997) The analgesic tramadol has minimal effect on gastrointestinal motor function. *Br J Clin Pharmacol* **43**(1): 71–75.

Wilder-Smith CH, Hill L, Osler W et al (1999a) Effect of tramadol and morphine on pain and gastrointestinal motor function in patients with chronic pancreatitis. *Dig Dis Sci* **44**(6): 1107–16.
Wilder-Smith CH, Hill L, Wilkins J et al (1999b) Effects of morphine and tramadol on somatic and visceral sensory function and gastrointestinal motility after abdominal surgery. *Anesthesiology* **91**(3): 639–47.
Williams BA, Hough KA, Tsui BY et al (2011) Neurotoxicity of adjuvants used in perineural anesthesia and analgesia in comparison with ropivacaine. *Reg Anesth Pain Med* **36**(3): 225–30.
Williamson OD, Sagman D, Bruins RH et al (2014) Antidepressants in the treatment for chronic low back pain: questioning the validity of meta-analyses. *Pain Pract* **14**(2): E33–41.
Wilsey B, Marcotte T, Deutsch R et al (2013) Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain* **14**(2): 136–48.
Wilson JA, Nimmo AF, Fleetwood-Walker SM et al (2008) A randomised double blind trial of the effect of pre-emptive epidural ketamine on persistent pain after lower limb amputation. *Pain* **135**(1-2): 108–18.
Wilson-Poe AR, Pocius E, Herschbach M et al (2013) The periaqueductal gray contributes to bidirectional enhancement of antinociception between morphine and cannabinoids. *Pharmacol Biochem Behav* **103**(3): 444–49.
Wilson-Smith A, Chang N, Lu VM et al (2018) Epidural Steroids at Closure After Microdiscectomy/Laminectomy for Reduction of Postoperative Analgesia: Systematic Review and Meta-Analysis. *World Neurosurg* **110**: e212-e21.
Wolf M, Tamaschke C, Mayer W et al (2003) [Efficacy of Arnica in varicose vein surgery: results of a randomized, double-blind, placebo-controlled pilot study]. *Forsch Komplementarmed Klass Naturheilkd* **10**(5): 242-7.
Wong MH, Stockler MR & Pavlakis N (2012) Bisphosphonates and other bone agents for breast cancer. *Cochrane Database Syst Rev* **2**: CD003474.
Woodhouse A, Ward ME & Mather LE (1999) Intra-subject variability in post-operative patient-controlled analgesia (PCA): is the patient equally satisfied with morphine, pethidine and fentanyl? *Pain* **80**(3): 545–53.
Wright AW, Mather LE & Smith MT (2001) Hydromorphone-3-glucuronide: a more potent neuro-excitant than its structural analogue, morphine-3-glucuronide. *Life Sci* **69**(4): 409–20.
Wu L, Huang X & Sun L (2015) The efficacy of N-methyl-D-aspartate receptor antagonists on improving the postoperative pain intensity and satisfaction after remifentanil-based anesthesia in adults: a meta-analysis. *J Clin Anesth* **27**(4): 311–24.
Wuytack F, Smith V & Cleary BJ (2016) Oral non-steroidal anti-inflammatory drugs (single dose) for perineal pain in the early postpartum period. *Cochrane Database Syst Rev* **7**: Cd011352.
Xiao JP, Li AL, Feng BM et al (2017) Efficacy and Safety of Tapentadol Immediate Release Assessment in Treatment of Moderate to Severe Pain: A Systematic Review and Meta-Analysis. *Pain Med* **18**(1): 14-24.
Xiao Y, Wu L, Zhou Q et al (2015) A randomized clinical trial of the effects of ultra-low-dose naloxone infusion on postoperative opioid requirements and recovery. *Acta Anaesthesiol Scand* **59**(9): 1194-203.
Xie M, Li XK & Peng Y (2017) Magnesium sulfate for postoperative complications in children undergoing tonsillectomies: a systematic review and meta-analysis. *J Evid Based Med* **10**(1): 16-25.
