9

Other specific patient groups

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9.1 | The pregnant patient

9.1.1 | Management of acute pain during pregnancy

Pregnant women with pain that is severe enough to need pharmacological treatment (over the counter or by prescription) represent a challenging group as medications given to them almost always cross the placenta. While most medications are safe, there are particular times of concern, notably the period of organogenesis (wk 4 to 10) and just before birth. Where possible, nonpharmacological treatment options should be considered before analgesic medications are used. Most of the data reported in this setting are from episodes of prolonged use (eg for chronic conditions) and there is a lack of data on the risk of short-term exposure such as in the treatment of acute pain during pregnancy. Ongoing analgesic use requires close liaison between the pregnant woman, the health professional managing the pregnancy, and the health professional managing the pain.

9.1.1.1 | Medications used in pregnancy

Studies of analgesic use during pregnancy are often confounded by the indication (the condition the analgesic was being taken for may alter birth and childhood outcomes), recall bias and the lack of an active comparator. This is evident in various cohort studies discussed below that have explored the associations of analgesic medication use and different pregnancy or birth outcomes and childhood issues and results should be interpreted with caution.

Medication use during pregnancy is common and the data on which to make clear statements about fetal risk is limited (Daw 2011 **Level IV SR**, 17 studies, n unspecified; Lupattelli 2014 **Level IV**, n=9,459; Black 2019 **NR**; Price 2017 **NR**). Medications that may be prescribed during pregnancy have been categorised according to fetal risk by the TGA (TGA 2011 **GL**) in Australia, and the same categories are used in New Zealand (Medsafe 2013 **GL**). The categories used are listed in Table 9.1. It is important to note that the system is not hierarchical and that medications in Category B are not necessarily safer than those in Category C. The classification of some of the medications that might be used in pain management is summarised in Table 9.2. A list of these medications, including regular updates, is maintained by the TGA (TGA 2020 **GL**) .

The United States has moved away from a '*letter based*' categorisation of medication safety in pregnancy to providing a description of risk about individual agents that providers can then use to discuss risk with their patients (FDA 2014 **GL**).

Paracetamol

Paracetamol is classed a Category A medication by the TGA and is regarded as the analgesic of choice during pregnancy (Bisson 2019 **GL**) as no increased prevalence of congenital anomalies has been reported with its use (Rebordosa 2008 **Level III-3**; Scialli 2010 **NR**).

There was also no association of paracetamol with an increased risk of spontaneous abortion (OR 1.2; 95%CI 0.8 to 1.8) (Li 2003 **Level III-2**). However, it has been suggested that its potential influence on prostaglandin synthesis may have adverse effects in women at high risk of pre-eclampsia (Sahlman 2019 **Level III-2**, n=2,508; Zelop 2008 **NR**). A yet to be replicated Danish cohort study suggested an increased risk of preterm birth following paracetamol exposure in early pregnancy in mothers with pre-eclampsia (OR 1.55; 95%CI 1.16 to 2.07), but not in women without pre-eclampsia (OR 1.08; 95%CI 0.97 to 1.20) (Rebordosa 2009 **Level III-3**, n=98,140).

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Childhood asthma

Paracetamol exposure has also been examined as a potential contributor to the increasing prevalence of childhood asthma, although there are likely multiple confounders. Plausibility is related to the potential for paracetamol to cause depletion of glutathione, an airway antioxidant. In observational cohort studies any paracetamol use during the first trimester was associated with an increased risk of childhood asthma (pooled OR 1.39; 95%CI 1.01 to 1.91) (5 studies) (Cheelo 2015 **Level III-2 SR**, 11 studies, n=3,663,454). However, there was marked between-study heterogeneity (I^2=63%) and only one of the studies adjusted for maternal respiratory tract infections. The association was weakened when adjustments for a range of factors, including respiratory infections was made.

Cryptorchidism

Association between paracetamol exposure in utero and cryptorchidism has been of interest due to the potential for paracetamol to act as an endocrine disrupter. A systematic review finds little evidence for an association between 'ever' use of analgesia and risk of cryptorchidism (pooled crude OR 1.11; 95%CI 1.00 to 1.23), including when separated into subgroups of case-control studies (OR 1.23; 95%CI 0.85 to 1.78) or cohort studies (OR 1.09; 95%CI 0.97 to 1.22) (Gurney 2017 **Level III-2 SR** [PRISMA], 10 Studies, n=501,456). There was a high degree of heterogeneity among studies.

Other childhood issues

Cohort studies have identified weak associations between intrauterine exposure to paracetamol and other childhood issues including neurodevelopmental conditions such as ADHD and ASD (for details see section 10.4.1).

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.

Overall there is insufficient evidence to warrant changing guidelines on early life paracetamol exposure at this time.

Nonsteroidal anti-inflammatory drugs

Nonselective NSAIDs and coxibs are Category C medications, except celecoxib which is Category B3.

Spontaneous abortion

Exposure to an nsNSAID or coxib was not identified as an independent risk factor for spontaneous abortion (Daniel 2014 **Level III-2**, n=65,457 [n=4,495 exposed to NSAIDs]). There was an increased risk with indomethacin found (aHR 2.8; 95%CI 1.70 to 4.69), but the authors warn that this is possibly due to reverse causation bias, as indomethacin is a tocolytic medication used in preterm labour. This is supported by the finding that the association with indomethacin use disappeared when omitting all indomethacin use during the last four d before the spontaneous abortion. The same authors found in a further analysis of the same database associations of spontaneous abortion with use of nsNSAIDs in general, and specifically for diclofenac and indomethacin, which disappear again when exposures occurring on the day before the spontaneous abortion for nsNSAIDs and when exposures in the last week for indomethacin are excluded (Daniel 2015 **Level III-2**, n=65,457 [n=4,495 exposed to NSAIDs]). The authors regard these results as confirmation of an indication bias of these findings.

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Congenital malformations

Intrauterine exposure to nsNSAIDs was not associated with increased risk for major congenital malformations (Daniel 2012 **Level III-2**, n=110,783 [n=5,267 exposed to NSAIDs]). This was also confirmed in another smaller study (Van Marter 2013 **Level III-3**, n=1,213) and four older cohort studies (Bloor 2013 **NR**). Major congenital malformations, structural heart defects and infant survival did not differ in offspring of women who took one of four different nsNSAIDs (ibuprofen, diclofenac, naproxen and piroxicam) during early pregnancy vs controls (Nezvalová-Henriksen 2013 **Level III-2**, n= 90,417 [n=6,511 exposed to NSAIDs]). The use in the second trimester of ibuprofen (aOR 1.7; 95%CI 1.3 to 2.3) or diclofenac (aOR 3.1; 95%CI 1.1 to 9.0) was associated with low birth weight, possibly related to maternal inflammatory conditions.

A cohort study of 174 women who took coxibs in the first trimester of pregnancy did not find a significantly increased risk of birth defects in their offspring (2.9% vs. 2.7%) (Dathe 2018 **Level III-2**, n=174).

While relatively safe to use in early and mid-pregnancy, NSAIDs can precipitate fetal cardiac and renal complications in late pregnancy, as well as interfere with fetal brain development and the production of amniotic fluid and thus should be discontinued from gestational wk 32 (Bloor 2013 **NR**).

Other neonatal and childhood issues

Fetal exposure to NSAIDs has been associated with persistent pulmonary hypertension in the newborn in one study (Alano 2001 **Level III-2**, n=40 [cases] vs n=61 [controls]), but not another (Van Marter 2013 **Level III-2**, n=377 [cases] vs n=836 [controls]). In the third trimester, associations between NSAID use and renal injury, oligohydramnios, necrotising enterocolitis and intracranial hemorrhage have also been reported (Bloor 2013 **NR**); the incidence may be increased with exposure occurring closer to delivery.

There is also an increased risk of premature closure of the ductus arteriosus (OR 15.04; 95%CI 3.29 to 68.68) (Koren 2006 **Level I** [Cochrane], 8 RCTs, n=438).

Ibuprofen use in the second (aOR 1.5; 95%CI 1.2 to 1.9) and third trimesters (aOR 1.5; 95%CI 1.1 to 2.1) was also associated with asthma in 18 mth old children (Nezvalová-Henriksen 2013 **Level III-2**, n= 90,417 [n=6,511 exposed to NSAIDs]).

One observational study showed an increased association between maternal aspirin use during pregnancy and the development of psychotic symptoms during adolescence (Gunawardana 2011 **Level III-3**, n=6,437]). However, this association may be related to the presence of maternal indications, for which the aspirin is taken, rather than the aspirin itself being causative itself (Khandaker 2013 **Level III-2 SR**, 21 studies, n unspecified)**.**

Conventional Opioids

Large increases in the use of prescription opioids in Western countries has been reflected in women of child bearing age and is a major public health concern affecting pregnant women and their infants (Lind 2017 **Level III-2 SR**, 68 studies, n unspecified; Yazdy 2015 **NR**). Rates of opioid use in Australia and New Zealand are possibly less than those seen in North America. One Australian study estimated that 1% of pregnant women took prescription opioids in a two-week period (Miller 2019 **Level III-2,** n=192,617 [pregnant patients] vs n=5,448,771 [controls]). In comparison, a Canadian cohort (studied between 2001 and 2013) where opioid use was 6.7 % before pregnancy, reducing to 4.2%, 3.0% and 2.4% in first, second and third trimesters respectively (Falk 2017 **Level III-2**, n=174,848).

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Congenital malformations

The risk of congenital malformation related to opioid exposure in early pregnancy is difficult to clarify due to these being rare events and bias due to inaccurate self-reporting about opioid use (Yazdy 2015 **NR**).

Data from the long running US National Birth Defects Prevention Study (1997-2011) was used to calculate an adjusted odds ratios for risk of a range of birth defects in offspring exposed in the periconceptual period to paracetamol, NSAID or opioid (Interrante 2017 **Level III-2**, n=29,078 [treated patients] vs n=10,962 [controls]). In utero opioid exposure (n=196 [treated patients] vs n=110 [controls]) was associated with tetralogy of Fallot, perimembranous ventricular septal defect and atrio-ventricular septal defect (aOR range 1.8 to 2.3), whereas the use of both opioids and NSAIDs (n=191 and n=86) was associated with gastroschisis, cleft palate, spina bifida, hypoplastic left heart syndrome, and pulmonary valve stenosis (aOR range 2.0 to 2.9). It was not possible to tell whether the effects were due to the drug or confounding due to the condition for which the drug was taken.

The impact of periconceptual opioid exposure for all indications on the risk of neural tube defects was studied in a well-designed case control study. This found an overall increased risk vs non-malformed controls (aOR 2.2; 95%CI 1.2 to 4.2) and malformed controls (aOR 1.9; 95%CI 1.0 to 3.4) (Yazdy 2013 **Level III-2**, n=305 [cases] vs 7,125 [non-malformed controls] vs 13,405 [malformed controls]). When opioids were used for pain control, the most common indication reported, there was no significant increase in neural tube defects.

A systematic review of the risk of teratogenic effects with opioid exposure in utero analysed 30 studies where statistical analysis was presented (Lind 2017 **Level III-2 SR**, 68 studies, n unspecified). Seventeen of these 30 studies (10 of 12 case control studies and 7 of 18 cohort studies) found positive associations for a range of congenital malformations, with the most common being for orofacial clefts, ventricular or atrial septal defects and, for the cohort studies, club foot. The authors noted few of these studies were of high quality, and many had been performed before 1999, and could not differentiate between groups taking opioids for substance use disorder vs chronic pain.

Neonatal abstinence syndrome

Neonates exposed to regular opioid in utero, particularly in the last three mth of pregnancy, are at risk of neonatal abstinence syndrome (NAS) and should be monitored for it after delivery. A population based USA cohort study reported the risk of NAS in infants born to women prescribed opioids during pregnancy (Desai 2015 **Level III-2**, n=290,605 [1,705 cases of NAS]). The absolute risk was low (0.59%; 95%CI 0.56 to 0.62). Both the duration (cumulative dose) and timing (later use; in the 90 d prior to birth) increased the risk. Maternal history of opioid misuse or dependence, alcohol, psychoactive medication use or smoking were also associated with increased risk of NAS. Long-term known opioid misuse had higher absolute risk 22% (95%CI 20 to 24%) vs short-term known misuse (19%; 95%CI 18 to 21%).

The longer term impact of NAS is of concern but clouded by the complexity of the effects of medication, small sample sizes and lack of control for confounding variables such as poverty and maternal psychopathology (Conradt 2018 **NR**).

Other issues are the lack of appropriate tools for its assessment and the lack of early recognition of NAS symptoms resulting in possible underreporting and, as a consequence, inappropriate and too early neonatal discharge from hospital (Wolff 2014 **NR**). Guidelines for the management of NAS have been published (Wiles 2014 **GL**).

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Other neonatal issues

Preterm infants, prenatally exposed to opioids, had increased rates of intermittent hypoxaemia (defined as episodes with SpO_2<80% on continuous pulse oximetry), which persisted beyond the immediate postnatal period (Abu Jawdeh 2017 **Level III-2**, n=14 [exposed] vs n=68 [unexposed]).

A small study suggested that neonatal outcome was better in mothers receiving opioids for chronic pain rather than addiction, although differences in dose and other environmental factors may contribute (Sharpe 2004 **Level III-2**, n=43), but minimising the use of opioid therapy for chronic pain during pregnancy has been recommended (Chou 2009 **GL**).

Neurodevelopmental outcomes

Neurodevelopmental abnormalities resulting from opioid exposure are mechanistically plausible due to multiple effects of opioids on maternal and fetal physiology, as well as direct receptor mechanisms; potential confounders such as psychosocial issues leading to childhood deprivation must also be considered. A pilot study suggested that on MRI scans that brain volumes of opioid-exposed babies may be smaller than controls, in particular in specific regions such as basal ganglia (Yuan 2014 **Level IV**, n=16). Cognitive outcomes of children exposed to opioids in utero have been described, showing marked developmental functional impairments vs non-exposed children (Farid 2008 **NR**; Winklbaur 2008 **NR**).

However, a systematic review found no significant impairments for cognitive, psychomotor or observed behavioural outcomes after chronic intrauterine opioid exposure in infants (4 studies, n=423) and preschool children (3 studies, n=455) vs non-exposed controls (Baldacchino 2014 **Level III-2 SR** [PRISMA], 5 studies, n unspecified). There were significant limitations of this systematic review (small number of studies analysed, heterogeneous populations, small numbers within the individual studies).

The school age academic performance (NAPLAN testing) of Australian grade 3, 5 and 7 children (assessed from year 2000 to 2006) who had suffered neonatal abstinence syndrome (NAS) (n=2,234) vs a matched control cohort (n=4,330) and population results (n=598,265) found significantly poorer outcomes in NAPLAN testing (Oei 2017 **Level III-2**). The risk of not meeting minimum NAPLAN test result standards was independently associated with a history of NAS (aOR 2.5; 95%CI 2.2 to 2.7).

Beside impairment of general cognitive abilities, children exposed to heroin prenatally show problems in several behavioural areas, in particular with regard to attention, when assessed by parents and teachers at 4.5 and 8.5 y of age, but these are not specific and not more severe than the effect on cognitive function (Nygaard 2016 **Level III-2**, n=72 [exposed] vs 58 [not exposed]).

For the management of acute pain in pregnant patients with an addiction see Section 9.8.9 below.

Atypical Opioids

Among women identified from the Swedish Medical Birth Register 1997 to 2013, 1,751 mothers (n=1,776 infants) had used tramadol and 96 of the infants had a congenital malformation (Kallen 2015 **Level III-2,** n=1,682,846 [mothers]; n=1,797,678 [infants]). Tramadol was associated with increased odds ratios for cardiovascular defects (OR 1.56; 95%CI 1.04 to 2.29) and for pes equinovarus (club foot) (OR 3.63; 95%CI 1.61 to 6.89).

Alpha-2-delta ligands

Evidence regarding the effects of exposure to alpha-2-delta ligands in utero remains scant. While registries of antiepileptic drug and pregnancy outcomes were established in different countries ≈15 y ago, gabapentin and pregabalin have been used relatively rarely vs other antileptic agents and no relevant outcomes could be reported for the two medications (Veroniki 2017 **Level III-2 SR**, 29 studies, n=5,100).

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Data on gabapentin use in pregnancy suggest its safety currently, although the number of documented exposures is small (Guttuso 2014 **Level IV SR**, 6 studies & 2 case reports, n=294 [gabapentin exposures in first trimester]). The rate of congenital malformations (1.7%) was not different from the rate in comparable general populations (1.6 to 2.2%). There were also equivalent rates of premature birth (including maternal hypertension/eclampsia premature birth) and similar birth weight after correction for gestational age at delivery with gabapentin use vs the general population (n=261). Based on similarly small numbers in another study, gabapentin exposure was not associated with increased rates of small for gestational age infants (aOR] 2.03; 95%CI 0.68 to 6.01), low birth weight (aOR 1.86; 95%CI 0.56 to 6.15) or preterm delivery (aOR 1.214; 95%CI 0.501 to 2.946) (Wade 2015 **Level III-2**, n=53 [gabapentin exposures]). In contrast, another cohort study revealed no increased rate of malformations, but a higher rate of preterm births and birth weight <2,500 g in the gabapentin group (Fujii 2013 **Level III-2**, n=223 [gabapentin exposures] vs n=223 [unexposed controls]).

Of 477 infants exposed to pregabalin during the first trimester, 5.9% had congenital malformations vs 3.3% in non-exposed infants (RR 1.80; 95%CI 1.26 to 2.58). However, propensity score adjustment suggested no teratogenic effect of pregabalin (aOR 1.16; 95%CI 0.81 to 1.67), confirmed by analysis of a second database (n=174 [exposed to pregabalin]) (aRR 1.03; 95%CI 0.56 to 1.90) (Patorno 2017 **Level III-2**, n=1,323,432 [pregnancies followed]).

Data from the Medical Birth Registry of Norway showed no increase of congenital malformations with gabapentin (n=39) and pregabalin (n=30), however, based on very low numbers of exposures (Veiby 2014 **Level III-2**, n=2,600 [exposed to any anticonvulsant] vs n=774,012 [unexposed controls]). Similarly, a systematic review examining neurodevelopmental effects from intrauterine exposure to anticonvulsants could not provide information on gabapentin or pregabalin due to too few exposures (Bromley 2014 **Level III-2 SR** [Cochrane], 28 studies [22 prospective cohort, 6 registry-based studies], n unspecified).

Withdrawal syndromes can occur in neonates exposed during pregnancy to gabapentin (combined with other substances), with re-introduction of gabapentin being a suggested treatment for this syndrome (Carrasco 2015 **CR**).

Table 9.1 | TGA medicine categorisation according to fetal risk

A	Medicines which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
B1	Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
B2	Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

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B3	Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
C	Medicines which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
D	Medicines which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These medicines may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
X	Medicines which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Notes: For medicines in the B1, B2 and B3 categories, human data are lacking or inadequate and subcategorisation is therefore based on available animal data. The allocation of a B category does NOT imply greater safety than the C category. Medicines in category D are not absolutely contraindicated in pregnancy (eg anticonvulsants). Moreover, in some cases the 'D' category has been assigned on the basis of "suspicion".

Due to legal considerations in Australia, sponsoring companies have, in some cases, applied a more restrictive category than can be justified on the basis of the available data.

In some cases there may be discrepancies between the published product information and the information in this table due to the process of ongoing document revision.

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Table 9.2 | Categorisation of medicines used in pain management

Medicine	Cat	Comments
Opioids alfentanil, buprenorphine, dextromoramide, dextropropoxyphene, fentanyl, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, phenoperidine, remifentanil, tramadol	C	Opioid analgesics may cause respiratory depression in the newborn. Withdrawal symptoms in newborns have been reported with prolonged use of this class of medicines including tramadol
codeine, dihydrocodeine	A	Prolonged high-dose use of codeine prior to birth may produce codeine withdrawal symptoms in the newborn
Paracetamol	A	
Aspirin	C	Aspirin inhibits prostaglandin synthesis. When given late in pregnancy, it may cause

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Medicine	Cat	Comments
		premature closure of the fetal ductus arteriosus, delay labour and birth. Aspirin increases the bleeding time both in the newborn and in the mother because of its antiplatelet effects. Products containing aspirin should be avoided in the last trimester. Low-dose aspirin (100 mg/d) does not affect bleeding time.
Other nsNSAIDs diclofenac, diflunisal, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, nabumetone, naproxen, phenylbutazone, piroxicam, sodium salicylate, sulindac, tenoxicam, tiaprofenic acid	C	These agents inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation and delayed labour and birth. Continuous treatment with NSAIDs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.
Coxibs celecoxib parecoxib	 B3 C	
Local anaesthetics bupivacaine, cinchocaine, lignocaine (lidocaine), mepivacaine, prilocaine etidocaine, ropivacaine procaine hydrochloride levobupivacaine	 A B1 B2 B3	
Antidepressants *SSRIs:* citalopram, fluoxetine, fluvoxamine, sertraline,	 C	SSRIs have had limited use in pregnancy without a reported increase in birth defects. The use of SSRIs in the third trimester may result in a withdrawal state in the newborn.
paroxetine	D	Category changed Sept 2005
Tricyclic antidepressants: amitriptyline, clomipramine, desipramine, dothiepin (dosulepin), doxepin, imipramine, nortriptyline, protriptyline, trimipramin	 C	Withdrawal symptoms in newborn infants have been reported with prolonged maternal use of this class of medicines.
Other antidepressants:		

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Medicine	Cat	Comments
mirtazapine, moclobemide, nefazodone, duloxetine venlafaxine, desvenlafaxine	B3 B2	
Anticonvulsants carbamazepine	D	Spina bifida occurs in about 1% of pregnancies in which carbamazepine is used as monotherapy. Carbamazepine taken during pregnancy also has been associated with minor craniofacial defects, fingernail hypoplasia and developmental disability. Carbamazepine also can cause coagulation defects with consequent risk of haemorrhage in the fetus and the newborn, which may be preventable by the prophylactic administration of vitamin K to the mother prior to the birth.
phenytoin sodium	D	This medicine taken during pregnancy has been associated with craniofacial defects, fingernail hypoplasia, developmental disability, growth retardation and, less frequently, oral clefts and cardiac anomalies. This clinical pattern is sometimes called the “fetal hydantoin syndrome”. Phenytoin can also cause coagulation defects with consequent risk of haemorrhage in the fetus and the newborn, which may be preventable by the prophylactic administration of vitamin K to the mother prior to the birth.
sodium valproate	D	Sodium valproate is contraindicated in pregnancy. A broad range of congenital malformations can occur in babies born to women who take sodium valproate during pregnancy, and the risk of malformations increases with increasing dose of valproate. If taken in the first trimester of pregnancy, sodium valproate (valproic acid) is associated with a one to two percent risk of neural tube defects (especially spina bifida) in the exposed fetus. Sodium valproate should not be used during pregnancy and in women of child-bearing potential unless alternative treatments are ineffective or not tolerated because of the high risk of malformation and risk of developmental disorders in infants exposed to valproate before birth. Avoid use of valproate in women of child-bearing age for all non-

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Medicine	Cat	Comments
		seizure indications. For seizure indications, consider alternatives if they exist. Always use the lowest effective dose. Patients and prescribers should reconsider benefit and risk at regular treatment reviews, at puberty and urgently when a woman of child-bearing potential treated with valproate plans a pregnancy or becomes pregnant. Folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception; specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.
lamotrigine	D	Category changed June 2006
clonazepam	C	Clonazepam is a benzodiazepine. These medicines may cause hypotonia, respiratory depression and hypothermia in the newborn if used in high doses during labour. Withdrawal symptoms in newborns have been reported with this class of medicines.
gabapentin,	B1	Used for neuropathic pain
tiagabine, topiramate, pregabalin	B3	
Lamotrigine Levetiracetam	D B3	Anticonvulsants for partial complex seizures, possibly mood stabilising and antineuropathic
Antiemetics, antinauseants *Phenothiazines:* prochlorperazine, promethazine, thiethylperazine	C	When given in high doses during late pregnancy, phenothiazines have caused prolonged neurological disturbances in the infant.
Others: dimenhydrinate, diphenhydramine, metoclopramide	A	
dolasetron, granisetron, ondansetron	B1	
domperidone, hyoscine, hyoscine hydrobromide	B2	
tropisetron	B3	

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KEY MESSAGES

1. Short-term use of NSAIDs in late pregnancy is associated with an increase in the risk of premature closure of the ductus arteriosus (**U**) (**Level I** [Cochrane Review]).
2. The chronic use of opioids during pregnancy may be associated with some teratogenic effects, childhood neurocognitive delay and/or negative neurobehavioural outcomes; however, it is difficult to separate the influence of multiple confounders in this patient group (**Q**) (**Level III-2 SR**).
3. Retrospective epidemiological studies linking paracetamol use in pregnancy to later development of childhood asthma are inherently confounded (**U**); when adjusted for respiratory tract infections in the child the association is lost (**Q**) (**Level III-2 SR**).
4. The use of common nsNSAIDS during pregnancy is not associated with increased risk of major congenital malformations, structural heart defects or difference in infant survival (**N**) (**Level III-2**).
5. Exposure to an nsNSAID or coxib is not an independent risk factor for spontaneous abortion (**Q**) (**Level III-2**)
6. The safety of alpha-2-delta ligand use in pregnancy remains unclear; limited data has not raised safety concerns (**N**) (**Level III-2**).

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

☑ For pain management in pregnancy, nonpharmacological treatment options should be considered where possible before analgesic medications are used (**U**).

☑ Use of medications for pain in pregnancy should be guided by published recommendations; ongoing analgesic use requires close liaison between the patient, the health professional managing the pregnancy and the health professional managing the pain (**U**).

☑ Most of the data reported in this setting are from episodes of prolonged use (eg for chronic conditions) and there is a lack of data on the risk of short-term exposure such as in the treatment of acute pain (**N**).

☑ Studies of analgesic use during pregnancy may be confounded by the indication, recall bias and often the lack of an active comparator; this is exemplified by reported associations between NSAID use in pregnancy and low birth weight and asthma confounded by the maternal indications for their use (ie inflammatory diseases) (**N**).

☑ Nonselective NSAIDs and Coxibs should be used with caution in the last trimester of pregnancy and should be avoided after the 32nd week (**U**).

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

☑ Neonates exposed to regular opioid in utero, particularly in the last three months of pregnancy, are at risk of neonatal abstinence syndrome and should be monitored for it after delivery (**N**).

9.1.2 | Pain syndromes in pregnancy

9.1.2.1 | Musculoskeletal pain syndromes

Low back pain (LBP) or pelvic girdle pain (PGP) alone or in combination are common during pregnancy (Casagrande 2015 **NR**). Low back pain in pregnancy refers to pain in the lumbar spine without radicular component or pain reproduced with repeated range of motion activity. Pelvic girdle pain is experienced between the posterior iliac crest and the gluteal fold, particularly in the vicinity of the sacroiliac joint, may radiate to the posterior thigh or be perceived in the pubic symphysis (Vleeming 2008 **GL**). The endurance capacity for standing, walking and sitting is diminished. The pattern may change during the course of pregnancy and following delivery with 76% of women reporting some form of back or pelvic pain during singleton pregnancy (Weis 2018 **Level IV**, n=287). Point and period prevalence were respectively 15.7%/17.8% for LBP, 15.3%/33.4% for PGP and 27.9%/30.7% for the combination.

Risk factors for pelvic pain during pregnancy include previous LBP and pelvic trauma (Elden 2016 **Level IV**, n=371). The group with pre-existing pain may present a more complex picture that may be more resistant to interventions, although studies do not always examine this group separately. Recommendations to improve the consistency of reporting in research using a Core Outcome Set for PGP have been proposed (Wuytack 2018 **GL**).

Exercise

A Cochrane review of interventions to prevent or reduce pain severity, functional disability or absenteeism (in addition to usual prenatal care) examined 15 RCTs in LBP, 6 RCTs in PGP and 13 RCTs in LBP/PGP combination (Liddle 2015 **Level I** [Cochrane], 34 RCTs, n=5,121). For women with pregnancy related LBP, comparing land-based exercise with usual care provides low quality evidence for exercise leading to reduced LBP and disability (SMD -0.64; 95%CI -1.03 to -0.25) (7 RCTs, n=645). For PGP alone, low quality evidence shows no significant difference in the number of women reporting pain when comparing exercise with information about pain management and usual prenatal care (RR 0.97; 95%CI 0.77 to 1.23) (2 RCTs, n=374). For combined LBP and PGP, there was moderate quality evidence for reduced pain and related sick leave after participation in a 12 wk program of land-based exercise in various formats (RR 0.76; 95%CI 0.62 to 0.94) (4 RCTs, n=1,062).

Two further systematic reviews investigated the preventive beneficial effect of exercise. The first assessed prenatal exercise impact on LBP, PGP and lumbopelvic pain (Davenport 2019 **Level III-3 SR**, 23 RCTs & 9 studies, n=52,297) (13 RCTs overlap with Liddle 2015). Prenatal exercise does not reduce the incidence of these conditions (13 RCTs), either in pregnancy or the postpartum period, but exercise in pregnancy is associated with lower pain severity during pregnancy and the early postpartum period vs non-exercisers (SMD -1.03; 95%CI -1.58 to -0.48) (15 RCTs). Exercise in pregnancy reduces the risk of LBP in pregnancy by 9% (RR 0.91; 95%CI 0.83 to 0.99) (7 RCTs, n=1,175), whereas it has no protective effect on PGP (RR 0.99; 95%CI 0.81 to 1.21) (4 RCTs, n=565) or lumbopelvic pain (RR 0.96; 95%CI 0.90 to 1.02) (8 RCTs, n=1,737) (Shiri 2018 **Level I** [PRISMA], 11 RCTs, n=2,347) (7 RCTs overlap with Liddle 2015 and 9 RCTs overlap with Davenport 2019). However, exercise prevented new episodes of sick leave due to lumbopelvic pain (RR 0.79; 95%CI 0.64 to 0.99) (3 RCTs, n=1,168).

In a cohort prevention intervention study, not included in the above systematic reviews, women who undertook high impact exercise 3 to 5 times per wk had a lower risk of developing PGP in pregnancy vs non-exercisers (RR 0.86; 95%CI 0.77 to 0.96) (Owe 2016 **Level III-2**, n=39,184).

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Manual therapies

Manual therapy interventions (including craniosacral therapy, osteopathic manipulative treatment, chiropractic interventions, massage and partner-delivered massage) reduce the intensity of pregnancy-related back and pelvic pain vs usual care and relaxation, but not to sham interventions (Hall 2016 **Level I** [PRISMA], 10 RCTs, n=1,198).

Pelvic belts

Use of a soft vs rigid pelvic belt was examined in two small non-blinded RCTs, with no non-treatment arm. There was no difference in function but pain was reduced vs the previous 24 h (Flack 2015 **Level II**, n=20, JS 2). Combining data from both groups, function and pain were improved at three wks (MD -2.3/10; 95%CI -1.2 to -3.5). In de novo PGP, two different pelvic support belts were well tolerated and reduced pain intensity by 20/100 (Bertuit 2018 **Level II**, n=46, JS 2).

Magnesium

Oral magnesium therapy did not reduce the frequency or severity of painful leg cramps during pregnancy (Nygaard 2008 **Level II**, n=45, JS 2).

9.1.2.2 | Meralgia paraesthetica and other compressive neuropathies

These variable conditions comprise some or all of the sensations of pain, tingling and numbness in the lateral thigh affects pregnant women more than a nonpregnant population (OR 12.0; 95%CI 1.2 to 118.0) (van Slobbe 2004 **Level III-2**). Multiple therapies have been reported but have not been fully evaluated or compared, including ice packs, local infiltration with steroid and local anaesthetic, topical lignocaine or capsaicin, TENS, pharmacological therapy (TCAs, antiepileptics) and surgical intervention (Harney 2007 **NR**; Van Diver 1995 **NR**). Other compressive neuropathies, such as carpal tunnel syndrome and Bell's palsy, also occur more commonly during pregnancy (Sax 2006 **NR**).

9.1.2.3 | Diastasis symphysis pubis

Diastasis of the symphysis pubis is defined as the separation of the pubic bones. It may occur during pregnancy, and following either operative or non-operative delivery. This occasionally disabling disorder (sometimes also called osteitis pubis or diastasis pubis) has a quoted incidence of 1:600 (Taylor 1986 **Level IV**) and can produce persistent pain; but there are limited data to inform management (Aslan 2007 **NR**).

Severe traumatic separation is rare and is heralded by a sensation of the separation occurring, associated with severe pain and swelling at the pubic symphysis. Evidence regarding management is from case series (Urraca-Gesto 2015 **Level IV SR**, 4 studies & 14 case reports, n=47 [diastasis symphysis pubis]; Chawla 2017 **Level IV**, n=2). Recommended management often initially includes lateral decubitus bed rest with a pelvic girdle and analgesia followed by mobilisation and physiotherapy to reinstate mobility. Rarely surgery is required for cases that do not resolve with spontaneous treatment (Buitendyk 2018 **CR**).

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KEY MESSAGES

1. Exercise reduces low back and pelvic girdle pain during pregnancy (**S**) (**Level I** [Cochrane Review]).
2. Manual therapy interventions reduce intensity of pregnancy-related back and pelvic pain versus usual care and relaxation, but not to sham interventions (**N**) (**Level I** [PRISMA])

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

☑ The use of a pelvic support belt may reduce pelvic girdle pain during pregnancy (**N**).

9.1.3 | Management of acute pain during labour and after birth

Pain during labour and birth represents a complex interaction of multiple physiological and psychological factors involved in parturition. Women's desires for and expectations of pain relief during labour and delivery vary widely. High-quality pain relief does not necessarily equate with a high level of satisfaction. Non-analgesic interventions (eg support person during labour or education) can provide a significant improvement in satisfaction with the experience of labour and childbirth (Taheri 2018 **Level I** [PRISMA], 20 RCTs, n=22,800).

Severe pain during labour is one of several factors associated with post-traumatic stress symptoms following birth (Slade 2006 **NR**). Personality traits, anxiety and analgesic expectations partially predict labour pain, epidural analgesic consumption and satisfaction (Carvalho 2014 **Level IV**, n=39).

9.1.3.1 | Systemic analgesia in labour pain

Nonopioids

A variety of nonopioids (NSAIDs, paracetamol, antispasmodics, sedatives and antihistamines) have been investigated with regard to their effect in labour pain (Othman 2012 **Level I** [Cochrane], 19 RCTs, n=2,863). Most of these studies are very old (>30 y) and show very limited efficacy vs placebo and inferior efficacy vs opioids. Sedatives may have a limited benefit vs placebo with regard to analgesia and satisfaction. There is insufficient evidence for the effectiveness of nonopioids to manage pain during labour.

However, a few studies subsequent to this review show some efficacy of nonopioids in labour pain. IV paracetamol 1 g and IM tramadol 1 mg/kg provide similar analgesia in labour, but tramadol recipients had a longer first stage of labour and more sedation and nausea (Kaur Makkar 2015 Level II, n=60, JS 1). IV paracetamol 1 g reduced labour pain slightly at 2, 3 and 4 h after injection (Zutshi 2016 **Level II**, n=200, JS 4), but was inferior to IV morphine (Ankumah 2017 **Level II**, n=40, JS 3). As an adjunct to patient-controlled epidural analgesia (PCEA), IV paracetamol 1 g decreased mean epidural infusion rate (7.03 ml/h [0.83] vs 8.12 ml/h [1.34]) and demand bolus requirements (1.0 [0.93] vs 1.43 [SD 0.90]) (Gupta 2016 Level II, n=80, JS 5).

Opioids

Systemic opioids are used in labour, although practice varies, and their use in Australia is declining (21.8% at 2011) (Li 2011 **Level IV**).

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The following conclusions are for healthy women with an uncomplicated pregnancy giving birth at or near term when parenteral opioids were compared to no treatment, placebo, another opioid or TENS (Smith 2018b **Level I** [Cochrane], 61 RCTs, n>8,000):

- Parenteral opioids provide moderate pain relief in labour;
- Maternal satisfaction is variable where reported;
- Opioids cause sedation, nausea and vomiting;
- For most outcomes there was no good quality evidence of differences between treatment groups.

There was insufficient evidence to assess the safety of opioids in labour. The quality of the evidence for pain and pain relief outcomes was predominantly poor or very poor.

Opioid analgesia vs epidural analgesia provides inferior pain relief overall (5 RCTs, n=1,133), with less maternal satisfaction (17 RCTs, n=1,911) (Anim-Somuah 2018 **Level I** [Cochrane], 40 RCTs, n=12,389).

IN or SC fentanyl was preferred by parturients to IM pethidine, when surveyed six wk after birth (Fleet 2017 **Level II**, n=116, JS 2)

Remifentanil intravenous PCA

In comparison to other systemic opioids, remifentanil offers an advantage due to its rapid metabolism. In some countries, remifentanil IV PCA is used for labour analgesia as an alternative to both epidural analgesia and other systemic opioids (Devabhakthuni 2013 **NR**). In the UK, 49% of obstetric wards use IV PCA with remifentanil as the most common agent followed by morphine and fentanyl. In Belgium, 36% of obstetric wards use IV PCA, with remifentanil being the most commonly used opioid (77%).

Remifentanil IV PCA in women with low-risk pregnancies (higher risk groups were excluded) was compared with other forms of parenteral analgesia in labour (Weibel 2017 **Level I** [Cochrane], 19 RCTs, n=3,569):

Satisfaction

- Women receiving remifentanil IV PCA are more satisfied with pain relief than women having other forms of opioids (IV/IM) (SMD 2.11; 95%CI 0.72 to 3.49) (4 RCTs, n=216), but satisfaction is less than for women in the epidural group (SMD 0.22; 95%CI 0.04 to 0.40);

Note: reversal of conclusion
This reverses the Level I key message in the previous edition of this document; preceding RCTs had described remifentanil IV PCA as providing superior satisfaction vs epidural techniques.

Pain relief

- Remifentanil IV PCA vs other opioids administered IV/IM provides better pain relief at 1 h (SMD -1.58/10; 95%CI -2.69 to -0.48);
- Remifentanil IV PCA vs epidural analgesia shows higher pain scores at 1 h (SMD 0.57; 95%CI 0.31 to 0.84) (6 RCTs, n unspecified);

Additional analgesia

- Remifentanil IV PCA lowers the risk of needing additional analgesia vs other opioids (IV/IM) (RR 0.57; 95%CI 0.4 to 0.81), while there is no evidence that remifentanil IV PCA reduces the requirement for additional analgesia vs other opioids via PCA;
- Remifentanil IV PCA is associated with a higher risk of needing rescue analgesia vs epidural analgesia (RR 9.27; 95%CI 3.73 to 28.03) (6 RCTs, n=1,037);

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Adverse events

- Data on adverse events is limited. Low quality evidence demonstrates women receiving remifentanil IV PCA experience more maternal respiratory depression vs epidural analgesia (SMD 0.91; 95%CI 0.51 to 1.62) (3 RCTs, n=687);
- Newborns of mothers receiving remifentanil IV PCA vs epidural analgesia, do not have an increased risk of Apgar scores < 7 at 5 min (5 RCTs, n=1,322).

There is mostly low-quality evidence to inform practice; further work is needed on maternal and fetal safety outcomes (maternal respiratory depression, Apgar score) and on optimal mode and regimen of remifentanil administration (Weibel 2017 **Level I** [Cochrane], 19 RCTs, n=3,569). A concurrent SR, comparing remifentanil IV PCA to epidural analgesia, finds higher pain scores at 1 h (WMD 1.33/10; 95%CI 0.30 to 2.36) and increased rates of hypoxaemia (OR 7.48; 95%CI 3.42 to 16.36); there were no differences at 2 and 3 h for analgesia, satisfaction or adverse effects except for overall reduced rates of pruritus (OR 0.54; 95%CI 0.32 to 0.89) (Lee 2017 **Level I** [PRISMA], 8 RCTs, n=2,351) (7 RCTs overlap).

Parturients having remifentanil IV PCA vs IM pethidine prn had lower pain scores (MD 13.9/100; 95%CI 21.4 to 6.4), lower conversion to epidural analgesia (19 vs 41%) but with a greater frequency of needing supplemental oxygen (41 vs 1%) (Wilson 2018 **Level II**, n= 401, JS 3). Remifentanil IV PCA achieved better median pain relief scores vs inhaled nitrous oxide (N_2O) (2.5/10 vs 0.5) (Volmanen 2005 **Level II**, n=15, JS 3).

As a potent opioid, remifentanil carries the risk of severe maternal respiratory depression (Van De Velde 2016 **NR**; Muchatuta 2013 **NR**). Oxygen desaturation (<90%) is frequent (70% of women studied) even when continuous supplemental oxygen is administered (Messmer 2016 **Level IV**, n=61). A number of respiratory (Bonner 2012 **CR**; Pruefer 2012 **CR**) and even cardiorespiratory arrests (Marr 2013 **CR**) have been reported with its use. Therefore, use of remifentanil IV PCA is only recommended if there is one-on-one continuous presence of a midwife, with both continuous oxygen saturation and cardiotocograph (CTG) monitoring (as an indirect method of detecting global hypoxaemia) (Goudra 2013 **NR**; Muchatuta 2013 **NR**). In view of these risks and the monitoring required, remifentanil IV PCA should not be regarded as an alternative to epidural analgesia based purely on economic considerations or convenience (Kranke 2013 **NR**). Remifentanil IV PCA has been recommended when neuraxial techniques are contraindicated.

9.1.3.2 | Inhalational analgesia

A meta-analysis of inhaled analgesia for pain management in labour compared various volatile agents (flurane derivatives) and N_2O to each other, placebo or no analgesia (Klomp 2012 **Level I** [Cochrane], 26 RCTs, n=2,959). Flurane derivatives (multiple volatiles studied, most recently sevoflurane) provide better pain relief than inhaled N_2O in first stage of labour; they result in lower pain intensity (MD 14.4/100; 95%CI 4.4 to 24.4) (3 RCTs, n=70) and higher pain relief scores (MD -16.3/100; 95%CI -26.9 to -5.8) (2 RCTs, n=70) but cause more drowsiness. Inhaled N_2O causes more nausea vs flurane derivatives (RR 6.60; 95%CI 1.85 to 23.52) (2 RCTs, n=98). However, trial design was often poor including lack of blinding for volatile agents.

Subgroup analysis of inhaled N_2O shows minimal difference in analgesic effect 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 subsequent systematic review confirms some analgesic efficacy in labour, but only two studies were of good quality (Likis 2014, **Level IV SR**, 58 studies, n=20,266) (1 RCT overlap). Inhaled N_2O provides less pain relief than epidural analgesia, but more than pethidine, bathing, showering or acupuncture. Maternal satisfaction with analgesia during their birth experience is heterogeneous and difficult to assess. A majority of women using inhaled N_2O report a positive

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experience (57%), but also report less satisfaction with analgesia (54%) vs epidural analgesia (94%) (Likis 2014, **Level IV SR**, 58 studies, n=20,266). The maternal adverse effects of inhaled N_2O are nausea (RR 43.1; 95%CI 2.6 to 707) (1 RCT, n=509), vomiting (RR 9.1; 95%CI 1.2 to 69) (2 RCTs, n=619), dizziness (RR 114; 95%CI 7.1 to 1,834) (1 RCT, n=509) and drowsiness (RR 77.6; 95%CI 4.8 to 1,255) (1 RCT, n=509) (Klomp 2012 **Level I** [Cochrane], 3 RCTs [N_2O], n=819); the wide confidence interval in the latter two outcomes suggests significant uncertainty in the estimate. Apgar scores are not different for inhaled N_2O vs no analgesia.

9.1.3.3 | Neuraxial analgesia in labour pain

Ultrasound guidance for epidural and intrathecal needle insertion

The use of ultrasound as an aid to improve successful placement of an epidural catheter or intrathecal needle is helpful. It can reduce the risk of failed (RR 0.21; 95%CI 0.10 to 0.43) or traumatic intrathecal needle and epidural catheter positioning (RR 0.27; 95%CI 0.11 to 0.6) and the number of needle insertions and redirections (Shaikh 2013 **Level I** [PRISMA], 14 RCTS, n=1,334)

Epidural analgesia

Epidural analgesia vs systemic opioid analgesia

Epidural analgesia vs opioid analgesia (Anim-Somuah 2018 **Level I** [Cochrane], 40 RCTs, n=12,389 [34 RCTs vs opioids, n=10,440]):

- Provides better pain relief overall (SMD -2.64; 95%CI -4.56 to -0.73) (5 RCTs, n=1,133), with a higher proportion rating their pain relief as 'excellent' or 'very good' (RR 1.47; 95%CI 1.03 to 2.08) (17 RCTs, n=1,911);

Note: reversal of conclusion

This reverses the Level I key message in the previous edition of this document; a preceding meta-analysis had described no difference in maternal satisfaction with epidural analgesia vs systemic opioid analgesia.

- Achieves substantial decreased need for additional analgesia vs opioid analgesia (RR 0.10; 95%CI 0.04 to 0.25) (16 RCTs, n=5,099);
- Achieves lower rate of respiratory depression needing supplemental oxygen administration (RR 0.23; 95%CI 0.05 to 0.97) (5 RCTs, n=2,031);
- Achieves less nausea and/or vomiting (RR 0.62; 95%CI 0.45 to 0.87) (15 RCTs, n=4,440);
- Increases duration of first stage (MD 32.28 min; 95%CI 18.34 to 46.22) (9 RCTs, n=2,259) and second stage of labour (MD 15.4 min; 95%CI 9.0 to 21.8) (16 RCTs, n=4,979);
- May increase oxytocin augmentation (RR 1.12; 95%CI 1.00 to 1.26) (19 RCTs, n=8,351);
- Increases the rate of assisted vaginal delivery (RR 1.44; 95%CI 1.29 to 1.60) (30 RCTs, n= 9,948). However, a post-hoc analysis (assessing only trials after 2005, which used lower concentrations of local anaesthetic) found no increase in assisted vaginal birth (RR 1.19; 95%CI 0.97 to 1.46);
- Does not increase the rate of Caesarean section overall (RR 1.07, 95%CI 0.96 to 1.18) (33 RCTs, n=10,350) or the rate of Caesarean section for fetal distress (RR 1.32, 95%CI 0.97 to 1.79) (12 RCTs, n=5,753);
- Reduces the risk of fetal acidosis (cord pH<7.2) (RR 0.81; 95%CI 0.69 to 0.94) (8 RCTs, n=4,783) and need for naloxone administration to newborns (RR 0.15; 95%CI 0.10 to 0.23) (10 RCTs, n=2,645); with no increase in admission to a special care/neonatal

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intensive care unit (8 RCTs, n=4,488) and no increase in the rate of Apgar score < 7 at 5 min (1 RCT, n=60);
- Does not increase long-term backache (2 RCTs, n=814), headache (4 RCTs, n=1,938), postnatal depression (1 RCTs, n=313) or itching (8 RCTs, n=2,900).

The most common complications caused by epidural analgesia are maternal hypotension (RR 11.34; 95%CI 1.87 to 67.95) (10 RCTs, n=4,212), motor block (RR 31.67; 95%CI 4.16 to 245) (3 RCTs, n=322), urinary retention (RR 14.18; 95%CI 4.52 to 44.45) (4 RCTs, n=343) and maternal fever (RR 2.51; 95%CI 1.67 to 3.77) (9 RCTs, n=4,276) (Anim-Somuah 2018 **Level I** [Cochrane], 40 RCTs, n=12,389).

These Cochrane review results are influenced by substantial heterogeneity for pain relief, maternal satisfaction, need for additional means of pain relief, length of second stage of labour and oxytocin augmentation. This heterogeneity did not seem to relate to subgroup or sensitivity confounders, where data could be analysed. None of these studies reported on the rare, serious adverse effects of epidural analgesia (see Sections 5.6.5.1 to 5.6.5.3). However, despite evidence for safety, in a case series of women before childbirth, 39% expressed concerns about neuraxial analgesia and 46% of 129 women deciding against epidural analgesia did so because of concerns about the technique (Toledo 2013 **Level IV**, n=509). Safety data from the above Cochrane review could help inform pregnant women about these concerns.

Epidural vs no analgesic pharmacological treatment

Epidural analgesia vs no analgesic pharmacological treatment (Anim-Somuah 2018 **Level I** [Cochrane], 40 RCTs, n=12,389 [7 RCTS vs no pharmacological treatment, n=897]):
- Epidural analgesia results in less pain (SMD -9.55; 95%CI -12.91 to -6.19) (2 RCTs, n=120);
- Epidural analgesia achieves a higher proportion rating their satisfaction with pain relief as excellent or very good (RR 1.32, 95%CI 1.05 to 1.65) (1 RCT, n=70);
- Epidural analgesia is associated with a lower Caesarean section rate vs placebo or no treatment (RR 0.46, 95%CI 0.23 to 0.90) (5 RCTs, n=578);
- There are no differences between groups for the following outcomes: nausea and vomiting (2 RCTs), pruritus (1 RCT), fever (1 RCT), shivering (1 RCT), drowsiness (1 RCT), and urinary retention (2 RCTs);
- Other maternal adverse events and fetal outcomes were not reported.

