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Drabinski T *et al.* 2020 (evidence-based health economic model)<sup>1</sup>



Trentino KM *et al.* 2020 (retrospective cohort study)<sup>2</sup>



Wan S *et al.* 2020 (retrospective cohort study)<sup>3</sup>



Kaserer A *et al.* 2019 (retrospective cohort study)<sup>4</sup>

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ECDC, European Centre for Disease Prevention and Control; PBM, patient blood management; RBC, red blood cell; WHO, World Health Organization. **References:** 1. Drabinski T *et al.* *Adv Ther.* 2020;37:3515-36. 2. Trentino KM *et al.* *Anaesthesia.* 2021;76(3):357-65. 3. Wan S *et al.* *J Arthroplasty.* 2020;35:3084-88. 4. Kaserer A *et al.* *Anaesthesia.* 2019;74(12):1534-41. 5. Shander A *et al.* *Anesth Analg.* 2020;131(1):75-85. 6. WHO interim guidance: Maintaining a safe and adequate blood supply during the pandemic outbreak of coronavirus disease (COVID-19), March 2020. 7. ECDC rapid risk assessment: Novel coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK - sixth update, March 2020. 8. Leahy MF *et al.* *Transfusion.* 2017;57(6):1347-58. 9. Keding V *et al.* *World J Surg Oncol.* 2018;16:159. 10. Khalafallah AA *et al.* *Lancet Haematol.* 2016;3(9):e415-25. 11. Deppe AC *et al.* *J Surg Res.* 2016;203(2):424-33. 12. Althoff FC *et al.* *Ann Surg.* 2019;269(5):794-804. 13. Gani F *et al.* *Ann Surg.* 2019;269(6):1073-79. 14. Spahn DR *et al.* *Lancet.* 2019;393(10187):2201-12. 15. Froessler B *et al.* *Ann Surg.* 2016;264(1):41-6. HQ-FCM-2100014 February 2021

## Guidelines

# An international multidisciplinary consensus statement on the prevention of opioid-related harm in adult surgical patients

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## Summary

This international multidisciplinary consensus statement was developed to provide balanced guidance on the safe peri-operative use of opioids in adults. An international panel of healthcare professionals evaluated the literature relating to postoperative opioid-related harm, including persistent postoperative opioid use; opioid-induced ventilatory impairment; non-medical opioid use; opioid diversion and dependence; and driving under the influence of prescription opioids. Recommended strategies to reduce harm include pre-operative assessment of the risk of persistent postoperative opioid use; use of an assessment of patient function rather

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than unidimensional pain scores alone to guide adequacy of analgesia; avoidance of long-acting (modified-release and transdermal patches) opioid formulations and combination analgesics; limiting the number of tablets prescribed at discharge; providing deprescribing advice; avoidance of automatic prescription refills; safe disposal of unused medicines; reducing the risk of opioid diversion; and better education of healthcare professionals, patients and carers. This consensus statement provides a framework for better prescribing practices that could help reduce the risk of postoperative opioid-related harm in adults.

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## Recommendations for best clinical practice

- 1 All patients undergoing surgery should be assumed to be at risk of developing persistent postoperative opioid use and opioid-induced ventilatory impairment and may need interventions to mitigate those risks.
- 2 Consider optimising management of pre-operative pain and psychological risk-factors before surgery, including weaning of opioids where possible. Ensure realistic expectations of postoperative pain control, both in hospital and after discharge.
- 3 Provision of opioid analgesia should be guided by functional outcomes, rather than unidimensional pain scores alone.
- 4 Multimodal analgesia should be optimised and patients educated about the use of non-pharmacological and non-opioid analgesia to reduce the amount and duration of opioids required to restore function.
- 5 Long-acting opioids should not be used routinely for acute postoperative pain.
- 6 A patient-centred approach should be used to limit the number of tablets and the duration of usual discharge opioid prescriptions, typically to less than a week.
- 7 Automated post-discharge repeat prescriptions for opioids should be avoided. Perform a patient review if more opioids are requested.
- 8 Hospitals should have strategies to mitigate the occurrence of opioid-induced ventilatory impairment. Specifically, all inpatients receiving postoperative

opioids must have their level of sedation assessed at appropriate and repeated intervals.

- 9 Modifiable factors that have been identified as increasing the risk of opioid-induced ventilatory impairment and persistent postoperative opioid use should be addressed. These factors include medicines with sedative properties; long-acting opioids; and reliance on unidimensional pain scores alone to guide prescribing and titration.
- 10 Patients should be advised on safe storage and disposal of unused opioids and directed to avoid opioid diversion to other individuals (e.g. sharing with friends and family).