Xu G, Xu S, Cheng C et al (2016a) Local Administration of Methylcobalamin and Lidocaine for Acute Ophthalmic Herpetic Neuralgia: A Single-Center Randomized Controlled Trial. *Pain Pract* **16**(7): 869-81.
Xu G, Xu S, Tang WZ et al (2016b) Local Injection of Methylcobalamin Combined with Lidocaine for Acute Herpetic Neuralgia. *Pain Med* **17**(3): 572-81.
Xu XS, Smit JW, Lin R et al (2010) Population pharmacokinetics of tapentadol immediate release (IR) in healthy subjects and patients with moderate or severe pain. *Clin Pharmacokinet* **49**(10): 671–82.
YaDeau JT, Brummett CM, Mayman DJ et al (2016) Duloxetine and subacute pain after knee arthroplasty when added to a multimodal analgesic regimen. *Anesthesiology* **125**(3): 561-72.
YaDeau JT, Paroli L, Fields KG et al (2015) Addition of Dexamethasone and Buprenorphine to Bupivacaine Sciatic Nerve Block: A Randomized Controlled Trial. *Reg Anesth Pain Med* **40**(4): 321-9.
Yaksh TL (1981) Spinal opiate analgesia: characteristics and principles of action. *Pain* **11**(3): 293–346.
Yaksh TL & Allen JW (2004) Preclinical insights into the implementation of intrathecal midazolam: a cautionary tale. *Anesth Analg* **98**(6): 1509–11.
Yaksh TL, Fisher CJ, Hockman TM et al (2017) Current and Future Issues in the Development of Spinal Agents for the Management of Pain. *Curr Neuropharmacol* **15**(2): 232-59.
Yaksh TL & Rudy TA (1976) Analgesia mediated by a direct spinal action of narcotics. *Science* **192**(4246): 1357–58.
Yanagihara Y, Ohtani M, Kariya S et al (2003) Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. *Biopharm Drug Dispos* **24**(1): 37–43.
Yang L, Du S & Sun Y (2017a) Intravenous acetaminophen as an adjunct to multimodal analgesia after total knee and hip arthroplasty: A systematic review and meta-analysis. *Int J Surg* **47**: 135-46.
Yang Y, Young JB, Schermer CR et al (2014) Use of ketorolac is associated with decreased pneumonia following rib fractures. *Am J Surg* **207**(4): 566-72.
Yang Y, Zeng C, Wei J et al (2017b) Single-dose intra-articular bupivacaine plus morphine versus bupivacaine alone after arthroscopic knee surgery: a meta-analysis of randomized controlled trials. *Knee Surg Sports Traumatol Arthrosc* **25**(3): 966-79.

Yassen A, Olofsen E, Romberg R et al (2006) Mechanism-based pharmacokinetic-pharmacodynamic modeling of the antinociceptive effect of buprenorphine in healthy volunteers. *Anesthesiology* **104**(6): 1232–42.
Yayac M, Li WT, Ong AC et al (2019) The Efficacy of Liposomal Bupivacaine Over Traditional Local Anesthetics in Periarticular Infiltration and Regional Anesthesia During Total Knee Arthroplasty: A Systematic Review and Meta-Analysis. *J Arthroplasty* **34**(9): 2166-83.
Ye F, Wu Y & Zhou C (2017) Effect of intravenous ketamine for postoperative analgesia in patients undergoing laparoscopic cholecystectomy: A meta-analysis. *Medicine (Baltimore)* **96**(51): e9147.
Yee K & Cox RG (2013a) Safety of perioperative dexamethasone administration in children: time for reflection? *Can J Anaesth* **60**(9): 833–39.
Yee MM, Josephson C, Hill CE et al (2013b) Cytochrome P450 2D6 polymorphisms and predicted opioid metabolism in African American children with sickle cell disease. *J Pediatr Hematol Oncol* **35**(7): e301–05.
Yeomans ND, Graham DY, Husni ME et al (2018) Randomised clinical trial: gastrointestinal events in arthritis patients treated with celecoxib, ibuprofen or naproxen in the PRECISION trial. *Aliment Pharmacol Ther* **47**(11): 1453-63.