Epidural vs acupuncture

Epidural analgesia vs electrical acupoint stimulation results in lower pain scores (SMD -53/100; 95%CI -58 to -48) (1 RCT, n=60) (Anim-Somuah 2018 **Level I** [Cochrane], 40 RCTs, n=12,389).

Epidural versus continuous midwifery support (one-to-one, with non-epidural analgesia):

All 493 women receiving epidural analgesia, and 494 out of 499 women receiving continuous midwifery support rated their pain relief as 'excellent or very good' (RR 1.01, 95% CI 1.00 to 1.02); however, pain intensity was not reported (1 RCT, n=992) (Anim-Somuah 2018 **Level I** [Cochrane], 40 RCTs, n=12,389). No woman receiving epidural analgesia requested additional means of pain relief vs 262 out of 499 receiving continuous midwifery support (1 RCT, n=992).

Timing of epidural

A meta-analysis assessed outcomes of early vs late initiation of epidural analgesia for labour, showing no clinically significant differences dependent on timing of epidural analgesia (Sng 2014 **Level I** [Cochrane], 9 RCTs, n=15,752). Specifically, there are no differences in rate of instrumental birth (RR 0.93; 95%CI 0.86 to 1.01) (8 RCTs, n=15,379), duration of second stage of labour (MD -3.22 min; 95%CI -6.71 to 0.27) (8 RCTs, n=14,982) or adverse fetal outcomes.

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The use of labour epidural analgesia given to every parturient at the onset of labour (routine use), when compared to maternal request for epidural analgesia, found no significant increase in Caesarean deliveries (34.8% vs 26.7%; 95%CI -0.1 to 16.3) (Wassen 2015 **Level II**, n= 493, JS 3). There was more hypotension (difference 9.5%; 95%CI 4.2 to 14.9) and motor blockade (difference 6.8%; 95%CI 1.1 to 12.5) in the routine use group.

Local anaesthetic concentrations

Epidural analgesia with low concentrations of bupivacaine (≤0.1%) or ropivacaine (≤0.17%) vs non-epidural methods of analgesia shows no differences in the duration of the first or second stage of labour, or the rate of instrumental birth or Caesarean section (Wang 2017 **Level I** [PRISMA], 10 RCTs, n=1,809).

A prior meta-analysis favours lower concentrations of bupivacaine (≤0.1%) (8 RCTs, n=852) or ropivacaine (≤0.17%) (3 RCTs, n=293) over higher concentrations for epidural analgesia in labour (Sultan 2013 **Level I**, 11 RCTs, n=1,145). Low concentrations are associated with fewer assisted vaginal births (OR 0.70; 95%CI 0.56 to 0.86), a shorter second stage of labour (WMD -14.03 min; 95%CI -27.52 to -0.55), less motor block (OR 3.9; 95%CI 1.59 to 9.55), greater ability to ambulate (OR 2.8; 95%CI 1.1 to 7.14), and less urinary retention (OR 0.42; 95%CI 0.23 to 0.73) but no difference in Caesarean section rate (OR 1.05; 95%CI 0.82 to 1.33).

However, lower vs higher concentrations may be associated with increased pruritus (OR 3.36; 95%CI 1.00 to 11.31) and are associated with a higher rate of Apgar scores <7 at 1 min (OR 1.53; 95%CI 1.07 to 2.21), but not persisting at 5 min. No differences are apparent for pain, nausea and vomiting, hypotension, fetal heart rate abnormalities or need for neonatal resuscitation.

Comparison of ropivacaine vs bupivacaine (alone or with fentanyl)

Use of bupivacaine vs ropivacaine as the sole agent for epidural analgesia shows no difference with regard to mode of birth, maternal satisfaction or neonatal outcomes (Halpern 2003 **Level I**, 23 RCTs, n=2,074).

The combination of fentanyl, with either ropivacaine or bupivacaine, exhibits comparable efficacy and safety (Li 2015 **Level I**, 9 RCTs, n=556). However, ropivacaine with fentanyl resulted in a significantly lower frequency of motor block (OR 0.31; 95%CI 0.18 to 0.51) despite a longer second stage than bupivacaine/fentanyl (MD 6.87; 95%CI 10.98 to 2.77). The concentrations used varied widely (by a factor of 30), and equipotent concentrations were not compared.

Adjuvant dexamethasone

The analgesic effect of dexamethasone when added to epidural local anaesthetic improves analgesia, but this may be due to a systemic effect. The addition of dexamethasone 8 mg to epidural analgesia in labour (levobupivacaine with fentanyl via PCEA) resulted in a reduced requirement for the PCEA solution (7.0 ml ± 1.2 vs 8.4 ml ± 2.6) (Dhal 2018 **Level II**, n=60, JS 5). The addition of dexamethasone 4 mg to single dose epidural levobupivacaine extended the duration of analgesia (81.6 min ± 14.4 vs 63.8 min ± 12.8) (Wahdan 2019 **Level II**, n=60, JS 4), this may be due a systemic effect (see also Section 4.12.2).

Adjuvant dexmedetomidine

The addition of dexmedetomidine to epidural local anaesthetic improved labour analgesia as bolus 0.5mcg/kg (Zhao 2017 **Level II**, n=80, JS 3) or infusion 0.5mcg/mL (Zhang 2018 **Level III-2 EH**, n=60). An RCT has compared 0.25, 0.5, 0.75 and 1 mcg/mL (with no local anaesthetic only arm) and the optimum dose is uncertain (Wangping 2017 **Level II**, n=100, JS 3) (see also Section 4.9.1).

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Adjuvant neostigmine

Adding neostigmine (in widely varying doses) to local anaesthetics (bupivacaine or ropivacaine) ± 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, n=275), but not epidural neostigmine (11 RCTs, n=911), 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 (see also Section 4.13.2).

Technique of epidural administration

Patient-controlled epidural analgesia (PCEA) for labour pain

PCEA can provide effective analgesia but the optimal settings are not clear (Leo 2008 **Level IV**; Loubert 2011 **NR**). A meta-analysis of PCEA in labour concluded that dilute concentrations of bupivacaine (0.125%) or ropivacaine (≤ 0.16%), with and without background infusion provide acceptable analgesia (6 RCTs, n=789) and that use of large bolus doses (6 RCTs, n=588) and background infusions (7 RCTs, n=573) with PCEA may improve analgesia and result in reduction of unscheduled clinician interventions vs other interventions (Halpern 2009 **Level I**, 30 RCTs, n=4,033 [bupivacaine vs ropivacaine 11 RCTs, n=2,083]).

A meta-analysis comparing PCEA with and without a background infusion shows that continuous background infusion was associated with increased instrumental vaginal birth (RR 1.66, 95%CI 1.08 to 2.56), prolonged second stage of labour (WMD 12.3 min, 95%CI 5.1 to 19.5), reduced requirement for physician-administered boluses (RR 0.35, 95%CI 0.25 to 0.47), with no difference in Caesarean section rate (RR 0.83, 95%CI 0.61 to 1.13) (Heesen 2015 **Level I** [PRISMA], 7 RCTs, n=891).

Programmed intermittent epidural boluses (PIEB)

PIEB for analgesia in labour reduces breakthrough pain incidence vs continuous epidural infusion (20 vs 33%) (RR 0.60; 95%CI 0.39 to 0.92) (Sng 2018 **Level I**, 10 RCTs, n=797). There are no differences for Caesarean section and assisted vaginal delivery rates, duration of labour or Apgar scores. Hourly local anaesthetic dose in the PIEB group is reduced, but the clinical significance of the difference is unclear (MD −1.1 mg/h; 95%CI −1.8 to −0.4) (12 RCTS, n=1,121). Maternal satisfaction is higher in the PIEB group (5 of 7 RCTs, n=570; data unable to be pooled for effect size). See also Section 5.6.1.5.

Combined spinal-epidural (CSE) and dural puncture epidural analgesia for labour pain

CSE analgesia provides slightly more rapid onset of pain relief than epidural techniques alone (Simmons 2012 **Level I** [Cochrane], 37 RCTs, n=3,274). In comparison to traditional epidural techniques (local anaesthetic concentration ≥0.25% bupivacaine), the time to onset is shorter (MD -2.9 min; 95%CI -5.1 to -0.7) (2 RCTs, n=129), with reduced need for rescue analgesia (RR 0.31; 95%CI 0.14 to 0.70) (1 RCT, n=42), lower rates of urinary retention (RR 0.86; 95%CI 0.79 to 0.95) (1 RCT, n=704) and instrumental birth (RR 0.81; 95%CI 0.67 to 0.97) (6 RCTs, n=1,015). However, a comparison of CSE with low-dose epidurals (local anaesthetic concentration equivalent to bupivacaine <0.25%; reflecting current practice) shows a faster onset of effect (MD -5.4 min; 95%CI -7.3 to -3.6) (5 RCTs, n=461), but no difference in maternal satisfaction (RR 1.01; 95%CI 0.98 to 1.05) (7 RCTs, n=520) and an increased rate of mild pruritus (RR 1.80; 95%CI 1.22 to 2.65) (11 RCTs, n=959).

The risk of unilateral block is reduced after CSE vs epidural analgesia (RR 0.48, 95%CI 0.24 to 0.97) (Heesen 2014 **Level I** [PRISMA], 10 RCTs, n=1,722).

Non-reassuring fetal heart rate tracings may be more common with CSE than epidural analgesia alone (RR 1.31, 95%CI 1.02 to 1.67) (Hattler 2016 **Level I** [PRISMA], 17 RCTS, n=3,947). The

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mechanism of this effect may be from an abrupt transient reduction in circulating catecholamines (Segal 2008 **BS**).

CSE techniques may be associated with a lower failure rate (6.6%) than standard epidural analgesia (1.6%) (Booth 2016 **Level III-3**, n=2,395).

Dural puncture epidural analgesia is a technique similar to CSE, where dural puncture is performed but no medication is injected intrathecally. There appears to be no certain benefit for this technique vs standard epidural analgesia (Heesen 2019 **Level I** [PRISMA], 5 RCTs, n=581).

Intrathecal analgesia for labour pain

Single-injection intrathecal opioids

Single-injection IT opioids are as effective as epidural local anaesthetics for the management of pain in early labour and they do not affect the rate of nausea or mode of delivery (Bucklin 2002 **Level I**, 7 RCTs, n=332). IT opioids increase the risk of fetal bradycardia (NNH 28) and maternal pruritus (NNH 1.7) in comparison with non-IT opioid analgesia (Mardirosoff 2002 **Level I**, 24 RCTs, n=3,513). Adding IT morphine ≤250 mcg to single bolus IT labour analgesia with bupivacaine/fentanyl or bupivacaine/sufentanil prolongs duration of analgesia (60.6 min, range 3 to 155) with no effect on SMD of pain intensity (Al-Kazwini 2016 **Level I** [PRISMA], 5 RCTs, n=286).

Respiratory depression related to epidural or IT opioids during labour is rare (Carvalho 2008 **NR**); see Section 5.7.1.3 for more details.

Intrathecal catheters for labour analgesia

IT microcatheters (24- to 28-gauge) are used infrequently for labour analgesia but may be useful in some specific cases, such as those patients who are morbidly obese, have significant cardiac disease or previous spinal surgery (Palmer 2010 **NR**). Continuous IT medication infusion improved early analgesia, with no differences in neonatal or obstetric outcomes but more technical difficulties vs epidural administration (Arkoosh 2008 **Level II**, n=429, JS 3); this trial used 28-gauge catheters and there were no safety concerns. Subsequent case series have used larger catheters: two have used 23-g successfully (Tao 2015 **Level IV**, n=113; Tao 2011 **Level IV**, n=7) with the larger study reporting a low PDPH rate (2.6%) and a failure rate of 11%, while a further study described a higher failure rate (20%) with 22-g and 24-g catheters (n=92) and a higher incidence of PDPH (29%), requiring a blood patch in 18% of these patients (Alonso 2009 **Level IV**). The authors of this study concluded the risks outweigh the benefits of IT microcatheters as a primary method for labour analgesia.

Placement of an epidural catheter (20- to 22-g) in women who have experienced an unintentional dural puncture is widely practised. A study comparing IT placement with epidural placement of an epidural catheter after unintentional dural puncture (n=97) reported a similar PDPH incidence (72 vs 62%) but easier establishment of neuraxial analgesia with the IT method (Russell 2012 **Level III-1**). Another study found a lower rate of PDPH (42% for IT placement vs 62% for epidural placement) (OR 2.3; 95%CI 1.04 to 4.86) (Verstraete 2014 **Level III-2**, n=128).

Comparison of intrathecal ropivacaine with bupivacaine

Single dose IT ropivacaine 0.15%/sufentanil 0.2mcg/mL vs IT bupivacaine 0.125%/sufentanil 0.2mcg/mL for labour pain resulted in lower pain scores (over the time period from 10 min until full cervical dilatation), and higher satisfaction (94.7% vs 84%) (Li 2018 **Level II**, n=300, JS 2).

9.1.3.4 | Regional analgesia in labour pain

Paracervical block and pudendal nerve block are the most commonly performed local anaesthetic PNBs, with a long history of use for pain management in labour.

Local anaesthetic nerve blocks (11 RCTs paracervical; 1 RCT pudendal), using various agents, are effective (8 RCTs), and superior to placebo (1 RCT, n=200), opioid (2 RCTs, n=129) and nonopioid

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analgesia (1 RCT, n=100) (Novikova 2012 **Level I** [Cochrane], 12 RCTs, n=1,549); however it is noted that these findings are based on RCTs of unclear quality and limited numbers. Adverse effects are more common in comparison with placebo (1 RCT, n=200). There is no difference in quality of analgesia and satisfaction with analgesia between different local anaesthetics (4 RCTs, n=789). Specifically in comparison to placebo, paracervical blocks with lignocaine 2% are associated with higher patient satisfaction (RR 32.3; 95%CI 11 to 99) but more adverse effects (RR 29.0; 95%CI 1.8 to 480) (Novikova 2012 **Level II** [Cochrane], 1 RCT [vs placebo], n=200). In comparison with opioids (IM pethidine or fentanyl IV PCA), nerve blocks provide better pain relief (RR 2.52; 95%CI 1.65 to 3.83), without an increase in the rate of assisted vaginal birth (RR 1.02; 95%CI 0.56 to 1.87) or of Caesarean section (RR 0.23; 95%CI 0.03 to 1.87) (Novikova 2012 **Level I** [Cochrane], 2 RCTs [vs opioids], n=129).

Paracervical block was equally efficacious but required supplementation more frequently than epidural analgesia (Manninen 2000 **Level II**, n=44, JS 3) and was less effective than single-injection IT analgesia (Junttila 2009 **Level III-2**). Serious fetal complications may occur (Shnider 1970 **NR**), so this technique should be limited to hospitals without other obstetric anaesthesia services (Levy 1999 **Level III-2**) or for patients with contraindications to neuraxial techniques (Junttila 2009 **Level III-2**).

9.1.3.5 | Complementary and other methods of pain relief in labour

Continuous or one-to-one support by a midwife or trained layperson during labour reduces analgesic use, rate of instrumental and operative birth and dissatisfaction, especially if the support person is not a member of the hospital staff, was present from early labour, or if an epidural analgesia service was not available (Hodnett 2013 **Level I** [Cochrane], 22 RCTs, n=15,288). The effect of continuous midwifery support, with and without epidural analgesia is described above (9.1.3.3).

A qualitative systematic review has assessed women's experiences of pharmacological and non-pharmacological pain relief for labour (Thomson 2019 **Level IV SR**, 24 studies, n unspecified). Overall, experiences were mixed with pharmacological methods assessed as effective, but with adverse effects, while non-pharmacological were described as not as effective, but facilitating bonding.

For some nonpharmacological or complementary therapies there is weak evidence of effectiveness vs standard care:

- Water immersion during labour has limited benefit. There is no difference in mode of delivery (spontaneous, instrumental or Caesarean), perineal trauma or blood loss. There is a small reduction in the requirement for regional analgesia (epidural, intrathecal, paracervical) vs no immersion (39% vs 43%) (RR 0.91; 95%CI 0.83 to 0.99) (5 RCTs; n=2,439) (Cluett 2018 **Level I** [Cochrane] 15 RCTs, n=3,663). Other maternal outcomes were not reported. There is insufficient evidence to determine the impact on neonatal intensive care unit admissions (2 RCTs, n=1,511) or neonatal infection rates (5 RCTs, n=1,295).

- Acupuncture/Acupressure in labour (Smith 2020 **Level I** [Cochrane], 28 RCTs, n=3,960) (see also Section 7.3.2.3):
  - Acupuncture vs sham does not reduce pain scores (2 RCTs, n=325), but does increase satisfaction with pain relief (RR 2.38; 95%CI 1.78 to 3.19) (1 RCT, n=150) and decreases use of pharmacological analgesia (RR 0.75; 95%CI 0.63 to 0.89);

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- Acupuncture vs usual care reduces pain scores (4 RCTs, n=495) and use of pharmacological analgesia (6 RCTs, n=1,059) but does not improve satisfaction (2 RCTs, n=343);
- Acupuncture vs no treatment reduces pain scores (1 RCT, n=163);
- Acupuncture vs water injection does not reduce use of pharmacological analgesia (1 RCT, n=128);
- Acupressure vs sham lowers pain scores (MD -1.93/10; 95%CI -3.31 to -0.55) but has no effect on use of pharmacological analgesia (6 RCTs, n=472);
- Acupressure vs usual care reduces pain scores (SMD -1.07; 95%CI -1.45 to -0.69) (8 RCTs, n=620) and improves satisfaction (1 RCT, n=105);
- Acupressure vs both placebo and usual care reduces pain scores (SMD -0.42; 95%CI -0.65 to -0.18) (2 RCTs, n=322) and marginally increases satisfaction with analgesia (1 RCT, n=212);
- There was no effect on Caesarean section rate;
- Overall, evidence was of low quality with no study at a low risk of bias on all domains. There is a need for high-quality research that includes sham controls and comparisons to usual care.

Massage vs standard care reduces pain during first stage of labour (SMD −0.81, 95%CI −1.06 to −0.56) (6 RCTs, n=362), but not second (SMD −0.98/10; 95%CI −2.23 to 0.26) (2 RCTs, n=124) or third stages (SMD −1.03/10; 95%CI −2.17 to 0.11) (2 RCTs, n=122) (Smith 2018a **Level I** [Cochrane], 10 RCTs, n=1,055). Massage also lessens anxiety during the first stage of labour (MD -16.27; 95%CI −27.03 to −5.51) (1 RCT, n=60), increases sense of control (MD 14.05; 95% CI 3.77 to 24.33) (1 RCT, n=124) and satisfaction (unable to quantify due to methodology) (see also Section 7.5.2).

The use of birth ball (Swiss ball) exercises for labour pain relief improves pain vs non-use (SMD -0.9/10; 95% CI -1.3 to -0.6) (Makvandi 2015 **Level I**, 3 RCTs, n=205). The quality of the studies was mixed, with most providing little information on the exact methods they used**;**

Hypnosis (eight antenatal and one intrapartum intervention) for labour pain reduces analgesic use (RR 0.73; 95%CI 0.57 to 0.94) (8 RCTs, n=2,916), but has no effect on rate of spontaneous vaginal birth (6 RCTs, n=2,361), sense of coping with labour (1 RCT, n=420) or satisfaction with pain relief when combined with either pethidine (1 RCT, n=72) or epidural analgesia (1 RCT, n=127) (Madden 2016 **Level I** [Cochrane], 9 RCTs, n=2,954);

Note: reversal of conclusion
This reverses the Level I key message in the previous edition of this document; a preceding meta-analysis had described no effect of hypnosis in the management of labour pain.

Relaxation techniques (including yoga, music or audio) has limited and low to very low quality evidence for reduction in labour pain or improved satisfaction (Smith 2018a **Level III-1 SR** [Cochrane], 15 studies, n=1,731).

For the following interventions, the evidence is not supportive.

- Biofeedback does not affect the use of pharmacological pain relief or the rates of assisted vaginal birth or Caesarean section (Barragan Loayza 2011 **Level I** [Cochrane], 4 RCTs, n=186);
- Sterile water injections, intra- or subcutaneously, vs saline injection do not reduce labour pain during the first stage of labour, or affect mode of birth or other maternal or fetal outcomes (Derry 2012 **Level I** [Cochrane], 7 RCTs, n=766);

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- Aromatherapy has no effect on any primary or secondary outcomes in labour (Smith 2011 **Level I** [Cochrane], 2 RCTs, n=535);
- In labour, TENS has no effect on pain, interventions or outcomes vs sham TENS (10 RCTs) or routine care (7 RCTs), when applied to the back (13 RCTs, n=1,150) or cranium (2 RCTs, n=140), with the exception of a reduction of reports of severe pain when applied to acupuncture points (2 RCTs, n=190) (Dowswell 2009 **Level I** [Cochrane], 17 RCTs, n=1,466). The findings of no analgesic effect were confirmed by two subsequent meta-analyses (Bedwell 2011 **Level I**, 14 RCTs, n=1,456) (14 RCTs overlap) (Mello 2011 **Level I**, 9 RCTs, n=1,076) (3 RCTs overlap) (see also Section 7.2).

9.1.3.6 | Analgesia for forceps delivery

Rates of assisted vaginal birth vary throughout the world (10–15% in high-resource settings). Neuraxial analgesia is commonly used for forceps delivery in these settings but local infiltration and pudendal nerve block are also used, while the rate of general anaesthesia is very low (Osterman 2011 **Level IV**). Studies in this setting are limited and old (Nikpoor 2013 **Level I** [Cochrane], 4 RCTs, n=388). Three of these RCTs compared diazepam to other agents for provision of general anaesthesia, without finding clinically relevant differences. In one RCT, IT analgesia vs pudendal nerve block resulted in more women regarding their analgesia as adequate (RR 3.36; 95%CI 2.46 to 4.60), with fewer reporting severe pain (RR 0.02; 95%CI 0.00 to 0.27) (Nikpoor 2013 **Level I** [Cochrane], 1 RCT [IT]: Hutchins 1980 **Level II**, n=183, JS 1). The authors conclude that there is a lack of evidence to guide practice.

9.1.3.7 | Pain after Caesarean section

Pain after Caesarean section has been treated by multiple analgesic techniques and multimodal analgesia is recommended (Sutton 2017 **NR**); a multimodal bundle of standardised use of preoperative paracetamol, postoperative comfort education, simethicone PO, postoperative gum chewing and use of abdominal binders reduced morphine requirements by 61% (Burgess 2019 **Level III-1**, n=9,313). This approach led to more women receiving less than 20 tablets of oxycodone (5 mg or 10 mg) at discharge (96.7% vs 26.3).

Pain on POD 1 may be higher than that from many other types of major surgery (Gerbershagen 2013 **Level III-2**, n=456 [Caesarean sections] of total n=70,764).

When asked to rate their pain after Caesarean section, patients using pain scores had increased pain reporting and a worse experience during the postoperative period than the comfort score reporting group (Chooi 2013 **Level II**, n=300, JS 4).

Important considerations in this patient group include transfer of medications via breast feeding, and facilitating postoperative mobility of the mother for care of the neonate.

Systemic analgesia

Oral analgesia

A meta-analysis of oral analgesia (opioids, tramadol, paracetamol, NSAIDs, coxibs, gabapentin) for pain after Caesarean section identified mainly small RCTs with contradictory results, not permitting definitive conclusions regarding the most effective or safest approach (Mkontwana 2015 **Level I** [Cochrane], 8 RCTS, n=962). Opioids and nonopioids showed little effect in comparison to placebo and each other with significant heterogeneity except for ketoprofen 100 mg (RR 0.55; 95%CI 0.39 to 0.79) (1 RCT, n=72). This Cochrane review states based on a single RCT that gabapentin reduces the need for additional analgesia vs placebo (Short 2012 **Level II**, n=132, JS 5). However, the results were incorrectly calculated and the conclusion replaced by a subsequent systematic review (including this trial) which finds: gabapentin 600 mg improves pain scores on

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movement at 24 h only (MD -11.58/100 VAS; 95%CI -23.04 to -0.12) and increases satisfaction scores after Caesarean section, with no difference in opioid use, nausea, vomiting, pruritus or sedation (Felder 2019 **Level I** [PRISMA], 6 RCTs, n=656). Oral oxycodone was as effective as IV PCA piritramide (opioid) in this setting, but there was no placebo comparator (Dieterich 2012 **Level II**, n=239, JS 3). Oral naproxen or tramadol were similarly effective, with fewer adverse effects with naproxen (Sammour 2011 **Level II**, n=120, JS 3). A study comparing oral oxycodone with IT morphine on top of background oral nonopioid analgesia found comparable analgesia and less pruritus, but lower maternal satisfaction (McDonnell 2010 **Level II**, n=111, JS 5).

Parenteral analgesia

IV paracetamol, given before the commencement of Caesarean section, vs placebo reduces postoperative pain (measured immediately after surgery or during the recovery period) (SMD −0.72/10; 95%CI −1.31 to −0.13) and reduces postoperative opioid consumption (SMD −0.46; 95%CI -0.828 to -0.092) (Ng 2019 **Level I** [PRISMA], 5 RCTs, n=409). In women having either Caesarean section or hysterectomy, IV paracetamol vs oral paracetamol reduced LOS (-11%), use of opioids (-1.6 mg daily morphine equivalent) and opioid-related adverse effects (Urman 2018 **Level III-3**, n=29,124).

Parenteral (but not oral or rectal) NSAIDs vs placebo after Caesarean section reduce pain scores at 12 and 24 h, opioid requirements, drowsiness and sedation, but not PONV (Zeng 2016 **Level I**, 22 RCTs, n=1,313). In combination with IV PCA morphine, parecoxib and ketorolac had similar efficacy, but without a placebo control (Wong 2010 **Level II**, n=66, JS 2).

As mentioned above, IV PCA piritramide (opioid) was as effective as oral oxycodone, but with no placebo comparator (Dieterich 2012 **Level II**, n=239, JS 3). A continuous IV infusion of tramadol vs IV PCA tramadol resulted in higher tramadol consumption and lower patient satisfaction (Demirel 2014 **Level II**, n=40, JS 1).

Dexmedetomidine (by IV or neuraxial routes) vs placebo for Caesarean section improves sensory block and duration of postoperative analgesia (4 RCTs [IT local anaesthetic], n=352) and reduces PONV and shivering (RR 0.26; 95%CI 0.11 to 0.60), with no harmful effects on umbilical blood gases and Apgar scores at 1 and 5 min (Zhang 2017 **Level I** [PRISMA], 6 RCTs, n=458). Review of further systemic dexmedetomidine studies reveal beneficial effects on PONV and shivering (Bao 2017 **Level I**, 12 RCTs, n=986) (2 RCT overlap); however, IT dexmedetomidine reduces only shivering, without an effect on PONV (Miao 2018 **Level I** [PRISMA], 6 RCTs, n=360) (2 & 3 RCTs overlap). Dexmedetomidine had an opioid-sparing effect when combined with sufentanil PCA (Nie 2014 **Level II**, n=120, JS 5); this was more pronounced when dexmedetomidine was continued in the PCA after an initial bolus than if an initial bolus only was administered.

IV dexamethasone 10 mg reduced nausea and vomiting following Caesarean section under bupivacaine/morphine spinal anaesthesia, with fewer complaints of pain at rest and on movement in the first 24 h vs saline control (Cardoso 2013 **Level II**, n=70, JS 5). However, IV dexamethasone 8 mg vs placebo had no effect on opioid consumption after Caesarean section (Ituk 2018 **Level II**, n=52, JS 5).

Low-dose ketamine bolus and subsequent low-dose infusion for 12 h resulted in an opioid-sparing effect for 24 h without any further benefits or improved long-term outcome (Suppa 2012 **Level II**, n=56, JS 4). However, three different intraoperative IV bolus doses of ketamine (0.25, 0.5, and 1 mg/kg) had no effect on postoperative pain, opioid requirements or long-term outcomes after Caesarean section (Bilgen 2012 **Level II**, n=140, JS 4). Similarly, there were no obvious benefits when IV ketamine 10 mg was added to IT morphine and IV ketorolac (Bauchat 2011 **Level II**, n=188, JS 5). In contrast, IV ketamine 0.15 mg/kg given in addition to a bupivacaine spinal anaesthetic resulted in a longer duration and better quality of early postoperative analgesia (Menkiti 2012 **Level II**, n=60, JS 4). There are conflicting RCTs examining the effect of low dose ketamine on

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reduction of pain after Caesarean section and no conclusion about efficacy can be made in this patient group (Rahmanian 2015 **Level II**, n=160, JS 2; Behdad 2013 **Level II**, n=60, JS 4; Han 2013 **Level II**, n=40, JS 2).

Epidural analgesia

Epidural local anaesthetics

A comparison of four different concentrations of ropivacaine (0.2, 0.1, 0.05, or 0.025%) with fentanyl 3 mcg/mL and adrenaline 0.5 mcg/mL, showed that the very low concentration 0.025% is effective for PCEA after Caesarean section (Cohen 2015 **Level II**, n=48, JS 5). All patients receiving this concentration could ambulate, and none had urinary retention.

PCEA with 0.2% ropivacaine vs epidural morphine 2 mg every 12 h, provided equivalent analgesia (Chen 2011 **Level II**, n=120, JS 5); although it resulted in more motor weakness, this did not impair ambulation. Other adverse effects (pruritus, nausea, vomiting and urinary retention) occurred more often after epidural morphine, resulting in improved satisfaction scores with PCEA ropivacaine. Intrathecal morphine may be more cost-effective than PCEA after Caesarean section (Vercauteren 2002 **Level II**, n=53, JS 2). No differences were found between PCEA with 0.1% levobupivacaine vs 0.06% combined with fentanyl 2 mcg/mL (Chen 2014 **Level II**, n=80, JS 4).

Epidural opioids

After Caesarean section, single-dose epidural morphine (1 to 8 mg) increases the time until rescue analgesic is required and decreases pain and postoperative morphine requirements for 24 h vs systemic opioid analgesia (Bonnet 2010 **Level I** [QUOROM], 10 RCTs, n=431); however, there is an increased incidence of pruritus (RR 2.7; 95%CI 2.1 to 3.6) and nausea (RR 2.0; 95%CI 1.2 to 3.3). The requirement for rescue IV opioid reduces as the morphine dose increases from 1.25 to 3.75 mg, with no apparent additional benefit from 5 mg (Palmer 2000 **Level II**, n=60, JS 5). Epidural morphine 1.5 mg was noninferior to 3 mg and caused fewer adverse effects (Singh 2013b **Level II**, n=90, JS 5). Extended-release epidural morphine 10 mg decreased supplemental opioid use and improved functional ability scores for 48 h vs 5 mg of conventional epidural morphine (Carvalho 2005 **Level II**, n=79, JS 3).

Epidural magnesium

Bupivacaine/morphine/magnesium for epidural administration was superior to bupivacaine/morphine or bupivacaine/magnesium with regard to pain relief, time to rescue analgesia and patient satisfaction (Sun 2012 **Level II**, n=200, JS 5), but the neurotoxicity of neuraxial magnesium has not been adequately investigated (Albrecht 2013b **Level I** [PRISMA], 25 RCTs [IV magnesium], n=1,461).

Intrathecal analgesia

Intrathecal opioids

IT morphine and other opioids effectively reduce pain and analgesic requirements post Caesarean section (Dahl 1999 **Level I**, 15 RCTs, n=535).

Lower-dose (50 to 100mcg) vs higher-dose intrathecal morphine (>100 to 250mcg) has shorter time to first request for analgesia (MD 4.5 h; 95%CI 1.9 to 7.1) but with less nausea and vomiting (OR 0.44; 95%CI 0.27 to 0.73]) and pruritus (OR 0.34; 95%CI 0.20 to 0.59) (Sultan 2016 **Level I**, 11 RCTs, n=480). Acknowledging the combined sample size is small, there is no difference in pain score at 12 h nor in morphine consumption at 24 h after surgery. Thus, the higher dose provides some additional analgesic benefit at the expense of greater adverse effects.

A retrospective study of IT morphine 200 mcg vs 100 mcg had similar findings with sparing of additional opioids, but more nausea requiring treatment and more pruritus (Wong 2013 **Level III-2**, n=241).

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IT morphine 100 mcg added to IT fentanyl vs IT fentanyl alone was superior with regard to analgesia and its duration as well as patient satisfaction, despite increased adverse effects (pruritus, nausea and vomiting) (Sawi 2013 **Level II**, n=60, JS 4).

IT hydromorphone 40 mcg produced similar outcomes to IT morphine 100 mcg () (Beatty 2013 **Level III-2,** n=114) and IT diamorphine 250 mcg similar outcomes to IT morphine 100 mcg (Barkshire 2001 **Level II**, n=60, JS 4).

IT tramadol 10 mg vs IT fentanyl 10 mcg added to spinal anaesthesia with bupivacaine increased the duration of analgesia and reduced postoperative shivering (Subedi 2013 **Level II**, n=80, JS 5).

Other intrathecal medications

IT clonidine in doses of 15 to 30 mcg added to IT hyperbaric bupivacaine improved early analgesia after Caesarean section, with reduced morphine consumption during the first 24 h, but increased intraoperative sedation (van Tuijl 2006 **Level II**, n=106, JS 5; Paech 2004 **Level II**, n=232, JS 5).

IT midazolam gave short duration postoperative analgesia (Prakash 2006 **Level II**, n=60, JS 3). The safety of both these medications with respect to neurotoxicity is not established.

Safety of neuraxial opioids after Caesarean section

The prevalence of OIVI (author-reported, individual study definition) 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.

Other regional techniques

Peripheral regional blocks are useful analgesic techniques after Caesarean section (Mitchell 2019 **NR**; Patel 2019 **NR**). Local anaesthetic techniques in general (wound infiltration, bupivacaine-soaked gelatin sponge placement or catheter infusions, ilioinguinal/ iliohypogastric block, TAP block) reduce opioid consumption following Caesarean section performed under general or regional anaesthesia vs placebo (Bamigboye 2009 **Level I** [Cochrane], 20 RCTs, n=1,150). The reduction in opioid consumption is most beneficial where abdominal nerve blocks are used to supplement regional anaesthesia (MD -25.8 mg; 95%CI -50.4 to -5.4) (4 RCTs, n=175).

Wound infiltration or infusion

After Caesarean section, either continuous wound infusion or single-dose infiltration with local anaesthetics vs placebo reduces parenteral morphine consumption at 24 h (MD -9.69 mg; 95%CI -14.85 to -4.52) and pain at 24 h at rest (MD -0.36/10; 95%CI -0.58 to -0.14) and with movement (MD -0.61/10; 95%CI -1.19 to -0.03) with no difference between the techniques (Adesope 2016 **Level I** [PRISMA], 21 RCTs, n=1,435). These effects are not shown in patients receiving IT morphine and only with catheter placement below the fascia. PONV and pruritus are not reduced. RCTs not included in this systematic review confirm these results. Continuous wound infiltration with ropivacaine was superior to epidural morphine with regard to pain relief, adverse effects, need for nursing care and hospital LOS (O'Neill 2012 **Level II**, n=58, JS 3). Combining a pre- with a postincisional wound infiltration with lignocaine 1% had superior efficacy to a pre- or postincisional infiltration alone (Fouladi 2013 **Level II**, n=281, JS 4).

There is benefit from adding diclofenac (Lavand'homme 2007 **Level II**, n=92, JS 3) or low-dose ketorolac, but not hydromorphone, to a 48 h continuous bupivacaine wound infusion (Carvalho

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2013 **Level II**, n=60, JS 5). Ketorolac reduced pain scores and need for analgesia and also inflammatory cytokines (IL-6 and IL-10) in the wound exudate. Adding tramadol (1.5 mg/kg) to levobupivacaine wound infiltration reduced pain scores early in the postoperative period but there was no systemic control group (Demiraran 2013 **Level II**, n=90, JS 4). SC pethidine or tramadol improved analgesia and were opioid sparing vs infiltration of bupivacaine 0.25% or placebo (Jabalameli 2016 **Level II**, n=120, JS 3). Placing a multi-orifice catheter for wound infiltration with ropivacaine/ketoprofen below the superficial abdominal fascia resulted in improved analgesic efficacy vs placement above (Rackelboom 2010 **Level II**, n=56, JS 5).

The number of factors influencing efficacy of local anaesthetic wound infiltration in post Caesarean section analgesia - catheter placement (superficial versus deep to transversalis fascia), local anaesthetic dose (high /low volume and concentration) and methods of administration (intermittent boluses versus continuous infusion) - need to be evaluated with further studies.

Ilioinguinal-iliohypogastric block (II-IH block)

Bilateral II-IH block (local anaesthetic vs saline placebo) used in addition to IT morphine improved analgesia, lowered analgesic requirements and increased satisfaction (Wolfson 2012 **Level II**, n=34, JS 5). However in another study, US-guided II-IH blocks with bupivacaine, combined with IT morphine (variable dosing), conferred no further benefit (Vallejo 2012 **Level II**, n=50, JS 4). US-guided II-IH blocks vs TAPB provided similar early analgesia with similar adverse event rates; however at later time points (24 h and 48 h), analgesia was superior with US-guided II-IH block (Jin 2019 **Level III-1**, n=242).

Transversus abdominis plane block (TAPB)

After Caesarean section, TAPB vs placebo (9 RCTs) or no block (3 RCTs) reduces pain at rest at 6 h (-3.6/10; 95%CI -6.3 to -0.9), to a lesser extent at 24 h (-1.1/10; 95%CI -2.1 to -0.01) and morphine requirements at 2 to 24 h (Champaneria 2016 **Level I SR** [PRISMA], 18 RCTs, n=1,353). TAPB/IT morphine vs IT morphine only reduces pain at rest (-0.5/10; 95%CI -1.0 to -0.1) and with movement (-1.0/10; 95%CI -1.7 to -0.4).

In a preceding SR, TAPB has varying outcomes depending on the comparator, and if added to multimodal analgesia (IT morphine, or placebo, in combination with paracetamol and NSAID and/or PCA opioids) (Fusco 2015 **Level I** [PRISMA], 11 RCTs, n=727) (9 RCTs overlap with Champaneria 2016). TAPB in addition to multimodal analgesia may not confer additional analgesic benefit. This uncertainty is affected by the heterogeneity of analgesic treatment in RCTs. Opioid related side effects may be reduced. In this systematic review the outcomes were not suitable for quantitative assessment; TAPB reduces opioid consumption vs IT opioid (3 of 4 RCTs), time to first analgesic request (5 of 7 RCTs), PONV (10 of 10 RCTs) and pruritus (4 of 7 RCTs). TAPB alone and with IT opioid does not improve postoperative analgesia vs IT opioid (3 RCTs each), but TAPB/IT opioid vs placebo reduces pain intensity (4 RCTs).

Following Caesarean section, local anaesthetic TAPB reduces postoperative opioid requirements for 24 h and pain scores for 12 h but only when IT morphine is not used (Mishriky 2012 **Level I** [PRISMA], 9 RCTs, n=524) [7 RCT overlap with Fusco 2015]; Abdallah 2012 **Level I** [PRISMA], 5 RCTs, n=312 (all 5 RCTs overlap)); IT morphine provides better analgesia than TAP blocks but with an increased rate of adverse effects.

RCTs with small patient numbers of TAPB used in combination with IT morphine have shown no (McKeen 2014 **Level II**, n=83, JS 5) vs early 0–24 h analgesic benefit (Lee 2013a **Level II**, n=51, JS 5; Onishi 2013 **Level III-2**; Singh 2013a **Level II**, n=60, JS 5). The latter study compared high-dose (3 mg/kg) with low-dose ropivacaine (1.5 mg/kg) and found only high-dose ropivacaine produced benefits for up to 12 h.

Single-dose US-guided TAPB and continuous wound infusions were compared in women having Caesarean section under spinal anaesthesia without morphine (Chandon 2014 **Level II**, n=65,

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JS 3). The trial was abandoned after a generalised seizure in the TAPB group; however, there were no differences between the groups with regard to analgesia and pain at 1 mth. In a similar study, there was also no difference in morphine use or pain when TAPB and SC wound infiltration with bupivacaine 0.25% and adrenaline were compared (Telnes 2015 **Level II**, n=60, JS 5).

With regard to TAPB technique and duration of effect, the posterior approach (4 RCTs) reduced opioid consumption and rest and dynamic pain scores over 48 h vs controls; longer than that from a lateral approach where rest pain scores only were lower than controls at 12 h (8 RCTs) (Abdallah 2013 **Level I** [PRISMA], 12 RCTs [8 Caesarean sections], n=641). Subanalysis of the varying agents and dose equivalents administered was not performed.

TAPB are associated with high peak plasma concentrations of local anaesthetic after 30 min (Torup 2012 **PK**) and mild toxicity is reported after total doses of ropivacaine of ≥2.5 mg/kg (Griffiths 2013 **Level IV**) and convulsions after 150 mg of levobupivacaine (Weiss 2014 **CR**).

Quadratus lumborum (QL) block

Quadratus lumborum block after Caesarean section in comparison to TAPB provided effective and prolonged analgesia with a mean time to first analgesic request of 68.8 h (SD 1.74) vs 13.3 h (SD 1.21) (Verma 2019 **Level II**, n=60, JS 3)

Risk of chronic pain following Caesarean section

Persistent postsurgical pain has been reported in 1 to 18% of women following Caesarean section (Landau 2013 **NR**). In two studies with detailed follow-up, the incidence of persistent pain was 14.6% at 2 mth, reducing to 4.2% at 12 mth (n=426) (Liu 2013 **Level IV**) and 11% at 8 wk, reducing to 0.6% at 12 mth (n=381) (Ortner 2014 **Level III-2**). For repeat Caesarean section, preoperative scar hyperalgesia (seen in 41% of patients) is a risk factor for postoperative pain (Ortner 2013 **Level III-2**). Patients with chronic postsurgical pain had higher rates of general vs spinal anaesthesia (37% general vs 17% in the no-pain group; p=0.02); in this study the incidence of significant pain at 10 mth postoperatively was 5.9 % (Nikolajsen 2004 **Level III-2**). A variety of regional analgesia techniques reduces CPSP at 3 to 8 mth following Caesarean section (NNT 19) (OR 0.46; 95%CI 0.28 to 0.78) (4 RCTs, n=551) (Weinstein 2018 **Level I** (Cochrane), 63 RCTs, n=3,027).

Prior Caesarean section is also a risk factor for chronic pelvic pain (Latthe 2006 **Level III-3 SR**, 63 studies, n=64,286). See also Section 1.4.

KEY MESSAGES

Neuraxial and regional analgesia for pain in labour

1. Epidural and combined spinal-epidural analgesia provides superior pain relief for labour and delivery compared with all other analgesic techniques (**S**) along with improved maternal satisfaction (**R**) (**Level I** [Cochrane Review]).
2. Epidural analgesia compared to systemic opioid reduces maternal nausea and/or vomiting (**N**) and need for maternal oxygen supplementation (**N**), but increases the duration of the first and second stage of labour slightly (**Q**) (**Level I** [Cochrane Review]).
3. Epidural analgesia compared to systemic opioid does not increase the rate of Caesarean section (**S**), long-term backache (**S**), headache (**N**), pruritus (**N**) or postnatal depression (**N**) (**Level I** [Cochrane Review]).

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4. Epidural analgesia compared to systemic opioids reduces the risk of fetal acidosis (**S**) and the need for neonatal naloxone administration with no increase in special care/neonatal intensive care unit admissions (**N**) (**Level I** [Cochrane Review]).
5. Epidural analgesia may increase the rate of assisted vaginal delivery (**U**), but not with contemporary techniques of epidural analgesia (use of low-concentrations of local anaesthetics) (**Q**) (**Level I** [Cochrane Review]).
6. Lower concentrations of local anaesthetics for epidural analgesia in labour result in a shorter duration of second stage of labour, fewer assisted vaginal deliveries, greater ambulation and less urinary retention than higher concentrations (**S**) (**Level I** [Cochrane Review]).
7. Early versus late initiation of epidural analgesia leads to no clinically significant differences in outcome (**S**) (**Level I** [Cochrane Review]).
8. In comparison with epidural analgesia, combined spinal-epidural analgesia reduces time to effective analgesia (**U**), does not increase maternal satisfaction (**U**), increases the incidence of mild pruritus (compared to low-dose epidurals) (**U**) (**Level I** [Cochrane Review]) and reduces the risk of unilateral block (**N**) (**Level I** [PRISMA]).
9. Local anaesthetic nerve blocks (in particular paracervical blocks) provide better analgesia than placebo, nonopioids and opioids for labour pain, but at an increased rate of adverse effects (**U**) (**Level I** [Cochrane Review]).
10. Non-reassuring fetal heart rate tracings can be more common with combined spinal-epidural analgesia than epidural analgesia in labour (**N**) (**Level I** [PRISMA]).
11. Ultrasound guidance improves the success of epidural catheter insertion and intrathecal needle placement and reduces traumatic insertions (**N**) (**Level I** [PRISMA]).
12. Patient-controlled epidural analgesia provides effective analgesia for labour (**U**) but optimal settings (**U**) (**Level I**) and the need for a background infusion remain unclear (**U**) (**Level I** [PRISMA]).
13. Programmed intermittent epidural bolus versus continuous epidural infusion reduces the incidence of breakthrough pain without increasing adverse outcome (**S**) (**Level I** [PRISMA]).
14. Dural puncture epidural analgesia does not appear to offer benefit over standard epidural analgesia (N) (**Level I** [PRISMA]).
15. There is no difference between the use of bupivacaine and ropivacaine for epidural analgesia in labour for any outcome (**U**), except ropivacaine may reduce the incidence of motor block (**Q**) (**Level I**).
16. Single-injection intrathecal opioids provide comparable early labour analgesia to epidural local anaesthetics, with increased pruritus but no difference in nausea (**U**) (**Level I**). Adding single injection intrathecal morphine (≤250 mcg) to local anaesthetic combined with shorter acting opioids increases time to first analgesic request, but is associated with increased adverse effects **(N)** (**Level I**).

Systemic analgesia for pain in labour

17. Analgesic concentrations of inhaled volatile anaesthetics provide superior analgesia in labour but more drowsiness, compared to inhaled nitrous oxide (**U**) (**Level I** [Cochrane Review]).

18. Inhaled nitrous oxide has some analgesic efficacy in labour pain (**U**), increases maternal adverse effects (nausea, vomiting, dizziness) (**U**) but has no adverse effects on the newborn (**U**) (**Level I** [Cochrane Review]); pain relief is comparable to pethidine but inferior to epidural analgesia (**U**) (**Level IV SR**).
19. Use of nonopioid analgesics alone for labour analgesia is not supported by current evidence (**U**) (**Level I** [Cochrane Review]).
20. Parenteral opioids other than remifentanil intravenous PCA provide moderate analgesic effects in labour pain (**S**), are inferior to epidural analgesia (**S**) and cause increased adverse maternal effects (sedation, nausea, vomiting) (**S**) and adverse effects on the newborn remain unclear (**Q**) (**Level I** [Cochrane Review]).
21. Remifentanil intravenous PCA is inferior to epidural analgesia (**U**), but provides better analgesia in labour compared to other parenteral opioids (**S**) (**Level I** [Cochrane]).

Complementary and other methods of pain relief in labour

22. Continuous or one-to-one support by a midwife or trained layperson during labour reduces analgesic use, rate of assisted and operative birth and dissatisfaction (**S**) (**Level I** [Cochrane Review]).
23. Immersion in water during labour may reduce the requirements for regional and neuraxial analgesia, with no difference in other maternal outcomes and insufficient evidence for neonatal outcomes compared to no immersion (**W**) (**Level I** [Cochrane Review]).
24. Relaxation by use of yoga, music or audio has limited benefit for pain relief or satisfaction in labour (**Q**) (**Level I** [Cochrane Review]).
25. Acupuncture and acupressure for labour pain may reduce pain, use of pharmacological pain relief and increase satisfaction with pain management vs standard care or placebo (**Q**) (**Level I** [Cochrane Review]); Caesarean section rates are unchanged (**R**) (**Level I** [Cochrane Review]).
26. Acupressure (vs sham) reduces labour pain, but has no effect on the use of pharmacological analgesia (**Q**) (**Level I** [Cochrane Review]).
27. Massage may decrease pain in the first stage of labour pain compared to standard care (**S**) (**Level I** [Cochrane Review]).
28. Transcutaneous electrical nerve stimulation has no effect on pain, interventions or outcomes in labour (**U**) (**Level I** [Cochrane Review]).
29. Biofeedback, sterile water injections intra- or subcutaneously and aromatherapy have no effect on labour pain or other outcomes (**U**) (**Level I** [Cochrane Review]).
30. Use of a birth ball may improve labour pain (**N**) (**Level I**).
31. Heat packs may reduce labour pain during the first and second stages (**N**) (**Level I** [Cochrane Review]).
32. Hypnosis (mostly antenatal interventions) may reduce analgesic requirements for labour pain (**R**) (**Level I** [Cochrane Review]).