## Why was this consensus statement developed?

Opioids are effective anti-nociceptive medicines that form an integral component of balanced multimodal analgesic strategies for the management of acute pain in postoperative patients [1, 2]. However, over the past decade it has been increasingly appreciated that, in efforts to improve pain relief after surgery, peri-operative prescribers have unwittingly contributed to persistent postoperative opioid use in some patients [3]. The economic and social repercussions of the opioid crisis are well documented in the USA [4], but it is now a phenomenon across many countries [5]. One study has shown that although 91% of patients in the USA were prescribed opioids postoperatively, only 5% of patients in seven other countries received such prescriptions [6]. However, comprehensive

global data are not available and it is conceivable that postoperative opioid usage in other countries may increase if left unchecked [7]. In addition to the social and economic costs of opioid misuse, there are personal costs, with many people dying from opioid overdose [8, 9]. These opioid-related deaths are predominantly a result of opioid-induced ventilatory impairment [4].

Over the past two decades, guidelines for the management of postoperative pain initially promoted the unrestricted titration of opioids to unidimensional pain scores, often as part of the now-discredited 'Pain as the 5th Vital Sign' campaign [10–13]. With rising concern that peri-operative opioid use may accidentally contribute to harm from persistent postoperative opioid use; opioid-induced ventilatory impairment; opioid misuse and diversion; and driving under the influence of prescription opioids, there is increasing enthusiasm for opioid-free anaesthesia and analgesia [1, 14, 15]. Currently, opioid-free techniques are poorly defined, with limited evidence to support the adjuvants recommended [16]; thus opioids will continue to be an important element of pain management in many postoperative patients. It is, therefore, necessary to focus on opioid stewardship and the multiple components of the healthcare system needed to deliver these medicines safely, rather than relying solely on opioid-free techniques [4].

This international multidisciplinary consensus statement was developed to provide balanced guidance on the safe peri-operative use of opioids, facilitating optimal functional recovery and reducing the risk of opioid-related harm in adult surgical patients. While intra-operative strategies are important, they are complex and heterogeneous, and beyond the scope of this document.

### **How does this consensus guideline differ from other available statements?**

This consensus statement discusses the judicious and safe use of peri-operative opioids from the moment of contemplation of surgery until full recovery with analgesic medicines weaned safely and deprescribed. In addition, it proposes strategies that should be implemented by individual clinicians as well as multidisciplinary teams to promote recovery through the use of multimodal opioid-inclusive analgesia, while simultaneously discussing those aiming to reduce the risk of harm from persistent postoperative opioid use. The topics of non-medical opioid use and opioid diversion and dependence, including in friends and family [17], are also covered. Furthermore, unlike other guidelines, strategies required to reduce the other significant, albeit less commonly discussed, harm associated with peri-operative opioid use, namely opioid-

induced ventilatory impairment – both in hospital and after discharge [18] – are included, as well as the need to consider the risks associated with driving under the influence of prescription opioids [19, 20].

This guidance should assist healthcare professionals and hospitals across the world to implement effective opioid stewardship practices that achieve a balance between the administration of sufficient opioid analgesia to facilitate recovery and restoration of function, while concurrently minimising the risk of opioid-related harms.

### **Methods**

This is an international multi-disciplinary consensus statement. Authors were selected based on clinical or academic expertise, and included anaesthetists, pain specialists, surgeons, a primary care physician, nurse and pharmacist from Australia, India, Italy, the Netherlands, the UK and the USA. Attempts to include authors from several other countries, regions and subspecialties were unsuccessful, but the authorship provides a broad reach of peri-operative clinicians over four continents. Evidence to formulate recommendations was identified by performing a directed literature review of data relevant to persistent postoperative opioid use; opioid-induced ventilatory impairment; non-medical opioid use; diversion and dependence; and driving under the influence of prescription opioids. Observational and interventional studies, as well as systematic reviews related to the topics of interest, were sought. Although a formal systematic review was not conducted, analysis and interpretation of the relevant studies was performed. Recommendations were made based on best evidence or, in the absence of such, on expert opinion, although no grading of the evidence was made. All recommendations were then included in a three-round Delphi process [21]. The first round involved the development of a long list by the authors. In the second round, all authors voted to include or remove each recommendation. Comments regarding content and clarity were also made. Recommendations that had  $\geq 50\%$  consensus for inclusion proceeded to the third round and were revised to address the comments. Following the third round, those recommendations with  $\geq 75\%$  consensus were chosen. Finally, these 10 recommendations for best clinical practice were ratified and included in the guidelines.

### **Persistent postoperative opioid use**

The search for a reliable definition of persistent postoperative opioid use has provided enough inconsistency to fuel two recent systematic reviews [22,

23]. For the purposes of this document, persistent postoperative opioid use is defined as patients taking any opioids prescribed for postoperative pain for longer than 90 days after surgery. This aligns with the International Classification of Diseases 11th Revision (ICD-11) definition of chronic postsurgical pain as pain that persists beyond 3 months after surgery, that is, past normal healing time [24]. Studies, mainly undertaken in North America, have demonstrated that 0.1–26% of opioid-naïve patients, and 35–77% of patients with previous opioid exposure continue to take opioids for more than 3 months

postoperatively when healing is complete and acute pain would have ceased [23].

