Yeung SST & Adcock L (2018) *Methoxyflurane in Pre-Hospital Settings: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines.* https://www.ncbi.nlm.nih.gov/books/NBK537959/pdf/Bookshelf_NBK537959.pdf Accessed 10 May 2020
Yildiz K, Efesoy SN, Ozdamar S et al (2011) Myotoxic effects of levobupivacaine, bupivacaine and ropivacaine in a rat model. *Clin Invest Med* **34**(5): E273.
Yiu-Cheung C (2012) Acute and chronic toxicity pattern in ketamine abusers in Hong Kong. *J Med Toxicol* **8**(3): 267–70.
Yoganarasimha N, Raghavendra T, Amitha S et al (2014) A comparative study between intrathecal clonidine and neostigmine with intrathecal bupivacaine for lower abdominal surgeries. *Indian J Anaesth* **58**(1): 43–47.
Young A & Buvanendran A (2012) Recent advances in multimodal analgesia. *Anesthesiol Clin* **30**(1): 91–100.
Yousef AA & Aborahma AM (2017) The Preventive Value of Epidural Calcitonin in Patients with Lower Limb Amputation. *Pain Med* **18**(9): 1745-51.
Youssef N, Orlov D & Alie T, et al (2014) What epidural opioid results in the best analgesia outcomes and fewest side effects after surgery?: a meta-analysis of randomised controlled trials. *Anesth Analg* **119**(4): 965–77.
Ystrom E, Gustavson K, Brandlistuen RE et al (2017) Prenatal Exposure to Acetaminophen and Risk of ADHD. *Pediatrics* **140**(5).
Yue C, Wei R & Liu Y (2017) Perioperative systemic steroid for rapid recovery in total knee and hip arthroplasty: a systematic review and meta-analysis of randomized trials. *J Orthop Surg Res* **12**(1): 100.
Yuhara H, Corley DA, Nakahara F et al (2014) Aspirin and non-aspirin NSAIDs increase risk of colonic diverticular bleeding: a systematic review and meta-analysis. *J Gastroenterol* **49**(6): 992–1000.
Zacher J, Altman R, Bellamy N et al (2008) Topical diclofenac and its role in pain and inflammation: an evidence-based review. *Curr Med Res Opin* **24**(4): 925–50.
Zaman B, Hojjati Ashrafi S, Seyed Siamdoust S et al (2017) The Effect of Ketamine and Dexamethasone in Combination with Lidocaine on the Onset and Duration of Axillary Block in Hand and Forearm Soft Tissue Surgery. *Anesth Pain Med* **7**(5): e15570.
Zaric D, Nydahl PA, Adel SO et al (1996) The effect of continuous epidural infusion of ropivacaine (0.1%, 0.2% and 0.3%) on nerve conduction velocity and postural control in volunteers. *Acta Anaesthesiol Scand* **40**(3): 342–49.
Zeiler FA, Teitelbaum J, West M et al (2014) The ketamine effect on intracranial pressure in nontraumatic neurological illness. *J Crit Care* **29**(6): 1096–106.
Zeng C, Li YS, Wei J et al (2016) Analgesic effect and safety of single-dose intra-articular magnesium after arthroscopic surgery: a systematic review and meta-analysis. *Sci Rep* **6**: 38024.
Zeng X, Jiang J, Yang L et al (2017) Epidural Dexmedetomidine Reduces the Requirement of Propofol during Total Intravenous Anaesthesia and Improves Analgesia after Surgery in Patients undergoing Open Thoracic Surgery. *Sci Rep* **7**(1): 3992.
Zhang C, Li C, Pirrone M et al (2016) Comparison of Dexmedetomidine and Clonidine as Adjuvants to Local Anesthetics for Intrathecal Anesthesia: A Meta-Analysis of Randomized Controlled Trials. *J Clin Pharmacol* **56**(7): 827-34.
Zhang J, Ding EL & Song Y (2006) Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. *JAMA* **296**(13): 1619–32.
Zhang J, Li X, Gao Y et al (2013) Effects of puerarin on the inflammatory role of burn-related procedural pain mediated by P2X(7) receptors. *Burns* **39**(4): 610–18.
Zhang X, Donnan PT, Bell S et al (2017a) Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis. *BMC Nephrology* **18**(1): 256.