Pain relief after Caesarean section

33. Local anaesthetic wound infiltration, in particular abdominal nerve blocks, reduces opioid consumption following Caesarean section (**U**) (**Level I** [Cochrane Review]).

34. Local anaesthetic transversus abdominis plane blocks reduce postoperative opioid requirements and pain scores after Caesarean section but only when intrathecal morphine is not used (**S**) (**Level I** [PRISMA]).
35. In relation to controls only and with no direct comparison between the two approaches, local anaesthetic transversus abdominis plane blocks performed by a posterior approach provide a longer duration of benefit versus the lateral approach after lower abdominal incision surgery including Caesarean section (**U**) (**Level I** [PRISMA]).
36. Intravenous paracetamol given before incision reduces opioid analgesic requirements after Caesarean section (**N**) (**Level I** [PRISMA])
37. Epidural (**U**) (**Level I** [QUOROM]) and intrathecal morphine (**U**) (**Level I**) and patient-controlled epidural analgesia (**U**) (**Level II**) provide effective analgesia after Caesarean section, but neuraxial morphine increases the rate of pruritus and nausea compared with systemic administration (**U**) (**Level I** [QUOROM]).
38. Intrathecal morphine (range of 100 mcg to 250 mcg) increases time to first analgesic request after Caesarean section, but pain scores and opioid consumption are unchanged, and postoperative nausea, vomiting and pruritus increased (**N**) (**Level I**).

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

☑ Remifentanil IV PCA for relief of labour pain carries a risk of maternal respiratory depression; use is recommended only if there is one-on-one continuous presence of a midwife, continuous oxygen saturation monitoring and continuous cardiotocograph monitoring (as an indirect method of detecting global hypoxaemia) (**U**).

☑ Transversus abdominis plane blocks after Caesarean section may result in high plasma concentrations of local anaesthetic and potential toxicity; minimum effective doses should be used (**U**).

9.1.4 | Pain management during lactation

Several general principles apply when administering analgesic and antiemetic medications for pain management during lactation:

- The choice of medications should be based on knowledge of their potential impact on breastfeeding and on the breastfed infant secondary to transfer in human milk;
- The lowest possible effective maternal dose of analgesic for the shortest possible duration is recommended (Reece-Stremtan 2017 **GL**);
- Breastfeeding is best avoided at times of peak medication concentration in milk and the infant should be observed for effects of medication transferred in breast milk.

A useful regularly updated peer reviewed resource is the USA National Library of Medicine's Drugs and Lactation Database (LactMed®) (https://www.ncbi.nlm.nih.gov/books/NBK501922/) (LactMed **GL**); this replaces the previously associated Toxicology Data Network (Toxnet) and LactMed@NIH smartphone/mobile applications.

Importantly, the use of many analgesic and antiemetic medications during lactation is off-label and the effects have not been adequately investigated, leaving clinical decisions to be made

on evidence derived from pharmacokinetic or observational studies, case reports and anecdotes. For most medications, information on infant outcome is inadequate (based on single dose or short-term administration or on case reports) or absent, so maternal consent is advisable and caution is warranted.

The principles of the passage of medications in human milk (LactMed **GL**; Verstegen 2019 **NR**; Ilett 2005 **NR**) including medications relevant to pain management (Ito 2018 **NR;** Bar-Oz 2003 **NR**; Spigset 2000 **NR**) have been reviewed. The maternal plasma concentration, which is influenced by the dose and the ability of the mother to metabolise the medication, is an important determinant of medication concentrations in breast milk. High lipid solubility, low molecular weight, low protein binding and the unionised state favour secretion into breast milk. Most medications have a milk-to-plasma ratio of ≤1 (Ito 2000 **NR**). Relative infant dose (RID) is a weight-adjusted time averaged (eg daily) dose of drug in milk ingested by the infant, expressed as a percentage of the time averaged maternal therapeutic dose on a body weight basis; a RID of 100% is the same as directly receiving a therapeutic dose per weight.

Infant exposure is often 0.5 to 4% of the maternal dose but infant medication metabolism may be impaired and much of the data is from single maternal dose studies rather than chronic therapy (LactMed **GL**; Berlin 2005 **NR**). A safe level of infant exposure to a medication has been arbitrarily defined as no more than 10% of the therapeutic dose for infants (or the adult dose standardised by weight if the infant dose is not known) (Ito 2000 **NR**). Until mature milk breastfeeding is established, only very small volumes of colostrum are secreted, so early breastfeeding is unlikely to pose a hazard (as overall dose is low including in the setting of lipophillic medications when concentrated vs plasma)(LactMed **GL**).

Guidelines include the following general recommendations (Mitchell 2020 **GL**; Martin 2018 **GL**; Reece-Stremtan 2017 **GL**). These recommendations are limited by the sparse clinical trial data in this patient population. Guidance is based on the experience of historical use, case series and pharmacokinetics (usually presented as relative infant dose [RID]% in breast milk related to the weight-adjusted maternal dose).

- Intracellular junctions between lactocytes close after 7 to 10 d postpartum. Exposure to maternal medications may be highest during 3 to 10 d postpartum;
- Opioids are the most concerning group of analgesics – dose and duration should be limited;
- Analgesic effectiveness needs to be weighed against adverse effects and safety concerns (particularly for opioids) because when maternal pain is well treated, breastfeeding outcomes are improved;
- There are differences in risk between different opioids. Codeine should be avoided as some mothers who are ultrarapid metabolisers produce higher concentrations of morphine with transfer into breast milk. Warnings against codeine use have been made (TGA 2016 **GL**) and extended to tramadol by some regulatory bodies (Medsafe 2020 **GL**; FDA 2019 **GL**) (see also Sections 10.4.4.5 and 10.4.4.12);
- Long acting opioids, and those with active metabolites (eg pethidine, morphine), have been associated with respiratory depression, cyanosis and bradycardia in neonates. Inconclusive evidence suggests doses of cumulative epidural fentanyl >150mcg may be associated with less successful breastfeeding;
- Mothers of healthy full-term infants can breastfeed as soon as they have recovered from anaesthesia. However, infants at risk of sensitivity (eg low birth weight, premature) should probably not be breastfed/receive maternal breast milk until 6 to 12 h after anaesthesia;
- Breastfed infants of mothers on high dose or long-term opioids need observation for drowsiness, poor feeding and neonatal abstinence syndrome (NAS);

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- Neonatal observation and monitoring is warranted if there is evidence of maternal CNS depression;
- Regional anaesthesia should have a lower risk than general anaesthesia for babies of breastfed mothers, because systemic absorption is very low, and postoperative regional analgesia may minimise the requirement for opioid analgesia;
- Neuraxial morphine and multimodal analgesia (including regional techniques such as transversus abdominis plane block and wound infiltration with local anaesthetic) reduces systemic opioid requirements.

Advice about specific agents includes:

- Paracetamol is widely used. Transfer into milk is low and appears to be less than the dosage given to infants;
- Aspirin in doses < 81mg/d has undetectable concentrations in human milk. Its use as chronic anti-platelet therapy is considered safe. Variable transfer into milk reflects nonlinear metabolism at higher analgesic dosages and these should be avoided (Mitchell 2020 **GL**);
- nsNSAIDs and Coxibs have a low transfer into milk (low %RDI) however they should be avoided in infants with ductal dependent cardiac lesions;
    - Concentrations in breast milk after oral ketorolac are low, but have not been measured after parenteral administration;
    - For diclofenac, limited studies demonstrate undetectable concentrations after oral or IM administration;
    - For naproxen, milk transfer is low and safe with short-term use (<1 wk), but there have been reports of neonatal GI disturbances after prolonged maternal use;
    - For indomethacin, milk transfer is low and is considered safe in the postpartum period;
- The effect of epidural analgesia on breastfeeding is uncertain (French 2016 **SR Level III-2**, 23 studies, n=36,128);
    - There is minimal data on effects of inhaled nitrous oxide by mothers on neonates. A review reported no adverse effect on suckling.

9.1.4.1 | Nonopioids

Paracetamol

The weight-adjusted maternal dose of paracetamol transferred to the newborn was 1.85% of a 1 g dose (Notarianni 1987 **Level IV PK**). Although glucuronide conjugation may be deficient in the newborn, the medication is considered safe as there have been no reports of adverse effects and concentrations in breast milk are a fraction of the recommended neonatal doses.

NSAIDs

Short-term maternal NSAID use during lactation appears safe for the healthy term infant; aspirin <150 mg/d maybe indicated for long-term use (Bloor 2013 **NR**). Despite similar proportional transfer to paracetamol, salicylates are eliminated slowly by the newborn, cause platelet dysfunction and have been associated with Reye's syndrome; aspirin in analgesic doses cannot be recommended as safe (Bar-Oz 2003 **NR**).

NSAIDs must be considered individually but, in general, concentrations in breast milk are low because they are weak acids and extensively plasma protein bound. In particular, ibuprofen has very low transfer (<1% weight-adjusted maternal dose), is short acting, free of active metabolites and has the best documented safety (Ito 2000 **NR**). Ibuprofen is therefore considered the ideal agent in this group (Montgomery 2012 **GL**).

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Diclofenac and ketorolac are minimally transported into breast milk and short-term or occasional use is compatible with breastfeeding (Rathmell 1997 **NR**). The safety of naproxen is less clear but it is also considered compatible. Indomethacin has been associated with central maternal adverse effects, such as agitation and psychosis, in previously healthy postnatal women (n=32) (Clunie 2003 **Level IV**).

Following a single 200 mg dose of celecoxib, <0.5% of the weight-adjusted maternal dose was present in breast milk, suggesting that breastfeeding during routine dosing poses a minimal risk (Gardiner 2006 **Level IV PK**; Hale 2004 **Level IV PK**). The relative infant dose of parecoxib and valdecoxib after a single dose of maternal parecoxib is very low (<1%) and neonatal neurobehavioural scores are within the normal range (Paech 2012 **Level IV PK**).

9.1.4.2 | Conventional and atypical opioids

With some provisos, the short-term use of opioids (2 to 3 d) is generally considered safe during lactation as most opioids are secreted into breast milk in low doses (LactMed **GL**; Ito 2018 **NR**; Hendrickson 2012 **NR**); the RID of opioids is usually low in the range of 1% to 5%, although individual variations exist (Ito 2018 **NR**).

Conventional opioids

An association between opioid exposure in breast milk and episodes of apnoea and cyanosis in infants has been described (Naumburg 1988 **Level IV**), leading some to suggest that opioids should be avoided if the newborn experiences such events during the first week of life. Cases of infant toxicity due to human milk exposure are reported (LactMed **GL**; Madadi 2007 **CR**), mostly involving codeine in infants <2 mth of age, therefore infants should be monitored for drowsiness (Hendrickson 2012 **NR**) (see also Sections 1.7.3 and 4.1.1).

RID (relative infant dose) of morphine is 2 to 3%, however, M6G exposure might be higher (Ito 2018 **NR**). The oral bioavailability in the infant is low (about 25%), so smaller amounts reach the infant's plasma (Feilberg 1989 **Level IV PK**). In mothers treated with IV PCA morphine for 48 h following Caesarean section, concentrations of morphine and M6G were low in breast milk, suggesting minimal medication would be transferred to the newborn (Baka 2002 **Level IV PK**). Compared with IV PCA pethidine (meperidine), there is significantly less neurobehavioural depression with IV PCA morphine (Wittels 1990 **Level III-2**). Overall, short-term morphine use post-partum is compatible with safety in breast feeding (Ito 2018 **NR**).

Pharmacokinetic studies suggest the more lipophilic opioids, such as fentanyl and alfentanil, are unlikely to cause problems. Following a single dose of IV fentanyl, the weight-adjusted maternal dose received by the newborn was 3%, concentrations in colostrum became undetectable within several hours and the nursing infant appeared unaffected (Steer 1992 **Level IV PK**; Nitsun 2006 **Level IV PK**).

Breastfed infants whose mothers received IV PCA pethidine were less alert and oriented to auditory cues after Caesarean section than infants of mothers receiving morphine (Wittels 1997 **Level III-2**, n=47). As norpethidine (normeperidine) accumulates in breast milk with repeated use and has a very slow neonatal elimination, pethidine use during breastfeeding is not recommended (Ito 2000 **NR**). The American Academy of Pediatrics (AAP) recommends against use of IV pethidine in breastfeeding mothers (Sachs 2013 **GL**). Pethidine PCEA results in much lower plasma concentrations than systemic pethidine, with lower infant exposure to pethidine and norpethidine (1.8%) (Al-Tamimi 2011 **Level IV PK**) and may be a low risk method during very early lactation (Sakalidis 2013 **Level III-2**).

Caution has been advised regarding the use of codeine during breastfeeding (FDA 2019 **GL**; TGA 2016 **GL**). Codeine has a milk-to-plasma ratio of slightly more than 1 and was previously suggested to be generally safe with short-term use, but should be used with caution when dosing

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is repeated (Meny 1993 **PK**; Hendrickson 2012 **NR**). A case-control study that included a newborn who died while breastfed by a mother taking codeine, has highlighted that breastfed infants of mothers who are extensive or ultrarapid metabolisers (20–40% of the population, depending on ethnicity, with duplications of CYP2D6 gene) are at increased risk of life-threatening CNS depression (Madadi 2009 **Level III-2**). A number of similar cases have been reported and healthcare workers and breastfeeding mothers should be aware of this risk (Madadi 2008 **Level IV**, n=35). A relationship between infant CNS symptoms (decreased alertness, lethargy, poor feeding) and maternal symptoms, codeine dose and, in some cases CYP2D6 phenotype, has been identified (Madadi 2009 **Level III-3**, n=72 [17 symptomatic]). Pharmacokinetic simulation suggests potentially toxic morphine concentrations can be reached in the newborn within 4 d of repeated maternal codeine administration (Willmann 2009 **PK**).

Oxycodone shows a relative infant dose (RID) of 1.5 to 8.5%; it has high oral bioavailability and is concentrated in human breast milk, so breastfed infants may receive >10% of a therapeutic dose, and a USA guideline cautions against its use (Sachs 2013 **GL**), while others suggest a maximum maternal daily dose of 30 to 40 mg (LactMed **GL**; Mitchell 2020 **GL**). Poor CYP2D6 metabolisers may have decreased clearance of oxycodone and ultrarapid metabolisers higher concentrations of the more potent metabolite oxymorphone, leading to sedation (Samer 2010 **Level II PK**, n=10 [5-arm crossover], JS 5). The safety with repeated maternal dosing has been questioned (Ito 2000 **NR**; Lam 2012 **Level III-2**); a case of opioid toxicity in a breastfed newborn of a mother taking oxycodone has been reported (Timm 2013 **CR**). Oxycodone use during breastfeeding resulted in increased rate of CNS depression of the newborn vs paracetamol (20.1 vs 0.5%) (OR 46.16; 95%CI 6 to 344) but no difference to codeine (16.7%) (OR 0.79; 95%CI 0.46 to 1.38) (Lam 2012 **Level III-2,** n=533). As a component of multimodal analgesia in the first 72 h after Caesarean section, there may be minimal risk to breastfeeding infants as only a low volume of milk is ingested during this period. Only 1 of 44 newborns had detectable plasma concentrations and none were over sedated despite maternal exposure up to 90 mg/d (Seaton 2007 **Level III-3**).

After IN hydromorphone exposure of the mother, 0.67% of the maternal dose of hydromorphone (adjusted for body weight) is transferred into breast milk (Edwards 2003 **Level IV PK**).

Hydrocodone is metabolised in small quantities to a more potent metabolite, hydromorphone, and ultrarapid metabolisers exist. The RID is 2.4% (Sauberan 2011 **Level IV PK**) and possible infant toxicity has been reported (Hendrickson 2012 **NR**).

Methadone is considered compatible with breastfeeding; even with high methadone doses, breast milk concentrations were relatively low at 2.1–3.5% (Bogen 2011 **Level IV PK**). Plasma concentrations of methadone were low in infants of breastfeeding mothers on methadone-maintenance programs and no effect on infant neurobehavioural outcomes were found on d 3, 14 and 30 following birth (Jansson 2008 **Level III-3**). Breastfeeding reduced NAS in newborns of mothers on methadone substitution and is encouraged (McQueen 2011 **Level III-2**).

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Atypical opioids

Buprenorphine has very low passage into breast milk and the combined RID of both buprenorphine and its active metabolite norbuprenorphine is <1% (Ilett 2012 **Level IV PK**). When used for drug substitution therapy in breastfeeding mothers, buprenorphine did not lead to adverse effects in newborns up to 4 wk postnatally (Gower 2014 **Level IV**).

Information regarding tapentadol in lactaction is limited to 4 case reports of infant exposure during breastfeeding, with no adverse reactions reported (LactMed **Level IV**).

Tramadol (100 mg every 6 h) on d 2–4 after Caesarean section was associated with a milk-to-plasma ratio of 2.2, a relative infant dose of 2.9% and no detectable behavioural effects in the infants (Ilett 2008 **Level III-2**). However, as with other medications, these data cannot be directly extrapolated to long-term use at later postpartum stages when the volume of ingested milk is higher. The use of tramadol during pregnancy and in lactation has been reviewed (LactMed Database 2019 **GL**; Bloor 2012 **NR**); the opinion being that during early lactation short-term use of tramadol appears unlikely to cause harm to healthy term infants. However, the USA's FDA has elected to apply the same warning as for codeine to tramadol (FDA 2019 **GL**); New Zealand has followed this lead (Medsafe 2017 **GL**), but not the Australian TGA to date.

10.1.4.3 | Other analgesics and medications related to pain relief

Epidural local anaesthetics

After epidural administration, local anaesthetics showed acceptable milk-to-plasma ratios of 1.1 for lidocaine (lignocaine), 0.34 for bupivacaine (Ortega 1999 **PK**) and 0.25 for ropivacaine (Matsota 2009 **PK**). These are considered safe (Rathmell 1997 **NR**), including for anaesthesia and analgesia during very early lactation (Hirose 1996 **Level II**, n=30, JS 2; Matsota 2009 **Level IV**, n=25). Use of epidural analgesia (local anaesthetic ± fentanyl) during labour (Chang 2005 **Level III-3**) or as PCEA after Caesarean section (Matsota 2009 **Level IV**) did not influence neurobehavioural scores in healthy term infants.

The possible effect of epidural analgesia on breastfeeding is complex and may not only be related to medications administered, with selection bias (lack of randomised trials), nonstandardised breastfeeding evaluations and failure to control for confounding variables making firm conclusions impossible (Szabo 2013 **NR**). In a study of 1,054 nulliparous women randomised to different methods of epidural analgesia in labour and matched with 351 nonepidural controls, there was no association with breastfeeding initiation (Wilson 2010 **Level III-2**, n=1,405). However, epidural analgesia in labour was associated with an increased risk of breastfeeding cessation at 30 d after adjusting for demographic and intrapartum factors (HR 1.26; 95%CI 1.1 to 1.44) (Dozier 2013 **Level III-2**, n=772).

Alpha-2 agonists

The effects of clonidine on breastfeeding have not been studied, but a single neuraxial dose is unlikely to have any adverse effect. As a neuraxial adjuvant, it may reduce requirements for systemic opioids in the postpartum period (Martin 2018 **GL**).

Dexmedetomidine has been used as an adjuvant infusion during Caesarean section; a breastfeeding infant would receive a negligible dose of 0.04 to 0.098% RID (Nakanishi 2017 **Level IV PK**).

Alpha-2 delta ligands

The alpha-2-delta ligands are increasingly popular analgesics for acute pain after operative birth, especially among women with neuropathic pain, opioid tolerance or where opioid dose minimisation is recommended. For gabapentin, the milk-to-plasma concentration was 0.86, the RID was 2.4% and no adverse effects were noted in the infant (Ohman 2005 **Level IV PK**). While

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suggestive of safety during lactation, a careful individual risk-benefit analysis was suggested (Kristensen 2006 **CR PK**). There are also limited human data on pregabalin during breastfeeding. Pregabalin is a small molecule that undergoes negligible metabolism and is thus expected to be excreted in breast milk. A breastfed infant of a mother on long-term pregabalin (for epilepsy) had serum concentrations of about 8% of the maternal concentrations, although no adverse effects were observed (Ohman 2011 **Level IV PK**). During a much later stage of lactation, the mean milk-to-plasma ratio was 0.53 to 0.76; and 0.2% of the maternal daily dose was secreted into breast milk, representing 7% of the body weight normalised maternal dose (Lockwood 2014 **Level IV PK**). The medication was well tolerated and the overall safety of anticonvulsants in breastfeeding mothers is regarded as high, with continuation of breastfeeding recommended (Reimers 2012 **NR**). Gabapentin is considered the safer of the two agents given its less likely transfer in breast milk (Reece-Stremtan 2017 **GL**).

Ketamine

Ketamine has limited data on transfer to breast milk. Given the uncertainty over neurodevelopmental effects with infant/toddler ketamine anaesthesia exposure, concerns exist over its use (Yan 2014 **Level III-3**). There is insufficient evidence to support its long-term safety when this agent is used as an infusion in breastfeeding mothers (Martin 2018 **GL**). A single study found there was no effect on duration of breast feeding (Suppa 2012 **Level II**, n=56, JS 4).

Antiemetics

There is very little information about antiemetic use and breastfeeding and, in almost all cases, the manufacturers (approved product information) do not recommend their use during lactation; although in practice most antiemetics are used, with the best data for metoclopramide (Pistilli 2013 **NR**). Metoclopramide is used both for cancer chemotherapy and to increase milk production, so although it concentrates in human milk the RID is much lower than the therapeutic dose in paediatrics (Kauppila 1983 **Level IV PK**) and authors have reported the absence of adverse effects in newborns whose mothers were exposed (Pistilli 2013 **NR**). Animal studies suggest possible CNS effects in the newborn but human anecdotal experience is favourable with medications such as metoclopramide, domperidone and dexamethasone. Ondansetron (and other 5HT-3 blockers), dexamethasone, and metoclopramide are recommended over the more sedating agents prochlorperazine and promethazine, which are considered safe, but could cause maternal sedation (Martin 2018 **GL**).

Laxatives

Stool softeners and laxatives (docusate, senna and bisacadoyl) are minimally absorbed from the gastrointestinal tract, and are thus considered safe for use during lactation (LactMed **GL**).

See Table 9.3 for recommendations.

Table 9.3 | The breastfeeding patient and medications used in pain management

Medication	Comments
Opioids Buprenorphine, codeine, dextropropoxyphene, fentanyl, hydromorphone, methadone, morphine, oxycodone, tramadol	Safe to use occasional doses, but avoid codeine. Use repeated doses with caution, especially if infant is premature or <4 wk old; monitor mother and infant for sedation and other adverse effects
Paracetamol	Safe to use

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Medication	Comments
Aspirin	Avoid due to theoretical risk of Reye's syndrome (safe for low-dose antiplatelet use < 150 mg/d)
Other NSAIDs Non-selective NSAIDs (nsNSAIDs), COX-2 Selective inhibitors(coxibs)	 Safe to use, ibuprofen is preferred Limited data; appear safe
Ketamine	Limited data
SSRIs: Sertraline, citalopram, fluoxetine, escitalopram, fluvoxamine, paroxetine	SSRIs are used in postnatal depression (some consider sertraline the preferred antidepressants in breastfeeding); avoid fluoxetine because of its long half-life
TCAs: Amitriptyline, clomipramine, dothiepin (dosulepin), doxepin, imipramine, nortriptyline, trimipramine	TCAs have been used to treat postnatal depression. Avoid doxepin if possible; a single case of neonatal respiratory depression has been reported
SNRIs Duloxetine, venlafaxine, desvenlafaxine	Low concentrations in milk: check baby for sedation and adequate weight gain. Consider using an alternative to duloxetine until more is known about it
Anticonvulsants Carbamazepine	 Safe to use; monitor infant for drowsiness and poor suckling
Phenytoin sodium	Safe to use
Sodium valproate	Should be safe to use (one report of adverse effects); consider monitoring baby for petechial rash
Clonazepam	Risk of sedation in infant; contact specialised information service
Tiagabine	Contact specialised information service
Gabapentin, pregabalin, lamotrigine, topiramate	Pass into breast milk (see above); contact one of the pregnancy drug information centres
Antiemetics, antinauseants *Phenothiazines:* Prochlorperazine	 Safe to use
Promethazine	Limited data but short-term use appears safe. Sedation of mother is main concern
Metoclopramide	Safe to use (used to stimulate lactation)

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Medication	Comments
Granisetron, ondansetron, tropisetron	Contact specialised information service; no data but 1–2 doses after birth appear safe
Domperidone	Used during first months of breastfeeding to stimulate lactation; mother may be less drowsy than with metoclopramide
Droperidol, haloperidol	Avoid if possible, or contact one of the pregnancy medication information centres; if used, monitor infant for sedation

Source: Modified information taken with permission from data published in Australian Medicines Handbook 2020; see also LactMed and Mitchell 2020.

KEY MESSAGES

1. Local anaesthetics, paracetamol and several NSAIDs, in particular ibuprofen, are considered to be safe in the lactating patient (**U**) (**Level IV**).
2. Morphine, fentanyl, methadone, and short-term oxycodone immediately after delivery are considered to be safe in the lactating patient and are preferred over pethidine (**U**) (**Level IV**).
3. Repeated dosing of codeine or oxycodone in lactating patients should be avoided if possible and the infant monitored for central nervous system depression (**S**) (**Level IV**).

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

☑ Prescribing medications during lactation requires consideration of possible transfer into breast milk, uptake by the infant and potential adverse effects for the infant; it should follow available prescribing guidelines (**U**).

☑ Breastfed neonates and infants may become sedated from the transfer of maternal medications; in this case, observation and monitoring of the infant and seeking medical advice is warranted. Maternal sedation may be an early warning sign (**N**).

9.1.5 | Pain in the puerperium

Pain during the puerperium is common and of multiple aetiologies, most often being perineal or uterine-cramping pain initially, and breast pain from postpartum d 4. In the first 6 mth postpartum, backache was reported by 44% of women and perineal pain by 21% (Brown 1998 **Level IV**). Headache has multiple aetiologies, mainly primary causes such as tension, migraine and musculoskeletal headache and, in a large observational study was reported by 40% of women one wk after delivery (Goldszmidt 2005 **Level IV**, n=985). Severe perineal and uterine pain limited mobility during maternal-infant bonding and perineal trauma and pain was associated with delayed resumption of sexual intercourse after birth (Williams 2007 **Level IV**). Breast, especially nipple, pain may result in abandonment of breastfeeding (Morland-Schultz 2005 **Level**

III-3 SR). Chronic postnatal pain is also a risk factor for postnatal depression (Gaudet 2013 **Level IV**).

9.1.5.1 | Perineal pain

Perineal pain - prevention and physical treatments

Many obstetric and surgical factors contribute to perineal trauma and episiotomy. After adjusting for parity, perineal trauma and length of labour, women with instrumented vs unassisted vaginal deliveries reported more perineal pain (Thompson 2002 **Level IV**; Fahey 2017 **NR**). Restrictive use vs routine mediolateral episiotomy reduced the rate of episiotomy from 75 to 28% and reduced the risk of severe perineal trauma and the requirement for suturing but did not influence the incidence or degree of perineal pain (Carroli 2009 **Level I** [Cochrane], 8 RCTs, n=5,541).

In comparison with interrupted suturing methods, continuous suturing reduced pain incidence for up to 10 d (particularly suturing of all layers) (RR 0.65; 95%CI 0.60 to 0.71) (4 RCTs, n=2,488) but not for skin only (RR 0.89; 95%CI 0.73 to 1.07) (2 RCTs, n=1,217) and reduced postpartum analgesic use (RR 0.70; 95% CI 0.58 to 0.84) (for all layers 2 RCTs and skin only 2 RCTs, n=2,973) (Kettle 2007 **Level** [Cochrane], 7 RCTs, n=3,822).

There is only limited evidence to support the effectiveness of local cooling treatments (ice packs, cold gel pads, cold/iced baths) for relieving perineal trauma pain vs various alternatives or no interventions (East 2012 **Level I** [Cochrane], 10 RCTs, n=1,825). Ice packs provided superior analgesia vs no treatment for 24–72 h postpartum (RR 0.61; 95%CI 0.41 to 0.91) (1 RCT, n=208).

Although improvement in perineal pain has been reported with US, there is insufficient evidence to fully evaluate efficacy (Hay-Smith 2000 **Level I** [Cochrane] 4 RCTs, n=659). Ear acupressure did not relieve perineal trauma pain in the first 48 h after birth (Kwan 2014 **Level II**, n=266, JS 5)

For women without prior vaginal birth, antenatal perineal massage (from 35 wk gestation) reduced the incidence of perineal trauma requiring suturing (NNT 15; 95%CI 10 to 36) and the requirement for an episiotomy (NNT 21; 95%CI 12 to 75) (Beckmann 2013 **Level I** [Cochrane], 4 RCTs, n=2,497). Effects on acute postpartum pain have not been reported, but a reduction in the incidence of perineal pain at 3 mth postpartum was found in women who used antenatal perineal massage and had previously given birth vaginally (NNT 13; 95%CI 7 to 60) (1 RCT, n=376).

Perineal pain - pharmacological treatments

More women with perineal pain experience pain relief from paracetamol than from placebo (RR 2.14; 95%CI 1.59 to 2.89) (Chou 2013 **Level I** [Cochrane] 11 RCTs, n=1,367); fewer women require additional analgesia (RR 0.34; 95%CI 0.21 to 0.55) (8 RCTs, n=1,132).

A single dose of NSAID vs placebo provided adequate pain relief at 4 h (RR 1.9; 95%CI 1.64 to 2.23) (10 RCTs, n=1,573) and 6 h (RR 1.92; 95%CI 1.69 to 2.17) (17 RCTs, n=2,079) after administration (Wuytack 2016 **Level I** [Cochrane], RCTs 28, n= 4,181). NSAIDs were more effective than paracetamol at 4 h (RR 1.54; 95%CI 1.07 to 2.22) (3 RCTs, n=342), but not at 6 h after administration.

Suppositories of nsNSAIDs reduce perineal pain in the first 48 h postpartum more effectively than placebo (Hedayati 2003 **Level I** [Cochrane], 3 RCTs, n=249). Rectal indomethacin was as effective as rectal diclofenac (Yildizhan 2009 **Level** II, n=200, JS 3). IV dexketoprofen was as effective as IV paracetamol (Akil 2014 **Level II**, n=95, JS 5). Both oral celecoxib and diclofenac reduced perineal pain, with celecoxib showing a slight advantage with respect to pain scores at rest and the incidence of gastrointestinal symptoms (Lim 2008 **Level II**, n=329, JS 5).

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Topical local anaesthetics (lignocaine, cinchocaine, pramoxine plus hydrocortisone preparations) or placebo did not improve perineal pain in the 24 h postpartum (Hedayati 2005 **Level I** [Cochrane], 8 RCTs, n=976). The use of systemic analgesics was not standardised across these studies and maybe a confounding factor. Following mediolateral episiotomy repair under epidural analgesia, a pudendal block with ropivacaine improved pain scores and reduced the proportion of women requiring additional analgesia (Aissaoui 2008 **Level II,** n=42, JS 4).

9.1.5.2 | Postpartum breast and nipple pain

Painful breasts are a common reason for ceasing breastfeeding (Amir 2003 **NR**). Management is firstly directed toward remedying the cause, whether this is infant-related (incorrect attachment, sucking, oral abnormalities), lactation-related (breast engorgement, blocked ducts or forceful milk ejection), nipple trauma, dermatological or infective problems (candida or mastitis) or other causes. There is insufficient evidence to recommend glycerine gel dressings, breast shells with lanolin, lanolin alone or an all-purpose nipple ointment for treatment of nipple pain (Dennis 2014 **Level III-1 SR** [Cochrane], 4 studies, n=656). Irrespective of treatment, nipple pain resolves by 7 to 10 d postpartum for most women. Guidance regarding the usual duration of pain may help women to continue to breastfeed.

Symptomatic treatments for breast engorgement have been assessed (Mangesi 2016 **Level III-3 SR**, 13 studies, n=919): acupuncture (2 studies), acupressure (1 study), scraping therapy (*Gua Sha*) (1 study), cabbage leaves (3 studies), cold gel packs (1 study), electromechanical massage (1 study) and pharmacological treatments (3 studies) did not result in a faster resolution of symptoms vs no treatment.

Mastitis is defined by at least two breast symptoms (pain, redness or lump) and at least one of fever or flu-like symptoms. The incidence is 17–33% of breastfeeding women, most episodes occurring in the first 4 wk postpartum (Amir 2007 **Level IV**). Infective mastitis is most commonly due to *Staphylococcus aureus* and noninfective mastitis is equally common. There is insufficient evidence to confirm the efficacy of antibiotics in relieving symptoms, with only two trials meeting the inclusion criteria for analysis (Jahanfar 2013 **Level I** [Cochrane], 2 RCTs, n≈125).

9.1.5.3 | Postpartum uterine pain

Uterine pain or "after pains" often worsen with increasing parity and are experienced by most multiparous women. Uterine contraction results from the release of oxytocin from the posterior pituitary gland, especially in response to breastfeeding. Lower abdominal pain may be mild to severe, accompanied by back pain and is described as throbbing, cramping and aching. Ergot alkaloids during the third stage of labour increase the requirement for analgesia for pain after birth due to persistent uterine contraction (RR 2.53; 95%CI 1.34 to 4.78), but also decreases mean blood loss and the incidence of postpartum haemorrhage vs no uterotonic medications (Liabsuetrakul 2007 **Level I** [Cochrane], 6 RCTs, n=3,941).

NSAIDs are superior to placebo (3 RCTs, n=204) and paracetamol (1 RCT, n=48) for the relief of "after pains" following vaginal birth (Deussen 2011 **Level I** [Cochrane], 18 RCTs, n=1,498). Paracetamol is no better than placebo (1 RCT, n=48). Data on opioids are contradictory and do not permit an assessment of their efficacy for this indication.

High-intensity TENS was more effective than low-intensity TENS for treating postpartum uterine pain but also produced more local discomfort (Olsen 2007 **Level III-2**).

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KEY MESSAGES

1. Routine episiotomy does not reduce perineal pain (**U**) (**Level I** [Cochrane Review]).
2. Continuous suturing of all layers compared with interrupted suturing for repair of episiotomy or second-degree tears reduces perineal pain and analgesic use in the postpartum period (**U**) (**Level I** [Cochrane Review]).
3. Paracetamol and NSAIDs are effective in treating perineal pain after childbirth compared with placebo (**S**) (**Level I** [Cochrane Review]).
4. NSAIDs, but not paracetamol, are effective in treating pain from uterine cramping after vaginal birth (**U**) (**Level I** [Cochrane Review]).
5. There is limited evidence to support the effectiveness of local cooling treatments in treatment of perineal pain after childbirth (**U**) (**Level I** [Cochrane Review]).
6. Topical local anaesthetic preparations are not effective for perineal pain after childbirth (**U**) (**Level I** [Cochrane Review]).
7. There is insufficient evidence to recommend any specific treatments for nipple pain and breast engorgement (**U**) (**Level I** [Cochrane Review]).

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

☑ Pain after childbirth requires appropriate treatment as it coincides with new emotional, physical and learning demands and may trigger postnatal depression (**U**).

☑ Management of breast and nipple pain should target the cause (**U**).

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9.2 | The older patient

The need to manage acute pain in older patients is becoming more common as the population ages. Advances in anaesthetic and surgical techniques mean that increasingly older patients, including patients >100 y old (Konttinen 2006 **Level IV**), are undergoing major surgery (Kojima 2006 **Level IV**). Medical conditions are more likely in older people and may lead to acute pain; these include acute exacerbations of arthritis, osteoporotic fractures of the spine, cancer and also pain from other acute medical conditions including ischaemic heart disease, herpes zoster and peripheral vascular disease. Furthermore, older adults are more likely to undergo potentially painful medical procedures, and experience trauma as well as surgery.

Adults of advanced age are a particularly vulnerable group. Factors that can combine to make effective control of acute pain in the older person more difficult than in younger patients include: a higher prevalence of coexistent diseases and concurrent medications, which increases the risk of drug-drug and disease-drug interactions; the presence of common geriatric syndromes, including cognitive impairment and frailty; age-related changes in physiology, pharmacodynamics and pharmacokinetics; altered responses to pain; and difficulties with assessment of pain, including problems related to cognitive impairment (Gibson 2018 **NR**).

National guidelines on pain management in the elderly have been developed (APS 2019 **GL).** Specific geriatric perioperative guidelines have been developed for general surgery (Mohanty 2016 **GL**) and hip fracture surgery (ACSQHC 2016 **GL**).

Furthermore, the elderly may fail to report pain because they think it is a normal part of ageing, or they acquiesce to family members/medical staff or have fears about intervention or the unwanted effects of analgesics, especially opioids (Fine 2012 **GL**). Sensory impairment and social isolation may further impair the effective treatment of pain. Lastly, the relative paucity of dedicated age-specific research on pain and its management, including the lack of randomised controlled trials conducted in older populations compounds vulnerability due to the lack of appropriate evidence to help guide clinical practice (Reid 2015 **NR**). Information on the safety, efficacy and pharmacokinetics in the elderly patient (>65 y) is often missing from drug registration trials and regulatory body documents. A structured cross-sectional review of publicly available initial drug registration data (FDA) found that limited data on older patients was present in the following areas: pharmacokinetics (62%) and safety (42%) and efficacy (45%) (Ruiter 2019 **Level IV SR**).

9.2.1 | Physiology and perception of pain

Several reviews summarise the age-related changes that occur in the neurophysiology of nociception and pain perception (Gagliese 2005 **Level III-2**; Gibson 2018 **NR**; Farrell 2012 **NR**; Gibson 2004 **NR**; Yezierski 2012 **NR BS**). Compared with a younger person's nervous system, there are extensive changes in the older person's structure, neurochemistry and function of both peripheral and central nervous systems, including neurochemical deterioration of the opioid and serotonergic systems. Therefore, there may be changes in nociceptive processing, including impairment of pain-inhibitory systems.

9.2.1.1 | Neurophysiological changes

In the peripheral nervous system there is a decrease in the function and density of both myelinated and, particularly, unmyelinated peripheral nerve fibres (Kemp 2014 **EH**; Heft 2017 **NR**). There are also increased number of fibres with damage or degeneration and conduction velocity

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slowing. In rats, reductions in substance P, CGRP and somatostatin levels have been reported (Yezierski 2012 **NR BS**). Similar structural and neurochemical changes have been noted in the CNS. In older humans, there are sensory neuron degenerative changes and loss of myelin in the dorsal horn of the spinal cord as well as reductions in substance P, CGRP and somatostatin levels. Age-related loss of neurons and dendritic connections is seen in the human brain, particularly in the cerebral cortex; including those areas involved in nociceptive processing. The synthesis, axonal transport and receptor binding of neurotransmitters also change. Opioid-receptor density is decreased in the brain but not in the spinal cord, and there may be decreases in endogenous opioids. However, the functional consequences of such age-related changes remain a subject of debate. Functional MRI studies show more age-related similarities than differences in the magnitude of activation in response to acute noxious mechanical stimulation (Cole 2010 **EH**; Farrell 2012 **NR**). A specific difference that has been identified was reduced activation in the middle insular cortex and primary somatosensory cortex in response to noxious heat (Tseng 2013 **EH**).

Variations in pain perception are best determined in controlled situations where the severity of the noxious stimulus is standardised, and psychopathology (such as impaired cognitive function or mood) is absent (Radinovic 2014 **Level IV**; Kunz 2009 **EH**). Assessment of variation can be done with experimental pain stimuli or, to a lesser extent, with standard medical procedures such as venipuncture and wound dressings.

Studies of the effects of experimental pain stimuli (brief noxious stimuli without tissue injury) on pain thresholds are conflicting and results depend on the type of stimulus used. Psychophysical studies using experimental pain provide limited evidence for a modest increase in pain threshold (ie reduced sensitivity to mild pain) with advancing age, particularly for thermal pain stimuli (Tseng 2013 **EH**; Gibson 2004 **NR**) and radiant more than contact heat (Lautenbacher 2017 **Level III-2 SR EH** [PRISMA], 31 studies [pain threshold], n=2,912; 9 studies (pain tolerance threshold], n=11,295). The results for electrical, mechanical and ischaemic stimuli are equivocal, with reports of no change or even decreased pain thresholds in adults of advanced age (El Tumi 2017 **Level III-2 SR EH** [PRISMA], 12 studies, n unspecified). Of note, there were racial differences similar to those found in younger patients and increased decrement in the lower extremities (Riley 2014 **Level III-3 EH**). The applicability of these experimental observations to pain occurring with tissue injury remains uncertain. These findings could indicate some deficit in the early warning function of pain with reduced capacity to identify a painful stimulus and that it might cause tissue injury (Hadjistavropoulos 2014 **NR**; Gibson 2006 **NR**). For example, in patients with an acute myocardial infarction, greater intensity of chest pain was inversely correlated with lower pain threshold (Granot 2007 **Level III-3 EH**); presentation and treatment of those patients with less pain may therefore be delayed.

Studies looking at age-related changes in pain tolerance are limited, but in general, using a variety of experimental pain stimuli, there is a reduced ability in older people to endure or tolerate intense pain (Farrell 2012 **NR**; Gibson 2003 **NR EH;**). Lessened ability to tolerate pain could mean that severe pain may have a greater impact on the more vulnerable older person.

Also, in the elderly, there are significantly smaller increases in pain thresholds following prolonged noxious stimulation and a prolonged recovery from hyperalgesia (Zheng 2009 **EH**; Gibson 2006 **EH**; Zheng 2000 **EH**). Using experimental pain stimuli in the elderly, there is a lower threshold for temporal summation (Lautenbacher 2012 **Level III-2 SR EH**, 25 studies, n= 13,580; Naugle 2017 **Level III-2 EH**, n=189; Gibson 2004 **EH**); older subjects showed temporal summation with trains of brief electrical stimuli at all stimulation frequencies, unlike younger subjects where this was not seen at the lower frequencies. Temporal summation of thermal stimuli was increased in older subjects vs younger subjects. Summation was more prolonged but otherwise temporal summation of pressure pain showed no age-related effects. After topical application of capsaicin, the magnitude and duration of primary hyperalgesia was similar in both older and younger

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subjects but secondary hyperalgesia (tenderness) resolved more slowly in older people. The proposed underlying mechanism for these findings is impaired descending inhibitory mechanisms and reduced capacity to down-regulate after sensitisation thereby leading to prolonged recovery in the older person (Gagliese 2005 **NR**). Findings from human psychophysical studies support the contention of impaired function in endogenous pain inhibitory systems in older adults (Riley 2017 **Level III-2 EH**, n=17; Grashorn 2013 **Level III-2 EH**, n=64), and this is also consistent with many earlier animal studies (Gagliese 2000b **BS**).

9.2.1.2 | Clinical implications

Several clinical reports (summarised in Cole 2006 **Level III-3 EH**; Pickering 2005 **NR**; Gibson 2003 **NR**) suggest that pain symptoms and presentation may change in the older patient; pain becomes a less frequent or a less severe symptom of a variety of acute medical conditions. Examples of differences in reports of acute pain are commonly related to abdominal pain (eg associated with infection, peptic ulcer, cholecystitis, or intestinal obstruction) or chest pain (eg myocardial ischaemia or infarction or pneumonia) and are in general agreement with the experimental finding of increased pain thresholds in the older person.

Compared with the younger adult with the same clinical condition, the older adult may report less pain or atypical pain, report it later or report no pain at all (Pickering 2005 **NR**). Examples in older patients include the absence of right upper quadrant or epigastric pain in 85% with cholecystitis, in 30% of those with peptic ulcer disease and up to 90% with pancreatitis, while in those with advanced peritonitis, pain may be a symptom in only 55%. Chest pain is absent, or pain is atypical, in up to 33% of older patients with acute myocardial infarction and 50% with unstable angina. This suggests a contradiction to data on experimental pain (reduced tolerance to intense pain – see Section 9.2.1.1 above); however, many clinical states are characterized by moderate to strong pain, but not intense pain (approaching tolerance levels). Age-related decrease in the efficiency of ascending pathways (noted by an increased pain threshold) and a concomitant decrease in the efficiency of descending inhibitory pathways (as noted by reduced pain tolerance) may explain this discrepancy.

Pain intensity after surgery may also be less. Older patients, matched for surgical procedure, reported less pain in the postoperative period: pain intensity decreased by 10–20% each decade after 60 y of age (Thomas 1998 **Level III-2**). Older men undergoing radical prostatectomy reported less pain on a present pain intensity scale and MPQ (but not a VAS) in the immediate postoperative period and used less PCA opioid than younger men undergoing the same procedure (Gagliese 2003 **Level III-2**). In a study of pain following IV cannula placement (a relatively standardised pain stimulus), older patients reported significantly less pain than younger patients (WMD -15/100; 95%CI -26 to -4) (Li 2001 **Level III-2**). An observational study of patients undergoing painful procedures (wound care, drain and femoral sheath removal, tracheal suctioning, turning, and central line insertion) found there was no age-related difference in pain scores (NRS) between the young and the elderly (>65 y), however the younger patients reported more pain-related distress (Stotts 2007 **Level III-2**, n=5,957).

9.2.2 | Assessment of pain

The need for specific methods to assess pain in the elderly is recognised in national guidelines (Schofield 2018 **SR GL).** These also emphasise the need for education of healthcare staff in the use of patient appropriate pain assessment tools (Sirsch 2020 **SR GL**).

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Even though cognitively impaired patients are just as likely as cognitively intact patients of the same age to have painful conditions and illnesses, the number of pain complaints and the reported pain intensity decreases with increasing cognitive impairment (Radinovic 2014 **Level IV**; Hadjistavropoulos 2014 **NR**; Lukas 2012 **NR**). Reasons for this could include diminished memory, impairment of capacity to report, or it could be that less pain is experienced.

Dementia

Studies in patients with dementia suggest that they may not experience less pain (Monroe 2014 **Level III-2**; Hadjistavropoulos 2014 **NR**). Functional MRI responses following mechanical pressure stimulation showed no evidence of diminished pain-related activity in patients with Alzheimer's disease vs age-matched controls, indicating that pain perception and processing were not diminished in these patients (Cole 2006 **Level III-2**). Moreover, in those with dementia, facial expressions are increased in response to controlled levels of noxious stimulation (Kunz 2009 **Level III-2 EH;** Kunz 2007 **Level III-2 EH**) and immediately following a uniform clinical pain stimulus, such as venipuncture, pain on mobilisation (Hadjistavropoulos 2014 **NR**) or dental local anaesthetic injection (Hsu 2007 **Level III-2**). The increased facial expressions in response to pain could suggest an increased sensitivity to pain in persons with dementia (Kunz 2007 **Level III-2**) or that facial actions represent a different aspect of the pain experience: a reflexive, automatic response which may be disinhibited in persons with cognitive impairment. In support of this conclusion, persons with dementia have also been found to display enhanced nociceptive flexion withdrawal reflexes (RIII) (Kunz 2009 **Level III-2 EH;** Kunz 2007 **Level III-2 EH**). In contrast, autonomic responses typically associated with the onset of acute pain (ie increased heart rate, blood pressure, galvanic skin resistance, breathing) appear to be blunted in persons with dementia (Plooij 2011 **Level III-2 SR EH,** 6 studies, n=395). Much of the typical elevation in autonomic indices occurs in anticipation of an impending painful stimulus, yet this anticipatory response is lacking in those with dementia (2 studies, n=135). Group differences in the poststimulus autonomic response, particularly in heart rate change, are less obvious (1 study, n=95) or unchanged (2 studies, n=103) including to stronger intensity pain (1 study, n=40).

Another study assessed the placebo component of analgesic therapies by looking at the effect of both "overtly applied" and "covertly applied" local anaesthetic on pain after venipuncture in patients with Alzheimer's disease (Benedetti 2006 **Level III-2**). The patients with reduced Frontal Assessment Battery scores (a measure of frontal executive function) had a reduced placebo component to their pain relief and dose increases were required to produce adequate analgesia.

Undertreatment of acute pain is more likely to occur in cognitively impaired patients (Forster 2000 **Level III-2**; Morrison 2000 **Level III-2**; Feldt 1998 **Level III-2**), although this may be improving (Paulson 2014 **Level III-2**).

Delirium

Acute perioperative neurocognitive disorders include delayed neurocognitive recovery (dNCR - formerly postoperative cognitive dysfunction) and delirium (Evered 2018 **NR**). From a pain management perspective, delirium is the more significant. Delirium is an acute deterioration in cognitive state associated with a fluctuating course, inattention, confusion and altered conscious state. It is most common in the elderly, especially those with pre-existing cognitive impairment, and occurs in medical patients and in up to 65% of postoperative patients. Delirium is associated with increased postoperative morbidity, impaired rehabilitation and prolonged hospital LOS (O'Regan 2013 N**R**). It is also prevalent during acute illnesses in the older person. It is estimated that delirium can be prevented in up to 40% of hospitalised patients; risk factors including age,

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infection, emergency surgery, pre-existing cognitive impairment, metabolic disturbance, polypharmacy and unrelieved pain (Thompson 2018 **Level IV**, n=668; American Geriatrics Society 2015 **GL**).

Delirium presents clinically in both hyperactive and hypoactive forms, of which the latter is more common (Rudolph 2011 **NR**) and mixed forms can occur. Although restlessness and agitation (hyperactive delirium) may trigger assessment, which identifies a trigger associated with pain, the more frequent hypoactive delirium may mask pain, especially in the elderly.

Effective pain management contributes to strategies to reduce the incidence of delirium, but some analgesics, especially opioids, also contribute to delirium either through anticholinergic activity (eg pethidine) or by causing sedation and confusion (Swart 2017 **Level III-2 SR,** 6 studies, n 22,000; American Geriatrics Society 2015 **GL**).

9.2.2.2 | Measurement of pain

Patient self-report measures of pain

Unidimensional measures of pain intensity are more commonly used to quantify pain in the acute pain setting than multidimensional measures (see also Section 2.2). Unidimensional measures used in younger adult populations, and which have been shown to be appropriate for use in the older patient, include the VNRS, FPS, VDS alone and with calorimetry (Iowa pain thermometer) and the NRS, with equivocal support for use of the VAS (Hadjistavropoulos 2014 **NR;** Paulson 2014 **NR**). Completion rate is high for VNRS in the older patient but this decreases with increasing cognitive impairment. Several studies confirm that VDS is often the preferred tool and use of familiar words such as “none, slight, mild, moderate, severe and extreme” is felt to be the most reliable in the older patient, including those with mild to moderate cognitive impairment. Trialling of different self-assessment scales may be warranted including in those with severe impairment and the patients may need more time to understand and respond to questions regarding pain. Immediate reports of present pain may be reasonably accurate and as valid as those of cognitively intact patients but recall of past pain is less likely to be as reliable. Further comparative studies in the elderly include patients with fractured hips (Leino 2011 **Level IV**) and after cardiac surgery (Pesonen 2008 **Level IV**), where VAS was also the least reliable and the VDS and Red Wedge Scale were most applicable.

Other measures of pain

Assessment of pain in noncommunicative patients is more difficult. Behaviours such as restlessness, frowning and grimacing or sounds such as grunting or groaning have been used in attempts to assess pain. In cognitively intact adults, some of these behaviours have been shown to correlate with patient self-report of pain (Bell 1997 **NR**). However, they may not always be valid indicators of pain in the nonverbal adult (Farrell 1996 **NR**) and can be difficult to interpret (Herr 2011 **NR**; Herr 2006 **NR**).

There is some argument that observations of facial expressions and sounds may be accurate measures of the presence of pain but not pain intensity in patients with advanced dementia (Herr 2006 **NR**), although this position has been challenged in recent studies (Lukas 2013 **Level III-2**).

More than 28 different observational pain assessment scales have been developed and used in patients with varying degrees of dementia (Lichtner 2014 **Level IV SR of SRs**, 8 SRs; Herr 2011 **NR**). Scales with the strongest evidence of utility include: FPSs, Abbey Pain Scale, Pain Assessment in Advanced Dementia (PAINAD) (a simple, reliable and validated five-item observational tool), Pain Assessment Checklist for Seniors with Limited Ability to Communicate and Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale.

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For more detailed and critical review of pain-assessment tools for use with nonverbal adults see (Lichtner 2014 **Level IV SR of SRs**, 8 SRs; Hadjistavropoulos 2014 **NR**; Herr 2011 **NR**; Herr 2006 **NR**; Zwakhalen 2006 **NR**).

See also Section 2.2.

9.2.3 | Pharmacokinetic and pharmacodynamic changes

The changes in physiology and effects on pharmacokinetics and pharmacodynamics in older people, and consequent alterations that might be required in some drug regimens are summarised in Table 9.4. The information in this table centres on opioids, given their widespread use. These changes have variable prevalence and are generally attributable to ageing alone but may be compounded by the higher incidence of degenerative and other concurrent diseases in older people.

Assessment of the pharmacodynamic changes associated with ageing is difficult. When such studies have been done with opioids, most have used a surrogate measure of effect other than clinical pain relief. For example, in studying the effects of fentanyl and alfentanil on the EEG, the pharmacokinetics were shown to be unaffected by age, but the sensitivity of the brain to these opioids was increased by 50% in the older person (Scott 1987 **EH**). It is unclear whether this can be attributed to changes in the number or function of opioid receptors in the CNS (in older rats there are fewer mu- and kappa-opioid receptors) (Yezierski 2012 **NR BS**; Vuyk 2003 **NR**), or whether it is due to an increased penetration of opioids into the CNS. Some of the changes that may lead to increased drug sensitivity in the older patient are discussed below; see Section 9.2.2 above.

Table 9.4 | Physiological changes in older people, resulting changes of pharmacokinetic variables and consequences for pharmacological treatment

Body system or process	Parameter and changes	Resulting pharmacokinetic/ pharmacodynamic changes	Changes in pharmacological treatment
Body composition	body fat 10–50%	for lipophilic medicines V_d $t_{1/2}$	calculate doses of lipophilic medicines on total body weight
	muscle 20%	no relevant effect	none
	body water 10%	for hydrophilic medicines V_d	calculate doses of hydrophilic medicines based on lean body weight
	plasma volume ↔	None	none
Liver	Liver size 25–40%	bioavailability of oral medicines hepatic CL of high extraction medicines (eg morphine)	↔ IV bolus dose oral dose of some medicines
	Hepatic blood flow 25–40%		

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Body system or process	Parameter and changes	Resulting pharmacokinetic/ pharmacodynamic changes	Changes in pharmacological treatment
	Phase 1 metabolism ↓ 25%	↓ hepatic CL of some low extraction medicines (eg ibuprofen	↑ maintenance doses of some medicines (eg morphine)
Kidney	Kidney size ↓ 30%	↓ clearance of renally excreted medicines ↔ effect on opioids, but often ↓ clearance of metabolites (eg morphine [M6G], tramadol [M1])	↑ maintenance dose of renally excreted medicine (alpha-2-delta ligands: gabapentin, pregabalin) or medicines with renally excreted metabolites (morphine, tramadol, pethidine) monitor for accumulation of renally excreted medicines
	Renal blood flow ↓ 10% / decade		
	GFR ↓ 30–50%		
	Creatinine clearance (Cl) ↓ 50–70%		
Heart	Cardiac output ↔ or ↓ to 20%	↓ central compartment volume ↑ peak concentration after IV bolus	initial IV bolus doses IV injection speed
CNS	Cerebral blood flow, volume and metabolism ↓ 20%	↑ distribution to the CNS ↑ apparent volume in the CNS	minimal clinically relevant changes for most drugs, but: ↑ bolus doses of medicines during titration ↑ maintenance doses of some medicines
	Blood brain barrier transport ↑ (medicine specific effect)	↑ apparent volume in the CNS ↑ apparent increase in CNS sensitivity	
Absorption of Medicines	oral and transmucosal absorption	no relevant effect of ageing	however ↓ oral bioavailability of some medicines due to first-pass effect
	IM absorption	↔	none
	SC absorption	↔	none
	transdermal absorption	↑ hydrophilic medicines ↔ lipophilic medicines	no clinically relevant effect for TD opioids
Protein binding of medicines	Plasma albumin ↓ 20%	↑ unbound fraction of medicines	

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Body system or process	Parameter and changes	Resulting pharmacokinetic/ pharmacodynamic changes	Changes in pharmacological treatment
	Alpha-1-acid glycoprotein 30–50%	cerebral uptake of medicines ↔ hepatic clearance of high extraction medicines hepatic clearance of low extraction medicines	possibly changed clearance and oral bioavailability possibly changed cerebral effects

Source: Modified and adapted from Macintyre 2008 and Coldrey 2011

9.2.4 | Drugs used in the management of acute pain in older people

In general, there is limited evidence about the use of analgesic medications in older patients; as because of their age, comorbidities or concurrent medications, they are often specifically excluded from clinical trials (McLachlan 2011 **NR**).

The American Society of Geriatrics publishes and regularly updates a list of drugs that can be associated with increased adverse effects when used in the elderly: American Geriatrics Society Updated Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults (American Geriatrics Society 2019 **GL**). This list comprises drugs that should be prescribed with caution in the elderly, as well as drug-drug interactions and drugs which have additional risk in specific disease states.

Drugs used to treat pain which are on the list include:

- Pethidine – may cause delirium
- nsNSAIDs – risk of GI bleeding in high risk groups, including > 75 y
- Drugs with anti-cholinergic effects – tricyclic antidepressants (TCA), hyoscine
- Falls risk – opioids, antidepressants (TCA, SSRI, SNRI), clonidine (CNS effects, orthostatic hypotension)
- Opioids in combination with gabapentin or pregabalin – this combination increases risk of sedation, OIVI and death.
- Heart failure – caution with nsNSAIDs and Coxibs (avoid if symptomatic heart failure)
- Cognitive impairment – drugs with anticholinergic effects eg TCAs
- Chronic kidney disease (GFR < 30 mL/min) – nsNSAIDs, Coxibs
- Hyponatraemia or Risk of Syndrome of inappropriate antidiuretic hormone secretion (SIADH) – SNRIs, SSRIs, TCAs, Tramadol

Concern is often expressed about the safety of pharmacological approaches to pain management in older adults due to the increased risk of adverse drug reactions. Analgesics may be responsible for >5% of adverse drug reactions and can lead to emergency department visits in the older population (Oscanoa 2017 **Level IV SR**, 42 studies, n> 7,000,000 [> 265,000 admissions]; Shehab 2016 **Level IV**, n=42,585); only anticoagulants and antidiabetic agents result in more frequent admissions (Shehab 2016 **Level IV**, n=42,585). Older patients are particularly vulnerable to adverse drug reactions because of the age-associated changes in pharmacokinetics and pharmacodynamics. In addition, comorbid medical conditions and geriatric syndromes that commonly occur in older people can increase adverse drug reactions (eg for NSAIDs) (Bhala 2013

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Level I, 754 RCTs, n=353,809). For instance, the presence of frailty, defined as "*a progressive age-related decline in physiological systems, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health-outcomes*" (WHO 2015 **NR**) may raise several concerns in formulating an appropriate pharmacological treatment of pain (Lohman 2017 **Level IV**, n=3,652). Frailty is often characterised by the coexistence of multiple diseases states, resulting in multiple medications with increasing risk of drug-drug and drug-disease interactions, and an associated increase in the risk of adverse drug reactions (Onder 2018 **GL**). The known association between frailty and inflammation may potentially down-regulate drug metabolism and transporter pathways, thereby impacting upon the clinical pharmacology of analgesics (McLachlan 2011 **NR**). Likewise, frailty is often characterized by chronic undernourishment, which could alter the distribution of some drugs as well as changes in pharmacokinetic parameters (Onder 2018 **GL**). Therefore, when pain medications are prescribed in older adults it is important to consider their potential side effects, but also possible interacting drugs or diseases in order to prevent ADRs.

While this and the following section concentrate on the use of analgesic drugs and techniques in the older patient, physical and psychological strategies should also be employed as with other patients (APS 2019 **GL**; Abdulla 2013 **GL**; Makris 2014 **NR**).

9.2.4.1 | Paracetamol, nonselective NSAIDs and Coxibs

Paracetamol is recommended as a first-line therapy in older adults for both mild to moderate pain (Abdulla 2013 **GL**; O'Neil 2012 **GL**; American Geriatrics Society 2009 **GL**; Makris 2014 **NR**). There is inconsistent evidence on the effect of ageing and frailty on clearance of paracetamol, with earlier authors recommending no dose adjustment (Bannwarth 2001 **PK**; Miners 1988 **PK**; Divoll 1982 **PK**) but more recent reviews recommending that dose adjustment is prudent (McLachlan 2011 **NR**; Mitchell 2011b **NR**). In a small cohort comparison, spot paracetamol plasma concentrations on d 5 of 3–4 g/d therapy were in the therapeutic range in 21 of 23 older and frail older patients and elevated in 2 (but less than twice therapeutic range) (Mitchell 2011a **Level III-3**, n=71). Plasma alanine aminotransferase (ALT) levels after 5 d were not elevated in any of the older and frail participants. Overdose may lead to severe hepatotoxicity and the wide availability of paracetamol often marketed under different names, presentations and combinations may increase this risk in older persons living at home (Tittarelli 2017 **NR**). A detailed review of paracetamol induced liver injury found no good quality evidence to indicate that older patients are at increased risk of liver injury when treated with paracetamol at normal doses (Caparrotta 2018 **NR**)

NSAIDs may offer more effective control of inflammatory pain, but older patients are more likely to suffer gastric and renal adverse effects following administration of nsNSAIDs (Abdulla 2013 **GL**) and may also be more likely to develop cognitive dysfunction (Juhlin 2005 **Level II**, n=14, JS 4; Pilotto 2003 **Level III-2**; Peura 2004 **NR**) (see also Section 4.2). In elderly (age >65 y) medical inpatients, use of nsNSAIDs was a significant risk factor for renal function deterioration occurring in 6.1% of patients exposed; other risk factors were loop diuretics, hypernatraemia and low serum albumin levels (Burkhardt 2005 **Level IV**, n=343). Use of oral nsNSAIDs often does not align with current clinical guidelines in the older population and particularly regarding the prolonged duration of use and lack of PPI coadministration (Gnjidic 2014 **Level III-2**).

NSAIDs should be used with care in elderly patients given their cardiovascular, gastrointestinal and renal adverse effects, and patients should be monitored closely (O'Neil 2012 **GL**; Fine 2004 **GL**; Makris 2014 **NR**). 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 challenge the assumption that opioids are safer in this population (Solomon 2010

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Level III-2, n=12,840). This study found 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. Overall the nsNSAID cohort appeared to have the lowest risk for adverse effects.

Coxibs have a significantly lower incidence of upper gastrointestinal complications (Jarupongprapa 2013 **Level I**, 9 RCTs, n=7,616) and have no antiplatelet effects (Munsterhjelm 2006 **Level II EH**, n=18, JS 4), which might be of some advantage in the older patient. The risk of other adverse effects, including effects on renal function (Zhang 2006 **Level I**, 114 RCTs, n=116,094), hypertension and exacerbation of cardiac failure may be lower too, at least for celecoxib (see Section 4.2.2.2). Compared with paracetamol and placebo, only transient reduction of creatinine clearance was seen after 3 d treatment with parecoxib 40 mg/d in elderly patients undergoing major orthopaedic surgery (Koppert 2006 **Level II**, n=75, JS 5).

Use of both coxibs and nsNSAIDs (possibly lowest with naproxen and celecoxib) can increase the risk of cardiovascular and cerebrovascular events (Trelle 2011 **Level I**, 31 RCTs, n=116,429) and regular use of nsNSAIDs may interfere with the clinical benefits of low-dose aspirin (for details see Section 4.2). Extra precautions are therefore required in older patients.

Topical nsNSAID agents may be a preferred route of administration (due to lower systemic levels and less gastrointestinal adverse effects) in older adults where there is appropriate and localised pain (Massey 2010 **Level I** [Cochrane] 47 RCTs, n=3,455; Klinge 2013 **Level I**, 6 RCTs, n=600; Zacher 2008 **Level I**, 19 RCTs, n> 3,000; Makris 2014 **NR**) (significant overlap between all three SRs) (see also Section 4.2.3.6).

9.2.4.2 | Conventional and atypical opioids

Despite the age-related changes listed in Table 9.4, there may be few differences in the older patient in fentanyl (Scott 1987 **EH**), morphine, oxycodone (Villesen 2007 **PK**) and buprenorphine pharmacokinetics (Kress 2009 **NR**).

After oral administration, the bioavailability of some drugs may be increased, leading to relatively higher plasma concentrations (Gupta 2012 **NR**; Mangoni 2004 **NR**).

Opioid dose

Older patients require less opioid than younger patients to achieve the same degree of pain relief (Gagliese 2000a **Level IV**; Woodhouse 1997 **Level IV**; Macintyre 1996 **Level IV**; Upton 2006 **PK**); however, a large interpatient variability still exists and doses must be titrated to effect in all patients. The decrease is much greater than would be predicted by age-related alterations in physiology and seems to have a significant pharmacodynamic component (Gupta 2012 **NR**; Macintyre 2008 **NR**).

In the clinical setting, there is evidence of an age-related 2 to 4-fold decrease in morphine and fentanyl requirements (Gagliese 2000a **Level IV**; Woodhouse 1997 **Level IV**; Macintyre 1996 **Level IV**). The decrease is in agreement with previous findings that the sensitivity of the brain to fentanyl and alfentanil was increased by 50% in older people (Scott 1987 **EH**). It has been suggested that doses of fentanyl, sufentanil and alfentanil should be reduced by up to 50% in older patients (Shafer 1997 **NR**); reductions in the doses of other opioids are also advised (Macintyre 2008 **NR**). In general, patients aged 80 y should receive 50% of the opioid dose of a 40-y-old patient due to pharmacodynamic changes and increased sensitivity (Gupta 2012 **NR**).

In patients >75 y, the elimination half-life of tramadol is slightly prolonged (Scott 2000 **NR**); lower daily doses have been suggested (Barkin 2005 **NR**). Awareness and consideration of drug interactions in the elderly is necessary, particularly with the high incidence of polypharmacy and antidepressant use (Makris 2014 **NR**).

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Opioid metabolites

Reduced renal function in the older patient could lead to a more rapid accumulation of active opioid metabolites (eg M6G, M3G, H3G, nordextropropoxyphene, norpethidine and M1) (see Section 4.1).

Adverse effects of opioids

The concern regarding respiratory depression in older people, especially those with respiratory disease, often leads to inadequate doses of opioid being given for the treatment of their pain. However, as with other patients, significant respiratory depression can generally be avoided if appropriate monitoring (in particular, of sedation) is in place (see Section 4.3.1.4).

The incidence of nausea/vomiting and pruritus in the postoperative period lessens with increasing age (Quinn 1994 **Level IV**). In older patients, IV PCA fentanyl may cause less postoperative cognitive dysfunction than morphine (Herrick 1996 **Level II**, n=96, JS 2). There is an increased risk of delirium in the elderly with use of pethidine (Swart 2017 **Level IV SR**, 3 studies [pethidine], n=877) and tramadol (Swart 2017 **Level IV SR**, 1 study [tramadol]: Brouquet 2010 **Level IV**, n=133) and a potential protective effect with fentanyl and hydromorphone; however, the underlying studies are small and of low quality. However, administration of an appropriate opioid medication is often associated with higher levels of cognitive function and undertreatment of postoperative pain with lower levels (Morrison 2000 **Level III-2**, n=541; Lynch 1998 **Level IV**). Constipation is a common adverse effect of treatment with opioids and is a relevant consideration in older adults, many of whom already exhibit altered gastrointestinal function. Prophylactic management of constipation should be commenced whenever opioids are prescribed (Hunold 2013 **Level IV**; Makris 2014 **NR**).

See also Section 4.3.1.4

9.2.4.3 | Local anaesthetics

Age-related decreases in clearance of bupivacaine (Veering 1987 **Level III-2**; Veering 1991 **PK**) and ropivacaine (Simon 2006 **PK**) have been shown. Older patients may be more sensitive to the effects of local anaesthetic agents because of a slowing of conduction velocity in peripheral nerves and a decrease in the number of neurons in the spinal cord (Sadean 2003 **NR**). Localised neuropathic pain may be suitable for treatment with topical lignocaine (lidocaine) patch, in particular in older patients with increased comorbidities and polypharmacy, as systemic adverse effects are rare (Finnerup 2015 **GL Level I** [PRISMA], 229 RCTs, n unspecified; Fine 2012 **GL**; Makris 2014 **NR**).

9.2.4.4 | Ketamine

There are no good data on the need or otherwise to alter ketamine doses in the older patient. In aged animals, however, changes in the composition of the NMDA-receptor site and function have been reported (Clayton 2002 **BS**; Magnusson 2002 **BS**; Vuyk 2003 **NR**). Young and elderly rats, given the same dose of ketamine on a mg/kg basis showed similar EEG changes but these changes were quantitatively greater in the older rats (Fu 2008 **BS**). These data suggest that, apart from any pharmacokinetic changes, the older person may be more sensitive to the effects of ketamine and doses may need to be lower in this patient group.

9.2.4.5 | Tricyclic antidepressants

Clearance of TCAs may decrease with increasing patient age and lower initial doses are recommended in older people (Ahmad 2002 **NR**).

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Older people may be particularly prone to the adverse effects of TCAs (Abdulla 2013 **GL**; Fine 2004 **GL**; Ahmad 2002 **NR**) including sedation, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, and increased risk of mortality and dementia (Coupland 2019 **Level III-2**, n=284,343; Fox 2011 **Level III-2**). Adverse effects appear to be most common with amitriptyline, and so nortriptyline may be preferred in this patient group (Argoff 2005 **NR**; Ahmad 2002 **NR**). Clinical conditions that may require TCAs to be administered with caution are more common in older people and include prostatic hypertrophy, narrow-angle glaucoma, cardiovascular disease and impaired liver function; ECG abnormalities may be a contraindication to the use of TCAs in older people (Ahmad 2002 **NR**).

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

9.2.4.6 | Serotonin–norepinephrine-reuptake inhibitors

Duloxetine has been shown to be effective and safe for the treatment of painful diabetic peripheral neuropathy in older patients (mean age 60 y) (Goldstein 2005 **Level II**, n=547, JS 4). Duloxetine was effective and well tolerated for the treatment of osteoarthritis pain of the knee in older patients (mean age 62 y) (Chappell 2009 **Level II**, n=231, JS 4).

9.2.4.7 | Anticonvulsants

As liver and renal function decline with increasing age, elimination of anticonvulsants such as carbamazepine and gabapentin may be reduced (Ahmad 2002 **GL**). As with TCAs, initial doses should be lower than for younger patients and any increases in dose should be titrated slowly.

The "second generation" drugs such as gabapentinoids and topiramate may be less likely to result in adverse effects in the older patient (Argoff 2005 **NR**), although the relatively high frequency of adverse effects such as somnolence and dizziness with pregabalin may be a problem in this group of patients (Goodman 2017 **NR**; Guay 2005 **NR**). However, pooled data from RCTs with pregabalin in neuropathic pain showed an increase of adverse effects only with increasing doses, but not related to the age of patients (Semel 2010 **Level III-3**, n=2,516 [65 to 74 y: n=766] & [≥75 y: n=514]). Efficacy was comparable to that in younger age groups; the lack of drug interactions may be an advantage in particular in older patients.

9.2.5 | Patient-controlled analgesia

PCA is an effective method of pain relief in older people but its use may be limited by the presence of cognitive impairment or development of postoperative delirium (Mann 2000 **Level II**, n=70, JS 3; Gagliese 2000a **Level III-2**; Mann 2003 **NR**). Compared with younger patients (mean age 39 y), older patients (mean age 67 y) self-administered less opioid than the younger group but there were no differences in pain relief achieved, satisfaction with pain relief and pain scores or concerns about pain relief, adverse drug effects, risks of addiction or use of the equipment (Gagliese 2000a **Level III-2**).

Compared with IM morphine analgesia in older men, PCA resulted in better pain relief, less confusion and fewer severe pulmonary complications (Egbert 1990 **Level II**, n=83, JS 2). In older patients, PCA also resulted in significantly lower pain scores vs intermittent SC morphine injections (Keita 2003 **Level II**, n=40, JS 3).

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9.2.6 | Epidural analgesia

In the general patient population, epidural analgesia can provide the most effective pain relief of all analgesic therapies used in the postoperative setting (see Section 5.6). Epidural analgesia significantly reduces many of the complications that occur in the elderly after surgery (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044). Older patients given epidural PCA using a mixture of bupivacaine and sufentanil had lower pain scores at rest and movement, higher satisfaction scores, improved mental status and more rapid recovery of bowel function vs use of IV PCA (Mann 2000 **Level II**, n=70, JS 3). After hip fracture surgery, epidural analgesia with bupivacaine and morphine also provided better pain relief both at rest and with movement but this did not lead to improved rehabilitation (Foss 2005 **Level II**, n=60, JS 5). Epidural analgesia, after colectomy for cancer in patients aged >65 y of age, may be associated with improved long-term survival (Cummings 2012 **Level III-2**, n=42,151). Patients having colectomy for cancer had better 5-y survival in the epidural group vs the nonepidural group (61 v 55%; HR 0.91; 95%CI 0.87 to 0.94). In a retrospective study, epidural analgesia was associated with reduced cancer recurrence in patients aged >64 y having colectomy (Gottschalk 2010 **Level III-2**). The postulated mechanism is reduced impairment of immune function in patients having epidural analgesia, although overall data are contradictory (see also Section 5.6.1.2).

Older patients are more likely to have ischaemic heart disease where coronary blood flow may be reduced rather than increased in response to sympathetic stimulation. In a study of patients (average age 67 y) with multivessel coronary artery disease, high (T2 to T3) thoracic epidural analgesia using 0.5% bupivacaine instituted before CABG surgery was able to partly normalise myocardial blood flow in response to sympathetic stimulation (Nygard 2005 **Level III-2**). In a small trial of perioperative analgesic regimens initiated preoperatively for hip fracture repaired under spinal anaesthesia, older patients who had received epidural bupivacaine/fentanyl analgesia had significantly better postoperative pain relief than those who were given IM oxycodone; there was no difference in the number of patients who developed postoperative continuous ECG-detected ischaemia or hypoxia (Scheinin 2000 **Level II**, n=77, JS 3). However, the number of episodes and total duration of ischaemia in each patient was markedly greater in the oxycodone group.

Epidural morphine requirements decrease as patient age increases (Ready 1987 **Level IV**). However, a comparison of PCA epidural fentanyl in patients aged >65 y with those aged 20–64 y showed no difference in fentanyl requirements or pruritus; although pain relief on coughing at 24 h was better in the older patient group (Ishiyama 2007 **Level III-3**).

Age is also a determinant of the spread of local anaesthetic in the epidural space and the degree of motor blockade (Simon 2004 **Level III-2**; Simon 2002 **Level III-2**). Thus, smaller volumes may be needed to cover the same number of dermatomes than in a younger patient. When the same volume of local anaesthetic was given, the concentration required to produce effective motor block decreased as patient age increased (Li 2006 **Level III-1**). Combinations of a local anaesthetic and opioid are commonly used for epidural analgesia, so it would seem reasonable to use lower infusion rates in older patients (Macintyre 2008 **NR**).

Older patients may be more susceptible to some of the adverse effects of epidural analgesia, including hypotension (Simon 2002 **Level III-2**; Crawford 1996 **Level IV**; Veering 2006 **NR**).

9.2.7 | Intrathecal opioid analgesia

IT morphine using a variety of doses provided more effective pain relief after major surgery vs other opioid analgesia, although the risk of respiratory depression and pruritus was greater (Meylan 2009 **Level I**, 27 RCTs, n=645).

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With neuraxial opioids, advanced patient age is considered by some to be a risk factor for respiratory depression and it has been suggested that patients >70 y be monitored in an ICU setting (Gwirtz 1999 **Level IV**). However, others report that older patients (average age 69 y) given up to 200 mcg IT morphine at the time of spinal anaesthesia for peripheral vascular and other surgery have been safely nursed on general wards by nursing staff who have received additional education and managed by an APS according to strict guidelines (Lim 2006 **Level IV**).

The optimal dose of IT morphine for older patients remains unknown. The evidence for the "best" dose is provided by data from small trials and remains inconsistent. IT morphine doses of 200 mcg given in addition to general anaesthesia in older patients (average age 70 y) undergoing abdominal aortic surgery led to better postoperative analgesia and reduced postoperative analgesia requirements vs general anaesthesia only (Blay 2006 **Level II**, n=30, JS 4). No conclusion could be made about adverse effects, as total patient numbers were small. A comparison of three doses of IT morphine (50 mcg, 100 mcg and 200 mcg) given to older patients after hip surgery concluded that the 100 mcg dose provided the best balance between good pain relief and pruritus (Murphy 2003 **Level II**, n=60, JS 4). There was no difference seen in the incidences of nausea and vomiting or respiratory depression.

Use of IT morphine 300 mcg in addition to IV PCA morphine in elderly patients led to better pain relief and PCA morphine requirements vs PCA morphine alone (Beaussier 2006 **Level II**, n=59, JS 5). However, sedation was increased and there were no differences in time to ambulation, hospital LOS or incidence of confusion.

9.2.8 | Other regional analgesia

The advantages of regional block in older patients include improved pain relief and a reduction of the adverse effects of opioids (Halaszynski 2009 **NR**). After hip fracture fixation, those who received patient-controlled femoral nerve analgesia, in addition to regular paracetamol and metamizol, were less likely to develop postoperative delirium, were able to sit at the bedside at an earlier stage, and required no SC morphine vs those getting paracetamol and metamizol only (28% required additional morphine analgesia) (Rosario 2008 **Level III-3**).

The duration of action of sciatic nerve (Hanks 2006 **Level III-2**) and brachial plexus blocks (Paqueron 2002 **Level III-2**) is prolonged in the older patient.

In older (>65 y) patients undergoing urological surgery via a flank incision, PVB of the lumbar plexus using either ropivacaine or bupivacaine has been shown to provide good analgesia with no changes in the patients' heart rate or blood pressure (Akin 2005 **Level II**, n=60, JS 1).

Unlike epidural analgesia, age did not influence the spread of bupivacaine in the thoracic paravertebral space (Cheema 2003 **Level III-2**).

KEY MESSAGES

1. Topical nsNSAIDs for localised pain provide effective analgesia (**U**) (**Level I** [Cochrane Review] with lower plasma concentrations and fewer gastrointestinal adverse effects than oral nsNSAIDs (**U**) (**Level I**); this may improve safety in the elderly.
2. PCA and epidural analgesia are more effective in older people than conventional opioid regimens (**U**) (**Level II**).
3. Experimental pain thresholds to thermal stimuli are modestly increased in older people (**U**) (**Level III-2 SR**).

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4. Reported frequency and intensity of acute pain in clinical situations may be reduced in the older person (**U**) (**Level III-2**).
5. Common unidimensional self-report measures of pain can be used in the older patient in the acute pain setting, but need to be appropriate for the individual patient; the verbal descriptor and numerical rating scales are preferred in patients who can self-report (**U**) (**Level III-2**), while in the older patient with cognitive impairment, specific pain assessment tools are more appropriate (**N**) (**Level IV SR**).
6. Undertreatment of acute pain is more likely to occur in cognitively impaired patients (**U**) (**Level III-2**).
7. The use of nsNSAIDs and coxibs in older people requires caution, although use of opioids may result in more complications (**U**) (**Level III-2**); paracetamol is the preferred nonopioid analgesic (**U**) (**Level III-2**).
8. The under-representation of older patients in clinical drug trials limits information about efficacy, safety and pharmacokinetics of many types of medications including analgesic medications **(N) (Level IV SR**}
9. The older patient is at increased risk from adverse effects of medications including many analgesics (**N**) (**Level IV**).
10. Delirium is common in elderly hospitalised patients, including after surgery; risk factors include inadequate pain management and excessive use of opioids and other sedating analgesics (**N**) (**Level IV**).
11. There is an age-related decrease in opioid requirements; significant interpatient variability persists (**U**) (**Level IV**).
12. The age-related decrease in opioid requirements is related more to the changes in pharmacodynamics that accompany ageing than to the changes in pharmacokinetics (**U**) (**Level IV).**

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

☑ The assessment of pain and evaluation of pain relief therapies in the older patient may present problems, arising from differences in reporting, cognitive impairment and difficulties in measurement (**U**).

☑ Measures of present pain may be more reliable than past pain, especially in patients with some cognitive impairment (**U**).

☑ The physiological changes associated with ageing are progressive; while the rate of change can vary markedly between individuals and is related to frailty, these changes may decrease the dose (maintenance and/or bolus) of drug required for pain relief and may lead to increased accumulation of active metabolites (**U**).

☑ The high prevalence of frailty in the older patient is an independent risk factor for increased adverse drug effects to analgesic medications (**N**).

☑ The use of regional analgesics techniques, as an alternative to systemic analgesics, can confer benefits of improved pain relief, and minimise adverse effects (cognitive, pulmonary) (**N**).

☑ Cognitive impairment in the older patient may limit the appropriate use of PCA (**N**).

9.3 | Culturally responsive care for Culturally and Linguistically Diverse patients

Growth in the cultural, linguistic and religious diversity of the Australian community reflects the diversity of migrant communities from many countries, this being a clear shift from early migrant communities predominantly of European background. The 2016 Census states that about 49% of Australians were born overseas or have at least one parent born overseas and 21 % speak a language other than English with slight variations across states (ABS 2017). The Aboriginal and Torres Strait Islander community comprises 2.8% of the total population. The five most common languages spoken at home (other than English) were Mandarin (2.5%), Italian (1.2%), Vietnamese (1.2%), Arabic (1.4%), Cantonese (1.2%) and Greek (1.0%). The top five non-Christian religions in 2016 were Islam (2.6% of the population), Buddhism (2.4%), Hinduism (1.9%), Sikhism (0.5%) and Judaism (0.4%). The New Zealand 2018 census (Stats NZ 2019) shows the following ethnic groups: European (64.1%), Māori (16.5%), Chinese (4.9%), Indian (4.7%), Samoan (3.9%); with the top 3 foreign countries of birth being England (4.5%); Peoples Republic of China (2.9%) and India (2.5%) and the languages spoken at home (other than English) were te reo Māori (4%), Samoan (2.2%), Northern Chinese (including Mandarin) (2%), and Hindi (1.5%).

Economic globalisation and current world events are compelling many communities to seek a home elsewhere. This facilitates ongoing migration, which has a direct impact on the cultural diversity of many countries. A major '*immigration nation*', Australia has been made home by over 7.5 million people since 1945 (Phillips 2017 **NR**). Recent migration patterns and the humanitarian program in Australia have resulted in the arrival of a variety of cultural groups, the majority of which came from Iraq, Syria, Afghanistan and Myanmar in 2016-17 (Refugee Council of Australia 2019).

Culture, language and religious convictions have an impact on the clinical encounter. This background drives a need to understand different cultures when considering pain assessment and management. This extends beyond the language spoken, because an individual's culture, faith and migration history influence their linguistic expression, metaphorical language, beliefs, attitude, need for social support, framework of meaning, health literacy, expectations, perception, methods of communication, norms of behaviour and pain relief preferences. This also applies to the culture and attitudes of the health professional (Xu 2018 **Level III-2**; Al-Harthy 2016 **Level III-2**; Holt 2018 **Level IV**; Park 2017 **Level IV**; Martin 2017 **Level IV**; Rahavard 2017 **NR**; Brady 2017 **NR**; Brady 2016 **NR**; Pillay 2015 **NR**). These principles, and culturally competent practices, are supported by the ANZCA Statement on Cultural Competence PS 62 (ANZCA 2017 **GL**). Similarly, culturally competent practices are endorsed by The Australian Medical Council, the Medical Board of Australia, and the Medical Council of New Zealand (Medical Board of Australia 2014 **GL**).

Consequently, a health professional needs to consider their own cultural assumptions and preconceived biases as well as address the cross-cultural elements that underpin their patients' individual responses. A person's empathy and ability to perceive pain in the other differs across cultures (Atkins 2016 **Level III-3**; Rosa 2018 **NR**). Some evidence shows variation in assessment and the severity of pain particularly in the case of African American patients; ethnicity can influence the health care relationship (Vigil 2016 **Level IV**; Hirsh 2015 **Level IV**). Investigation into medication adherence and patient–physician ethnicity/language concordance supports the need for cultural responsiveness (Ali 2017 **Level IV**; Ohana 2015 **Level IV**). The need for cross-cultural sensitivity is particularly important when addressing verbal and nonverbal indicators of pain and being aware

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of stoic and emotive responses to pain as they may have different meaning across cultures (Ford 2015 **Level IV**). Overall, researchers have found significant cultural differences in self-care when managing pain which affects pain-relief seeking behaviour (Xu 2018 **Level III-2)**. These behavioural differences occur as it relates to ethnicity (Meints 2016 **Level III-3 SR,** 19 studies, n=6,489; Meints 2018 **Level III-2 EH**; Meints 2017 **Level III-2 EH**, n=172). On a broader scale, some cultural attitudes may limit pain-relief seeking behaviour (Wechkunanukul 2016 **Level IV SR**, 10 studies, n=1,511,382). Similarly, a patient may vocalise (Burri 2018 **Level III-2**; Meints 2015 **Level III-2 EH**, n=190; Brady 2016 **NR**), or appear stoic in managing pain (Cagle 2017 **NR**). For example, it may be perceived by some patients as inappropriate to use a nurse's time to ask for pain relief as it may be seen as a weakness/shameful, or an unnecessary interruption of their time (Carrion 2015 **Level III-3**). In some collectivist cultures, the concept of patient autonomy is foreign and interdependence is preferred. This behaviour may result in patients waiting for a health professional to offer pain relief as the latter is seen as the primary medical decision maker (Martin 2017 **Level IV**; Pillay 2014 **NR**). Health literacy influences a patient's ability to understand and act on medical advice (Xu 2018 **Level III-3 SR,** 23 studies, n=6,110; Teo 2018 **Level III-3**; Wilkinson 2014 **Level IV**). Cross-cultural perception of pain may be a learned behaviour with links that have been made between culture and pain-related caregiver behaviours (Kristjansdottir 2018 **Level III-3**). This may explain why, cross-culturally, there is a difference in how a patient might approach their ability to manage their pain (or not). A recent study highlighted that the cross-cultural perception of the causation of pain as something external, impeded the capacity to express it in biomedical terms: *'The women reported that not eating the right food, old age and stress could cause pain, with an overlying belief that pain was often caused by hard work or tiredness.'* (Holt 2018 **Level IV**). Spiritual coping needs to be considered as well; faith informs many patients to respond to pain positively without seeking pain relief. Hindu culture, for instance, understands pain and suffering within the context of gaining better karma (Dewar 2015 **Level IV**). Buddhism emphasises the need for stoicism and fatalism, articulating that pain has the ability to strengthen the body, purify the soul and deepen the spirit (Cheng 2017 **NR**; Waikakul 2016 **NR**). Prayer has also demonstrated a powerful way of tolerating pain in both the African American and Latino community (Meints 2015 **Level III-2 EH**, n=190; Gagnon 2014 **NR**). Research about the impact of the refugee experience on patients with health professionals, advises to provide care with great cultural sensitivity, and that mental health symptoms and chronic pain are commonly experienced by refugee patients (Crosby 2013 **NR**).

Communication problems caused by variable linguistic (and non-verbal) proficiency of either the patient or the health professional, make it difficult to adequately assist patients with interactive pain management (eg PCA use, requesting analgesia when needed), to gain consent for invasive analgesic techniques (eg epidural or regional catheters) and to assess their pain (Taylor 2017 **Level III-2**; Ali 2017 **Level IV;** Ford 2015 **Level IV**). When language is an obstacle, there should be caution when using nonprofessional interpreters (eg family, friends), because their linguistic ability/accuracy in the other language has not been tested and may be variable. In addition, nonprofessional interpreters may inadvertently omit, edit and impose their own values when conveying the information to the clinician, and the patient may be reluctant to openly express themselves in front of people they know.

Direct correlation with longer length of hospital admission, as well as higher readmission rates, longer delay times, not to mention poorer outcomes in emergency treatment (eg lower likelihood of receiving analgesia or attending to hospital, lower self-reported quality of life and poorer end-of-life care) have been made with failure to use an interpreter (Wechkunanukul 2016 **Level III-2 SR**, 10 studies, n=1,511,382; Taylor 2017 **Level III-2**; Asghar 2016 **Level III-2**; Kilkenny 2018 **Level III-3**; Santos 2013 **Level III-3**; Silva 2016 **Level IV SR**, 10 studies, n unspecified; van Rosse 2016 **Level IV**; Lindholm 2012 **Level IV**). This is in addition to poorer outcomes due to possible delays in seeking

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help, which can be culturally influenced as well (Wechkunanukul 2016 **Level IV SR**, 10 studies, n=1,511,382)

The use of alternative methods of communication through translation apps such as Google Translate in the clinical setting is either not advised or non-conclusive with the risk to the patient being considered too great (Silvera-Tawil 2018 **Level IV**; Panayiotou 2019 **NR**). The use of health-care specific language translation apps may therefore only be considered as an alternative option in low risk situations such as non-clinical communication in the sub-acute setting (eg daily routine communication) when formal healthcare interpreter services are not available. An accredited healthcare interpreter should always be engaged to communicate the important points in the continuum of patient care. To date only two language translation apps, "Talk to Me" and "CALD Assist" are regarded safe to use when communicating with culturally and linguistically diverse patients in the sub-acute setting. Both apps incorporate basic questions around pain and were developed in Australia (in November 2019 only available for Apple IOS 10 [iPad] in the case of CALD Assist and both [iPad] and [iPhone] in the case of "Talk to Me"), therefore incorporating languages reflecting the local migrant communities (Panayiotou 2019 **NR**).

Cultural differences in response to pain in both experimental and clinical settings have been reported. A person's expression of pain is something that will not change irrespective of the length of settlement in a host country (Zborowski 1969 **NR**). In addition, the pain experience is socialised and therefore one will encounter cultural variances in language of distress when experiencing pain. Studies conducted using experimental pain stimuli found that cultural differences indeed influenced clinically relevant pain (Lee 2016 **Level III-2**), pain tolerance and threshold (Kim 2017 **Level III-2 EH SR**, 41 studies, n unspecified; Mahadeva 2015 **Level III-3**; Aufiero 2017 **EH**; Morris 2015 **EH**). In a cohort study on large colorectal and lung cancer, African American patients reported higher sensitivity to pain than Caucasian patients (Martinez 2014 **Level III-2**). Similarly, African American and Latino/a patients were found to experience a greater 'ethnicity effect' when it came to pain related anxiety, severity and vocalising pain than their Caucasian counterparts (Gagnon 2014 **NR**).

Several systematic reviews looked at the perception of pain across cultures and the effect of patient ethnicity on pain response, assessment and management across a variety of clinical pain settings (Lee 2019a **Level III-2 SR** [PRISMA], 14 studies, n=11,733; Xu 2018 **Level III-3 SR,** 23 studies, n=6,110; Rahavard 2017 **Level III-3 SR**, 42 studies, n unspecified; Kim 2017 **Level III-3 EH SR**, 41 studies, n unspecified; Krupic 2019 **Level IV SR**, 10 studies, n unspecified; Hampton 2015 **Level IV SR**, 5 studies, n unspecified). A review of the cultural impact on the pain management of Chinese cancer patients highlighted that analgesic use, adherence and pain reporting in Chinese cancer patients is poor, as it is culturally influenced by feelings of '*fatalism, desire to be good, low pain control belief, pain endurance beliefs, and negative effect beliefs*.' (Xu 2018 **Level III-3 SR**, 23 studies, n=6,110). Similarly, another study compared opioid consumption after major abdominal surgery between Hong Kong patients and Caucasian patients in Australia found that the Hong Kong patients requested less opioid, but that their pain scores were higher (Konstantatos 2012 **Level III-2**). Further marked disparities in effective pain treatment were reported; in the United States, African Americans and Hispanics were less likely to receive opioid analgesics and were more likely to have their pain undertreated vs Caucasian patients (Groenewald 2018 **Level IV**; Dickason 2015 **Level IV**). This disparity was reported for all types of pain visits, was more pronounced with increasing pain intensity and was unaffected by adjustment for pain severity. A study which looked at a patient receipt of an opioid prescription after a dental diagnosis, found that indeed ethnicity also mattered (Janakiram 2018 **Level IV**).

Interestingly, the research that focused on analgesic prescriptions to children in US ED's, raises the point that the level of opioids is dependent on whether the patient has an ethnic-concordant health care provider (Groenewald 2018 **Level IV**). This may explain the differences

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reported in patients of different ethnic groups attending EDs and requiring analgesia (Lee 2019a **Level III-2 SR** [PRISMA], 14 studies, n=11,733), while some studies find little to none (Ly 2019 **Level III-2**; Jacob 2017 **Level III-2**; Shavit 2018 **Level IV**; Shavit 2016 **Level IV**).

Prescription of opioids also varied with patient ethnicity independent of health professional bias. There are innate genetic factors that may explain pain disparity in Indian, Malay and Han Chinese patients, which demonstrates that opioid requirements are indeed ethnicity dependent and have to be administered as such (Somogyi 2016 **Level IV**).

To ensure culturally responsive care, it is imperative that health professionals continually improve their cultural competence by increasing their cross-cultural knowledge, skills and self-awareness through cultural competency training (Jongen 2018 **Level IV SR** [PRISMA], 64 studies [16 studies specific to health work force], n unspecified). Additionally, it is important to use accredited healthcare interpreters to improve communication between health professionals and patients who have difficulty communicating in the main language (Berger 2014 **Level IV**; Cadoret 2014 **NR**). Other strategies used to facilitate cross-cultural pain education and management include bilingual handouts describing varying methods of pain control and Visual Analog Scale (VAS) with carefully chosen anchor terms or the use of faces scales (see Chapter 2). With some studies showing a preference for the Faces Pain Scale – Revised, these scales might not be effective on their own (Pathak 2018 **Level IV**). A comparative study involving the assessment of Verbal Descriptor Scale (VDS), the Visual Analog Scale (VAS), the Faces Pain Scale (FPS), the McGill Pain Questionnaire-Short Form (MPQ-SF) and the Brief Pain Inventory-Short Form (BPI-SF) found that more than a single tool may be needed to ensure diagnostic accuracy and consistency in assessing severe pain in patients of CALD backgrounds (Ham 2015 **Level IV**). A series of pain scales in a number of different languages has also been produced by the British Pain Society to assist in the assessment of people whose first language is not English and these are available on their website (BPS 2014 **GL**). Limitations with the latter are that it is not available in Italian (one of the largest cultural groups in Australia) and it assumes a certain level of literacy of the patient. While there is evidence of differences in pain reports and analgesic use in different cultures or ethnic groups, this should not be used to stereotype patients or promote assumptions about differences in assessment and management of pain or response to pain therapies. Rather, it should only be used to inform of possible cultural preferences. Culturally responsive care in this context is used as an extension of person-centred care and therefore provision of effective analgesia requires not a culturally specific approach but a sensitivity to a patient's ethnicity, spirituality, cultural practices and beliefs, level of acculturation and their behavioural expression of pain. The large individual differences in pain behaviours and analgesic requirements that exist in any patient group mean that pain is best assessed and managed on an individual basis rather than on the basis of what might be expected in a patient from a particular cultural, ethnic or spiritual background (Cadoret 2014 **NR**).

KEY MESSAGES

1. Disparities in assessment, analgesic requirements and effective treatment of pain exist across ethnic groups (**S**) (**Level III-2 SR**).
2. Ethnic and cultural background of both healthcare professional and patient can influence the ability to assess and treat acute pain (**N**) (**Level III-2 SR**).

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

☑ Cultural competence of health professionals supported by specific training improves health outcomes for culturally and linguistically diverse patients (**U**).

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- ☑ Pain assessment and management should be done on an individual patient basis. Differences between ethnic and cultural groups should not be used to stereotype patients but should only be used to inform of possible cultural preferences (**U**).
- ☑ Multilingual printed information and pain measurement scales are useful in managing patients from different cultural or ethnic backgrounds (**U**).
- ☑ If language proficiency poses a communication barrier, then an accredited health care interpreter should be included when conducting a pain assessment, to ensure correct assessment; the use of friends, family or staff member should be avoided (**N**).
- ☑ The use of health-care specific language translation apps may be only considered as an alternative option in non-clinical situations in the sub-acute setting (eg daily routine communication) when formal healthcare interpreter services are not available (**N**).