Zhang X, Wang D, Shi M et al (2017b) Efficacy and Safety of Dexmedetomidine as an Adjuvant in Epidural Analgesia and Anesthesia: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Clin Drug Investig* **37**(4): 343-54.
Zhang Y, Qin QR & Hui LT (2018) Motor blocks and operative deliveries with ropivacaine and fentanyl for labor epidural analgesia: A meta-analysis. *J Obstet Gynaecol Res* **44**(12): 2156-65.

Zhang Y, Wang Y & Zhang X (2017c) Effect of pre-emptive pregabalin on pain management in patients undergoing laparoscopic cholecystectomy: A systematic review and meta-analysis. *Int J Surg* **44**: 122-27.
Zhao J, Wang Y & Wang D (2018) The Effect of Ketamine Infusion in the Treatment of Complex Regional Pain Syndrome: a Systemic Review and Meta-analysis. *Curr Pain Headache Rep* **22**(2): 12.
Zhao SZ, Chung F, Hanna DB et al (2004) Dose-response relationship between opioid use and adverse effects after ambulatory surgery. *J Pain Symptom Manage* **28**(1): 35–46.
Zhong HY, Yang ZY, Zhang W et al (2020) Effects of Adding Oxycodone to Ropivacaine on Labor Analgesia: A Randomized Controlled Trial. *Clin J Pain* **36**(2): 96-100.
Zhou G, Ma L, Jing J et al (2018) A meta-analysis of dexamethasone for pain management in patients with total knee arthroplasty. *Medicine (Baltimore)* **97**(35): e11753.
Zhou HY, Chen SR & Pan HL (2011) Targeting N-methyl-D-aspartate receptors for treatment of neuropathic pain. *Expert Rev Clin Pharmacol* **4**(3): 379–88.
Zhou M, Chen N, He L et al (2017) Oxcarbazepine for neuropathic pain. *Cochrane Database Syst Rev* **12**: CD007963.
Zhu J, Xie H, Zhang L et al (2018a) Efficiency and safety of ketamine for pain relief after laparoscopic cholecystectomy: A meta-analysis from randomized controlled trials. *Int J Surg* **49**: 1-9.
Zhu M, Liang R, Pan LH et al (2013) Zoledronate for metastatic bone disease and pain: a meta-analysis of randomized clinical trials. *Pain Med* **14**(2): 257–64.
Zhu Y, Yao R, Li Y et al (2018b) Protective Effect of Celecoxib on Early Postoperative Cognitive Dysfunction in Geriatric Patients. *Front Neurol* **9**: 633.
Zink W & Graf BM (2004) Local anesthetic myotoxicity. *Reg Anesth Pain Med* **29**(4): 333-40.
Zohar E, Luban I, Zunser I et al (2002) Patient-controlled bupivacaine wound instillation following cesarean section: the lack of efficacy of adjuvant ketamine. *J Clin Anesth* **14**(7): 505–11.
Zollner C, Mousa S, Klinger A et al (2008) Topical fentanyl in a randomized, double-blind study in patients with corneal damage. *Clin J Pain* **24**(8): 690–96.
Zou Z, An MM, Xie Q et al (2016) Single dose intra-articular morphine for pain control after knee arthroscopy. *Cochrane Database Syst Rev*(5): Cd008918.
Zou Z, Jiang Y, Xiao M et al (2014) The impact of prophylactic dexamethasone on nausea and vomiting after thyroidectomy: a systematic review and meta-analysis. *PLoS One* **9**(10): e109582.
Zuehl AR (2018) Continuous intrathecal morphine infusion for pain management in a patient with burn injury. *Burns Open* **2**(4): 213-16.
Zuurman L, Roy C, Schoemaker RC et al (2008) Effect of intrapulmonary tetrahydrocannabinol administration in humans. *J Psychopharmacol* **22**(7): 707–16.
Zwisler ST, Enggaard TP, Mikkelsen S et al (2010) Impact of the CYP2D6 genotype on post-operative intravenous oxycodone analgesia. *Acta Anaesthesiol Scand* **54**(2): 232–40.