9.3.1 | Aboriginal and Torres Strait Islander Peoples

Evidence from the Australian Institute of Health and Welfare highlights that when compared to non-Indigenous Australians; "*Indigenous Australians, on average, have worse heal*th", experience "*large disparities in health outcomes*" and "*report greater difficulty in accessing affordable health services that are close by*" (AIHW 2018 **NR**). Despite limited and predominantly weak levels of evidence regarding acute pain and its management in Indigenous Australians; this chapter seeks to identify key themes, barriers, concerns and opportunities for improvement (see also Table 9.5).

Importantly for clinicians navigating this chapter, findings drawn from patient populations may not be generalisable beyond the cohort where they were originally documented; however, exploration of these original papers may provide guidance to practitioners working with these populations. Additionally, examples selected from the literature for this chapter are not to suggest a universal approach to pain assessment, but instead highlight heterogeneity in this population, the need to counter racial profiling and ensure delivery of individualised care. There is a need for personalised care and variable patient preferences were identified for different mediums of patient information regarding lower back pain (Lin 2017 **Level III-1**); it was suggested that the need for "*communication to be individualised, flexible, and patient centred*".

The ramifications of profiling on pain management have been highlighted within the literature. One example regards pain experience related to vulvar cancer surgery where "*Although pain was noted as an issue by the Indigenous women, one of the health professionals interviewed did not see it as an issue and indicated that Indigenous peoples have high pain thresholds.*"(McGrath 2015 **Level IV**). Practitioners should be aware that historical literature which suggests high pain tolerance or pain threshold has been broadly criticised by contemporary authors, who have highlighted a potential risk of harm to patients if these beliefs are followed (McGrath 2015 **Level IV**; Fenwick 2004 **Level IV**; Fenwick 2006 **NR**).

Contemporary studies have instead identified unique, culturally appropriate pain behaviours among Indigenous patients (Fenwick 2004 **Level IV**) which may have been misinterpreted by health practitioners as "*a high pain threshold*" (McGrath 2015 **Level IV**). Examples of culturally appropriate pain behaviours may include **"***verbal and nonverbal silence in response to pain*" as reported in a study of postoperative pain in Central Australian Indigenous women (Fenwick 2004 **Level IV**). Multiple authors highlight study populations where pain may not be vocally communicated in a manner "*expected*" by Western health professionals which suggests that health professionals may be required to change their methods of assessment in order to identify

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pain expression in this population (McGrath 2006 **Level IV**; Fenwick 2004 **Level IV**; Honeyman 1996 **Level IV**). Other examples of "*silent*" pain performance may include the feigning of sleep, turning a head away or grimacing, also documented in a Central Australian study (Fenwick 2001 **Level IV**). Authors propose multiple reasons for this style of pain expression; ranging from respect for the health professional (Fenwick 2006 **NR**), an individual's position within their community (McGrath 2006 **Level IV**), a belief that the practitioner can "*see within*" the patient akin to the skills of a traditional healer (Fenwick 2004 **Level IV**), fear of the healthcare system (Fenwick 2001 **Level IV**) or due to fear of the cause of pain (Fenwick 2004 **Level IV**). Examples of the latter include cohorts where "*illness and pain are understood in relation to the external world and can be caused by such things as, breaking of tradition or violation of taboos, crossing into forbidden land or speaking to the wrong relative at the wrong time… possibly making the (pain) sufferer too ashamed to complain*" (Fenwick 2004 **Level IV**). Beliefs regarding the cause of pain must however be contrasted with the findings in regional and remote Western Australia, where the majority of participants with chronic low-back pain believed their pain resulted from problems in spinal anatomy or structure (Lin 2013 **Level IV**). Drawing from this evidence, clinicians need to acknowledge the breadth of pain expression and associated beliefs and how this may influence the establishment of appropriate pharmacological and non-pharmacological therapeutic regimes.

Consideration should also be given to the systemic factors which may also play a role in an individual's decision to report pain. Examples from the literature include patients being reluctant to disclose pain due to "*a lack of established trust relationships with health care providers*", perception that they were not listened to by health professionals and that negative stereotypes were affecting their treatment (Strong 2015 **Level IV**). Additionally, some patients may become "*quiet and withdrawn*" when hospitalised and may therefore "*not be sufficiently assertive to indicate their need for pain relief"* (McGrath 2015 **Level IV**). The impact of historical factors influencing an individual's decision to express pain must also not be overlooked (Fenwick 2006 **NR**).

9.3.1.1 | Assessment

Problems with the utility of frequently used assessment tools have been identified in a variety of studies exploring pain assessment in Aboriginal and Torres Strait Islander patients. In a review of the impact of an Acute Pain Service on postoperative pain, a higher proportion of patients were able to complete a verbal rating scale than a numerical pain scale (Sartain 1999 **Level III-3**). This was expanded by later authors who suggested that in some patient populations, linguistic nuances may favour the use of verbal rating scales and recommend the use of verbal descriptors based on the patient's language (Fenwick 2006 **NR**).

Not appreciating individual differences in pain expression or an individual's expectations regarding the assessment of their pain may lead to inadequate pain management. (Fenwick 2006 **NR**) An example from postoperative pain management in Central Australian Aboriginal women, highlighted that non-Aboriginal nurses expected pain to be expressed in a manner familiar to their own culture (e.g. vocalising pain); whereas the Aboriginal women expected pain to be interpreted in a manner similar to traditional healers such as "*to see within*" (Fenwick 2004 **Level IV**).

One particular challenge which may further exacerbate cultural differences and expectations across the patient/health care professional's interaction involves the role of communication. A prospective study identified that anaesthetists were more likely to be unsure if Aboriginal or Torres Strait Islander patients understood explanations vs non-Aboriginal patients (Howe 1998 **Level III-3**); subsequently leading to a higher rate of change to the patient's proposed treatment plan. From a patient perspective, patients were noted to experience "*difficulty describing their*

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pain problems to health professionals, in making themselves understood and in understanding what they were being told" (Strong 2015 **Level IV**). Adding to this, language barriers and the use of jargon have been identified as potential impediments to communication (Strong 2015 **Level IV**; Lin 2014 **Level IV**). Suggestions for health practitioners to address this include personalising communication (as discussed above), avoiding the use of jargon (Strong 2015 **Level IV**; Lin 2014 **Level IV**), consider the use of visual aids ((Strong 2015 **Level IV**; Lin 2014 **Level IV**; Cusack 2013 **Level IV**), and investing in trust development (Mitchell 2018 **Level IV**; Strong 2015 **Level IV**; McGrath 2006 **Level IV**; Fenwick 2006 **NR**).

The health professional may be required to modify their methods of history-taking within some populations in order to improve communication (Fenwick 2001 **Level IV**). Resources developed for pain management in Central Australian Aboriginal people highlight that asking two questions in one sentence or asking questions with obvious answers may cause confusion or result in no answer being forthcoming from the patient respectively. They recommend the health professional ask one question at a time and avoid asking "*nonsense*" questions where the answer is clear, such as asking about the presence of pain when the experience of pain is obvious. Likewise, health professionals should be aware that periods of silence may occur following asking questions of some Australian Aboriginal people, possibly out of respect for the individual asking the question (Taylor 2014 **NR**; Fenwick 2006 **NR**). Alternate suggestions for health professionals include using a conversational style of history taking (Lin 2014 **Level IV**; Lin 2013 **Level IV**; Taylor 2014 **NR**; Fenwick 2006 **NR**), which is noted by some authors to improve patient-practitioner trust (Fenwick 2006 **NR**).

9.3.1.2 | Treatment

Negative interactions with health care professionals may "*deter Indigenous people from seeking further services*" (Strong 2015 **Level IV**). Conversely, the development of trust between the healthcare provider and patient is noted to improve information disclosure and "*participants taking an active role in their management*" (Lin 2014 **Level IV**).

Variation in treatment or inconsistent use of pain relief has been identified in the literature. Examples include a recent publication which identified the inconsistent use of pain reducing techniques for children receiving repeated penicillin injections during acute rheumatic fever management (Mitchell 2018 **Level IV**). In this paper the author notes that only a minority of patients were able to "*negotiate about the pain of their injection*" with the children's ability to negotiate being linked to "*a trusting relationship with clinicians*". As a result, for repeated procedures Mitchell suggests "*a decolonising stance would ensure that pain reduction measures are mandated for every instance*" referencing current paediatric procedural pain management guidelines (RACP 2006 **GL**). Additionally, one study suggested that Indigenous Australian patients may be less likely to receive complex analgesia than non-indigenous patients in the postoperative period (RR 0.45; 95%CI 0.18 to 1.15]) (Howe 1998 **Level III-3**). Another author suggests Indigenous Australian patients receiving vulvar cancer treatment were "*were undermedicated for pain*" (McGrath 2015 **Level IV**). These findings have not been explored further, and the implications remain unclear.

Finally, higher levels of medical comorbidities such as renal failure have been identified within the Indigenous Australian population (Howe 1998 **Level III-3**; AIHW 2011 **Level IV**). These comorbidities may influence analgesic choice as reflected within other chapters.

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Table 9.5 | Barriers to effective Pain Management:

Barrier	Recommendations to address these barrier
Communication difficulties during patient/health care practitioner interaction	
Pain expression in Aboriginal and Torres Strait Islander Peoples may not reflect that which is expected by the health professional's cultural background (Fenwick 2004 **Level IV**)	• Health practitioners should understand nuances of pain expression and beliefs within such populations. Using frameworks such as cultural safety/cultural competency may be of assistance (The Wardliparingga Aboriginal Research Unit of the South Australian Health and Medical Research Institute 2017 **GL**; Fenwick 2006 **NR**) • Seek the assistance of caretakers in assessment of pain (Fenwick 2006 **NR**)
Language difficulties may exist between the patient and health care practitioner (Lin 2014 **Level IV**; Strong 2015 **Level IV**)	• Seek the assistance of an Aboriginal health worker or interpreter to assist in the bilateral communication between patient and health care team (Howe 1998 **Level III-3**; Cusack 2013 **Level IV**; Taylor 2014 **NR**) • Provide support, give information and improved explanations to patients (Strong 2015 **Level IV**; McGrath 2006 **Level IV**) • Avoid jargon (Lin 2014 **Level IV;** Strong 2015 **Level IV**) • Consider visual aids, (Strong 2015 **Level IV**; Lin 2014 **Level IV**) however this should be personalised to the individual. (Lin 2017 **Level III-1**)
Systemic factors may affect pain disclosure by the patient to health care practitioner (Fenwick 2006 **Level IV**; Strong 2015 **Level IV**)	• Develop trust with the patient (Mitchell 2018 **Level IV**; Strong 2015 **Level IV**; McGrath 2006 **Level IV**; Fenwick 2006 **NR**) • Consider cross-cultural competency/cultural safety Frameworks (see above) • Consider input from Aboriginal Health Workers • Consider self-exploration of practitioner's own culture, and the impact this can have on patients of other cultures (process of becoming culturally sensitive) (Fenwick 2006 **NR**)
Racial Profiling	• Acknowledge that previous views about pain tolerance can be harmful to patient care (McGrath 2015 **Level IV**; Fenwick 2004 **Level IV**; Fenwick 2006 **NR**)
Assessment Use of culturally inappropriate measures (Fenwick 2004 **Level IV**)	• The verbal pain descriptors may be a better choice of pain measurement tool than numerical rating scales in some Aboriginal Australian Peoples (Fenwick 2006 **NR**)
Treatment Potential variation, under-treatment or disparities	• Recognition of the risk of harm due to racial profiling (see above)

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treatment of pain for Indigenous Australian patients (Lin 2018 **Level IV SR**, 18 studies n unspecified; Howe 1998 **Level III-3**; McGrath 2015 **Level IV**)	• Taking a "decolonising stance" to address power imbalance, examples include ensuring "that pain reduction measures are mandated for every instance" (Mitchell 2018 **Level IV**) of paediatric procedure related pain as guided by current guidelines. (RACP 2006 **NR**)

KEY MESSAGES

1. Verbal descriptor scales may be a better choice of pain measurement tool than verbal numerical rating scales in some Aboriginal and Torres Strait Islander Peoples (**U**) (**Level III-3**).
2. Medical comorbidities such as renal impairment are more common in Aboriginal and Torres Strait Islander Peoples and may influence the choice of analgesic agent (**U**) (**Level IV**).

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

☑ Heterogeneity between differing populations of Aboriginal Peoples may require tailoring of the service delivered to the population and individual being serviced (**U**).

☑ Pain expression in Aboriginal and Torres Strait Islander Peoples may not reflect that which is expected by the health professional's cultural background. This places the onus on the health professional to understand nuances of pain expression and beliefs within such populations (**U**).

☑ Aboriginal and Torres Strait Islander Peoples are at increased risk of underrecognition and undertreatment of pain (**N**).

9.3.2 | Māori peoples

Māori peoples make up 16.5% (775,836 people) of the New Zealand population (Stats NZ 2019 **NR**). In 1840 in New Zealand, the Treaty of Waitangi, Māori and the Crown contracted to recognise British sovereignty in exchange for guarantees that indigenous rights to customary resources would be protected. This treaty has impacted on the health resources for this indigenous population (Durie 2012 **NR**). Cultural factors play a role in pain experiences in terms of a person's pain expression, threshold and tolerance (McGavock 2012 **NR**; Davidhizar 2004 **NR**) and also influence interaction with health professionals and adherence to advice provided (Magnusson 2011 **Level IV**, n=15). Māori views on health and healing, and the care of Māori people who are in pain, are different to the biomedical views prevalent in Western culture (McGavock 2012 **NR**). Māori perceive pain as a multidimensional experience affecting them physiologically, psychologically and socially (Magnusson 2011 **Level IV**, n=15). For example, in the Te Whare Tapa Whā model, health is seen as the interaction between te taha tinana (physical health), te taha hinengaro (mental health), te taha wairua (spirituality) and te taha whānau (family) (Pitama 2011 **NR**; Durie 1985 **NR**). Commonly used and widely accepted descriptors and phrases relating to pain and established pain measures in Western medicine are appropriate to use when assessing Māori patients (Magnusson 2011 **Level IV**; Pitama 2011 **NR**).

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Demographic data of patients attending for an initial assessment in 2015 were requested from all District Health Boards that offered a multidisciplinary chronic pain service (Lewis 2018 **Level III-3**, n=2002). Māori patients scored significantly worse than patients of European descent on all clinical assessment measures. Māori vs to non- Māori had higher pain, and greater disability, increased levels of stress, anxiety and depression, lower self-efficacy to manage pain, greater levels of pain-related fear and more catastrophic thoughts that were related to pain. In another study, data were collected via a comprehensive questionnaire given to consecutive new patients seen at a New Zealand multidisciplinary Pain Service over a four-year period (Burri 2018 **Level III-3**, n=798). Cross-cultural comparison discovered that Māori patients reported highest pain levels, the largest number of pain sites, the greatest pain interference, as well as highest levels of stress, anxiety, depression, and psychological distress, when vs all other ethnicities.

There has been limited data published about Māori perspectives on pain (Magnusson 2011 **Level IV**). Some of the quantitative research of Māori health has covered acute experimental pain (Azariah 1984 **Level III-2 EH**), acute postoperative pain (Mahmoud 2006 **Level IV**), pain associated with giving birth (Nelson 2006 **Level IV**), dental pain in children (Jamieson 2006 **Level III-2**) and prescription rates for analgesia (Crengle 2005 **Level III-2**).

Using the ischaemic arm test, Māoris were able to tolerate ischaemic pain for longer durations vs their European counterparts (Azariah 1984 **Level III-2 EH**, n=60). After accounting for various behavioural and material factors, Māori children were more likely to experience dental pain (OR 1.35; 95%CI 1.08 to 1.70) in a model considering demographic factors only, and Pacific Islander children were less likely to have received a general anaesthetic for dental work than New Zealand European children (OR 0.44; 95%CI 0.24 to 0.82) (Jamieson 2006 **Level III-2**, n=3,275).

Māori women were less likely to receive a range of medical interventions during childbirth, including Caesarean sections or epidural analgesia, vs non-Māori women (Harris 2007 **Level III-2**; Sadler 2002 **Level III-2**; Nelson 2006 **Level IV**). Māori and Pacific Islander women had a 15% epidural analgesia rate vs 25% in other New Zealand women, despite the fact that Māori and Pacific women were more likely to have pre-existing health conditions that would dictate a higher need for epidural analgesia (Nelson 2006 **Level IV**). A retrospective observational study was conducted in New Zealand Māori and New Zealand Europeans with data collected over 21 mth on patients who had received intrathecal morphine for postoperative pain management (Woods 2018 **Level III-3**, n=96). New Zealand Māori experienced a significantly higher rate and intensity of pruritus than New Zealand Europeans which was less likely to be treated.

From accident registry data, high levels of adverse outcomes were observed three mths post-trauma among a Māori cohort (Maclennan 2013 **Level IV**, n=566). Almost half were experiencing problems with mobility. A majority were having difficulties performing their usual activities and most were suffering some or extreme pain or discomfort. Over half were experiencing an increased level of psychological distress as well. Prevalence of disability due to injury in a household survey was slightly higher among Māori (31.4%) than non-Māori (29.3%) aged ≥15 y (Office for Disability Issues and Statistics New Zealand 2010 **Level III-2**). Overall, these outcomes highlight the importance of improved prevention strategies and post-injury care.

New Zealand continues to have some of the highest healthcare inequalities in the world with Māori having a two to three times higher mortality from non-communicable disease than non-Māori populations (Lilic 2015 **Level III-2**; Kerr 2014 **Level III-2**; Di Cesare 2013 **Level IV**; Hsiang 2013 **Level IV**). Māori were slightly less likely to consult general practitioners for back pain or regional pain disorders than European New Zealanders but were more likely to present with gout (Taylor 2004 **Level III-3**). Māori have one of the highest prevalence of gout internationally. A qualitative general inductive approach guided by Māori community principles ('Kaupapa') was used on 12 Māori (aged 48-79 years) with gout (Te Karu 2013 **Level IV**). Many put up with the pain

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and put the needs of others before themselves. NSAIDs, prednisone, and colchicine were mostly used with allopurinol used late in the disease. This showed that early preventive treatment in a culturally sensitive health care system was needed. In a prospective observational study, patients with gout for <10 y were recruited from primary and secondary care settings (Dalbeth 2013 **Level III-2**, n = 291 [37 Māori, 35 Pacific Islanders and 219 who were neither Māori nor Pacific Islanders]). Māori and Pacific Islander participants had 9 y earlier age of onset, higher flare frequency and more features of joint inflammation. Māori and Pacific Islander patients also reported greater pain and activity limitation and lower health-related quality of life.

Similarly, joint replacement registry data collected between 2005 and 2009 demonstrated that Māori patients experience higher pain and poorer mobility on self-report questionnaires one year following total joint arthroplasty than non-Māori patients (Singleton 2013 **Level III-2**). A validated Monte Carlo computer simulation model estimated quality-adjusted life years (QALYs) lost due to knee osteoarthritis in the New Zealand (NZ) adult population (aged 40 to 84 y) over their lifetimes until death (Abbott 2017 **NR**). Data were obtained from the NZ Health Survey, NZ Burden of Diseases, NZ Census, and from the relevant literature. QALY losses were found to be lower for Māori than non-Māori due to lower life expectancy. A prospective cohort study of rotator cuff repairs (March 2009 to December 2010) from the New Zealand Rotator Cuff Registry showed that Māori present younger with more pain and with significantly poorer function (Maher 2017 **Level III-2**, n=1,383). Māori suffer disproportionately from the pain of ischaemic heart disease with hospitalisation rates for Māori found to be 1.4 times that of non-Māori (Curtis 2010 **Level III-2**); mortality rates were more than twice that of non-Māori.

Alongside inequalities in access to, and quality of care, Māori also experience greater discrimination than non-Māori (Harris 2006 **Level III-2**). Research on acute pain suggests that experiences of Māori may differ from those of other New Zealanders in terms of tolerance, healthcare access or treatment, including receipt of pain-relief medication (McGavock 2012 **NR**). Given entrenched health disparities across a wide range of conditions and diseases, Māori carry a disproportionate burden of pain. The development and implementation of cultural competence training should provide pathways for health professionals to work more effectively with Māori patients (Pitama 2011 **Level IV**).

KEY MESSAGES

1. Experimental ischaemic pain is tolerated for longer in Māori people than in European New Zealanders (**U**) (**Level III-2**).
2. Māori people report higher levels of pain and/or disability with dental pain, gout and after trauma and joint replacement surgery than European New Zealanders (**U**) (**Level III-2**).

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

☑ High healthcare inequalities exist regarding access and quality of care (across age ranges, genders and for various medical conditions) between the Māori and Pacific Islander peoples compared with New Zealanders of European origin (**S**).

☑ Māori culture embraces the multidimensional aspects of pain experiences (**S**).

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9.4 | The patient with sleep-disordered breathing including obstructive sleep apnoea

Sleep-disordered breathing (SDB) is a spectrum of disorders where partial or complete cessation of breathing occurs many times during sleep. Obstructive sleep apnoea (OSA) is the most common form of SDB and is the condition most studied in surgical patients. As the prevalence of OSA is increasing and numbers of patients having surgery is large, the population at risk is significant (Memtsoudis 2013 **NR**). Acute pain management in a patient with OSA presents several potential problems; identification of patients at significant risk, choice of the most appropriate form of analgesia, the most suitable location in which to provide care and the level of monitoring required. These difficulties arise primarily from the risk of exacerbating OSA by the administration of opioid or other medicines with sedative effects (in particular benzodiazepines, but also butyrophenone or phenothiazine antiemetics and alpha-2-delta ligands). Importantly, patients with OSA suffer sleep disturbance on postoperative night one, and an increased frequency of SDB on postoperative night three (Chung 2014 **Level III-2**, n=38).

The prevalence of moderate and severe OSA in the general adult population is estimated to be 6 to 17%, and in older age groups (>60y) 49% or more (Senaratna 2017 **Level IV SR,** 24 studies, n=3,807). However, a large proportion of OSA patients remain clinically undiagnosed and untreated. There is a variable prevalence in the surgical population, with an estimated 60 to 70% prevalence in patients undergoing bariatric surgery of which one-third have moderate or severe OSA, and would benefit from CPAP (de Raaff 2017 **GL**). Therefore, many patients with undiagnosed OSA will have had treatment for acute pain without significant morbidity. The risk will depend on the severity of OSA, the nature and extent of surgery, the type of anaesthesia and analgesia and the extent of postoperative monitoring.

Patients with known OSA are at increased risk of postoperative complications vs other patients (Memtsoudis 2013 **NR**). However, the main risk may lie more with the body size and build of the patient, especially those who are morbidly obese, rather than the fact they have a specific diagnosis of OSA (Loadsman 2009 **NR**).

The simple to use STOP-Bang screening questionnaire has been validated for the identification of patients with OSA (Nagappa 2017 **Level III-2 SR** [PRISMA], 10 studies, n=23,609). A score 3 has been demonstrated to have high sensitivity for detecting moderate to severe OSA, whereas patients with a score <3 are considered to be low risk. Patients at high risk of OSA (STOP-BANG ≥3) have been demonstrated to have higher rates of perioperative complications. Specifically, in 7,877 high risk patients for OSA vs 15,732 low risk patients undergoing different surgeries, postoperative complications (6.86% vs 4.62: OR 3.93; 95%CI 1.85 to 7.77) and LOS (5.0 d ± 4.2 vs 3.4 ± 2.8: MD 2.01 d; 95%CI 0.77 to 3.24) are increased. Similarly, preoperative apnoea-hypopnoea index (AHI) and identification of nocturnal hypoxemia by oxygen desaturation index (ODI), cumulative sleep time percentage with SpO_2 <90% (CT90), minimum SpO_2, mean SpO_2, and longest apnoea duration are associated with postoperative complications (Suen 2019 **Level IV SR**, 21 studies, n unspecified).

A large retrospective database study using the USA Nationwide Inpatient Sample compared postoperative respiratory outcomes in surgical patients either with or without OSA based on ICD-9 coding on discharge and matched by propensity scoring (Memtsoudis 2011 **Level III-2**, n=6,051,703). Coding for OSA was associated with respiratory complications after both orthopaedic and general surgery: aspiration pneumonia (OR 1.41; 95%CI 1.35 to 1.47 and OR 1.37; 95%CI 1.33 to 1.41 respectively), acute respiratory distress syndrome (OR 2.39; 95%CI 2.28 to 2.51 and OR 1.58; 95%CI 1.54 to 1.62 respectively) and requiring intubation/mechanical

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ventilation (OR 5.20; 95%CI 5.05 to 5.37 and OR 1.95; 95%CI 1.91 to 1.98 respectively). The relative contribution of each component of perioperative care (eg type of analgesia or anaesthesia) is impossible to ascertain. Several other studies have analysed patient outcomes using the Nationwide Inpatient Sample database. These studies found:

- SDB was independently associated with postoperative cardiopulmonary complications (atrial fibrillation, intubation with mechanical ventilation, noninvasive ventilation) but not with an increased rate of in-hospital death (Mokhlesi 2013b **Level III-2**, n=1,058,710);
- For the subgroup of bariatric surgery patients, a diagnosis of SDB/OSA was surprisingly negatively associated with inhospital mortality (OR 0.34; 95%CI 0.23 to 0.50) (Mokhlesi 2013a **Level III-2**), n=91,028), while being positively associated with increased risk of atrial fibrillation (OR 1.25; 95%CI 1.11 to 1.41), need for intubation (OR 4.35; 95%CI 3.97 to 4.77) and of noninvasive ventilation (OR 14.12; 95%CI 12.09 to 16.51);
- For patients having shoulder arthroplasty, there was no association with adverse outcomes (Griffin 2013 **Level III-2**, n=22,988);
- In patients having revision hip or knee arthroplasty, OSA was associated with increased inhospital mortality (OR 1.9; 95%CI 1.3 to 2.8), as well as pulmonary embolus (OR 2.02; 95%CI 1.3 to 2.9) and wound complications (D'Apuzzo 2012 **Level III-2**, n=258,455).

OSA has been associated with a higher risk of postoperative cardiac adverse effects (OR 2.07; 95%CI 1.23 to 3.50) and acute respiratory failure (OR 2.43; 95%CI 1.34 to 4.39) (Kaw 2012 **Level III-2 SR**, 13 studies, n=3,942). Desaturation and ICU transfer were also more likely, but these two findings were hindered by a high degree of heterogeneity in the studies.

Following outpatient surgery, there was no association between preoperative diagnosis of OSA and an increase in adverse effects or unplanned hospital admission (Bryson 2012b **Level III-2**, n=674; Sabers 2003 **Level III-3**, n=234).

A major limitation of these studies is the reliance on existing diagnostic codes to identify patients with OSA using administrative data which may significantly underestimate the risk of undiagnosed OSA. This question was subsequently investigated. Patients presenting for general and vascular surgery were categorised into three groups: no diagnosis or low risk OSA; documented OSA without therapy or suspicion of OSA (STOP-Bang ≥3); and diagnosis of OSA with treatment. Untreated OSA, was independently associated with an increase in cardiopulmonary complications (risk-adjusted rates 6.7% versus 4%; aOR 1.8), especially unplanned reintubation (aOR 2.5) and myocardial infarction (aOR 2.6) (Abdelsattar 2015 **Level III-2**, n=26,842). Furthermore, the available evidence was recently reviewed by the Society of Anesthesia and Sleep Medicine Task Force (USA) which concluded that despite the low level of evidence, the majority of studies suggest OSA is associated with an increased risk of postoperative complications, including pulmonary and cardiovascular complications (Opperer 2016 **Level III-2 SR** [PRISMA], 61 studies, n=8,969,583). These findings are confirmed by subsequent studies: The rates of a composite outcome (myocardial injury, cardiac death, heart failure, thromboembolism, atrial fibrillation, and stroke within 30 d of surgery) were 30.1% for patients with severe OSA, 22.1% for patients with moderate OSA, 19.0% for patients with mild OSA, and 14.2% for patients with no OSA (Chan 2019c **Level III-2**, n=1,364). The association between composite outcome and OSA was significant only for patients with severe OSA (aHR 2.23; 95%CI 1.49 to 3.34). A hospital registry study assessing a bundle intervention for perioperative screening and management of patients with suspected OSA (BOSTN) identified associations between high BOSTN score (2) and a number of outcomes vs low scores; increased risk of postextubation desaturation (aOR 1.34; 99.3%CI 1.21 to 1.48) and increased LOS (3.7 d vs 4.3: aRR 0.87; 99.3%CI 0.84 to 0.91) but reduced requirement for postoperative invasive ventilation (aOR 0.89; 95%CI 0.80 to 0.98) (Raub 2020 **Level III-2**, n=3,834).

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Despite the evidence presented above, in a Canadian survey, 50% of anaesthetists continue to rely on their clinical suspicion and only 30% on a screening tool to identify patients with OSA preoperatively (Cordovani 2016 **Level IV**, n=992). Furthermore, 47% did not know of or had no access to a specific institutional policy for perioperative management of OSA, and 40% would send a patient with OSA home after ambulatory surgery. An accompanying editorial criticises this situation on the basis of 12 perioperative deaths in OSA patients the author assessed as an expert witness (Benumof 2016 **Level IV**, n=12).

In light of the increased postoperative risks associated with OSA, recent studies have aimed to determine the effect of treatment on outcome. A prospective cohort study screened patients for OSA risk and after surgery instituted extra care and observation (options included continuous pulse oximetry, oxygen, CPAP/BiPAP and others) for those identified as high risk, but the actual usage of these interventions was not recorded (Lockhart 2013 **Level III-2**, n=14,962). There was no increase in 30 d or 1 y postoperative mortality; however, it is not possible to determine if this was due to the use of the targeted interventions.

9.4.1 | Opioids and obstructive sleep apnoea

One of the main concerns in patients with OSA is that administration of opioids for the treatment of acute pain may lead to an increase in the number and severity of obstructive episodes and oxygen desaturation. OSA is associated with an increased sensitivity to opioid analgesia, possibly due to upregulation of opioid receptors secondary to recurrent hypoxia, and increased sensitivity to pain, due to chronic sleep fragmentation, in both adult volunteers (Doufas 2013 **Level III-2 EH**, n=43) and children (Brown 2009 **NR**) (see also 10.10.3). Furthermore, CPAP treatment appears to reduce pain sensitivity in patients with OSA, likely by the restoration of sleep continuity and improved ventilation (Cozowicz 2018 **Level IV SR** [PRISMA], 40 studies, n unspecified).

Patients assessed to be at risk of having OSA (by history, BMI and physical examination) vs control patients had more obstructive events during the first postoperative night (39±22 vs 14±10 events/h) and spent more time with oxygen saturation levels <90% (Blake 2008 **Level III-2**, n=63). There was no difference between the groups in the cumulative morphine dose over that time or frequency of central and mixed apnoeas. Classification of risk for OSA correlated with an increased number of desaturation events per h in patients monitored for 48 h postoperatively (Gali 2009 **Level III-3**, n=693).

Furthermore, while perioperative morphine dose is predictive of central apnoeas regardless of OSA status, patients at risk of OSA experienced significantly more severe hypoxaemia, largely due to obstructive respiratory events (Cozowicz 2018 **Level III-SR** [PRISMA], 40 studies, n=223,368).

OSA was a risk factor for OIVI in surgical patients (OR 1.4; 95%CI 1.2 to 1.7) (Gupta 2018b **Level IV SR** [PRISMA], 12 studies, n = 841,424). In patients with OSA, opioids attenuated the arousal response to hypoxia and prolonged airway obstruction.

Two early studies concluded that opioid administration in the postoperative period led to episodes of pronounced oxygen desaturation while the patients were asleep, and this was more commonly the result of obstructive and central apnoea than a decrease in respiratory rate (Catley 1985 **Level III-2**, n=32; Clyburn 1990 **Level III-2**, n=10). Those studies, however, involved bolus doses of opioids in the PACU and subsequent infusion rates of IV morphine that would now be considered much larger than current practice. A subsequent study using continuous infusion doses of remifentanil calculated to be analgesic in volunteers with moderate OSA demonstrated a substantial increase in the number of central events, while the number of obstructive events was reduced (possibly secondary to the REM-suppressing effect of opioids); minimum arterial haemoglobin oxygen saturation during the night was significantly lower in patients receiving remifentanil (Bernards 2009 **Level II**, n=19, JS 4). In another study, the central apnea index and

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obstructive apnea index on postoperative night 1 were correlated with the first 24-h opioid requirements (Chung 2014 **Level III-2**, n=38).

Despite a Cochrane review (Mason 2015 **Level I** [Cochrane], 14 studies, n=293: including Bernards 2009 **Level II**), there remains a paucity of information regarding the effects of analgesics, including opioids, in the acute pain setting in patients with OSA and therefore limited data on which to base recommendations for their postoperative care (ASA 2014 **GL**).

The apparent ceiling effect on respiratory depression, but not analgesia in healthy young patients, has favoured the use of buprenorphine in patients with SDB. Buprenorphine has unique pharmacological properties - it is a mixed agonist-antagonist, with a higher affinity for the mu-opioid receptor and consequent long half-life (166 min) (White 2018 **Level I** [Cochrane], 28 studies, n=2,210). However, in the setting of acute pain management, buprenorphine was found to have no difference in pain scores or the incidence of respiratory depression or sedation vs morphine in adults (White 2018 **Level I** [Cochrane], 28 studies, n=2,210) and children (Murray 2018 **Level I** [Cochrane], 4 studies, n=195). Buprenorphine's effect on respiratory drive may have potentially profound adverse effects in acute pain management, especially in patients with SDB.

A small study in children undergoing adenotonsillectomy for OSA showed a trend to fewer episodes of postoperative desaturation in children given tramadol vs morphine, but the difference was only significant for the second h after surgery (Hullett 2006 **Level II**, n=66, JS 4). In patients with a BMI ≥28 and with signs or symptoms suggestive of OSA, there was no difference in the numbers of respiratory events (obstructive apnoeas, hypopnoeas or central apnoeas) in patients receiving IV morphine PCA and those receiving an "opioid-sparing" analgesic regimen (IV tramadol PCA, parecoxib and "rescue-only" morphine); however there was a correlation between >15 respiratory events/h and total morphine dose (Blake 2009, **Level II**, n=65, JS 4).

Multimodal, opioid-sparing, analgesia has also been examined in adult OSA patients undergoing elective lower extremity arthroplasty (Cozowicz 2019 **Level III-2**, n=181,182). Assessment of this higher perioperative risk population demonstrated a step-wise reduction in opioid dose prescription and PCA use (26.6% in opioid only vs 19.2%, 13.7%, and 7.7%) with increasing modes of multimodal analgesia over 10 y. With regards to postoperative complications, there were significantly reduced odds for postoperative mechanical ventilation (OR 0.23; 95%CI 0.16 to 0.32) and critical care admission (OR 0.60, CI 0.48; 0.75) with the addition of two or more non-opioid analgesic modes. Of note, the most commonly used components of multimodal analgesia included paracetamol, coxibs, nsNSAIDs, gabapentin or pregabalin, regional analgesia, ketamine and corticosteroids.

In a number of case reports, the use of opioid medications by various regimens (intermittent IM, IV PCA and PCEA) in patients with OSA appeared to be a common factor for complications, including death (Parikh 2002 **Level IV**, n=19; Ostermeier 1997 **Level IV**, n=3; Etches 1994 **Level IV**, n=8; Lofsky 2002 **NR**; Cullen 2001 **CR**; Reeder 1991 **CR**; VanDercar 1991 **CR**). However, caution is required when interpreting these reports. Most of the cases involved excessive opioid doses (eg excessive bolus dose or a background infusion with PCA) and/or inadequate monitoring for respiratory depression (Macintyre 2005 **NR**). It appeared there was an over-reliance on monitoring respiratory rate; and sedation levels were not checked and/or increasing sedation was not recognised as an early indicator of respiratory depression.

Examination of the legal literature provides a similar story. From analysis of the Anesthesia Closed Claims Project database, OSA or suspected OSA was identified in 24% of patients with postoperative OIVI (Lee 2015 **Level IV**, n=357). Furthermore, the majority of critical events (88%) occurred within 24 h of surgery and nearly half of patients had a continuous opioid infusion at the time of the event, highlighting the requirement for appropriate postoperative monitoring in high risk patients. A retrospective review of the legal literature between 1991 and 2010 found 24 cases in which OSA (a known diagnosis in 96%) was directly implicated in the postoperative

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adverse outcome (death in 45.6% and anoxic brain injury in 45.6%) (Fouladpour 2016 **Level IV**, n=24). The most common complications were respiratory arrest in an unmonitored environment and difficulty in airway management. Furthermore, opioid use was thought to play a role in 38% of cases. Finally, examination of case reports of critical complications (death, near-death, and critical respiratory events) in surgical patients with OSA reinforced the importance of early postoperative monitoring, with 80% of events occurring within the first 24 h and 67% on the general hospital ward (Subramani 2017 **Level IV**, n=60).

An updated ASA task force report (USA) on the perioperative management of patients with OSA concluded that there remains only limited evidence to evaluate the effects of various postoperative analgesia techniques in patients with OSA and no good comparisons between conventional opioids such as morphine, and tramadol or nonopioid analgesics (ASA 2014 **GL**). Expert opinion, however, consistently suggests that nonopioid analgesics and regional techniques should be considered, either as an alternative to opioids or to help limit the amount of opioid required both for adults (ASA 2014 **GL**) and children (Patino 2013 **NR**).

9.4.2 | Obesity as a risk factor

The prevalence of obesity continues to grow, from 5–8% in 1980 to 13% in 2015 (WHO 2017), and is strongly associated with OSA (Young 2004 **NR**). Using polysomnography, OSA was identified in 71% of patients presenting for bariatric surgery (Frey 2003 **Level IV**, n=40) and an estimated one third of these patients suffer from moderate to severe OSA (de Raaff 2017 **Level IV**, n=15 [experts surveyed]). It is still unclear if the use of PCA, with appropriate bolus doses and monitoring, in morbidly obese patients is less safe than regional analgesia or other systemic opioid analgesic techniques.

In patients having bariatric surgery, all of whom underwent preoperative polysomnography and were prescribed CPAP therapy preoperatively if indicated, complications were common (33%) but, while age, open surgery and BMI were associated with those complications, OSA severity was not (Weingarten 2011a **Level III-2**, n=797). In morbidly obese children having tonsillectomy, obesity was similarly associated with adverse outcome, independently of OSA (Gleich 2012 **Level III-2**, n=100).

For further information see Sections 9.5 and on paediatric patients see Section 10.10.3.

9.4.3 | Approaches to treatment

9.4.3.1 | Oxygen

While oxygen therapy alone may not prevent the disruptions of sleep pattern or symptoms such as daytime somnolence and altered mental function that may occur in patients with OSA, it can reduce the likelihood of significant hypoxaemia (Landsberg 2001 **Level III-3**, n=43; Phillips 1990 **Level III-3**, n=8). As patients with OSA are more at risk of hypoxaemia after surgery or when given opioids, the use of supplemental oxygen would seem appropriate (ASA 2014 **GL**) despite concerns about reducing respiratory drive during apnoeic periods and potential life-threatening respiratory depression (Lofsky 2002 **NR**) from removing hypoxaemia as a key trigger for respiratory arousal. However, in patients with newly diagnosed (AHI >5 per h on preoperative polysomnography) and untreated OSA, postoperative supplemental oxygen 3 L/min via nasal prongs improved oxygenation, and decreased the AHI, mainly due to a decrease in hypopnea index and, to a smaller degree, central apnoea index (Liao 2017 **Level II,** n=123, JS 3). Furthermore, there was no significant difference in $PaCO_2$ measured by transcutaneous CO_2 monitor, however, patients with COPD and obesity hypoventilation syndrome (OHS) (serum $HCO3^-$ level >30 mmol/L) were excluded from this study and a significant proportion of patients (11.4%)

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experienced CO_2 retention, especially those receiving supplemental oxygen on postoperative night one.

9.4.3.2 | Continuous positive airway pressure

The perioperative use of CPAP may theoretically help to reduce postoperative risk and is recommended for patients with OSA (ASA 2014 **GL**). The effectiveness of CPAP (used appropriately and in highly supervised environments) for the management of OSA in the postoperative setting was initially supported by case reports (Rennotte 1995 **Level IV**, n=16; Mehta 2000 **NR;** Reeder 1991 **CR**). However, a number of studies examining perioperative initiation of both fixed and autotitrated CPAP for patients considered or known to be at risk, have demonstrated very poor adherence by those accepting the therapy (Liao 2013 **Level II**, n=177, JS 2; Guralnick 2012 **Level IV**, n=211), with no obvious outcome benefit (O'Gorman 2013 **Level II**, n=133, JS 2). Poor patient adherence may be improved by initiation of CPAP prior to surgery with more effective education and individualisation of therapy.

The effective *de-novo* use of CPAP in the setting of acute pain management likely requires a higher level of supervision than that available in the general surgical ward; most reports of the successful use of postoperative CPAP utilise extended periods of high-dependency nursing with staff educated and experienced in its use (Rennotte 1995 **Level IV**, n=16; Mehta 2000 **NR;** Reeder 1991 **CR**). Established CPAP use may, however, be associated with a lower risk of perioperative complications, as cardiovascular complications in particular (cardiac arrest and shock) were increased in patients with untreated OSA vs those previously established on CPAP in a study using a Manitoban health administrative database (OR 2.20; 95%CI 1.16 to 4.17) (Mutter 2014 **Level III-3**, n=20,488).

In adult patients with OSA undergoing surgery, there was no significant difference in postoperative adverse events between CPAP and no-CPAP treatment groups, but postoperative CPAP reduced the AHI vs preoperative baseline AHI values without CPAP (37 ± 19 events/h vs 12 ± 16 events/h) (Nagappa 2015 **Level IV SR** [PRISMA], 6 studies, n=904). In patients in PACU following bariatric surgery, CPAP treatment decreased AHI, decreased oxygen desaturations, and increased the mean oxygen saturation by 3% (Zaremba 2016 **Level III-1**, n=45). Patients with a known diagnosis of OSA, who are currently using CPAP at home, should therefore have CPAP continued while in hospital (ASA 2014 **GL**). As such, the Society of Anaesthesia and Sleep Medicine guidelines recommend the perioperative usage of CPAP therapy (prescribed setting) to reduce the risk of postoperative respiratory failure and cardiac events in patients with OSA who are either adherent, or poorly adherent, to CPAP therapy (Chung 2016 **GL**).

In paediatric patients with CPAP intolerance and moderate to severe OSA, there are limited data that high-flow air via nasal cannula (10 to 50 L/min) reduced respiratory events, improved oxygenation, and reduced heart rate (Hawkins 2017 **Level III-2**, n=10).

Evidence indicates that the risk of CPAP causing gastric distension and anastomotic leaks after all types of oesophageal and upper abdominal surgery appears to be unfounded in adults (Weingarten 2011b **Level III-2**, n=797; Huerta 2002 **Level III-2**, n=1,067). In patients undergoing bariatric surgery postoperative CPAP usage was not a risk factor for suture line disruption and leakage (de Raaff 2018 **Level III-2**, n=2,153).

9.4.3.3 | Monitoring and environment

Advice on the most appropriate environment for the care of OSA patients requiring analgesia, along with the level of monitoring required, is based on expert opinion only and suggests that the severity of SDB, efficacy of any current therapy, relevant comorbidities (eg cardiac) and the analgesia required all be taken into consideration both for adults (ASA 2014 **GL**; Joshi 2012 **GL**) and

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children (Patino 2013 **NR**). The ASA recommends continuous pulse oximetry monitoring and supplemental oxygen use after discharge from the recovery room in patients at increased risk of respiratory compromise from OSA until baseline oxygen saturation can be maintained on room air (ASA 2014 **GL**). Recommendations for postoperative monitoring of OSA patients after bariatric surgery include a minimum of continuous pulse oximetry in a designated surgical ward or a medium care unit, independent of CPAP usage (de Raaff 2017 **GL**).

Continuous pulse oximetry monitoring has the potential disadvantage of delaying the detection of hypoventilation when supplemental oxygen is administered. However, when continuous pulse oximetry was compared with standard monitoring (intermittent nursing spot-checks) in postoperative patients prescribed opioids, the detection of oxygen desaturation was 15 times more common, with a trend toward less ICU transfer in the pulse oximetry group (Lam 2017 **Level I** [PRISMA], 9 RCTs, n unspecified).

See also Section 4.3.1.4.

KEY MESSAGES

1. Continuous pulse oximetry compared to intermittent nursing spot-checks detects more episodes of hypoxaemia in postoperative patients with obstructive sleep apnoea prescribed opioids (**N**) (**Level I**).
2. The STOP-Bang questionnaire has high sensitivity for the identification of patients at risk of moderate to severe obstructive sleep apnoea (**S**) (**Level III-2 SR**).
3. Patients with sleep-disordered breathing, including obstructive sleep apnoea, having surgery are at increased risk of adverse cardiac and respiratory effects (**S**) (**Level III-2 SR**), in particular cardiac arrest/shock, atrial fibrillation, aspiration pneumonia, acute respiratory distress syndrome and need for intubation, mechanical and noninvasive ventilation (**N**) (**Level III-2**) and increased hospital length of stay (**N**) (**Level III-2 SR**).
4. Patients with obstructive sleep apnoea have an increased risk of exacerbation of obstructive episodes and hypoxaemia during the postoperative period (**U**) (**Level III-2**), in particular in the first 72 hours with peaks on the first and third postoperative night (**N**) (**Level III-2**).
5. Morbidly obese patients may be at increased risk of postoperative hypoxaemia, independent of a diagnosis of obstructive sleep apnoea (**U**) (**Level III-2**).
6. Continuous positive airway pressure does not increase the risk of anastomotic leak after upper gastrointestinal surgery (**S**) (**Level III-2**).
7. Increasing severity of obstructive sleep apnoea is associated with increased risk of postoperative respiratory complications including opioid-induced ventilatory impairment (**Q**) (**Level III-3**).
8. The prevalence of obstructive sleep apnoea in the surgical patient population is high and the majority (80%) of these patients are undiagnosed (**S**) (**Level IV SR**).
9. Higher preoperative apnoea-hypopnoea index and identification of nocturnal hypoxemia are risk factors associated with postoperative complications in patients with sleep-disordered breathing (**N**) (**Level IV SR**).
10. Patients with obstructive sleep apnoea have increased sensitivity to pain that improves with use of continuous positive air way pressure (**N**) (**Level IV SR**).

11. Opioids in patients with obstructive sleep apnoea attenuate arousal to hypoxia and prolong airway obstruction, and thereby lead to more severe hypoxaemia (**S**) (**Level IV SR**).

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

- ☑ Preoperative screening for obstructive sleep apnoea combined with treatment (ideally instituted preoperatively) and increased postoperative observation may decrease postoperative morbidity and mortality (**S**).
- ☑ Management strategies that may increase the efficacy and safety of pain relief in patients with obstructive sleep apnoea include multimodal nonsedating opioid-sparing analgesia such as regional techniques, continuous positive airway pressure, monitoring and supervision (in a high-dependency area if necessary) and supplemental oxygen (**U**).
- ☑ Perioperative commencement of continuous positive airway pressure may be beneficial in patients with obstructive sleep apnoea but requires high levels of supervision; significant problems are poor patient acceptance and postoperative adherence (**U**).
- ☑ In patients with obstructive sleep apnoea, monitoring should be extended beyond 24 hours to capture the high-risk period for late postoperative hypoxaemia (**N**).

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9.5 | The Obese Patient

Over the past three decades, the prevalence of obesity has increased significantly and is a major public health concern worldwide (Arroyo-Johnson 2016 **NR**). Obesity is associated with many comorbidities, with obstructive sleep apnoea (OSA) and the risk of hypoventilation being of particular concern with regards to acute pain management. As more obese patients are presenting for surgery, the need to manage acute pain safely in these patients becomes increasingly relevant. Multimodal analgesia and opioid-sparing techniques provide superior pain relief, improve perioperative outcomes and enhanced recovery in bariatric surgical care.

9.5.1 | Definitions of obesity

Obesity can be defined according to either anthropometric or body composition diagnostic criteria (Lang 2017 **NR**). Body mass index (BMI) is commonly used to define obesity, calculated by using weight in kilograms divided by height in metres squared. Other methods, including waist circumference, central and peripheral fat mass have also been used (Engin 2017 **NR**). The World Health Organization has established an international adult classification of BMI, whereby a BMI of 30 kg/m2 or higher is defined as obese (Arroyo-Johnson 2016 **NR**). Obesity can be further sub-classified into class 1 (30 to 34.9 kg/m2); class 2 (35 to 39.9 kg/m2) and class 3 or morbid obesity (greater than 40 kg/m2) (Engin 2017 **NR**). Currently, there is no consensus on an international classification of obesity for the paediatric population.
See Section 10.10 for paediatric issues.

9.5.2 | Prevalence

In Australia, 67% of adults are currently overweight or obese (AIHW 2019c **Level IV**). In New Zealand, 30.9% of adults are obese with differences by ethnicity (66.5% of Pacific Islanders, 48.2% of Māori, 29.1% of European/Other and 13.8% of Asian) (NZ MoH 2019 **Level IV**); the adult obesity rate has increased from 29% in 2011/12. Worldwide, the prevalence rate for being overweight or obese between 1980 and 2013 increased 27.5% for adults and 47.1% for children, to a total of 2.1 billion individuals considered overweight or obese (Ng 2014 **NR**). It has been predicted that by 2030, up to 86% of adults in the USA will be overweight or obese (Wang 2008 **NR**).

9.5.3 | Morbidity associated with obesity

Obesity has been linked to decreased life expectancy by approximately 3 to 18 y and large increases in healthcare expenditures (Leung 2015 **NR**). For every 5 unit increase in BMI above 25 kg/m2, overall mortality increases by 29%, vascular mortality by 41% and diabetes-related mortality by 210% (Prospective Studies 2009 **Level IV SR**, 57 studies, n=894,576).

Body mass is an important determinant of respiratory function, which can manifest as reduced lung volume, derangements in lung and chest wall compliance, increased resistance and moderate to severe hypoxaemia (Wang 2008 **NR**). These physiological alterations are more marked in obese patients with OSA. In surgical patients, the OSA prevalence is 40% in obese female and 50% in obese males, and OSA incidence increases to approximately 70% in morbid obesity (Lang 2017 **NR**).

The incidence of hypertension, dyslipidaemia, type 2 diabetes mellitus and cerebrovascular disease are directly proportional to BMI (Engin 2017 **NR**)**.** Obesity is also associated with increased

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risk of several cancer types and certain pro-inflammatory conditions such as osteoarthritis and chronic pain (Belcaid 2019 **NR**).

Common characteristics in obese persons with pro-inflammatory conditions include fatigue, lethargy, social withdrawal, irritability as well as anxiety and depression (Seaman 2013 **NR**; Hoftun 2012 **Level IV**, n=7,373). Obesity is an independent risk factor for major depressive disorder (OR 5.25; 95% CI 1.41 to 19.58) (Kasen 2008 **Level IV**, n=544). Obese patients with high depression, anxiety and alexithymia levels rated their postoperative pain as more intense and requested more analgesia vs obese patients with normal psychological indicators (Aceto 2016 **Level IV**, n=120).

9.5.4 | Pharmacokinetic impact of obesity

Unfortunately, obese subjects are often excluded from clinical trials during the drug development process (Hanley 2010 **NR**). As a result, information regarding the impact of obesity of the pharmacokinetics and pharmacodynamics of the majority of drugs remains limited.

Absorption

Although gastric emptying and gut permeability are affected by obesity (Teixeira 2012 **Level III-2**, n=40; Cardoso-Junior 2007 **Level III-2**, n=38; Xing 2004 **NR**), oral bioavailability and absorption does not appear to be altered in obese individuals, and may increase in morbid obesity (Cheymol 2000 **NR**; Blouin 1999 **NR**).

Distribution

Total blood volume, cardiac output and plasma protein binding are increased in obesity (Cooney 2016 **NR**). Volume of distribution (Vd) changes in the obese patient appear to be drug-specific and for the most part, can be attributed to the physiochemical properties of the individual drug (Hanley 2010 **NR**). However, it is clear that Vd is influenced by many factors and its obesity related changes are therefore difficult to predict on the basis of drug properties such as lipophilicity alone (Belcaid 2019 **NR**; Smit 2018 **NR**).

Metabolism and Elimination

Obese patients appear to undergo TBW-proportional increases in phase II conjugation of paracetamol (Abernethy 1982 **Level III-2**). There is limited evidence of an increase in cytochrome P450 (CYP) 2E1 activity with obesity, with a reduction in activity noted after weight loss (Emery 2003 **Level III-2**, n=32; O'Shea 1994 **Level III-2**, n=24). The clinical relevance of this is unclear and probably not significant. Although hepatic clearance is usually unchanged or increased in the early stages of obesity, it could eventually become reduced due to hepatic steatosis, liver fibrosis and cirrhosis (Leykin 2011 **NR**; Adams 2000 **NR**)

The direct effect of obesity on renal clearance is unclear. Studies of creatinine have found increased, decreased or similar GFR estimates in obese versus non-obese individuals. Presently, there is no single, well validated weight descriptor to characterise drug clearance in the obese population (Belcaid 2019 **NR**; Hanley 2010 **NR**).

9.5.4.1 | Indirect measures of body composition

A number of indirect measures to assess body composition have been developed for clinical use, including BMI, total body weight (TBW), ideal body weight (IBW), lean bodyweight (LBW) and predicted normal weight (PNWT).

Methods for calculating indirect measures of body composition are as follows (Duffull 2004 **Level III-3 PK**):

- IBW (kg) = 45.4 (49.9kg if male) + 0.89 x (height in cm – 152.4)

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- LBW (kg) = 1.07 (1.1 if male) x TBW – 0.0148 (0.0128 if male) x BMI x TBW.
- PNWT (kg) = 1.75 (1.57 if male) x TBW – 0.0242 (0.0183 if male) x BMI x TBW – 12.6 (10.5 if male)

There is a lack of evidence regarding dose adjustments of analgesia in the obese and morbidly obese patient and no clear consensus on what measures to use (Budiansky 2017 **NR**). It is advisable not to use TBW to calculate doses in obese patients to avoid risk of overdosing. Additionally, it is important to consider that LBW does not increase proportionally with fat mass in obesity. Normal fat mass is a size descriptor that partitions total body mass into fat and fat-free components. It uses allometric theory to calculate the fraction of fat mass that will make fat equivalent to fat-free mass. The value of normal fat mass is drug specific and specific to a PK parameter (eg Vd or CL) (Anderson 2017 **NR PK**). Calculating normal fat mass for drug dosing has been proposed as a principle-based approach that explains size and body composition effects on PKs of all drugs in adults of all sizes.

9.5.5 | Drugs used in the management of acute pain in the obese patient

An overarching systematic review of pain management after laparoscopic gastric bypass surgery shows that the administration of NSAIDS (1 RCT, n=47), dexmedetomidine (2 RCTS, n=157), ketamine (1 RCT, n=60) and intraperitoneal (2 RCT, n=188) or subfascial/subcutaneous (1 RCT, n=40) local anaesthetics or by transversus abdominis plane block (TAP) (2 RCTs, n=157) may improve analgesia vs placebo/controls (Andersen 2014 **Level I** [PRISMA] 9 RCTs, n=644).

Specifically for laparoscopic sleeve gastrectomy, a systematic review identified paracetamol (2 RCTs, n=161), NSAIDs (1 RCT, n=28) and opioids as rescue analgesics as well as TAP block (5 RCTs, n=247), but preferably port-site infiltration instead (1 RCT, n=147) as evidence-based analgesic options (Macfater 2019 **Level I** [PRISMA], 18 RCTs, n unspecified.; alpha-2-delta ligands (3 RCTs, n=253), while effective, should be used with caution in this population due to the risk of increasing OIVI (Belcaid 2019 **NR**).

RCTs included in the above two systematic reviews are partially mentioned again in the following more detailed paragraphs.

9.5.5.1 | Paracetamol

IV paracetamol improves pain scores (MD -0.66/10; 95%CI -1.03 to -0.28) and reduces opioid consumption (MD -6.44 mg; 95%CI -9.26 to −3.61) during the first 24 h after laparoscopic bariatric surgery vs placebo (Lee 2019b **Level I** [PRISMA], 4 RCT, n=349 patients).

The use of paracetamol in morbidly obese patients undergoing laparoscopic sleeve gastrectomy reduces opioid consumption, hospital LOS and reduces the number of emergency representations postoperatively due to abdominal pain (Cooke 2018 **Level II**, n=127, JS 5; El Chaar 2016 **Level II**, n=100, JS 5). The combined use of IV paracetamol with IV ketorolac has been shown to provide similar analgesic efficacy vs hydromorphone patient-controlled analgesia (PCA) after gastric bypass surgery (Ziemann-Gimmel 2013 **Level III-3**, n=181).

Pharmacokinetics in morbidly obese young adults appears to be altered as serum concentrations are virtually undetectable two h after administration of 1000 mg IV paracetamol (Hakim 2019 **Level IV PK**, n=11). This suggests that morbidly obese patients may require dose adjustment, although there is currently no consensus on what dosing regimen to use.

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9.5.5.2 | Non-steroidal anti-inflammatories (NSAIDs)

In the absence of contraindications, the use of non-selective NSAIDs following bariatric surgery has been shown to reduce opioid consumption and improve pain scores and postoperative nausea and vomiting (PONV) (Govindarajan 2005 **Level II**, n=50, JS 2). IV ibuprofen vs IV paracetamol provided better reduction in pain scores and similar reductions in post-operative opioid consumption (Erdogan Kayhan 2018 **Level II**, n=80, JS 5). Intraoperative ketorolac was associated with reduced haemoglobin, although there was no difference in transfusion requirements (Klein 2012 **Level III-2**, n=162).

9.5.5.3 | Conventional Opioids

The use of conventional opioids for acute pain management in obese patients is a challenge due to the increased risk of OIVI. An opioid-sparing approach with multimodal techniques and individualised pain management may mitigate the risks.

Comparisons between opioids offer conflicting evidence and slight differences in outcomes. Sufentanil vs remifentanil infusions offered better quality of recovery (Aldrete score, psychomotor recovery) despite slower awakening times in morbidly obese patients undergoing laparoscopic gastroplasty (Bidgoli 2011 **Level II**, n=100, JS 5).

Studies comparing remifentanil and fentanyl in patients with class 2 and 3 obesity undergoing laparoscopic gastric banding surgery provided conflicting results, however remifentanil had predictably faster recovery of respiratory parameters (Kontrimaviciute 2012 **Level II**, n=66, JS 3; Bidgoli 2011 **Level II**, n=100, JS 5; De Baerdemaeker 2007 **Level III-3**, n=40).

Pharmacologic dosing models for fentanyl in morbidly obese patients have not yet been developed, but data suggest that fentanyl should be dosed based on LBW or IBW (Belcaid 2019 **NR**; Lang 2017 **NR**). One small trial demonstrated the pharmacokinetic mass versus TBW curve was essentially linear below 100 kg and approached a plateau above 140 kg (Shibutani 2004 **Level III-2 PK**, n=109). Prolonged infusions of fentanyl in obese patients have been associated with prolonged effects (Porhomayon 2013 **NR**). Remifentanil infusion dosing is governed by either IBW or LBW (Egan 1998 **Level III-2 PK**, n=24). Metabolism of morphine does not appear to be altered in morbidly obese patients, however, decreased elimination of active metabolites is evident, prolonging duration of action and exposure to these metabolites (de Hoogd 2017 **Level III-2**, n=40).

9.5.5.4 | Tramadol

After laparoscopic bariatric surgery, tramadol was superior to morphine in providing postoperative analgesia, with lower opioid requirements, lower hypopnoea episodes, earlier ambulation, early PACU discharge and shorter hospital LOS (Bamgbade 2017 **Level III-3**, n=412). Drawbacks for routine use include potential interactions with multiple antidepressants, which is particularly relevant as obesity is associated with a higher risk of developing depressive disorders (Kasen 2008 **Level IV**, n=544; Apovian 2016 **NR**).

9.5.5.5 | NMDA receptor antagonists

Intraoperative ketamine vs placebo improved early analgesia and reduced opioid requirements in patients undergoing laparoscopic gastric bypass surgery when added to remifentanil infusion) (Hasanein 2019 **Level II**, n=60, JS 3). Addition of low dose ketamine to morphine appears to significantly reduce opioid consumption and improve oxygen saturation and lung function vs patients using morphine alone (Kamal 2008 **Level II**, n=80, JS 4). The use of ketamine combined with clonidine or dexmedetomidine also reduces intra- and post-operative opioid consumption, along

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with reduction of PONV and earlier time to extubation. This combination may cause significant drowsiness however (Sollazzi 2009 **Level II**, n=50, JS 3). A single dose of ketamine (0.4 mg/kg) resulted in no significant difference in pain intensity, however a clinically significant improvement in the affective component of pain was observed (Wang 2019 **Level II**, n=100, JS 5).

There is limited data available regarding ketamine dosing in obese patients. One study examining dose adjustments for induction of anaesthesia suggests using LBW or IBW (Sollazzi 2009 **Level II**, n=50, JS 3).

Perioperative IV magnesium sulfate vs placebo lowered pain scores and morphine consumption in patients undergoing sleeve gastrectomy (Kizilcik 2018 **Level II**, n=80, JS 5).

9.5.5.6 | Alpha-2-delta ligands

A single preoperative administration of pregabalin 150 mg demonstrated reductions in morphine consumption and pain scores with a low incidence of adverse effects after laparoscopic sleeve gastrectomy (Cabrera Schulmeyer 2010 **Level II**, n=80, JS 5). A single dose of preoperative gabapentin was found to have similar effects after laparoscopic gastric bypass surgery in patients with morbid obesity (Hassani 2015 **Level II**, n=60, JS 5). Caution with the routine use of these agents is required in the obese population, as they are known to cause sedation and may increase the risk of OIVI (Belcaid 2019 **NR**).

9.5.5.7 | Alpha-2 agonists

Dexmedetomidine in class 3 obese patients undergoing bariatric surgery results in improved analgesia, reduced opioid requirements and PONV with the most common infusion dose being used at 0.2 to 0.4 mcg/kg/hr (Singh 2017 **Level I** [PRISMA], 6 RCTs, n=362). This is confirmed by a subsequent RCT; intraoperative dexmedetomidine infusion reduced pain scores, morphine consumption and improve the quality of recovery after laparoscopic sleeve gastrectomy (Sherif 2017 **Level II**, n=150, JS 5). Clonidine vs dexmedetomidine had comparable effects on pain scores, quantity of analgesic consumption, return to normal function and patient satisfaction after laparoscopic sleeve gastrectomy (Naja 2014 **Level II**, n=60, JS 5).

9.5.5.8 | Corticosteroids

In postoperative obese patients undergoing laparoscopic sleeve gastrectomy, the addition of dexamethasone 8 mg and haloperidol 2 mg to ondansetron 8 mg vs ondansetron 8 mg only reduced pain intensity, morphine consumption and nausea (Benevides 2013 **Level II**, n=90, JS 5).

9.5.5.9 | Systemic local anaesthetics

Intraoperative systemic lidocaine infusion in the 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).

9.5.5.10 | Cannabinoids

Self-reported marijuana use is associated with higher perioperative opioid use in the context of obesity and weight loss surgery (Bauer 2018 **Level III-2**, n=434).

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9.5.6 | Local and regional anaesthetic techniques used in the management of acute pain in the obese patient

9.5.6.1 | Wound infiltration including wound catheters

Continuous SC and subfascial infusion of bupivacaine provided similar analgesia to IV PCA pethidine with reduced opioid requirements following laparoscopic gastric bypass surgery (Cottam 2007 **Level II**, n=40, JS 2).

Intraperitoneal local anaesthetic infusions for bariatric surgery reduce postoperative pain, decrease opioid consumption (Andersen 2014 **Level I** [PRISMA] 2 RCTs [intraperitoneal], n=188); Omar 2019 **Level II**, n=100, JS 3; Sherwinter 2008 **Level II**, n=30, JS 5) and are associated with earlier mobilisation, earlier intake of oral fluids and a shorter hospital LOS (Ruiz-Tovar 2018 **Level II**, n=110, JS 5). However, spraying 20 mL of 2.5% (?dosing error in manuscript) bupivacaine vs placebo onto the diaphragm during a laparoscopic gastric bypass did not reduce pain or opioid consumption (Schipper 2019 **Level II**, n=127, JS 4).

Preperitoneal bupivacaine infiltration reduced acute pain intensity, opioid consumption and the incidence of chronic post-surgical pain after bariatric surgery (Boerboom 2018 **Level II**, n=100, JS 4).

9.5.6.2 | Continuous and single-injection peripheral nerve blocks

Obesity was associated with a higher rate of peripheral block failure using landmark techniques (Franco 2006 **Level III-3**, n=2,020) and lower rates of patient satisfaction (Hanouz 2010 **Level III-2**, n=605). The use of US-guided regional blocks in obese patients improved procedural time, efficacy and patient satisfaction vs nerve stimulation (Lam 2014 **Level II**, n=24, JS 5). Even with the use of US guidance, elevated BMI is associated with an increased time required for block placement and higher pain scores and opioid consumption in PACU (Schroeder 2012 **Level IV**, n=528).

Ambulatory hernia repairs under local anaesthesia appear to be feasible and safe in obese patients with a BMI up to 45 kg/m2 (Acevedo 2010 **Level III-3**, n=2,031).

There is conflicting evidence regarding the analgesic benefit of a single injection US-guided TAP blocks in morbidly obese patients undergoing laparoscopic bariatric surgery (De Oliveira 2014b **Level II**, n=19, JS 5; Wassef 2013 **Level II**, n=35, JS 3). There was a short-term reduction in pain scores by US-guided TAP blocks, however other parameters including opioid consumption, time to ambulation or hospital LOS were similar to placebo (Saber 2019 **Level II**, n=90, JS 5). Another RCT found no difference in pain scores or opioid consumption with US-guided TAP blocks (Albrecht 2013a **Level II**, n=70, JS 5). Continuous local anaesthetic infusions appear to be more successful, with reduced pain scores and opioid consumption, earlier oral intake and ambulation times with US- guided (Said 2017 **Level II**, n=90, JS 2) or laparoscopic guided TAP block catheter placement (Ruiz-Tovar 2018 **Level II**, n=140, JS 4).

Brachial plexus blocks have been shown to provide safe and effective analgesia in patients with morbid obesity (Melton 2017 **Level III-2**, n=28; Franco 2006 **Level III-3**, n=2,020; Schroeder 2012 **Level IV**, n=528; Schwemmer 2006 **Level IV**, n=70). However, concern has been raised regarding the safety of supraclavicular blocks following a case report of severe respiratory distress in a morbidly obese patient who received a US-guided block (Guirguis 2012 **CR**).

There is currently no evidence-based recommendation for peripheral nerve block local anaesthetic dosing in patients with morbid obesity. Based on expert opinion, IBW should be used (Leykin 2011 **NR PK**; Ingrande 2010 **NR PK;** Adams 2000 **NR**).

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9.5.6.3 | Neuraxial techniques

Neuraxial blocks are challenging in obese obstetric patients, with a significant increase in failure rate at times (Kula 2017 **Level IV**, n=2,485; Vaananen 2017 **Level IV**, n=842). US guidance is likely to improve success rate (Shaylor 2016 **Level IV**, n=63), and estimated epidural depth visualised on ultrasound is strongly correlated with actual distance upon successful needle placement (Balki 2009 **Level IV**, n=46). A handheld ultrasound device provides comparable depth estimates to a console ultrasound machine (Carvalho 2019 **Level III-2**, n=47).

Obese parturients report significantly lower efficacy from labour epidurals (Bonnet 2017a **Level IV**, n=9,337). After an accidental dural puncture, the incidence of postdural puncture headaches (PDPH) is less in obese parturients vs non-obese (Peralta 2015 **Level III-2**, n=518 [dural punctures]).

The effect of obesity on the spread and block height in spinal anaesthesia remains controversial (Ngaka 2016 **Level III-2**, n=50; Kim 2015 **Level III-2**, n=209). More extensive spread of spinal anaesthesia is noted in females with central obesity vs those with non-central obesity (Chang 2017 **Level III-2**, n=57).

The addition of IT morphine vs placebo as part of a multimodal analgesic regimen after laparoscopic bariatric surgery markedly reduced postoperative pain, systemic opioid consumption and hospital LOS (El Sherif 2016 **Level II**, n=100, JS 4).

Epidural administration of local anaesthetic in obese patients has been associated with increased risk of cephalad spread (Carvalho 2017 **Level II,** n=40, JS 5; Lamon 2017 **Level III-2**, n=5,015; Kim 2015 **Level III-2**, n=209; Vricella 2011 **Level III-2**, n=250), thus dose reductions are likely to be required.

Thoracic epidural infusions of morphine at 200 mcg/h have been used safely in patients with class 3 obesity (Zotou 2014 **Level II**, n=48, JS 5). A loading dose of epidural morphine appears to offer no additional benefit in pain control and prolongs delay to normal bowel function and ambulation. Post laparotomy, the use of a thoracic epidural offers better measurements on spirometry function tests and quicker recovery of respiratory function (von Ungern-Sternberg 2005 **Level III-2**, n=84). Thoracic epidural use in obese patients undergoing off-pump coronary artery bypass surgery was shown to provide better analgesia, early tracheal extubation and shorter ICU LOS (Sharma 2010 **Level II**, n=60, JS 3).

PCA morphine vs epidural analgesia in gastric bypass surgery resulted in similar pain control, time to ambulation, bowel recovery or hospital LOS (Charghi 2003 **Level III-3**, n=86). Epidural analgesia was associated with an increased incidence of wound infections (39% vs 15%).

9.5.7 | Non-pharmacological techniques used in the management of acute pain in the obese patient

Various non-pharmacological therapies have been assessed in small trials for their efficacy in improving postoperative pain, though none are common practice.

Pulmonary recruitment manoeuvres reduced pain intensity and opioid requirements in the first 24 h after laparoscopic bariatric surgery (Pasquier 2018 **Level II**, n=150, JS 5).

A single session of postoperative prefrontal repetitive transcranial magnetic stimulation vs sham was associated with a 40% reduction in PCA morphine use in gastric bypass surgery patients (Borckardt 2008 **Level II**, n=20, JS 5).

The use of lavender aromatherapy in the post-anaesthesia care unit has been found to reduce the total analgesic and opioid requirements of patients undergoing laparoscopic gastric banding (Kim 2007 **Level II**, n=54, JS 3).

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9.5.8 | Multimodal concepts

Introduction of a multimodal protocol for analgesia in laparoscopic sleeve gastrectomy (preoperative etoricoxib, intraoperative and postoperative paracetamol with optional postoperative tramadol) vs historic control (previous standard care) resulted in reduced opioid requirements, reduced adverse effects of opioids (8.8% vs 33%) with similar analgesic efficacy (Ng 2017 **Level III-3**, n=158).

KEY MESSAGES

1. Perioperative dexmedetomidine infusion reduces pain intensity, opioid requirements and PONV after bariatric surgery (**N**) (**Level I** [PRISMA]).
2. Intraoperative peritoneal local anaesthetic administration reduces pain intensity and opioid requirements after bariatric surgery (**N**) (**Level I** [PRISMA]).
3. Paracetamol (multi-dosing) r educes opioid requirements, hospital length of stay and representations for pain after bariatric surgery (**N**) (**Level II**).
4. Intraoperative systemic lidocaine infusions reduce pain intensity, opioid requirements and improve the quality of recovery after bariatric surgery (**N**) (**Level II**).
5. Epidural administration of local anaesthetics in obese patients has been associated with increased risk of cephalad spread (**N**) (**Level III-2**).
6. Obesity increases the failure rate of neuraxial and peripheral nerve blocks (**N**) (**Level IV**); ultrasound guidance improves the success rate (**N**) (**Level IV**).

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

☑ Obesity has significant detrimental effects on respiratory function and is linked to an increased rate of obstructive sleep apnoea (**N**).

☑ Obesity influences pharmacokinetic and pharmacodynamic parameters of analgesic medications leading to uncertainty about dosing and caution should be used with weight-based dosing (**N**).

☑ Multimodal analgesic techniques including use of regional techniques result in opioid-sparing effects and thereby improve safety of acute pain management after bariatric surgery (**N**).

9.6 | The patient with concurrent renal or hepatic disease

The efficacy and effectiveness of most analgesic medicines is altered by impaired renal or hepatic function. This change is not only because of altered clearance of the parent medicine, but also through the accumulation of therapeutically active or toxic metabolites. Some analgesic agents can aggravate pre-existing renal and hepatic disease, causing direct damage and thus altering their metabolism.

A brief summary of the effects that renal or hepatic disease may have on some of the medicines used in pain management, as well as alterations that might be required in analgesic medicine regimens, is given in Tables 9.6 and 9.7.

9.6.1 | Patients with renal disease

The degree to which analgesic medicine regimens require alteration in patients with renal impairment depends largely on the extent of renal impairment. Some medicines have active metabolites that are dependent on the kidney for excretion, and the medicine or its metabolites may further impair renal function.

A standard definition for chronic kidney disease (CKD) is provided by the US National Kidney Foundation (kidney.org) Kidney Disease Outcome Quality Initiative Advisory Board; patients with CKD should have either a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for ≥3 mth or structural/functional kidney damage with or without changes in GFR **(**Levin 2014 **GL**). This definition quantifies five stages from Stage 1 (kidney damage with normal or increased GFR) via Stage 2 (mild reduction in renal function and GFR), Stages 3 and 4 (moderate to severe impairment of renal function and reduction in GFR) to Stage 5 (end-stage kidney disease requiring dialysis or renal replacement therapy).

There is some limited information about the ability of dialysis to clear many medicines and/or their metabolites. Molecules are more likely to be removed by dialysis if they have a low molecular weight, greater water solubility and lower volume of distribution; while a higher degree of protein binding and use of lower-efficiency dialysis techniques will reduce removal (Trainor 2011 **NR**; Dean 2004 **NR**).

The available data indicate the following (see Table 9.6 for references):

- Analgesics that exhibit the safest pharmacological profile in patients with renal impairment are alfentanil, buprenorphine, fentanyl, ketamine, paracetamol (except with compound analgesics) and sufentanil. None of these medicines deliver a high active metabolite load or have a significantly prolonged clearance.
- Oxycodone can usually be used without any dose adjustment in patients with renal impairment. Its metabolites do not appear to contribute to any clinical effect in patients with normal renal function.
- Amitriptyline, bupivacaine, levobupivacaine, lignocaine, ropivacaine, clonidine, gabapentin, pregabalin, codeine, hydromorphone, methadone, morphine, tramadol and tapentadol have been used in patients with renal disease but may need dosing adjustment depending on the degree of impairment. For local anaesthetics and prolonged administration, a reduction in dose may be required. Levobupivacaine, with similar clearance mechanisms, and ropivacaine may be safer than bupivacaine due to their higher therapeutic ratio. Haemodialysis clears some medicines, and so a supplemental dose may be needed at the end of dialysis (eg gabapentin, pregabalin).

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- NSAIDs (both nsNSAIDs and coxibs), dextropropoxyphene and pethidine should not be used in the presence of significant renal impairment.
- Carbamazepine, sodium valproate and lamotrigine require no dose reduction. Caution is advised for the use of lamotrigine in patients with an eGFR <15 mL/min/1.73m^2
- Oxcarbazepine and topiramate require dose reduction in renal disease

Detailed reviews of pain management in patients with CKD have been published (Nagar 2017 **Level III-3 SR** [PRISMA], 12 studies, n unspecified; Sande 2017 **Level IV SR**, 18 studies, n unspecified; Davison 2019 **NR**; Pham 2017 **NR**; Nayak-Rao 2011 **NR**), also with an emphasis on the perioperative period (Tawfic 2015 **NR**) and on paediatric patients (Reis 2018 **NR**). Reviews of perioperative management (Trainor 2011 **NR**) and of prescribing for the dialysis patient has also been published (Smyth 2016 **NR**).

Additional information can be found in the *Australian Medicines Handbook* (AMH 2019 **GL**).

Table 9.6 | Analgesic medicines in patients with renal impairment

Medicine	Comments	Recommendations*
Opioids		
Alfentanil	No active metabolites 92% protein bound; increases in free fraction may result from alterations in protein binding (Sande 2017; Tawfic 2015)	No dose adjustment required unless renal failure is severe
Buprenorphine	Pharmacokinetics unchanged; predominantly biliary excretion of metabolites Pharmacokinetics also unchanged with dialysis (Davison 2019; Pham 2017; Sande 2017)	No dose adjustment required
Codeine	Accumulation of active metabolites can occur; prolonged sedation and respiratory arrest have been reported in patients with renal impairment No good data on removal by dialysis (Davison 2019; Pham 2017; Sande 2017)	Dose adjustment recommended or use an alternative opioid
Dextro-propoxyphene	Accumulation of active metabolite (nordextropropoxyphene) can lead to CNS and cardiovascular system toxicity. Contraindicated if creatinine clearance <40 mL/min. Blood concentrations not significantly changed during dialysis (Davison 2019; Niscola 2010)	Use of alternative agent recommended
Dihydrocodeine	Metabolic pathway probably similar to codeine Time to peak concentration and terminal half-life prolonged (Pham 2017; Craig 2008; Murtagh 2007)	Insufficient evidence: use not recommended

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Medicine	Comments	Recommendations*
Fentanyl	No active metabolites Not removed to any significant degree by dialysis (Davison 2019; Sande 2017; Pham 2017; Tawfic 2015)	No dose adjustment required; may be used in patients with severe renal impairment
Hydromorphone	Neurotoxicity from accumulation of H3G possible H3G is effectively removed during HD; PD no data (Davison 2019; Sande 2017; Pham 2017; Tawfic 2015)	Dose adjustment recommended or use alternative opioid
Methadone	Methadone and its metabolites are excreted in urine and faeces; in anuric patients it may be mostly in faeces High protein binding, high volume of distribution and moderate water solubility would suggest that it is likely to be poorly removed by HD (Davison 2019; Pham 2017; Opdal 2015; Nayak-Rao 2011)	Dose adjustment may be required in severe renal impairment
Morphine	Major metabolites M3G and M6G excreted via kidney and accumulate in renal impairment M6G is an opioid agonist that crosses the blood-brain barrier slowly; delayed sedation from M6G has been reported in renal failure Neurotoxicity from accumulation of M3G possible Oral administration results in proportionally higher metabolite load Morphine and its metabolites are cleared by most HD procedures but may not be significantly affected by PD M6G also removed but slow diffusion from CNS delays response (Davison 2019; Sande 2017; Pham 2017; Tawfic 2015)	Dose adjustment recommended or use alternative opioid
Oxycodone	The metabolite oxymorphone is active but plasma levels are normally negligible and therefore it has an insignificant clinical effect in patients with normal renal function Higher blood concentrations of oxycodone and metabolites with moderate to severe renal	No dose adjustment required in most patients Monitor and adjust if necessary

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Medicine	Comments	Recommendations*
	impairment; half-life significantly increased in end-stage renal disease Oxycodone and its metabolites are dialyzable (HD, no data on PD) (Davison 2019; Samolsky Dekel 2017; Pham 2017; Sande 2017)	
Pethidine	Norpethidine is the only active metabolite and is renally excreted; it is dialysable (HD) Accumulation of norpethidine can lead to neuroexcitation including seizures (Tawfic 2015; Craig 2008; Launay-Vacher 2005)	Use of alternative agent recommended
Sufentanil	Minimally active metabolite (Sande 2017; King 2011; Murphy 2005)	No dose adjustment required
Tramadol	Increased mu-opioid effects from active metabolite O-desmethyltramadol (M1) as renally excreted Tramadol is removed to some extent by HD (Davison 2019; Pham 2017; Tawfic 2015)	Dose adjustment recommended Use of alternative agent recommended in significant renal impairment
Tapentadol	Metabolised by glucuronidation Major metabolite will accumulate in renal failure but significance unknown Likely to be removable by HD (AMH 2019; Pham 2017; Xu 2010)	Do not use in severe renal impairment (Creatinine clearance <30 mL/min)
Nonopioids		
Paracetamol	Terminal elimination half-life may be prolonged Is dialysable (Nayak-Rao 2011; Kuo 2010; Craig 2008)	May need to increase dose interval if renal impairment is severe Some evidence that it may accelerate the rate of progression to chronic renal failure
NsNSAIDs and coxibs	Can affect renal function Behaviour during dialysis not clearly elucidated for most NSAIDs (Nayak-Rao 2011; Kuo 2010; Launay-Vacher 2005)	Some evidence that they may accelerate the rate of progression to chronic renal failure, in particular in dehydration.

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Medicine	Comments	Recommendations*
		Progression of renal disease more likely with nsNSAIDs than coxibs
Anticonvulsants		
Alpha-2-delta ligands	Gabapentin: impaired renal function reduces clearance in direct proportion to creatinine clearance; about 35% cleared by dialysis (Davison 2019; Asconape 2014)	Dose adjustment recommended on basis of creatinine clearance
	Pregabalin: Impaired renal function reduces clearance in direct proportion to creatinine clearance; highly cleared by dialysis (Davison 2019; Asconape 2014)	Dose adjustment recommended on basis of creatinine clearance
Carbamazepine	No dose adjustment necessary Highly protein bound, poorly dialysed (Bansal 2015)	No dose adjustment needed
Lamotrigine	Limited data (Bansal 2015)	Dose reduction if GFR<15 ml/min
Topiramate	Up to 80% renal excretion unchanged (Bansal 2015)	Dose reduction
Valproic acid	Hepatic elimination (Bansal 2015)	No dose reduction
Other medicines		
Local anaesthetics	There may be no significant difference in plasma concentration of levobupivacaine, bupivacaine or ropivacaine in patients with chronic renal failure unless renal failure is severe, or continuous infusions are used or repeated doses are used Increases in free fraction may result from alterations in protein binding Higher peak plasma concentrations of ropivacaine in uraemic patients but no difference in free fraction; uraemic patients have significantly higher alpha-1-acid glycoprotein plasma concentrations (AMH 2019; De Martin 2006; Jokinen 2005; Crews 2002)	Risk of toxicity may be affected by abnormalities in acid-base balance and/or potassium levels Doses may need to be reduced if prolonged or repeated administration (eg continuous infusions)

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Medicine	Comments	Recommendations*
Clonidine	Half-life is increased in severe renal failure 50% metabolised by the liver; remainder excreted unchanged by the kidney (Khan 1999; Lowenthal 1993)	Limited data; dose adjustment has been recommended
TCAs	Amitriptyline is metabolised in the liver to nortriptyline, the active agent Not significantly removed by dialysis (Davison 2019; Raymond 2008; Dargan 2005)	Limited data; metabolite accumulation may occur and increase the risk of adverse effects but little evidence to indicate need for dose reduction
SNRIs	Duloxetine Venlafaxine (AMH 2019; Raymond 2008)	Dose reduction if creatinine clearance <30 mL/min
Ketamine	Dehydronorketamine levels are increased but it has only 1% of potency of ketamine Ketamine is not removed well by HD (Davison 2019; Tawfic 2015)	Limited data; probable that no dose adjustment is required

*Note: * Doses must still be titrated to effect for each patient.*
HD – haemodialysis
PD – peritoneal dialysis

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9.6.2 | Patients with hepatic disease

Not all patients with hepatic disease have impaired liver function. In patients with hepatic impairment, most analgesic medicines have reduced clearance and increased oral bioavailability but the significance of these changes in the clinical setting has not been studied in depth.

Patients with cirrhotic liver disease may have renal impairment despite a normal serum creatinine. This can affect clearance of renally excreted medications and dose adjustment may be required.

The available data indicate the following (see Table 9.7 for references).

- While there are limited data, dose adjustments are usually not required for alfentanil, buprenorphine, fentanyl, morphine, oxycodone and sufentanil. However, all opioids carry an increased risk of toxicity and hepatic encephalopathy.
- Tramadol may need to be given at lower doses.
- Methadone should be used with caution in the presence of severe liver disease because of the potential for accumulation due to impaired clearance.
- Combination preparations of slow-release oxycodone and naloxone (Targin®) should be avoided in hepatic impairment as the reduced naloxone clearance leads to increased systemic levels and potential antagonism of the analgesic action of the oxycodone.
- The clearance of local anaesthetics may be significantly impaired; doses may need to be decreased if use is prolonged.
- Carbamazepine and valproate should be avoided in patients with severe hepatic impairment.
- It may be wise to reduce the dose of paracetamol in patients with significant degrees of hepatic impairment.

Detailed reviews of analgesic use in hepatic disease have been published (Dwyer 2014 **NR**; Imani 2014 **NR**; Bosilkovska 2012 **NR)** other detailed but lower quality reviews have also been published (Soleimanpour 2016 **NR**). Additional information can be found in the *Australian Medicines Handbook* (AMH 2019 **GL**).

Table 9.7 | Analgesic medicines in patients with hepatic impairment

Medicine	Comments	Recommendations*
Opioids		
Alfentanil	No significant difference in half-life found in children undergoing liver transplant In alcoholic cirrhosis, plasma clearance and protein binding decreased and elimination half-life increased after single dose (Davis 1989; Ferrier 1985)	Limited data: no dose adjustment required in most patients
Buprenorphine	Lower blood concentrations of buprenorphine and norbuprenorphine Chronic use in patients with HIV or HCV associated with increased incidence of hepatic enzyme rise (Tetrault 2016; Dwyer 2014; Johnson 2005)	Limited data: no dose adjustment required

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Medicine	Comments	Recommendations*
Dextro-propoxyphene	Reduced oxidation leading to reduced clearance (Tegeder 1999)	Limited data: dose adjustment may be required
Fentanyl	Disposition appears to be unaffected (Dwyer 2014; Chandok 2010)	Limited data: no dose adjustment required
Methadone	Increased half-life but limited significance (Dwyer 2014; Lugo 2005)	Limited data: no dose adjustment required in stable chronic liver disease
Morphine	Hepatic impairment does not appear to have a significant effect on morphine pharmacokinetics; even in patients with cirrhosis there is a large hepatic reserve for glucuronidation Blood concentrations of morphine but not morphine metabolites higher after liver resection; blood concentrations also higher in patients with liver cancer Increased oral bioavailability of morphine due to its normal high first pass metabolism when given via this route Morphine pharmacokinetics altered in Nonalcoholic Steatohepatitis (NASH) (Pierre 2017; Rudin 2007; Kotb 2005)	In most patients no dose adjustment required
Hydro-morphone	Increased half-life of hydromorphone (AMH 2019; Soleimanpour 2016; Chandok 2010)	Consider dose reduction
Oxycodone	Decreased oxycodone clearance with mild to moderate hepatic impairment Avoid fixed dose combination with naloxone (Targin®) in moderate to severe hepatic impairment as systemic absorption of naloxone may be increased (AMH 2019; Riley 2008; Kalso 2005)	Limited data: no dose adjustment required in most patients
Pethidine	Reduced clearance (Tegeder 1999)	Limited data: dose adjustment may be required; use not recommended
Sufentanil	No difference in clearance or elimination (Tegeder 1999; Chauvin 1989)	No dose adjustment required
Tramadol	Reduced clearance (Dwyer 2014; Kotb 2008; Tegeder 1999)	Limited data: dose adjustment may be

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Medicine	Comments	Recommendations*
		required if impairment is severe
Tapentadol	Elimination by hepatic glucuronidation (AMH 2019; Xu 2010)	Avoid in severe hepatic impairment (Child-Pugh score 10–15) Adjust dose in moderate hepatic impairment (Child-Pugh score 7–9)
Nonopioids		
Paracetamol	Metabolised in the liver; small proportion metabolised to the potentially hepatotoxic metabolite N-acetyl-p-benzoquinone imine. This is normally inactivated by hepatic glutathione Clearance is reduced (Hayward 2016; Dwyer 2014; Imani 2014; Graham 2013; Chandok 2010)	Commonly suggested that it should be used with caution or in reduced doses or frequency with active liver disease, alcohol-related liver disease and glucose-6-phosphate dehydrogenase deficiency However, others report that it can be used safely in patients with liver disease and is preferred to NSAIDs, and that therapeutic doses of paracetamol, at least for short-term use, are an unlikely cause of hepatotoxicity in patients who ingest moderate to large amounts of alcohol Dose reduction for chronic use
nsNSAIDs	Metabolised in liver. Altered metabolism and bioavailability in cirrhosis. Avoid if renal impairment present or risk of hepato-renal syndrome (Dwyer 2014; Imani 2014; Chandok 2010)	May be used in mild chronic liver disease Avoid in cirrhosis COX2 selective agents may be safer

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Medicine	Comments	Recommendations*
Anticonvulsants		
Alpha-2-delta ligands	Eliminated renally (Asconape 2014; Dwyer 2014; Chandok 2010)	Safe in liver disease
Carbamazepine	Transient rises in hepatic enzymes occur in 25–61% of patients treated; has been reported to cause hepatic failure (rare) Primarily metabolised in the liver (Asconape 2014; Ahmed 2006)	Dose adjustment may be required; use not recommended in severe hepatic impairment
Valproate	Transient rises in hepatic enzymes occur in 10–15% of patients treated; has been reported to cause hepatic failure (rare) Primarily metabolised in the liver (Asconape 2014; Ahmed 2006)	Dose adjustment may be required; use not recommended in severe hepatic impairment
Other medicines		
Local anaesthetics	Amide-type local anaesthetics undergo hepatic metabolism and clearance may be reduced in hepatic disease Increased plasma concentrations of ropivacaine after continuous infusion but not a single dose (AMH 2019; Jokinen 2007; Jokinen 2005; Bodenham 1990)	Limited data; dose adjustment may be required with prolonged or repeated use
TCAs	Amitriptyline is metabolised in the liver to nortriptyline, the active agent (Dwyer 2014; Chandok 2010)	Reduce dose if hepatic impairment is severe
SNRIs	Duloxetine Venlafaxine (Dwyer 2014; Chandok 2010)	Duloxetine should not be used in hepatic impairment Venlafaxine dose reduction in hepatic impairment Desvenlafaxine may be safer
Ketamine	In acute use, rare incidence of hepatic enzyme rise Prolonged infusion associated with hepatic enzyme rise Chronic use possibly associated with sclerosing cholangitis (Wong 2014; Noppers 2011)	Monitor hepatic enzymes when continuous infusion is prolonged beyond about five d

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*Note: *Doses must still be titrated to effect for each patient*

KEY MESSAGE

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

☑ Consideration should be given to the choice and dose regimen of analgesic agents in patients with hepatic and particularly renal impairment (**S**).

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9.7 | The opioid-tolerant patient

With increased opioid prescribing for chronic pain, partly due to an ageing population, and increased use and misuse of prescription opioids, increasing proportions of patients with acute pain are opioid-tolerant. The proportion of opioid-tolerant patients varies widely with country and context. For example, it is higher in those presenting for orthopaedic and spinal surgery (Hilliard 2018 **Level IV**, n=34,186).

9.7.1 | Definitions

Misunderstandings in the terminology related to addiction (see also Section 9.8 below), tolerance, and physical dependence may confuse health professionals and patients, leading to inappropriate and/or suboptimal acute pain management as well as stigmatisation (Patel 2017 **Level IV**, n=216). Terms such as addiction, substance abuse, substance dependence and dependence are often used interchangeably. Relevant terms are defined in Table 9.8.

The definitions of many of these terms were not developed for people suffering with chronic pain. Consensus statements from the IMMPACT and ACTTION panels address definitions for the patient with chronic pain (O'Connor 2013 **GL**; Smith 2013 **GL**) as follows:

- Misuse: opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects
- Abuse: intentional use of the opioid for a nonmedical purpose, such as euphoria or altering one's state of consciousness
- Addiction: Pattern of continued use with experience of, or demonstrated potential for, harm.

Table 9.8 | Definitions of relevant terms

Aberrant drug-related behaviours	"*Behaviours that may be suggestive of the development of abuse, addiction or misuse*" (Moore 2009)
Addiction	A disease that is characterized by aberrant drug-seeking and maladaptive drug-taking behaviours that may include cravings, compulsive drug use and loss of control over drug use, despite the risk of physical, social and psychological harm While psychoactive drugs have an addiction liability, psychological, social, environmental and genetic factors play an important role in the development of addiction Unlike tolerance and physical dependence, addiction is not a predictable effect of a drug "*Primary chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations*" (AAPM 2001 **GL**)
Chemical coping	"*The use of opioids to cope with emotional distress, characterized by inappropriate and/or excessive opioid use*" (Kwon 2015 **NR**)

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Dependence syndrome (ICD 10)	"*A cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state*" (AAPM 2001 **GL**)
Diversion	Sharing, selling or trading prescribed drugs to someone for whom they are not prescribed (Arria 2011 **Level IV**) Sourcing activities or paths which redirect psychoactive prescription drugs from legitimate production or medical-use environments into the hands of nonmedical consumers (Fischer 2010 **NR**)
Medication assisted treatment	Use of medications in combination with counselling and behavioural therapies for the treatment of substance use disorders (SAMHSA 2019 **GL**)
Non-medical prescription opioid use (NMPOU)	Used by National Survey on Drug Use (SAMHSA 2019 **GL**)
Opioid Induced Hyperalgesia (OIH)	"*State of nociceptive sensitization caused by exposure to opioids*" (Ramasubbu 2011 **NR**) Declining nociceptive threshold after opioid exposure without overt withdrawal signs (Mao 2015 **NR**)
Physical dependence	A physiological adaptation to a drug whereby abrupt discontinuation or reversal of that drug, or a sudden reduction in its dose, leads to a withdrawal (abstinence) syndrome Withdrawal can be terminated by administration of the same or similar drug
Pseudoaddiction	Behaviours that may seem inappropriately drug-seeking but are a result of undertreatment of pain and resolve when pain relief is adequate (Weissman 1989 **NR**)
Substance use disorder (SUD)	The essential feature of a substance use disorder is a cluster of cognitive, behavioural and psychological symptoms indicating that the individual continues using the substance despite significant substance-related problems (American Psychiatric Association 2013b)
Tolerance (pharmacological)	A predictable physiological decrease in the effect of a drug over time so that a progressive increase in the amount of that drug is required to achieve the same effect Tolerance develops to desired (eg analgesia) and undesired (eg euphoria, opioid-related sedation, nausea or constipation) effects at different rates
Tolerance (associative, psychological)	"*Can arise for all the central effects of opioids, including euphoria and dysphoria, sedation, analgesia and nausea. This type of tolerance involves learning, and its development is linked to environmental or contextual cues*" (Ballantyne 2017 **NR**)

*Source: Adapted from (AAPM 2001 **GL**) and the references in the table.*

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9.7.2 | Clinical implications of opioid tolerance and opioid-induced hyperalgesia

Opioid exposure can lead to desensitisation processes commonly described as opioid tolerance and pronociceptive processes referred to as opioid-induced hyperalgesia (OIH) (Mao 2015 **NR**). OIH may be modulated by amongst others NMDA and GABA receptors and possibly the innate neuroimmune system (Arout 2015 **BS NR**) as well as peripheral mu-opioid receptors (Weber 2017 **NR**).

The relative roles played by tolerance and OIH in the patient who is taking long-term opioids are unknown and both may contribute to increased pain (Higgins 2019 **Level III-3 EH SR** [PRISMA], 26 studies, n=2,706; Weber 2017 **NR**). It is also possible that different opioids vary in their ability to induce OIH and tolerance (see Section 4.1.1). Studies of OIH are confounded by factors such as pain modality tested, route of administration and opioid type (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**; Eyler 2013 **NR**). Illicit substance use, affective characteristics, and coping styles may also play a role (Higgins 2019 **Level III-3 EH SR** [PRISMA], 26 studies, n=2,706).

There are some features of OIH that may help to distinguish it from pre-existing pain. With OIH, pain intensity may be increased above the level of the pre-existing pain; the distribution tends to be beyond that of the pre-existing pain as well as being more diffuse; and QST may show changes in pain thresholds and tolerability (Higgins 2019 **Level III-3 EH SR** [PRISMA], 26 studies, n=2,706; Weber 2017 **NR**; Lee 2011 **NR**; Ramasubbu 2011 **NR**). 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, withdrawal and neuropathic pain.

OIH is identified by reduced pain tolerance to noxious thermal (hot and cold), but not electrical stimuli, in patients with chronic opioid exposure (Higgins 2019 **Level III-3 EH SR** [PRISMA], 26 studies, n=2,706); pain detection thresholds remain unchanged. However, an attempt to identify a quantitative sensory testing 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 2015b **Level IV EH SR**, 14 studies, n unspecified). The methods investigated include pain due to cold, heat, pressure, electrical stimulus, ischemia, and injection; only heat pain sensitivity showed some promise.

In subjects in methadone-maintenance programs, the presence of chronic pain may differentially increase pain thresholds and there may be a dose-related effect on abnormal pain processing (Chen 2009 **Level III-2 EH**; Peles 2011 **Level III-3 EH**; Hooten 2010 **Level IV EH**). In chronic pain patients on opioid treatment, patients with negative affect (ie more distressed) show more features of OIH (Edwards 2016 **Level III-2**, n=31). There is controversy about the impact of opioid cessation, with some evidence suggesting resolution of OIH after a few months opioid abstinence (Treister 2012 **Level III-3 EH**) and others showing that heat and pain perception remain abnormal even after abstinence for at least 6 mth (Prosser 2008 **Level III-2 EH**).

After intraoperative use of remifentanil (at ≥0.1 mcg/kg/min), there is evidence of acute opioid tolerance and OIH of limited clinical relevance (Kim 2014 **Level IV SR**, number of studies unspecified, n unspecified; Rivosecchi 2014 **Level IV SR**, 35 studies, n unspecified). Another meta-analysis confirms clinically small but statistically significant OIH only after high-dose remifentanil (≥0.3 mcg/kg/min) with insufficient data on fentanyl and sufentanil (Fletcher 2014 **Level I** [PRISMA] 27 RCTs, n=1,494). Patients had increased postoperative pain scores at 1 h (MD 9.4/100; 95%CI 4.4 to 14.5) up to 24 h (MD 3/100; 95%CI 0.4 to 5.6) and higher opioid requirements over 24 h (SMD 0.7; 95%CI 0.37 to 1.02). Overall, the effect of remifentanil is dose dependent (Angst 2015 **NR**). Gradual (by 0.6 ng/ml target concentration every 5 min) vs abrupt withdrawal of a remifentanil infusion (target concentration 2.5 ng/ml for 30 min) induced no OIH (pain similar to placebo) measured with the

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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 high-dose 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 2013b **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) as well as 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).

The challenge faced by the health professional is that if inadequate pain relief is due to OIH, reducing the 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 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 Section 9.8 below) (Edwards 2011 **Level III-2**; Macintyre 2015 **NR**; Gourlay 2008 **NR**).

9.7.3 | Patient groups

Four main groups of opioid-tolerant patients are encountered in acute pain settings.

1. Patients with chronic noncancer pain (CNCP) being treated with opioids, where acute presentations may be due to a new acutely painful condition (eg surgery, trauma) or to exacerbation of the underlying chronic condition (eg sickle cell crisis, pancreatitis) (Quinlan 2012 **NR**). Opioids for CNCP are associated with increased risk of acutely painful injuries, including fractures (Teng 2015 **Level III-2 SR**, 8 studies, n=500,819), other injury and overdose (Landsman-Blumberg 2017 **Level III-2**, n=21,203), with increasing risk as opioid dose increases (Bedson 2019 **Level III-2**, n=98,140; Murphy 2018 **Level IV**, n=19,480 [SAEs]). In USA veterans, chronic opioid use is more likely at younger ages, in males, in rural areas, in smokers, in the presence of back pain, and in those with post-traumatic stress disorder (PTSD) and major depression (Hudson 2017 **Level III-2**). Australian pharmaceutical benefit (PBS) scheme data show persistent opioid use is more likely if initiated with transdermal preparations, higher doses, in older patients, with comorbid depression (Sullivan 2018 **NR**) or psychotic illness, and if there is prior dispensing of pregabalin or benzodiazepines (Lalic 2019 **Level IV**, n= 769 334). Some of the patients in this group may exhibit features of OUD.

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2. Patients with cancer pain being treated with opioids, who may be at various stages of their illness including active treatment (eg surgery), palliation and in remission. In the latter case, survivors of cancer may experience specific issues relating to "survivorship" (Yazdani 2014 **NR**). Some of these issues will be similar to those in patients with chronic noncancer pain.
3. Patients with a OUD with current status ranging from using illicit prescription or non-prescription opioids and/or on an opioid-maintenance treatment program, or in remission; many patients with active or past OUD report chronic non-cancer pain (see also Section 9.8 below).
4. Patients who have developed acute or subacute opioid tolerance (or OIH) due to perioperative opioid administration, particularly opioids of high potency, in high dose and for "extended" periods (e.g. in an ICU).

Recognition of the presence of opioid tolerance or OIH may not be possible if the patient's history is not available or accurate (eg following major trauma with ICU admission or if the patient is unconscious at presentation). If a patient is requiring much larger than expected opioid doses and other factors that might be leading to the high requirements have been excluded, opioid tolerance or OIH should be considered.

(See Sections 10.6.3.1 and 10.7 for paediatric issues).

9.7.3.1 | Overlap between chronic pain (cancer- or non-cancer related) treatment and opioid use disorder

Chronic non-cancer related pain (CNCP)

The past twenty years have seen a multi-fold rise in opioid prescription for CNCP, primarily in developed countries (Karanges 2016 **Level IV**; Dowell 2016 **GL**). This is despite evidence of only small and probably clinically insufficient improvements in pain, physical function and social functioning, and no improvement in emotional functioning vs placebo, and no evidence of better outcomes than most non-opioid alternatives (Busse 2018 **Level I** [PRISMA], 96 RCTs, n=26,169). There is insufficient evidence of long-term benefit (Chou 2015 **Level IV SR**, 39 studies, n unspecified; Dowell 2016 **GL**).

Concurrently, there has been a rising incidence of opioid-related harms, including opioid use disorder (OUD), opioid diversion, traumatic injury such as road trauma, myocardial infarction, overdose (intentional and unintentional) and mortality (Els 2017 **Level I** [Cochrane] 14 SRs of 61 RCTs, n=18,679; Tucker 2019 **Level I** [PRISMA], 14 RCTs, n=3,071; Ray 2016 **Level III-2**, n=22,912 [prescription episodes]; Chou 2015 **Level IV SR**, 39 studies, n unspecified; Dowell 2016 **GL**). Adverse events are more likely at higher doses, typically greater than 100 mg oral MED/d (Chou 2015 **Level IV SR**, 39 studies, n unspecified; Dowell 2016 **GL**; Ballantyne 2017 **NR**) and with greater dose variability (Glanz 2019 **Level III-2**, n=14,898).

The relationship between CNCP and addiction exists on a continuum with a "*complicated reciprocity*" between the two conditions (Manhapra 2018 **NR**). Ballantyne defines "*complex persistent dependence*" in CNCP by the inability to taper opioids, accompanied by OUD-like behaviours on attempted cessation (Ballantyne 2012 **NR**). CNCP and addiction have overlapping mechanisms with disruption of reward in both, noting that acute pain in the context of CNCP may have "*positive reinforcing qualities*" (Elman 2016 **NR**).

Observed rates of OUD in CNCP depend on the definitions used. The varying criteria in DSM-IV, DSM-V, ICD-9, -10 and -11 classifications lead to different estimates (Kaye 2017b **NR**), noting that these definitions were not developed for those with concurrent pain (Campbell 2016 **Level IV**, n=1,134).

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- In those with CNCP, "misuse" prevalence was 21 to 29% (95%CI 13 to 38%), and "addiction" 8 to 9% (95%CI 3 to 17%) (Vowles 2015 **Level IV SR** [PRISMA], 38 studies, n=1,026,427).
- Using IMMPACT and ACTTION consensus statements in mixed studies of chronic non-cancer and cancer pain, the pooled incidence of "dependence/abuse" was 4.7% (95%CI 2.1 to 10.4%) (Higgins 2018 **Level IV SR** [PRISMA], 12 studies, n=310,408).
- The Australian POINT Study found 18% of community members with CNCP prescribed opioids met DSM-V 'opioid use disorder' criteria, 19% ICD-11 'dependence' criteria, and 24% the 'addiction' definition used in pain medicine, with substantial concordance (Campbell 2016 **Level IV**, n=1,134).

In USA veterans, chronic opioid use is more likely if younger, male, white, married, living in in a rural area, PTSD (OR 1.22; 95%CI 1.2 to 1.25), major depression (OR 1.14; 95%CI 1.12 to 1.17), tobacco use disorder (OR 1.18; 95%CI 1.15 to 1.2), back pain (OR 2.50; 95%CI 2.45 to 2.55), and with increasing pain severity (Hudson 2017 **Level IV**, n=1,397,946). American patients on higher opioid doses for musculoskeletal pain are less likely to be working, with greater depression, more fear-avoidance, decreased pain self-efficacy and greater primary care and pain clinic visits (Morasco 2017 **Level III-3**, n=517). Depressed patients are twice as likely to transition to long-term opioid use for CNCP; depression increases risk of abuse or non-medical prescription opioid use (although dose and duration contribute to this risk, duration is more important) (Sullivan 2018 **NR**).

These factors are similar to the factors that are associated with SUD. In patients presenting for surgery, a higher Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) score is associated with increased likelihood of preoperative prescribed and illicit opioid use and increased postoperative surgical site pain (Hah 2015 **Level IV**, n=107). OUD is more likely in the presence of psychosocial factors, particular if the person has a genetic predisposition (Kaye 2017b **NR**). Past-year "dependence" is increased in younger people and if there is a history of benzodiazepine dependence (Campbell 2015 **Level IV**, n=1,424). There is a strong association with psychiatric illness including mood disorders, antisocial personality disorder and PTSD, and a history of SUD (Kaye 2017b **NR**). In one USA series, of those prescribed opioids long-term, 73.1% had a comorbid psychiatric diagnosis (Glanz 2019 **Level III-2**, n=14,898).

In those with chronic pain and history of SUD, pain catastrophising is associated with greater likelihood of prescription opioid misuse (Morasco 2017 **Level III-3**, n=517). High-dose opioid prescription also increases the likelihood of self-reported heroin use (adjusted HR 2.54; 95%CI 1.26 to 5.10) in USA veterans, although long-term opioid prescription did not increase this risk (Banerjee 2019 **Level III-2**, n=3,570). In Canada, prescription of opioids is a common pathway to OUD requiring addiction treatment, more commonly in women; those taking this route are older and more educated with chronic pain a significant association (Sanger 2018 **Level III-2**, n=976). Addiction treatment outcomes may be worse in those with pain volatility (Worley 2015 **Level IV**, n=149). There is growing evidence that buprenorphine maintenance therapy may be preferred in those with combined CNCP and addiction (Berna 2015 **NR**) (see Section 9.8 below).

Screening for risk of OUD is addressed in Section 9.8.5 below.

Cancer pain

Those with cancer pain exist on a continuum in terms of disease stages, conforming roughly to three main groups – those undergoing active treatment with curative intent, those undergoing palliative care/treatment with reduced life expectancy and those in remission.

In a palliative care setting, physician-assessed "chemical coping", defined as "using prescribed opioids to control non-nociceptive symptoms", was found in 18% (95%CI 14 to 21%) and (on multivariate analysis) more likely in patients who were younger, CAGE ("cut-annoyed-

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guilty-eye" screening questionnaire for problematic alcohol use) positive, with better function, higher pain and lower wellbeing scores (Kwon 2015 **Level IV**). There was high prevalence of positive SOAPP-SF and CAGE in a palliative care clinic, noting approximately one quarter had no evidence of ongoing disease and one quarter had CNCP; there were also positive urine drug screens in those with cancer and active treatment (56% of the subsample) (Childers 2015 **Level IV**, n=323)

With improved oncological treatment, there is a growing population of cancer "survivors", defined by the American Cancer Society as survival at least 5 y following a cancer diagnosis. In this group, CNCP is common and multifactorial due to surgery, radiotherapy, chemotherapy and incidental causes (Carmona-Bayonas 2017 **NR**). An integrative review estimated that at least one in five cancer patients may be at risk of OUD (Carmichael 2016 **NR**). Cancer survivors are more likely than the general population to be prescribed long-term benzodiazepines and opioids, with such prescriptions often not conforming to professional guidelines (Fredheim 2019 **Level IV**, n=21,426). Particular issues arise in those with co-morbid psychiatric disorders including an addiction history (Carmona-Bayonas 2017 **NR**). Surveys of USA palliative care providers and hospice social workers found limited systems in place to screen for and manage OUD in this context (Merlin 2019 **Level IV**, n=157 [health care professionals]; Sacco 2017 **Level IV**, n=107 [US Medicare certified hospices]).

The American Society of Clinical Oncology practice guidelines recommend a universal precautions approach to chronic pain in survivors of adult cancers, with regular screening for pain, multidisciplinary care for complex situations, preference for non-opioids, opioid trials in selected patients with clear goals and regular risk assessment (Paice 2016 **GL** [based on SR of 63 studies]).

9.7.4 | Chronic opioid use and perioperative outcomes

9.7.4.1 | Effects on perioperative outcomes

A growing body of evidence, primarily in patients undergoing elective orthopaedic and spinal surgery and primarily retrospectively collected, shows an association between chronic preoperative opioid use and worse postoperative outcomes. This includes increased likelihood of 90-d complications (Sing 2016 **Level III-2**, n=174), revision arthroplasty following primary arthroplasty (Bedard 2018a **Level III-2**, n=17,695; Bedard 2018b **Level III-2**, n=35,894; Weick 2018 **Level III-2**, n=324,154; Ben-Ari 2017 **Level III-2**, n=32,636) and periprosthetic joint infection (Bell 2018 **Level III-2**, n=23,754).

In primary knee arthroplasty, preoperative opioid use was associated with poorer outcomes – longer hospital LOS, more additional surgeries for stiffness or pain, more referrals to pain specialists and worse knee society scores (Zywiel 2011 **Level III-2**, n=98). In spinal surgery, opioids increase the risk of 90 d wound complications, readmission and revision spinal fusion (Jain 2018a **Level III-2**, n=29,101; Jain 2018b **Level III-2**, n=24,610). Likewise, opioid abuse and dependence (defined by ICD-9 codes) are associated with increased aggregate morbidity (OR 2.3; 95%CI 2.2 to 2.4), surgical site infection (OR 2.5; 95%CI 2.0 to 3.0), pneumonia (OR 2.1; 95%CI 1.8 to 3.2) and prolonged LOS (OR 2.5; 95%CI 2.4 to 2.5) following joint arthroplasty and spinal fusion (Menendez 2015 **Level III-2**, n=9,307,348). Greater preoperative opioid use is associated with worse general health, quality of life and disability at 3 and 12 mth following spinal surgery (Lee 2014 **Level III-2**, n=583). However, evidence is conflicting, with multivariate analysis of spinal surgery showing preoperative opioid use not being associated with complications (identified on retrospective chart review), but only with increased LOS (Armaghani 2016 **Level III-2**, n=583). On multivariate analysis, preoperative opioid use is associated with longer LOS, more complications,

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more readmissions and increased (covariate-adjusted) costs following abdominal and other surgeries (Gupta 2018a **Level III-2**, n=16,016,842; Cron 2017 **Level III-2**, n=2,413; Waljee 2017 **Level III-2**, n=200,005).

Chronic opioids may also suppress the hypothalamic-pituitary-adrenal axis. As many as one in five patients on chronic opioids may have low cortisol levels, although is not clear which patients should be screened (Demarest 2015 **NR**). This led the US Food and Drug Administration (FDA) in 2013 to issue a warning to be added to all opioid labelling (FDA 2013 **GL**). Addisonian crises have been described in some postoperative patients (Fountas 2018 **NR**). Although the prevalence is unknown, the implications for perioperative care include investigation should patients present with symptoms and signs suggesting adrenal insufficiency.

9.7.4.2 | Strategies for outcome improvement

Preoperative opioid use may be a modifiable risk factor for perioperative outcomes. There is limited low quality evidence that ceasing opioids preoperatively may ameliorate perioperative risk (Jain 2018a **III-2**, n=29,101; Nguyen 2016 **Level III-2**, n=177).

Opioid tapering should be considered prior to elective surgery, although there is limited evidence as to the best strategy in terms of efficacy and safety (Eccleston 2017 **Level I** [Cochrane], 5 RCTs, n=278; Berna 2015 **GL**). Whatever strategy is used, it should consider patient-centred barriers (fear of withdrawal and that nonopioids might be ineffective) and facilitators (social support and a trusted practitioner) along with reassurance about long-term benefits (including improved pain and quality of life) (Goesling 2019 **Level IV**, n=49; Frank 2016 **Level IV**, n=24).

Expert advice is for shared decision making, reduction by 5 to 20% every 4 wk (Pergolizzi 2018 **GL**), and support for self-efficacy, resilience and alternative pain management strategies (McAnally 2017 **GL**). The USA Department of Veterans Affairs has developed an opioid tapering tool (U.S. Department of Veterans Affairs 2016 **GL**). Alpha-2 agonists such as clonidine are effective for withdrawal symptoms, although have side effects including hypotension (Gowing 2014 **Level I** [Cochrane], 25 RCTs, n=1,668).

In opioid-tolerant patients, improved compliance with enhanced recovery after surgery (ERAS) protocols may mitigate the impact of opioid tolerance on postoperative complications (Owodunni 2019 **Level III-2**, n=646). ERAS may provide a framework to reduce the risk of ongoing opioid use; it is multidisciplinary, patient-centred, includes multimodal analgesia (which decreases opioid reliance), includes site-specific regional analgesia, promotes more comprehensive preoperative assessment, and has formalised pathways for community transition; it is a logical extension for ERAS to guide use of post discharge opioids including tapering and follow-up (Stone 2017 **NR**).

9.7.5 | Chronic opioid use and sleep-disordered breathing

Opioids can affect ventilatory function via decreases in central respiratory drive, level of consciousness and upper airway tone causing opioid-induced ventilatory impairment (OIVI) (Macintyre 2011 **NR**).

Long-term opioid use is a risk factor for sleep-disordered breathing (SDB) (prevalence in this population 24%) (Correa 2015 **Level III-3 SR**, 8 studies, n=560); SDB (in particular central sleep apnoea) is strongly associated with morphine equivalent daily dose (high risk >200 mg MED/d) with body mass index inversely related to the severity of SDB. A study not included in this systematic review has similar findings (Rose 2014 **Level IV**, n=24); severe SDB (again mainly central sleep apnoea) was found in 46 % of patients on opioids in a dose-dependent fashion and of these 45% had daytime hypercapnia, indicating chronic respiratory failure.

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In patients undergoing methadone-maintenance treatment, SDB was common (35.2% OSA and 14.1% central sleep apnoea), but not related to methadone dose and subjective sleep complaints (Sharkey 2010 **Level IV**, n=71). Patients on methadone-maintenance programs were more likely to have sleep abnormalities, especially central sleep apnoea, than were matched controls, although the effect was confounded by greater use of benzodiazepines in the methadone group (Teichtahl 2001 **Level III-2**, n=19).

Particular care should be taken when the total opioid dose is rapidly escalated above the usual dose and when other sedative agents are coadministered (Macintyre 2011 **NR**).

See also Section 9.4 above.

9.7.6 | Assessment and management of acute pain

A number of articles, chapters and a book (Bryson 2012a **NR**) have been published outlining suggested strategies for the assessment and management of acute pain in the patient taking long-term opioids for chronic pain or because they have a SUD, perhaps treated in a drug treatment program. These focus on postoperative (Coluzzi 2017 **NR**; Simpson 2017 **NR**; Buckley 2014 **NR**; Tumber 2014 **NR**; Eyler 2013 **NR**; De Pinto 2012 **NR**; Geary 2012 **NR**; Quinlan 2012 **NR**; Schug 2012 **NR**; Huxtable 2011 **NR**) and post-traumatic pain (Karamchandani 2019 **NR**).

Evidence for the most appropriate assessment and management in these patients is very limited and the advice given in these papers remains based primarily on case series, case reports, expert opinion and personal experience. Opioid-tolerant patients are heterogeneous and thus difficult to study, and thus are often excluded from studies of acute pain management. The past few years have seen a growing number of RCTs in opioid-tolerant patients or inclusion of these patients in broader studies, often after spinal or orthopaedic surgery. However, details of the opioid tolerance and pre-existing pain are sometimes not well described. In general, assessment and management of these patients should focus on:

- Coordinated care that includes an interdisciplinary approach and liaison with other treating health professionals and specialist teams, as required,
- Effective analgesia;
- Use of strategies that may attenuate tolerance or OIH;
- Prevention of withdrawal;
- Appropriate discharge planning to ensure continuity of long-term care.

9.7.6.1 | Models of care and clinical pathways

Given that opioid-tolerant patients may present complex assessment and management challenges, there is an international trend towards improved perioperative coordination of care with interdisciplinary input. This aims to provide patient-centred care, robust preoperative risk stratification, planning, optimisation and consent, reduced practice variability and care continuity, including bidirectionally in transition from hospital to the community. These models promote safe opioid management that conforms to professional guidelines, by identifying those at risk, offering tapering strategies, ensuring ongoing follow-up, and promoting coordination and communication with other providers.

One such integrated model of care is the Perioperative Surgical Home, which has been extensively discussed in the literature (Kaye 2017a **NR**) and might be of particular value in the setting of high risk patients including the opioid-tolerant patient (Pozek 2017 **NR**). Other models have been described which involve pain medicine physicians (and others) early in the preoperative and then the postoperative phase; these are either described as a Transitional Pain Service (Huang 2015 **NR**; Katz 2015a **NR**) or an Acute Pain Outpatient Service (Tiippana 2016 **Level IV**, n=200). There are limited data supporting successful opioid reduction by such services (Huang

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2016 **Level IV**, n=51; Tiippana 2016 **Level IV**, n=200). There is the suggestion that such services could become an integrated part of the Perioperative Surgical Home (Vetter 2017 **NR**).

"Ambulatory pain physicians" based in ambulatory surgical centres could be another approach (Vadivelu 2016a **NR**), in particular as the management of opioid-tolerant patients in this setting is often even more complex (Vadivelu 2017 **NR**).

Interdisciplinary management of patients with aberrant opioid-related behaviour has been successfully implemented in the palliative care setting (Arthur 2018 **Level IV**, n=30). Peer-reviewed clinical pathways including standardised postoperative analgesia orders for opioid-tolerant patients developed with multidisciplinary input improved pain management and PACU discharge readiness (Naqib 2018 **Level III-3**, n=169). A Safer Opioid Prescribing Protocol (SOPP) introduced in an electronic medical record at a level 1 trauma centre improved prescribing of non-opioids and reduced high-dose opioid prescribing (Baird 2019 **Level III-3**, n=507).

9.7.6.2 | Assessment

Assessment using unidimensional measures is frequently inadequate, in particular in these complex patients (Radnovich 2014 **NR**; Gandhi 2011 **NR**). The need for multidimensional assessment is recognised in the ACTTION-APS-AAPM pain taxonomy which uses five dimensions (core criteria, common features, modulating factors, impact/functional consequences, putative pathophysiologic pain mechanisms) to better describe pain complexity (Kent 2017 **GL**). The USA is abandoning pain scores and pain as "the fifth vital sign", as an unintended consequence has been excess opioid administration to chase pain scores (viewed as a contributor to the opioid epidemic). This has been exacerbated by the direct link between pain self-report and reimbursement; the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey uses pain scores as a surrogate measure of care quality. Treating unidimensional scores may lead to increased adverse events like oversedation and should be avoided (Levy 2019 **NR**). This is in particular true in the setting of opioid-tolerance and chronic pain (Allen 2014 **NR**).

Other considerations in acute pain assessment in opioid-tolerant patients include:

- Psychological and social, as well as biological, triggers for pain deterioration in those with chronic pain should be identified (Quinlan 2012 **NR**);
- Specific factors that should be sought in all opioid-tolerant patients, those with chronic pain and those with SUD (see Table 9.9) (Huxtable 2011 **NR**);
- Practitioners determining the need for elective procedures (eg surgeons, physicians, radiologists) or for labour analgesia planning (obstetricians, general practitioners) should refer patients early for pain management planning and optimisation (Tumber 2014 **NR**);
- Previous records should be reviewed and information about prior experiences of acute pain management should be sought to avoid or optimise strategies that were ineffective and to replicate those that were effective (Tumber 2014 **NR**);
- Meaningful engagement of the patient and their family or other caregivers (Geary 2012 **NR**), is key to assessment, management and adherence to the proposed plan (Haber 2009 **NR**) through expectation management, addressing concerns and education;
- Communication should involve engagement, empathising, educating, enlisting and end by summarising, reviewing and indicating next steps (Jamison 2011 **NR**).

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Table 9.9 | Pain-related assessment in opioid-tolerant patient

Information from all opioid-tolerant patients	Additional information in patients with CNCP or cancer pain	Additional information in patients with a substance use disorder
Current treatment providers	Pain diagnosis	Opioid substitution therapies and doses (methadone, buprenorphine)
Opioid and nonopioid medications	Usual pain scores	Other prescribed or diverted prescription medicine or illicit substance use (polyabuse is common)
Dose verification of all relevant medications	Functional status	Routes of administration
Nonprescribed drugs (eg over-the-counter and illicit drugs, alcohol, nicotine)	Prognosis (cancer pain)	Where relevant, registered prescriber and dispensing pharmacy
Drug allergies and reactions	Psychospiritual issues (including end-of-life issues, anxiety, depression, coping style and strategies)	Medical and psychiatric comorbidities (eg blood-borne viruses, hepatic disease, other infections, chronic pain, personality disorder)
Experiences and expectations of acute pain management including goals of care	Where relevant, the authorized prescriber of any opioids	Concerns about opioids (especially for those in remission)
Support systems after discharge	Presence of invasive pain treatment (eg IT pump, spinal cord stimulator)	
	Medication misuse, evidence of aberrant drug-related behaviour or SUD	Comorbid chronic pain
	Expectations about their admission (eg expectation that chronic back pain will be improved after spinal surgery; palliative vs curative surgery in patients with cancer)	

Source: From Huxtable 2011; reproduced with permission and modified.

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9.7.6.3 | Effective analgesia

Even more than in other patients, the basis for successful pain management in opioid-tolerant patients must be the utilisation of multimodal and interdisciplinary analgesia strategies (Schug 2012 **NR**; Huxtable 2011 **NR**). However, opioids will often be needed and then require additional considerations.

Opioids

It is known that opioid use is usually significantly higher in opioid-tolerant vs opioid-naïve patients and that the interpatient variation in the doses needed is even greater. After a variety of surgical procedures, opioid-tolerant patients using PCA (Rapp 1995 **Level III-2**, n=3,508) or epidural analgesia (de Leon-Casasola 1993 **Level III-2**, n=116) require approximately three times the dose (on average with large standard deviations) vs their opioid-naïve counterparts. The increased acute opioid dosing required to address tolerance continues to be under-recognised. Opioid-tolerant patients with cancer (78% with metastatic disease) presenting acutely to an emergency department were frequently under-dosed, due primarily to "standard dose" administration failing to account for their opioid tolerance (Patel 2017 **Level IV**, n=216). Uptake of expert opinion about managing opioid-tolerant patients for ambulatory surgery is poor, with only 37% taking their usual long-acting opioid on day of surgery and many not receiving recommended non-opioids and adjuvants (Wilson 2015 **Level IV**, n=148).

Opioid-tolerant patients reported higher pain scores (both resting and dynamic) and remained under the care of an APS longer than other patients (Rapp 1995 **Level III-2**, n=3,508). Compared with opioid-tolerant patients with cancer pain, opioid-tolerant patients with noncancer pain had higher rest and dynamic pain scores and required longer APS input but there was no difference in opioid requirements (Rapp 1995 **Level III-2**, n=3,508). In addition, staff relied more on functional measures of pain than on pain scores to assess pain intensity in these patients (Rapp 1994 **Level IV**, n=482 [health care professionals]). Their postoperative pain is initially more intense and needs therefore more time to resolve than that in opioid-naïve patients (Chapman 2009 **Level III-2**, n=138).

The incidence of opioid-induced nausea and vomiting may be lower in opioid-tolerant patients, although the risk of excessive sedation/OIVI may be higher (Rapp 1995 **Level III-2**, n=3,508) and may be particularly likely if opioid doses are rapidly escalated above the baseline level (Huxtable 2011 **NR**).

Where possible, oral or sublingual opioids should be used in preference to parenteral opioids (Donroe 2016 **NR**). IV PCA is a useful modality for pain relief in a subset of opioid-tolerant patients, including those with a SUD, provided that pain intensity and opioid consumption are carefully monitored and background requirements are provided if the patient cannot take their usual opioid; larger bolus doses will often be needed (Macintyre 2015 **NR**; Huxtable 2011 **NR**; Mitra 2004 **NR**). The size of an appropriate dose (on an individual patient basis) has been calculated by one group of investigators by using a preoperative fentanyl infusion until the patient's respiratory rate was <5/min; pharmacokinetic simulations were then used to predict the size of the PCA bolus dose and the rate of a background infusion that would be required for postoperative analgesia (Davis 2005 **Level IV PK**). It may also be based on the dose of opioid the patient is already taking (Macintyre 2015 **NR**; Hadi 2006 **NR**). Regardless of the initial dose prescribed, subsequent doses will need to be titrated to effect for each patient, bearing in mind realistic expectations about pain control and optimisation of non-opioid and non-pharmacological strategies. Caution should also be exercised as high opioid use may result in OIH (see section above).

Neuraxial opioids have been used effectively in opioid-tolerant patients, although higher doses may be required without increasing adverse effects (de Leon-Casasola 1993 **Level III-2**).

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Effective analgesia using IT or epidural opioids will not necessarily prevent opioid withdrawal (Huxtable 2011 **NR**; Carroll 2004 **NR**).

Nonpharmacological strategies

Behavioural and cognitive techniques may minimise anxiety and reduce catastrophising, and physical techniques should also be considered (Tumber 2014 **NR**); however, there is limited evidence for their effectiveness in opioid-tolerant patients in acute pain settings

9.7.6.4 | Attenuation of tolerance and opioid-induced hyperalgesia

A number of strategies may attenuate opioid tolerance and OIH. These include:

- NMDA-receptor antagonists
- opioid-receptor antagonists;
- opioid rotation;
- other adjuvant medicines.

NMDA-receptor antagonists

As noted in Section 4.6, the NMDA receptor is involved in tolerance and OIH development (Chang 2007 **NR**). In rodents, the NMDA-receptor antagonist ketamine attenuates both the development of tolerance (Laulin 2002 **BS**; Shimoyama 1996 **BS**) and OIH (Van Elstraete 2011 **BS**; Minville 2010 **BS**; Haugan 2008 **BS**; Laulin 2002 **BS**).

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). This statement 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 placebo groups.

After spinal surgery in opioid-tolerant patients, perioperative ketamine resulted in significantly less pain but did not reduce PCA opioid use (Urban 2008 **Level II**, n=26, JS 3) and reduced opioid requirements and pain scores in the early postoperative period and at 6 wks (Loftus 2010 **Level II**, n=101, JS 4). For multilevel spinal fusion, ketamine decreased PCA hydromorphone use in opioid-tolerant but not opioid-naïve patients, with the effect primarily from 16 h postoperatively (Boenigk 2019 **Level II**, n=129, JS 5). Intraoperative S-ketamine in opioid-tolerant patients undergoing spinal surgery resulted in reduced PCA morphine use at 24 h (MD -42 mg; 95%CI -59 to -25) with reduced sedation and without increasing other adverse effects. Furthermore, at 6 mth there was improved back pain, longer walking distance and less disability (Nielsen 2017a **Level II**, n=150, JS 5). This beneficial effect was maintained at 1 y with lower opioid use, lower dynamic pain scores, greater likelihood of working and lower disability scores (Nielsen 2019 **Level II**, n=147, JS 5).

After noncancer general surgery in a similar patient group, a postoperative ketamine infusion at 0.2 mg/kg/h decreased average pain scores (13.5% decrease vs 15.5% increase) but not opioid use (Barreveld 2013 **Level II**, n=64, JS 4).

Consensus guidelines for the use of ketamine infusions in acute pain support its use for opioid-dependent or opioid-tolerant patients undergoing surgery to limit opioid use (Schwenk 2018 **GL**).

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Opioid receptor antagonists (low dose)

In rodents, ultra-low dose naloxone has been shown to attenuate opioid tolerance (Wang 2005 **BS**; Crain 2000 **BS**; Crain 1995 **BS**) and remifentanil-induced OIH (Aguado 2013 **BS**).

In the experimental pain setting in healthy volunteers, the coadministration of ultra-low doses of naloxone (La Vincente 2008 **EH**) or naltrexone (Hay 2011 **Level II EH**, n=10, JS 5) to buprenorphine significantly increased tolerance to cold-pressor pain.

Clinical studies have concentrated on the concurrent use of naloxone and an opioid given acutely, with conflicting results; improved postoperative pain and reduced opioid use as well as no differences in either have been reported (Angst 2006 **NR**; Sloan 2006 **NR**). The use of low-dose naloxone added to postoperative opioid analgesia (most commonly by PCA) decreases the risk of pruritus (OR 0.40; 95%CI 0.21 to 0.79) and nausea (OR 0.62; 95%CI 0.43 to 0.89), but not vomiting, pain intensity or opioid use (Murphy 2011 **Level I**, 8 RCTs, n=800). Use over 3 mth of a combination of oxycodone/ultra-low-dose naltrexone in patients with chronic pain vs oxycodone alone, showed that those given the combination had similar pain relief but with 12% lower daily oxycodone use, as well as less constipation, sedation, pruritus and physical dependence as assessed by a withdrawal scale (Webster 2006 **Level II**, n=719, JS 4). Low-dose naloxone (0.25 mcg/kg/h intraoperatively) also reduced postoperative opioid use when combined with high dose remifentanil (and improved time to bowel recovery) (Xiao 2015 **Level II**, n=75, JS 5).

Opioid rotation

Opioid rotation (also called "switching") is commonly used in the treatment of chronic noncancer and cancer pain when a change to another opioid can improve analgesia and reduce adverse effects (Mercadante 2012 **Level IV;** Nalamachu 2012 **NR**). Opioid rotation (eg using an opioid that is different from the preadmission opioid) may also be useful in the acute pain setting (Huxtable 2011 **NR**; Hadi 2006 **NR**). The underlying rationale is that different opioids do not act to the same degree on various opioid receptor subtypes, are metabolised differently, that cross-tolerance is likely to be incomplete (Huxtable 2011 **NR**; Mitra 2008 **NR**; Jage 2005 **NR**) and that the degree of OIH and tolerance appears to vary between opioids (see Section 4.3.1).

Adjuvants

Adjuvants are primarily used for their antitolerance, antiallodynic and antihyperalgesic effects (Huxtable 2011 **NR**).

In rats, intraoperative use of paracetamol, metamizol, ketoprofen and parecoxib abolished acute tolerance caused by remifentanil infusion (Benito 2010 **BS**). In an experimental pain setting using intradermal electrical pain stimuli, parecoxib given before but not during a remifentanil infusion modulated the hyperalgesia after withdrawal of remifentanil (Troster 2006 **Level II EH**, n=15, JS 5).

Gabapentin has also been shown to attenuate opioid tolerance (Aguado 2012 **BS**; Lin 2005 **BS**) and OIH (Wei 2012 **BS**) in rats and this effect was synergistic to ketamine (Van Elstraete 2011 **BS**). Pregabalin shows similar effects in animal models (Lyndon 2017 **BS**; Hasanein 2014 **BS**). In methadone-maintained patients, gabapentin increased cold-pressor pain threshold and pain tolerance (Compton 2010, **Level II EH**, n=26, JS 2). In the setting of OIH associated with remifentanil, 150–300 mg pregabalin preoperatively attenuated this effect after hysterectomy (Jo 2011 **Level II**, n=60, JS 5) and laparoscopic urological surgery (Lee 2013b **Level II**, n=93, JS 5).

Other adjuvants that may influence tolerance and OIH but for which there is limited evidence include alpha-2 agonists (clonidine and dexmedetomidine), buprenorphine (Lee 2011 **NR**; Ramasubbu 2011 **NR**; Patch III 2017 **CR**) and systemic lidocaine (Eipe 2016 **NR**). OIH /tolerance after remifentanil use was also reduced by propofol (6 RCTs, n=341) (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).

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Use of regional analgesia techniques to manage the early postoperative pain of total knee joint replacement did not reduce longer-term opioid use (1 y postop) in the overall population nor after stratification into opioid naïve patients, intermittent opioid users and chronic opioid users (Sun 2017 **Level IV**, n=120,080).

9.7.6.5 | Prevention of withdrawal

Withdrawal from opioids is characterised by excitatory and autonomic symptoms including abdominal cramping, muscle aches and pain, insomnia, dysphoria, anxiety, restlessness, nausea and vomiting, diarrhoea, rhinorrhoea and sneezing, trembling, yawning, watery eyes (epiphora) and piloerection (or "gooseflesh") (Rehni 2013 **NR**; Tetrault 2008 **NR**). Withdrawal-associated injury site pain (WISP), a temporary reactivation of pain at an old injury site that was pain-free prior to opioid initiation, has also been described (Rieb 2016 **Level IV**, n=47). The time of onset of withdrawal symptoms after cessation of the drug will depend on the duration of action of the opioid. To assess withdrawal, the use of validated withdrawal tools (Clinical Opioid Withdrawal Scale, Subjective Opioid Withdrawal Scale, Objective Opioid Withdrawal Scale) is recommended (Donroe 2016 **NR**) (See also Section 10.4.6.2 in children).

Withdrawal should be prevented by maintenance of normal preadmission opioid regimens (including on the day of surgery) or appropriate substitutions with another opioid or the same opioid via another route (Macintyre 2015 **NR**; Schug 2012 **NR**; Huxtable 2011 **NR**). It may be of benefit to check preadmission opioid doses with the patient's doctor or pharmacist; the use of unauthorised additional opioids (licit or illicit) or of lower doses than prescribed may affect both pain relief and the risk of adverse effects.

While multimodal analgesic regimens (eg NSAIDs, paracetamol, ketamine, tramadol, regional analgesia) are of analgesic benefit (Rajpal 2010 **Level III-3**), opioid-tolerant patients are at risk of opioid withdrawal if a purely nonopioid analgesic regimen or atypical opioids with low mu-receptor effects such as tramadol or tapentadol are used (Macintyre 2015 **NR**; Huxtable 2011 **NR**).

For this reason, opioid antagonists (naloxone, naltrexone) should be avoided as their use can precipitate acute withdrawal reactions (Schug 2012 **NR**; Alford 2006 **NR**).

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

During a 10-d buprenorphine detoxification procedure, gabapentin reduced opioid use vs placebo (Sanders 2013 **Level II**, n=30, JS 5) and in a dose of 1,600 mg/d reduced withdrawal symptoms in patients during methadone-assisted detoxification (Salehi 2011 **Level III-1**). Pregabalin attenuated naloxone-induced withdrawal symptoms in opioid-tolerant rats (Hasanein 2014 **BS**) and has also been used successfully to attenuate withdrawal symptoms from a number of drugs including alcohol and benzodiazepines, although data on opioid withdrawal are limited (Freynhagen 2016 **NR**). Pregabalin added to methadone in maintenance program patients reduced methadone requirements and withdrawal symptoms vs placebo (Moghadam 2013 **Level II**, n=60, JS 5).

9.7.6.6 | Discharge planning and transition to community care

Discharge planning for opioid-tolerant patients is optimally commenced prior to admission and must consider any regulatory requirements (eg the authority to prescribe an opioid may have to be delegated to a particular physician only), the duration of use of any additional opioids prescribed for short-term acute pain management and the weaning of those drugs and, in some patients, the potential for prescribed opioids to be abused, misused or diverted. Without robust discharge systems, there is a significant risk of unintended opioid dose escalation with attendant risks (Quinlan 2012 **NR**; Schug 2012 **NR**; Huxtable 2011 **NR**).

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Preoperative opioid use, especially at higher dose, is a significant risk factor for ongoing postoperative opioid prescription, even in circumstances where long-term prescription is not indicated (Dunn 2018 Level **III-2**, n=1,477; Goesling 2016 **Level III-2**, n=574). This was confirmed in an Australian population after total hip replacement, where longer preoperative opioid use increased the risk of persistent chronic use (opioid use for 157 to 224 d vs 94 to 157 d [OR=3.75; 95%CI 2.28 to 6.18] and >225 d [OR 5.18; 95%CI 2.92 to 9.19]) (Inacio 2016 **Level IV**, n=8,925). Similar findings are reported after spinal surgery, where preoperative opioid use increased the risk of prolonged postoperative requirements (OR 4.71; 95%CI 3.11-7.13) (Reid 2019 **Level III-3**, n=552). Opioid use in the year prior to elective colorectal surgery was the only risk factor for post-discharge opioid use within 1 y (Scow 2019 **Level IV**, n=367). After minor upper limb surgery (carpal tunnel release, trigger finger release, cubital tunnel release, and thumb carpometacarpal arthroplasty) 59% of patients filled an opioid prescription; patients preoperatively on opioids vs not on opioids filled more postoperative opioid prescriptions (66 % vs 59 %), were given longer-lasting prescriptions (24 d vs 5 d), received more refills (24 % vs 5 %) and 19 % vs 6% had at least one indicator of potentially inappropriate prescribing (Waljee 2016 **Level IV**, n= 296,452).

A "reverse analgesic ladder" approach is recommended, with the aim being stepwise return of the patient to their usual opioid regimen (Huxtable 2011 **NR**). Considerations include the likely duration of acute pain (and thus the amount of opioid that should be prescribed), the choice of opioid and its "abuse liability", and the use of nonopioid agents. In this context it is of note that postoperative pain resolved more slowly in opioid-tolerant than that in opioid-naïve patients (Chapman 2009 **Level III-2**).Appropriate use of nonopioid analgesics where possible, use of abuse-deterrent formulations, provision of small quantities and staged pharmacy supply, communication with the primary physician and other treating health care professionals (including a plan for cessation), and patient education and support must all be considered.

An ethical dilemma arises where the preadmission opioid regimen is not consistent with widely accepted professional guidelines for opioid prescription in chronic pain or SUD (Dowell 2016 **GL**; FPMANZCA 2015 **GL**). In these cases, and/or when there is a high risk of opioid misuse, referral to a pain specialist and/or an addiction service should be considered (Huxtable 2011 **NR**).

The USA CDC guidelines, although criticised, offer some good principles for opioid prescribing, which might be useful in the setting of discharging opioid-tolerant patients after an acute pain episode (Dowell 2016 **GL**):

- Preference for non-drug and non-opioid therapy;
- Defined goals including when opioids would be discontinued;
- Risks discussed at baseline and periodically;
- Immediate-release instead of slow-release opioids;
- Lowest effective dose – reassess at 50mg OME, avoid greater than 90 mg OME;
- For acute pain, lowest effective dose of IR for shortest duration;
- Reassess benefits and harms early and frequently;
- Evaluate risk of opioid-related harms before and episodically;
- Avoid concurrent benzodiazepines;
- If OUD, offer evidence-based treatment for this (see Section 9.8 below).

The Australian NPS MedicineWise program (NPS MedicineWise 2019 **GL**) recommends referral to an addiction or pain medicine specialist if the patient:

- is taking two or more psychoactive drugs in combination;
- is taking opioids and benzodiazepines;
- has serious psychiatric illness;
- mixes pharmaceutical and illicit drug intake;
- has been discharged from a general practitioner for problematic behaviour;

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- was recently discharged from a correctional service;
- shows evidence of high-risk behaviours.

For more details on opioid use and discharge medication see Sections 9.8., 8.13. and 10.4.5.

KEY MESSAGES

1. Alpha-2 agonists (clonidine and lofexidine) reduce opioid-withdrawal symptoms (**U**) (**Level I** [Cochrane Review]).
2. Remifentanil use leads to opioid-induced hyperalgesia (**U**), which is attenuated by 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**).
3. Gabapentin and pregabalin attenuate opioid-induced hyperalgesia/tolerance and reduce opioid-withdrawal symptoms (**U**) (**Level II**).
4. In opioid-tolerant patients, ketamine improves pain relief after surgery and reduces opioid requirements (**S**) (**Level II**).
5. Long-term opioid use is a dose-dependent risk factor for sleep-disordered breathing, which requires appropriate perioperative assessment, monitoring and management (**S**) (**Level III-2 SR**).
6. Long-term opioid use is associated with dose-dependent increased risks of injuries (**N**) (**Level III-2**) including fractures (**N**) (**Level III-2 SR**) and overdose (**N**) (**Level III-2**).
7. Preoperative opioid use is associated with worse outcomes after a variety of operations (**N**) (**Level III-2**).
8. Preoperative opioid tapering may ameliorate the risk of postoperative complications and morbidity (**N**) (**Level III-2**)
9. Preoperative opioid use is a risk factor for prolonged postoperative opioid use (**N**) (**Level III-2**).
10. Opioid-tolerant patients report higher pain scores, have slower pain resolution leading to longer hospital stay and increased readmissions but have a lower incidence of opioid-induced nausea and vomiting (**U**) (**Level III-2**).
11. Opioid-tolerant patients may have significantly higher opioid requirements and interpatient variation in the doses needed than opioid-naïve patients (**U**) (**Level III-2**).

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

☑ Usual preadmission opioid regimens should be maintained where possible or appropriate substitutions made (**S**).

☑ Liaison with all health care professionals involved in the treatment of the opioid-tolerant patient is important (**S**).

☑ Opioid-tolerant patients are at risk of opioid withdrawal if nonopioid analgesic regimens, tramadol or tapentadol alone are used (**U**).

- ☑ PCA settings may need to include a background infusion or other background opioid to replace the usual opioid dose and a higher bolus dose (**U**).
- ☑ Neuraxial opioids can be used effectively in opioid-tolerant patients, although higher doses may be required and these doses may be inadequate to prevent withdrawal (**U**).
- ☑ Adjuvants are used for their antitolerance, antihyperalgesic, and antiallodynic effects and there is some evidence upon which to base the choice of agent (**S**).
- ☑ In patients with escalating opioid requirements, management considerations are the development of tolerance or opioid-induced hyperalgesia (**S**).
- ☑ Following short-term opioid dose escalation for acute pain, a "reverse analgesic ladder" approach, using stepwise reduction to the patient's usual opioid regimen is recommended (**S**).
- ☑ For assessment of withdrawal reactions, the use of a validated withdrawal tool in opioid-tolerant patients is recommended; management strategies vary and include weaning, rotation and adjuvant use (**N**).

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9.8 | The patient with a substance use disorder

The information in this chapter overlaps with that in section 9.7 above and readers are referred to that section for information on definitions, implications of tolerance and opioid-induced hyperalgesia (OIH), overlap between chronic pain (non-cancer and cancer-related) and substance use disorders, impact of opioids on perioperative outcomes, and assessment and management of acute pain including models of care, clinical pathways and discharge planning.

Terminology

Whilst "addiction" was recommended in the consensus statement from the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine (AAPM 2001 **GL**; Ballantyne 2007 **NR**), more recently the use of the term "substance use disorder" (SUD) has been recommended by DSM-5 (American Psychiatric Association 2013a **GL**) and by ICD-11 (WHO 2018 **GL**).

For patients taking drugs that induce tolerance and physical dependence long-term, it is important to separate out these expected physiological phenomena (albeit potentially with psychological components in the case of "dependence"). This reduces the potential for stigmatisation of those who have physical dependence and tolerance (Ballantyne 2007 **NR**).

Problematic use in the setting of chronic pain is defined by the IMMPACT ACTTION consensus panels in terms of misuse, abuse and addiction (see Section 9.7.1 above)

A SUD exists when the extent and pattern of substance use interferes with the psychological and sociocultural integrity of the person (see Table 9.7). For example, there may be recurring problems with social and personal interactions or with the legal system, recurrent failures to fulfil work or family obligations, and these patients may put themselves or others at risk of harm (Haber 2009 **NR**).

The artificial divide between "good and bad drugs" is being eroded as there has been increasing misuse and abuse of legally prescribed drugs (notably prescription opioids) and drugs that were formally illegal have been legalised for therapeutic use (notably cannabinoids) (Nielsen 2017b **NR**). Although cannabis, cocaine and amphetamines are more widely abused, opioids contribute to 82% of fatal overdoses worldwide (UNODC 2016 **Level IV**)

Centres in many countries regularly monitor the use of illicit drugs, including prescription opioids and permit identification of current trends in drugs abused/misused. These include:

- internationally, the World Health Organization through the International Narcotics Control Board (https://www.incb.org) (INCB 2019);
- in Australia, the National Drug and Alcohol Research Centre (https://ndarc.med.unsw.edu.au) (Roxburgh 2018 **Level IV**), the annual overdose report from the Pennington Institute based on Australian Bureau of Statistics data (Penington Institute 2019 **Level IV**) and the annual pharmacotherapy statistics from the Australian Institute of Health and Welfare (https://www.aihw.gov.au) (AIHW 2019a **Level IV**);
- in New Zealand, the Centre for Social and Health Outcomes Research and Evaluation (https://shoreandwhariki.ac.nz/shore/) (SHORE 2014 **Level IV**);
- in the UK, the surveillance systems set up by the National Health Service under NHS Digital (https://digital.nhs.uk) which includes regular reports on drug misuse statistics;
- in the USA, the Substance Abuse and Mental Health Services of the US Department of Health and Human Services (https://www.samhsa.gov) (SAMHSA 2019), National Institute on Drug Abuse, and other schemes specifically tracking prescription opioid abuse, such as Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) (https://www.radars.org) (Murphy 2018 **Level IV**);

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- in Canada, the Canadian Institute for Health Information (CIHI) (https://www.cihi.ca/en) includes reporting on opioid prescription and related harms, and other substance use.

Pain management goals

Effective management of acute pain in patients with a SUD may be complex due to:

- psychological, social and behavioural characteristics associated with the disorder; noting that SUD is more common in those with comorbid psychiatric illness (Vietri 2014 **Level IV**, n=1,242; Webster 2017 **NR**);
- presence of the drug (or drugs) of abuse including intoxication or acute withdrawal syndromes;
- medications used to assist with drug withdrawal, relapse prevention and rehabilitation;
- complications of drug abuse including organ impairment, infectious diseases and increased risk of traumatic injury and other drug-related presentations; and
- the presence of tolerance and physical dependence which are expected physiological responses to chronic use of some substances.

Impact on outcomes

SUD can impact perioperative outcomes, implying that some patients will require deferral for optimisation prior to elective procedures (eg referral for substance use and chronic pain management). In elective spinal fusion, opioid dependence (ICD-9) prolonged LOS (adj OR 2.11; 95%CI 1.78 to 2.49), increased costs, resulted in higher infection rates, higher anaemia, and higher pulmonary insufficiency and this has implications for pain management and consent (Tank 2018 **Level III-2**, n=1,826,868).

Trauma outcomes are impacted by the types of substances abused, with increased mortality in those concurrently using benzodiazepines and opioids (Cheng 2016 **Level III-2**, n=10,166). Unaddressed opioid use disorder (OUD) and subsequent undertreatment of pain leads to premature discharge, worse medical outcomes, readmission, relapse and overdose (Ward 2018 **NR**).

For impact of chronic opioid use on outcomes see Section 9.7.4 above.

9.8.1 | CNS-depressant drugs

Although not inevitable, abuse of CNS-depressant drugs (eg opioids, alcohol, benzodiazepines) is often associated with physical dependence and tolerance (see Section 9.7 above). Withdrawal from CNS-depressant drugs produces symptoms of CNS and autonomic hyperexcitability, the opposite of the effects of the drugs themselves (Quinlan 2017 **NR**).

9.8.1.1 | Opioids including prescription opioids

Acute pain in those with an opioid use disorder (OUD) should be treated using the strategies outlined in Section 9.7 above and in the remainder of this section.

United States of America

In the USA, the Centre for Disease Control (CDC) has labelled the current trends in opioid use an "opioid epidemic", as reflected in rising prescription and other opioid use, and related harms. The CDC Opioids Portal (https://www.cdc.gov/opioids/strategy.html) describes three "waves" in this epidemic from the 1990s a rise in use of prescription opioids, from 2010 of heroin and from 2013 of synthetic opioids, especially illicitly-manufactured fentanyl.

From 2002 to 2010, there were large increases in overall opioid prescriptions, followed by a slight decrease from 2011 to 2013; diversion and abuse showed large increases from 2002 to 2010, then a plateau or decline; and there have been similar patterns for opioid-related deaths

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(Dart 2015 **Level IV**). The 2015 US National Survey on Drug Use and Health found that, in the general community, 37.8% had ever used prescription opioids, 4.7% had misused and 0.8% had an OUD; the most common reason for misuse was for physical pain relief (63.4%); misuse and use disorders were more common in the presence of unemployment, low income and behavioural health problems; 59.9% had used prescription opioids without a script and 40.8% had obtained them from friends or relatives (Han 2017 **Level IV**, n=52,200). Past-year rates of prescription opioid misuse amongst American adolescents and young adults have also risen (Jordan 2017 **Level IV SR** [PRISMA], 19 studies, n=503,845).

Patterns of heroin use in the USA have changed with recent users more likely to be introduced via prescription opioids, with reasons for the transition being that heroin is easier to access and cheaper, along with changing demographics of use (greater geographical spread and not now predominantly involving minorities) (Cicero 2014 **Level III-3**, n=2,851)**.** From 2013 to 2014 in the USA, there was a rapid increase in age-adjusted death rates involving fentanyl which coincided with increased availability of illicitly manufactured fentanyl, according to law enforcement reports; this underpins the need for public health, coroners and law enforcement to work together on this public health problem (Rudd 2016 **Level IV**).

Emergency departments (ED) are an important source of opioids for misuse and diversion with ED physicians amongst the top prescribers of opioids; 10% of diverted opioids originate from ED prescription, 10% of prescriptions have indicators of "inappropriate prescribing" (Lyapustina 2017 **NR**), noting that some providers prescribe opioids to expedite ED discharge (Pomerleau 2017 **Level IV**, n=443 [health care professionals]).

Systematic approaches to these issues in the USA have included support for prescribing decisions, reducing inappropriate access (eg Prescription Drug Monitoring Programs [PDMPs] and Opioid Analgesic Risk Evaluation and Mitigation Strategy [REMS]) (Bucher Bartelson 2017 **Level IV**), increasing access to overdose treatment and providing substance use treatment (Collins 2018 **NR**; Volkow 2014 **NR**).

Concerns have been raised about the inadvertent impact of such strategies on pain management and that some approaches are not evidence-based, leading to a call for pain specialists to advocate for patients to ensure adequate treatment especially for vulnerable populations (Pergolizzi 2019 **NR**) and to oppose forced opioid tapering (Darnall 2019 **NR**).

Other countries

Some authors have viewed the opioid epidemic as primarily a North American problem, with the main issues being opioid prescribing for inappropriate indications and in doses that are too high (Hauser 2016 **NR**). Although the worldwide literature shows that the highest growth in prevalence of prescription opioid use is in USA government-insured populations (Roland 2016 **Level IV SR** [PRISMA], 16 studies, n unspecified), there is ample evidence that other countries have a similar, albeit possibly less severe, issue. Prescription opioid use is also rising in the European Union, Canada and Australia (Quinlan 2017 **NR**; Hauser 2017 **NR**). Prediction estimates show opioid "dependence" is a global issue with high prevalence in Australia, New Zealand, Western Europe and North America; with lower estimates in Africa and Asia (Degenhardt 2014 **Level IV SR** [PRISMA], 31 studies, n unspecified). A comparison of five countries (USA, UK, France, Germany and Australia) via the Global Drug Survey 2015 (online anonymous) found country of residence accounted for <3% of the variance in opioid misuse or abuse (Morley 2017 **Level IV**, n=5,670). German data show that first opioid prescriptions increased by 37% from 2000 to 2010, noting professional guidelines are not always followed (Just 2016 **NR**).

In Australia in 2016, 11% of those aged 14 y had ever used a prescription opioid for non-medical purposes (3.7% in the past year); commonly multiple substances were used (alcohol in over 35%, smoking in approximately 25%, cannabis in nearly 20%); pharmaceutical opioids were

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responsible for more deaths and poisonings than heroin; there was a mortality peak in 1999, followed by decline and then 62% increase in death rate from 2007 to 2016 (AIHW 2018 **Level IV**).

Opioids contributed to two-thirds of drug-induced deaths in Australia; in 2016, 1,045 opioid-induced deaths occurred in Australia (6.6/100,000 people vs 3.8/100,000 people in 2007) (Roxburgh 2018 **Level IV**) and 75% of these were prescription opioids. 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]).

Comorbid disorders

In those who use prescription opioids non-medically, the prevalence of chronic non-cancer pain is 48 to 60% (Voon 2017 **Level IV SR** [PRISMA], 18 SRs, n unspecified). For those treated with buprenorphine for OUD, relapse is more likely with increased chronic pain severity (adj OR 1.15; 95%CI 1.06 to 1.24) (Griffin 2016 **Level II**, n=148, JS 2). Long term opioid prescription receipt is more likely in those with a prior diagnosis of ADHD (HR 1.53; 95%CI 1.48 to 1.58), nonopioid SUD (HR 3.15; 95%CI 3.06 to 3.24) and prior OUD (HR 8.70; 95%CI 8.20 to 9.24) (Quinn 2018 **Level IV**, n= 1,224,520).

Abuse deterrent formulations

More recently, focus has turned to the use of "abuse deterrent" or "tamper-resistant" formulations (Schaeffer 2012 **NR**); strategies that are being assessed include the use of technologies that prevent the release of active opioid when tablets are crushed or attempts are made to extract the drugs by other means, combinations of the opioid with an opioid antagonist such as naloxone or with a second substance with aversive effects (Passik 2014 **NR**; Webster 2011 **NR**). It is important to note that such formulations are not preventing abuse in principle but are making it more difficult to abuse these opioids by routes other than the oral one (ie injecting, snorting).

Studies of opioid abuse potential can be limited by methodological issues and best practice principles have been described (Setnik 2017 **NR**). Post-marketing surveillance is significantly challenging and future studies may need to compare one abuse deterrent formulation with another, as other formulations decline in use over time.

Slow-release oxycodone, reformulated to be abuse deterrent, was introduced to the USA in 2010 and was associated with reduced intentional abuse, diversion and overdose (Larochelle 2015 **Level III-3**; Dart 2015 **Level IV**); however, this coincided with an increase in heroin overdoses. From 2012 to 2014, 25 to 30% of those with an OUD reported past-month abuse of this reformulated product, reflecting transition to oral abuse (43%), successful defeat of the formulation with ongoing inhaled or injecting use (34%), or exclusive use of the oral route (23%) (Cicero 2015 **Level IV**, n=10,784).

In Australia, reformulated slow-release oxycodone was introduced in 2014. The National Opioid Medications Abuse Deterrent (NOMAD) cohort reported cheaper street prices and lower use via tampering (injection), but no change in harms (Larance 2018 **Level III-3**; Degenhardt 2015a **Level III-3**). Whilst some tampering continued, the agent was reported as less attractive for misuse (Peacock 2015 **Level III-3**, n=522).

9.8.1.2 | Alcohol and benzodiazepines

Excessive alcohol use predisposes to particular types of acute pain eg due to trauma (77% of screened Australian trauma patients had a probable alcohol-related injury or were engaging in risky drinking regularly [Browne 2013 **Level IV**, n=729]) and pancreatic disease (RR 1.37; 95%CI 1.19 to 1.58) (Alsamarrai 2014 **Level IV SR**, 51 studies, n 3,000,000). It may also lead to hepatic dysfunction, which may affect the metabolism of other drugs, including analgesics.

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Alcohol and/or benzodiazepine use disorders are relatively common, particularly in certain subgroups of the population. The Australian POINT study of patients with CNCP prescribed opioids found a 33% lifetime prevalence of alcohol use disorder, and 16% of those who drank in the prior 12 mth did so for pain control (Larance 2016 **Level IV**, n=1,514). Heroin users also take benzodiazepines to potentiate the effects of the opioid (Bluth 2016 **NR**); concurrent use of opioids and benzodiazepines increases the risk of opioid-related overdose (Dowell 2016 **GL**).

In terms of screening for benzodiazepine use, short-acting (eg midazolam) appear in urine drug screens for 12 h and long-acting (eg diazepam) for over 7 d (Quinlan 2017 **NR**).

There is no cross-tolerance between opioids and alcohol or benzodiazepines in animal studies (Bell 1998 **BS**). The effective concentrations of remifentanil were not different between alcoholic and non-alcoholic patients (Liang 2011 **Level II**, n=60, JS 5). There is therefore no pharmacological reason to use higher than "standard" initial opioid doses in patients with an alcohol or benzodiazepine dependence.

Prevention of withdrawal should be a clinical priority in all patients. Benzodiazepines are effective for alcohol withdrawal symptoms, especially prevention of seizures (Amato 2010 **Level I** [Cochrane], 64 RCTs, n=4,309). If benzodiazepines are administered for the treatment of withdrawal symptoms and signs, patient sedation levels must be monitored, especially if patients are receiving concurrent opioids or other sedating drugs (Macintyre 2011 **NR**). Excessive sedation will limit the amount of opioid that can be given safely.

There are inconclusive results on the effect of pregabalin on alcohol withdrawal (Guglielmo 2012 **Level IV SR**, 3 studies [withdrawal], n=271).

Naltrexone is used for treatment of alcohol use disorder and this complicates acute pain management (see Section 9.8.3.3).

9.8.1.3 | Cannabinoids

Recreational use

"Recreational" cannabis users had approximately 50% greater rescue pethidine requirements, as well as higher pain intensity and dissatisfaction scores, than nonusers over the first 6 h after orthopaedic surgery (Jefferson 2013, **Level III-2**).

Synthetic cannabinoids may contain a large number of components and are more potent than the naturally occurring drug, resulting in agitation, hypertension, hypokalaemia, vomiting and seizures (Tait 2016 **Level IV SR**, 106 studies, n>4,000 [26 deaths]).

Use for chronic pain

Despite Level I evidence that cannabinoids have limited efficacy and potential for harm in CNCP (Stockings 2018 **Level IV SR** [PRISMA], 47 RCTs and 57 studies, n=9,958), the Australian POINT study found that, over a 4 y period, one quarter of those prescribed opioids for CNCP had also used cannabis, usually for pain management, with 12% meeting criteria for cannabis use disorder (ICD-10 criteria) (Degenhardt 2015c **Level IV**, n=1,514). Those using cannabis were younger, with greater pain severity and interference, lower pain self-efficacy, greater concurrent benzodiazepine prescription and greater non-adherence to the prescribed opioid regimen (Campbell 2018 **Level IV**, n=1,514). Presence of (chronic) pain may make reducing cannabis use more difficult (Sznitman 2018 **Level IV**, n=18) (see also Section 4.11).

Withdrawal syndromes

Withdrawal is usually only seen in high-dose cannabis smokers in whom tolerance develops quickly (Beaulieu 2017 **NR**). Both DSM-5 and ICD-11 define cannabis withdrawal as part of use disorders and dependence (WHO 2018 **GL**; American Psychiatric Association 2013a **GL**).

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Withdrawal commences within 24-48 h and can last up to 3 wk; symptoms may include depressed mood, abdominal pain and headache, all of which can confound acute pain management (Bonnet 2017b **NR**).

Screening

In terms of screening for use, after single use, cannabis and its metabolites appear in urine drug screens for 3-4 d (Quinlan 2017 **NR**). With heavy or chronic use, they may appear in urine drug screens for up to 45 d.

For information about the use of cannabinoids for pain management see Section 4.11.

9.8.1.4 | Alpha-2-delta modulators (Gabapentinoids)

Increasingly, these are recognised as drugs of abuse with rising misuse rates (Crossin 2019 **Level IV**, n=1,201 [pregabalin misuse-related ambulance attendances]); Bonnet 2017c **Level IV SR** [PRISMA], 106 studies, n unspecified). Risk factors for abuse include prior substance abuse and psychiatric comorbidities. Rates of abuse are higher in opioid abusers than in the general population and use with opioids increases the risk of opioid-related death (OR 1.99; 95%CI 1.61 to 2.47) (Gomes 2017 **Level III-2**, n=5,875).

See also Section 4.8.1.1.

9.8.2 | CNS-stimulant drugs

Abuse of CNS-stimulant drugs (eg cocaine, amphetamines, ecstasy, ketamine) is associated with psychological rather than physical dependence and only a low degree of tolerance; these drugs do not exhibit any cross-tolerance with opioids (Buckley 2014 **NR**).

Cocaine and ecstasy (N-Methyl-3,4-methylenedioxyamphetamine or MDMA) are known to enhance the analgesic effects of morphine in animal studies (Gatch 1999 **BS**; Kauppila 1992 **BS**; Nencini 1988 **BS**). This effect may be age-dependent as exposure to methamphetamine in adolescent rats enhances morphine antinociception (and tolerance development) with inverse effects in adult rats (Cyr 2012 **BS**). In experimental-pain settings, subjects taking ecstasy have been shown to have a reduced pain tolerance (O'Regan 2004 **Level III-2 SR EH**); this was also true for abstinent previous users (lower pressure pain thresholds, increased cold pain ratings, increased pain ratings during testing of DNIC) (McCann 2011 **Level III-2 EH**). Those taking cocaine also had reduced cold pressor pain thresholds (Compton 1994 **Level III-2 EH**).

There are very few data from the clinical setting of any differences in opioid requirements. Compared with those with negative urine drug screens, trauma patients in intensive care who were urine screen positive for cocaine and/or amphetamines required similar opioid doses (Kram 2017 **Level III-2**, n=150).

Epidemiological data from the USA show rising rates of cocaine- and/or psychostimulant deaths since 2015; cocaine deaths are partially attributable to lacing with synthetic opioids (Kariisa 2019 **Level IV**). Analysis of urine drug tests in the USA show rising rates of fentanyl positivity in those positive for cocaine and methamphetamine, reflecting a growing risk to stimulant users of opioid-related overdose in that country (LaRue 2019 **Level IV**, n=1,000,000).

While behavioural and autonomic effects are seen during acute exposure, withdrawal symptoms are predominantly affective rather than physical (Quinlan 2017 **NR**). Stimulants are associated with particular types of acute pain (eg cocaine use and chest pain including acute coronary syndromes).

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9.8.2.1 | Nicotine

In volunteer studies, nicotine increases pain threshold (n=393) and tolerance (n=339) and has therefore an acute small to medium analgesic effect (Ditre 2016 **Level III-2 EH SR** [PRISMA], 13 studies, n unspecified). The authors speculate, that this could make smoking more rewarding and harder to give up.

In African-American smokers, smoking abstinence increased self-reported pain, with greater abstinence-induced pain in those with pre-existing CNCP (Bello 2018 **Level III-3**, n=214). In patients attending a Danish pain clinic, smoking rates were higher than those in the general population; compared with non-smokers, smokers and ex-smokers were more likely to use opioids and at higher doses, although were not more likely to have opioid addiction (Plesner 2016 **Level IV**, n=98). Opioid-dependent smokers are more likely to be nicotine-dependent, with greater severity of nicotine dependence (Parker 2018 **Level IV**, n= 58,971).

9.8.2.2 | Cocaine

Whilst cocaine use does not induce physical dependence, its regular use is very reinforcing (ie psychological dependence) which can be managed with tricyclic antidepressants (Bluth 2016 **NR**). "Withdrawal" is described as having three phases – "crash" within h to d, "acute" for up to 3 wk, and "extinction" over several mth (Beaulieu 2017 **NR**). Cocaine is also known to enhance the effects of morphine in animal studies.

Cocaine use may present with seizures, arrhythmias, coronary vasospasm, myocardial ischaemia or stroke (Vadivelu 2018 **NR**). Dexmedetomidine may be useful to achieve sympatholysis (Vadivelu 2016b **NR**).

Cocaine appears in urine drug screens for 48 to 72 h (Quinlan 2017 **NR**).

9.8.2.3 | Amphetamines and methamphetamine

Methamphetamines are highly addictive with long-term use leading to anxiety, mood disturbance, insomnia and sometimes psychosis, all of which can impact on acute pain (Becker 2018 **NR**). There are no effective pharmacotherapies, although there is low quality evidence for methylphenidate (2 RCTs, n=88) (Chan 2019a **Level I** [PRISMA], 34 RCTs, n unspecified).

Methamphetamines, used for ADHD, are increasingly drugs of abuse especially by school students, with non-medical regular users 1.8% of Australians aged 15 to 35 years, commonly declining by mid-30s (Chan 2019b **Level III-3**, n=1,755).

Withdrawal from methamphetamines is characterised by increased sedation and appetite that can last for a few days; the severity of sleepiness correlated with the amount used (calculated by cost per mth) and length of regular use (McGregor 2005 **NR**).

Amphetamines appear in urine drug screens for 48 h (Quinlan 2017 **NR**).

9.8.3 | Drugs used in the treatment of addiction disorders

Close liaison with all treating clinicians and drug and alcohol services should occur. In the case of those receiving opioid substitution therapy (OST), this may include arrangements with the usual prescriber and pharmacist for a "takeaway" dose on the day of elective surgery/procedure admission, as well as liaison at discharge to ensure continuity of ongoing therapy (Schug 2012 **NR**; Huxtable 2011 **NR**).

Good acute pain management is particularly important for patients on OST as acute pain exposure was associated with reduced retention in treatment (aOR 0.46; 95%CI 0.23 to 0.93) (Bounes 2013 **Level III-2**, n=323 [prescribers]). The presence of chronic pain increases the odds of

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craving in those on OST (aOR 3.10; 95%CI 1.28 to 7.50), which may impact outcomes in this subgroup of patients (Tsui 2016 **Level III-2**, n=105).

Continuity of OST is important, as all-cause and overdose-related mortality risk drops sharply in the first 4 wk of therapy, but rises substantially with cessation (Sordo 2017 **Level III-3 SR** [PRISMA] 19 studies, n=122,885 [methadone], n= 15,831 [buprenorphine]). With regard to mortality under OST, methadone vs buprenorphine use shows higher crude mortality, but also substantially higher relative risk reduction when time in-treatment is compared to time out-of-treatment (Bahji 2019 **Level III-3 SR** [PRISMA], 32 studies, n=150,235) (19 studies overlap with Sordo 2017). As in the previous systematic review, greatest mortality reduction occurred in the first 4 wk. Short-term detoxification is rarely effective and there is an increased risk of one-year mortality vs OST (Harrison 2018 **NR**).

A comparison of OST with methadone vs buprenorphine found no difference in self-reported opioid use or positive urine drug screens, no difference in retention (low quality evidence), but each was more effective than detoxification or psychological treatment alone (Nielsen 2016 **Level I** [Cochrane], 6 RCTs, n=607).

In Australia in 2017, 50,597 clients were receiving OST, of which 65% were male and 10% identify as Aboriginal and/or Torres Strait Islander (AIHW 2019b **Level IV**). Overall rates of OST have been stable since 2010 (20 clients per 10,000 population); there are 3,168 authorized prescribers (90 in prisons), and 2,852 dosing points (mostly pharmacies); overall there are roughly similar numbers of clients on methadone, buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®).

9.8.3.1 | Methadone

Methadone is a long-acting opioid agonist used in the management of patients with an opioid addiction (see Section 4.3.1.3). It is commonly prescribed in doses in the range 50–120 mg and once/d, which is adequate to suppress symptoms of opioid withdrawal.

In the acute pain setting, methadone should be continued, where possible, at the usual dose. If there is any doubt about the dose (eg there is suspicion that the patient is diverting all or part of the prescribed amount), it is prudent to give part of the reported dose and repeat this over the day if needed, monitoring the patient for sedation (Huxtable 2011 **NR**; Peng 2005 **NR**). If the patient is unable to take methadone by mouth, substitution with parenteral methadone or another opioid will be required in the short-term (Huxtable 2011 **NR**; Mitra 2004 **NR**). Parenteral methadone doses were 0.7 times the oral doses (Gonzalez-Barboteo 2008 **Level IV**); half to two-thirds of the oral maintenance dose can be given in equal divided doses by SC or IM injection 2 to 4 times/d or by continuous infusion (Huxtable 2011 **NR**; Alford 2006 **NR**).

The duration of any analgesic effect from the dose is much shorter (Alford 2006 **NR**); although this is sometimes not well understood by treating physicians (Bounes 2014 **Level IV**). Dividing the daily dose on a temporary basis (eg giving half the usual daily methadone doses twice a day or one third of the usual dose every 8 h) may result in a better analgesic effect (Basu 2007 **NR**). Divided doses or continuous infusion have been recommended for palliative care management of those on methadone OST (Taveros 2017 **Level IV SR** [PRISMA], 7 studies, n=142).

Care should also be taken with concurrent administration of other drugs that prolong the corrected QT interval; although this is thought to be an issue only with very high methadone doses (Andrews 2009 **NR**).

If patient receiving methadone OST require additional opioids at discharge, consider daily dispensing; overdose prevention education and nasal naloxone prescription have also been recommended in this circumstance (Ward 2018 **NR**).

Methadone appears in urine drug screens for 7 to 8 d after cessation (Quinlan 2017 **NR**).

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Patients taking methadone may have OIH (see section 9.7 above for more information including implications for management).

9.8.3.2 | Buprenorphine

Buprenorphine is a partial opioid agonist used effectively in the treatment of opioid addiction (Mattick 2014 **Level I** [Cochrane], 31 RCTs, n=5,430) and commonly prescribed for OUD in doses of 8 to 32 mg (Roberts 2005 **NR**). Regulatory controls on prescribers and those providing acute pain management vary by country and state.

Administered SL, it has a mean terminal half-life of 28 h (Johnson 2005 **NR**). It is usually given once every day or every second day, which is adequate to suppress symptoms of opioid withdrawal; like methadone the duration of any analgesic effect from the dose is much shorter (Alford 2006 **NR**).

Some preparations combine buprenorphine and naloxone (the latter is poorly absorbed by the SL route) (Orman 2009 **NR**); naloxone is added to buprenorphine with the aim of reducing parenteral abuse of the drug.

Furthermore, long-acting buprenorphine preparations are now becoming available worldwide (Harrison 2018 **NR**; Chavoustie 2017 **NR**). In Australia, two such preparations are registered for SC injection: a SC gel depot preparation (Buvidal) previously used in France (Vorspan 2019 **NR**) for weekly or monthly injection and Sublocade for monthly injection. There are multiple reasons why such preparations could be advantageous; they reduce need for frequent attendance at the dispensing facility, reduce inconvenience for patients and staff, reduce the risk of diversion and injecting and may result in better adherence. Guidelines for the use of these preparations in Australia are published (Lintzeris 2019 **GL**).

In opioid-naïve subjects, administration of buprenorphine resulted in decreased hyperalgesia following transcutaneous pain stimuli vs placebo, suggesting that unlike morphine and methadone, buprenorphine may exert an antihyperalgesic effect (Koppert 2005 **Level III-2**). However, both methadone-maintained and buprenorphine-maintained patients were similarly more sensitive to cold-pressor pain than opioid-naïve controls (Compton 2012 **Level III-2**).

Whilst there are still conflicting views in the literature regarding perioperative management of OST with buprenorphine, the evidence supports its continuation. A systematic literature search found limited evidence to support discontinuation (4 CR) and more support for continuation (1 Level III-1, 4 Level III-3, 3 Level IV) (Quaye 2019 **Level IV SR**, 8 studies & 4 CR, n unspecified). There is no evidence that the outcomes are worse if it is continued and limited evidence about relapse rates with discontinuation (Goel 2019 **Level IV SR** [PRISMA], 6 studies & 12 CR, n unspecified) (5 of 6 studies overlap). Significant risks of discontinuation include relapse and accidental overdose (Lembke 2019 **NR**).

As with methadone, dividing the daily doses on a temporary basis (every 8 or 12 h) may take advantage of the analgesic properties of buprenorphine (Alford 2006 **NR**).

If buprenorphine has been ceased (eg unconscious patient, intraoral surgery or trauma preventing SL administration), its reintroduction should be managed in consultation with the prescribing health professional who should also be involved in discharge planning to ensure continuity of long-term care and availability of usual replacement therapy on discharge (Huxtable 2011 **NR**).

With its metabolites, buprenorphine appears in urine drug screens for 8 d (Quinlan 2017 **NR**)

In-hospital or emergency department initiation

OST with methadone or buprenorphine are both better than clonidine and lofexidine in ameliorating withdrawal symptoms (Gowing 2017 **Level I** [Cochrane], 27 RCTs, n=3,048). This has implications for commencing OST in hospital or emergency departments.

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Comparison of in-hospital OST initiation of buprenorphine and continued outpatient follow-up with a 5-day detoxification protocol using buprenorphine showed the former led to more patients receiving treatment and less illicit opioid use at 6 mth post-discharge (RR 0.60; 95%CI 0.46 to 0.73) (Liebschutz 2014 **Level II**, n=139, JS 3).

Emergency department initiation of buprenorphine/naloxone for OUD may improve engagement with and retention in treatment (D'Onofrio 2015 **Level II**, n=329, JS 3).

Management of patients treated for CNCP with transdermal buprenorphine is addressed in 9.7.

9.8.3.3 | Naltrexone

Naltrexone is a pure opioid antagonist used in the management of patients with opioid or alcohol dependence. In the USA, it is available as tablets or in a long-acting injectable form.

There is good evidence for its effectiveness in alcohol dependence (Rosner 2010 **Level I** [Cochrane], 50 RCTs, n=7,793).

There is mixed evidence for its use in opioid use disorder. Neither oral naltrexone (Minozzi 2011 **Level I** [Cochrane], 13 RCTs, n=1,158) nor long-acting naltrexone implants (Larney 2014 **Level I**, 5 RCTs, n=576 & **Level IV SR**, 4 studies, n=8,358) have good evidence of efficacy and safety. On the contrary, there is a significant excess mortality in patients on oral naltrexone vs methadone-maintenance treatment (RR 3.5; 95%CI 2.2 to 5.8) (Degenhardt 2015b **Level III-2**). There is a limited evidence base for extended release naltrexone injections with no change in mortality, except for those recently released from correctional facilities (Babu 2019 **NR**). Compared with oral naltrexone, extended release naltrexone implant (both combined with CBT) for opioid use disorder results in better treatment retention at 6 mth (Sullivan 2019 **Level II**, n=60, JS 2).

The usual oral maintenance dose is 50 mg/d; orally administered, naltrexone has an apparent half-life of about 14 h and binds to opioid receptors for over 24 h following a single dose (Vickers 2006 **NR**); this can create difficulties in the acute pain setting as opioid agonists will be antagonised. It has been recommended that, where possible, naltrexone should be stopped for at least 24 h, and preferably 72 h, before surgery (Kampman et al 2015 **GL**; Harrison et al 2018 **NR**; Vickers 2006 **NR**; Mitra 2004 **NR**).

These difficulties are even greater when the patient has an active implant (Vickers 2006 **NR**; O'Brien 2006 **NR**); the duration of efficacy of the 1.1 g implant is approximately 95 d and that of the 2.2 and 3.3 g implants approximately 140 d (Ngo 2008 **PK**). In cases where effective opioid analgesia is required, removal of the implant might be considered (Sadleir 2011 **Level IV**).

In addition, a microsphere-based formulation of naltrexone incorporated into a biodegradable matrix for IM injection (XR-NTX) is now becoming available, and is approved by the FDA for alcohol and opioid dependence (Sudakin 2016 **NR**). For this preparation (380mg IM), the peak activity is at 7 d and duration of effect is 28 d (Harrison 2018 **NR**). Whilst it has proven difficult to provide analgesia during the first two wk post-injection, effective analgesia has been described in the last wk of the four. Elective surgery should be scheduled 4 wk after the last injection; with recommendations including a preoperative consultation with a pain and addiction specialist, development of a relapse risk management plan including with community provider input and education (Ward 2018 **NR**).

In patients receiving naltrexone therapy, multimodal analgesic regimens (eg NSAIDs, paracetamol, ketamine, tramadol, tapentadol, regional analgesia, lidocaine, dexmedetomidine, gabapentinoids, non-pharmacological strategies) should also be employed (Harrison 2018 **NR**).

There is experimental evidence of mu-opioid receptor upregulation following antagonist withdrawal (Millan 1988 **BS**) and abrupt discontinuation of naltrexone may therefore lead to a period of increased opioid sensitivity (Vickers 2006 **NR**). As the effect of naltrexone diminishes

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after it has been ceased, the opioid dose required for analgesia may also need to be decreased in order to avoid opioid overdose (in particular OIVI).

Planning around cessation and reintroduction of naltrexone should be done in consultation with the prescribing health professional and an acute pain service/specialist.

9.8.4 | The therapeutic relationship and behavioural management

Pain management in patients with SUD often presents significant challenges for both clinicians and patients. Patients fear being stigmatised or discriminated against; they are concerned about inadequate pain relief with their past experiences leading to physician distrust; and they fear experiencing withdrawal (especially whilst waiting in ED or after admission, before their usual drugs are prescribed) and relapse precipitated by acute opioid exposure (Quinlan 2017 **NR**; Buckley 2014 **NR**; Eyler 2013 **NR**; Roberts 2008 **NR**).

Providers experience mistrust, concerns about drug seeking, fear of overtreatment with adverse events, concerns about diversion, and risk of discharge against medical advice. Many health professionals (and some patients) have misconceptions about acute pain management in this setting (Bounes 2014 **NR**). Evidence for the most appropriate management of acute pain in patients with an addiction is limited and thus advice is based primarily on case series, case reports, expert opinion and personal experience.

In Canada, 48% of injecting drug users report having ever been denied pain medication as inpatients and this is positively associated with using illicit drugs whilst in hospital (adj OR 1.46; 95%CI 1.14 to 1.88) (Ti 2015b **Level IV**, n=1,053). Injecting drug users who discharge against medical advice experience inadequate pain and withdrawal management, often leading to continued drug use in hospital settings (McNeil 2016 **Level IV**, n=30). Risk factors for discharge against medical advice are recent injecting drug use, "pension day", Indigenous patients (although this is likely to be multifactorial), and day of the week (more likely on weekends); rates are lower with in-hospital methadone use, community-based hospital in the home, older age and more social support (Ti 2015a **Level IV SR** [PRISMA], 17 studies, n unspecified).

A more patient-centred approach has been recommended, with a (perhaps controversial) shift in focus for these patients from abstinence-based policies to risk reduction (McNeil 2016 **Level IV**). Integration of OUD treatment into hospital care (eg as occurring in some USA emergency departments) might reduce conflict between teams and reduce discharge against medical advice (Fanucchi 2016 **NR**). A multidisciplinary addiction consultative service (IMPACT = improving addiction care team) improved staff experiences as they felt relieved, viewed care as more humanised, understood addiction as a disease and valued the support provided by discharge referral pathways (Englander 2018 **Level IV**).

Inappropriate behaviours can be prevented to a significant extent by the development of a respectful, honest and open approach to communication and, as with all other patients, an explanation of treatment plans and the fact that complete relief of pain may not be a realistic goal, as well as involvement of the patient in the choice of plan (within appropriate boundaries) (Jones 2014 **NR**; Haber 2009 **NR**; Roberts 2008 **NR**). One communication framework is the "7 Es" (Becker 2016 **Level IV**): Express empathy, Elicit functional goals, Educate, Endorse an alternative plan, Enlist patient buy-in, Enact follow-up plan, and maintain Equanimity (calm, even-tempered, non-judgemental).

A proactive, rather than reactive, discussion about medications and behaviours is recommended (Haber 2009 **NR**) and sometimes limit setting (Huxtable 2011 **NR**). Episodes of acute pain may negatively impact upon long-term retention in addiction treatment programs and better acute pain control may improve such retention (Bounes 2013 **Level III-2**). Addiction "talking points" include the provider raising concerns, approaching management through the lens of it

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being best to have treatment from a specialist (as in any chronic disease), and "[caring] enough" to set boundaries (Allen 2014 **NR**).

9.8.5 | Assessment including screening for risk of opioid use disorder and mitigation strategies

The first step in managing patients with a SUD is identifying the problem, although obtaining an accurate history can sometimes be difficult. Risk factors for OUD include past or current substance abuse, untreated psychiatric disorders, younger age, social and family factors that encourage misuse (Webster 2017 **NR**). Risk factors for opioid overdose include those of middle age, opioid use disorder and other psychiatric comorbidities. At times, it may be in the setting of unsuccessful overdose that inpatient contact occurs.

Identification of patients abusing drugs or at risk of drug abuse may be difficult. The ability of health professionals to predict which patients may misuse or abuse opioids is poor (Jung 2007 **Level IV SR**, 6 studies, n unspecified) and patient self-report of drug use may not correlate with evidence from drug screening (Sehgal 2012 **NR**).

Screening tools are widely used in chronic settings especially in the USA; and increasingly are recommended prior to short-term therapy also (Ballantyne 2015 **NR**). These tools were largely developed in an outpatient (often pain clinic) setting, and are not validated for acute hospital settings including emergency departments, so as yet it is not clear who should be screened and with what tool (Duber 2018 **NR**). Opioid Risk Tool (ORT), Screener and Opioid Assessment for Patients with Pain (SOAPP-R) and Current Opioid Misuse Measure (COMM) are poor at predicting risk of subsequent aberrant behaviours in patients with CNCP in the emergency department (Chalmers 2019 **Level IV**). The SOAPP-R applied in emergency department patients, in whom discharge opioid prescribing was being considered, had sensitivity 54%, specificity 71%, positive predictive value 26% and negative predictive value 89% for identifying subsequent high-risk behaviour (Weiner 2016 **Level IV**, n=82). A further limitation is that self-reported tools can be manipulated (Kaye 2017b **NR**).

Polysubstance use is common and many patients use drugs from different groups, the most common being CNS-depressant drugs (such as opioids, alcohol, benzodiazepines and cannabinoids) and CNS-stimulant drugs (including cocaine, amphetamines and amphetamine-like drugs). The group from which the drugs come determines their withdrawal characteristics (if any) and their interaction with acute pain treatment (Peng 2005 **NR**; Mitra 2004 **NR**). Patients should be asked about the route of administration used, as some may be injecting prescription drugs intended for oral, TD or SL use. Verification of opioid doses should be undertaken where possible or else a divided dose given with monitoring of effect, in case the reported dose is incorrect or the drug is being wholly or partly diverted (Huxtable 2011 **NR**; Alford 2006 **NR**).

Recommendations include establishing a supportive non-judgemental environment, determining what drugs are misused, developing an analgesic plan (which optimise non-opioids, increases opioids if required with careful monitoring for adverse effects and change to oral analgesia from parenteral as soon as feasible), a withdrawal management plan (continuing OST or replacing, and consider withdrawal from other drugs), minimising stress and multidisciplinary discharge planning (Quinlan 2017 **NR**).

"Universal precautions" are increasingly recommended for acute pain settings (Webster 2017 **NR**). In this context, universal precautions encompass use of multimodal analgesia, abuse-deterrent formulations, urine drug screening, use of prescription drug monitoring programs (PDMP) and risk management strategies (eg REMS programs in the USA).

An acute admission offers an opportunity to engage with the chronic condition of SUD as well as to treat the acute issues; failure to engage is a missed opportunity (Donroe 2016 **NR**). Screening,

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Brief Intervention and Referral to Treatment (SBIRT) is promoted and commonly used in the USA (Kaiser 2016 **NR**)

Involvement of an addiction medicine specialist or service may be required; suggested referral criteria are (Nack 2017 **NR**):

- Abuse of medication
- Excessive alcohol use
- Unwilling to try other pain treatments
- Concurrent opioid and sedative prescriptions
- Psychiatric disorder
- On ORT with persistent pain.

9.8.6 | Transition to community care

In all cases, close liaison with other treating health professionals and drug and alcohol services is required. This is especially important if the management plan includes additional opioids for pain relief for a limited period after discharge or if any alteration has been made, after consultation with the relevant services, to methadone or buprenorphine doses while in hospital.

In many countries, regulatory requirements will dictate that only one physician has the authority to prescribe for these patients. However, restricted use of additional opioids after discharge may be possible in some circumstances. For example, it could be arranged for the patient to pick up a limited and progressively decreasing number of tablets daily or every other day, along with their usual methadone or buprenorphine (Peng 2005 **NR**).

For those with concurrent chronic pain, referral to an outpatient pain service may be required; the patient not currently in SUD treatment may require referral to a drug and alcohol service (Huxtable 2011 **NR**).

It is necessary to notify usual prescribers of medications used in hospital as these may appear in subsequent urine drug screens (Vadivelu 2016a **NR**).

For discharge medication see also Section 8.13.

9.8.7 | Patients in recovery from substance use disorders

Patients in drug-treatment programs or in drug-free recovery may be concerned about the risk of relapse if they are given opioids for the management of their acute pain (Eyler 2013 **NR**; Markowitz 2010 **NR**). However, there is no evidence that the use of opioids to treat acute pain increases the rate of relapse; a more likely trigger is unrelieved pain, although this is primarily based on expert opinion (Ward 2018 **NR**; Buckley 2014 **NR**; Markowitz 2010 **NR**; Alford 2006 **NR**)

IV opioids may present greater risk for relapse due to more rapid and higher peak concentrations and patients may be very reluctant to receive opioids (Quinlan 2017 **NR**). Those at particular risk of relapse when given opioids include younger patients, males and those using multiple illicit drugs, especially cocaine (Markowitz 2010 **NR**). Effective communication and planning, the use of multimodal analgesic strategies, reassurance that the risk of reversion to an active addiction is small, and information that ineffective analgesia can paradoxically lead to relapse in recovered patients, are important and help avoid undertreatment (Huxtable 2011 **NR**; Mitra 2004 **NR**).

The anxiety associated with surgery might trigger conditioned responses resulting in drug craving (Volkow 2016 **NR**). Those with prior maintenance opioid addiction treatment but prolonged abstinence demonstrate increased cold sensitivity, decreased tolerance and cravings (similar to their opioid-maintained counterparts); but they had greater sense of control over these cravings which may reflect that they have developed skills to cope with pain to avoid

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relapse (Wachholtz 2019 **Level III-2**, n=120). Expert opinion suggests that both uncontrolled pain and uncontrolled opioid access can trigger relapse (Ward 2018 **NR**).

9.8.8 | Acute pain in pregnant patients with an opioid use disorder

Many women with an addiction are of childbearing age (AIHW 2019a **Level IV**); the prevalence of prescription-opioid abuse is rising in this population (Klaman 2017 **GL**). The prevalence of neonatal abstinence syndrome (NAS) has risen in the USA and Canada (Filteau 2018 **Level IV**; Ko 2016 **Level IV**), although it has stabilised in Australia (Uebel 2016 **Level IV**, n=1,022,263) and England (Davies 2016 **Level IV**).

The management of acute pain in pregnant patients with an addiction must consider treatment of the mother, as well as possible effects on the foetus and newborn.

Identification of these patients during pregnancy allows time for assessment and appropriate management planning; however, this is not always possible as antenatal care is often suboptimal (Kampman 2015 **GL**; Jones 2014 **NR**). Routine screening may increase the rate of addiction detection (Jones 2014 **NR**) and validated screening tools include the 4Ps and CRAFFT (ACOG 2012 **GL**; Jones 2014 **NR**). Care is complicated in these patients by other factors related to their use of drugs such as respiratory infections, endocarditis, untreated cellulitis, abscesses, HIV/AIDS, hepatitis and social factors such as abuse, interpersonal violence and homelessness (Jones 2014 **NR**; Ludlow 2007 **NR**). Stabilisation with OST, as early as possible in pregnancy, is preferred to withdrawal management or abstinence due to risks to both mother and foetus with addiction relapse and treatment dropout (Klaman 2017 **GL**; Kampman 2015 **GL**).

Reviews of pain management in these patients (Buckley 2014 **NR**; Jones 2014 **NR**; Stanhope 2013 **NR**) as well as guidelines have been published (Klaman 2017 **GL**; Kampman 2015 **GL**). Collaborative team care is essential.

9.8.8.1 | Methadone

Methadone maintenance is regarded as the gold standard for antenatal OST (ACOG 2012 **GL**). Pregnant patients taking methadone as part of a drug-dependence treatment program should receive whatever dose is needed to prevent heroin use, and the dose may need to be increased in the third trimester because the physiological changes associated with pregnancy can alter drug pharmacokinetics (Jones 2012a **NR**; Ludlow 2007 **NR**).

9.8.8.2 | Buprenorphine

The largest study of OST in pregnancy, the Maternal Opioid Treatment Human Experimental Research (MOTHER) study compared methadone and buprenorphine and showed similar maternal outcomes (Jones 2012b **NR**, summarising results of 1 RCT: Jones 2012a **Level II**, n=175). Buprenorphine resulted in less foetal cardiac and movement suppression, lower rates of preterm labour, less severe NAS (a treatable condition), but lower maternal satisfaction and lower treatment retention rates, vs methadone maintenance (Bandstra 2012 **NR**, secondary analysis of 1 RCT: Jones 2012a **Level II**, n=175). When compared with methadone maintenance, buprenorphine maintenance may lead to better neonatal outcomes, but this might be due to systemic bias in studies (Brogly 2014 **Level III-2 SR** [PRISMA], 4 RCTs & 8 studies, n=1,380 [includes Jones 2012a]).

9.8.8.3 | Naltrexone

Although not recommended in professional guidelines, there is emerging evidence that neonatal outcomes may be no worse for those treated with implanted naltrexone when compare with

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OST (Kelty 2017 **Level III-2**, n=775). Issues with naltrexone include that its induction requires an opioid-free period after detoxification and it is also more challenging for peripartum pain relief (Tran 2017 **NR**).

In the absence of specific evidence, management of pain in the peripartum period should be extrapolated from the non-pregnant patient with reliance on non-opioids including regional blocks.

9.8.8.4 | Peripartum management

Methadone maintenance should be continued without interruption in the peripartum period; if for some reason the women is unable to take it orally, it can be given subcutaneously. As with any opioid-tolerant patient, additional opioids will be required for pain relief and the newborn will require high-level neonatal care because of the risk of NAS (Jones 2012a **NR**; Jones 2008 **NR**; Ludlow 2007 **NR**). Pain scores after Caesarean section are also higher (Meyer 2010 **Level III-3**).

Buprenorphine maintenance should be continued without interruption as it does not interfere with pain control after vaginal delivery or Caesarean section (Vilkins 2017 **Level III-2**, n=273; Hoyt 2018 **Level IV**, n=14; Leighton 2017 **Level IV**, n=4). These women will also have higher opioid requirements after surgery and the newborn is still at risk (albeit maybe a lower risk) of NAS (Jones 2012a **NR**; Jones 2010 **NR**; Ludlow 2007 **NR**).

Delivery should occur at a tertiary centre and needs clear criteria for opioid use, neonatologist involvement pre-delivery and consent during pregnancy regarding NAS (Pritham 2014 **NR**). Opioid requirements during labour were not significantly increased, although methadone- and buprenorphine-maintained patients had higher pain scores and higher opioid requirements postpartum than did controls (Meyer 2010 **Level III-3**). In another study, opioid-maintained patients required epidural analgesia more often than controls (38.1 vs 14.3%) but had no higher opioid requirements after Caesarean section (Hoflich 2012 **Level III-2**).

Opioid requirements and the risk of withdrawal, for the patient and the newborn, will be higher in patients still using heroin prior to childbirth (Ludlow 2007 **NR**). In all patients with opioid addiction, naloxone is not recommended except in situations of life-threatening overdose (Kampman 2015 **GL**).

Opioid requirements in those addicted to non-opioid substances should be similar to non-pregnant patients.

For further information on maternal and neonatal outcomes see Section 9.1.

KEY MESSAGE

1. Benzodiazepines are effective for alcohol-withdrawal symptoms, in particular reducing seizures (**U**) (**Level I** [Cochrane Review]).
2. Opioid substitution therapy with methadone or buprenorphine is better than clonidine and lofexidine in ameliorating withdrawal symptoms (**N**) (**Level I** [Cochrane Review]).
3. Methadone and buprenorphine maintenance regimens should be continued throughout acute pain episodes wherever possible (**S**) (**Level III-2 SR** [PRISMA]).
4. Poorly managed acute pain episodes may decrease retention in opioid-maintenance programs (**U**) (**Level III-2**).
5. To achieve better analgesic efficacy, daily methadone maintenance doses should be divided and given 8 to 12 hourly (**S**) (**Level IV SR** [PRISMA]).

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

- ☑ Pain management in patients with substance use disorder often presents significant challenges for both clinicians and patients. Patients fear being stigmatised or discriminated against, are concerned about inadequate pain relief with their past experiences leading to physician distrust; they fear experiencing withdrawal (before their usual drugs are prescribed) and relapse precipitated by acute opioid exposure. The challenges for the clinician Include mistrust, concerns about drug seeking, fear of overtreatment with adverse events, concerns about diversion, and risk of discharge against medical advice (**N**).
- ☑ A "universal precautions" approach is increasingly recommended for patients with substance use disorder in acute pain settings; it may include use of multimodal analgesia, abuse-deterrent formulations, urine drug screening, use of prescription drug monitoring programs and risk management strategies (**N**).
- ☑ An acute admission offers opportunity to engage with patients with substance use disorder as well as to treat the acute issues (**N**).
- ☑ There is no cross-tolerance between alcohol or benzodiazepines or central nervous system stimulants and opioids (**U**).
- ☑ Oral naltrexone should be stopped at least 24 hours, ideally 72 hours, prior to elective surgery (**U**); naltrexone implants may need surgical removal in cases of severe acute pain where opioid responsiveness is required (**U**).
- ☑ Patients who have ceased naltrexone therapy should be regarded as opioid naïve; in the immediate post-treatment phase they may be more opioid sensitive (**U**).
- ☑ To achieve better analgesic efficacy, daily buprenorphine maintenance doses could be divided and given 8 to 12 hourly (**U**).
- ☑ Nicotine has a small to medium analgesic effect in volunteers and smoking abstinence increased self-reported pain (**N**).

FOR C

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