There are many political, economic, commercial and societal drivers associated with prescribed opioid misuse [7, 25] (Fig. 1). An in-depth discussion of these factors is beyond the scope of this article.

## Reducing the risk: recommendations and rationale

As well as the presence of socio-economic factors influencing persistent postoperative opioid use, other



**Figure 1** Risk-factors for prescribed opioid misuse.

SETTING	MODIFIABLE RISK FACTORS	RECOMMENDATIONS OR RATIONALE
Pre-assessment clinic	 Pre-operative opioids	Patients taking long-term opioids are more likely to develop PPOU: wean or taper opioids before surgery
	 Psychological comorbidities	Psychological interventions may reduce pre-operative anxiety, depression and catastrophic thinking, thus decreasing postoperative pain and opioid requirements
	 Unrealistic expectations	Educate patients and carers about pain management, including non-pharmacological strategies and safe analgesic use
Postoperative period in hospital	 Reliance on unidimensional pain scores alone	Use functional outcomes to ensure that analgesic use leads to improved recovery
	 Abnormal pain trajectory	Patients whose pain is not following an expected trajectory should be identified early as this may signify postoperative complications, neuropathic pain or psychological distress
	 Reliance on opioid analgesia	Use multimodal analgesia and non-pharmacological techniques for pain relief
	 Long-acting opioids	Avoid initiating long-acting formulations; use short-acting opioids as needed only
	 Compound opioids	Do not prescribe compound tablets: give each drug separately
Preparation for discharge	 Over-emphasis on opioids for discharge medication	Educate patients and carers to use multimodal analgesia and non-pharmacological techniques for pain relief
	 Large number of opioid tablets	Limit the number of tablets given at discharge
	 Long duration of discharge opioid prescription	Limit the duration of opioids given at discharge
	 Lack of deprescribing advice	Educate patients and carers about reducing analgesia (opioids first)
Post-discharge	 Repeat prescriptions	The risk of PPOU increases considerably with each repeat prescription: review the patient before dispensing more opioids
	 Chronic postsurgical pain	Refer to a pain service if pain exceeds expected healing time
	 Unsafe storage of opioids at home	Unsecured opioids risk unintended overdose or diversion
	 Unsafe disposal of unused opioids	Educate patients and carers about safe disposal of unused opioids

**Figure 2** Modifiable risk-factors and suggested recommendations or rationale for persistent postoperative opioid use (PPOU).

factors are modifiable and can be attenuated to reduce harm (Fig. 2).

### Pre-operative factors

Even before the patient has surgery, some factors can be identified to enable interventions to mitigate harm from persistent postoperative opioid use.

#### Pre-operative opioid use

The strongest predictor of persistent postoperative opioid use is pre-existing chronic opioid use. The incidence of persistent postoperative opioid use can be up to 10 times higher in those taking opioids long-term before surgery than in opioid-naïve patients [23]. There appears to be a dose-dependent effect whereby higher doses increase the risk of persistent postoperative opioid use. In a study of patients undergoing hip or knee arthroplasty, an oral morphine equivalent dose of 60 mg.day<sup>-1</sup> or higher was associated with an 80% probability of persistent postoperative opioid use [26]. The reduction of opioids before surgery is likely to confer benefit both in the immediate and longer-term postoperative period [27], but rapid or forced tapers should be avoided [28, 29]. A pre-operative multidisciplinary team approach providing plans to taper opioid doses and improve patient pain, function

and psychological distress is possible and leads to decreases in pre-operative and postoperative pain, improvements in pre- and postoperative depression and anxiety, and better patient function [30, 31]. Referral to chronic pain management and/or addiction medicine services may be beneficial for some patients.

#### Pain and psychological disorders

The presence of pre-operative chronic pain is a significant risk-factor for persistent postoperative opioid use, as are affective disorders including anxiety, depression and catastrophic thinking [32]. Possibly as proxy measures, the pre-operative use of antidepressants or benzodiazepines has also been linked to higher rates of persistent postoperative opioid use [23, 32, 33]. Substance use disorders, including tobacco, alcohol and cocaine abuse, also increase the likelihood of persistent postoperative opioid use [32, 33].

In the early postoperative period, pre-operative anxiety, depression, catastrophising and emotional distress levels have also all been shown to correlate with higher pain intensity and opioid requirements [34, 35]. It is, therefore, recommended that pre-operative pain and psychological risk-factors should be optimised before surgery.

*Patient expectations*

Pre-operative patient education providing realistic expectations regarding pain after surgery, together with information around multimodal analgesia (incorporating non-pharmacological techniques as well as non-opioid analgesia) [36] and education about the risks and side-effects of opioids, can reduce postoperative opioid use and decrease the duration of opioids taken after discharge [37]. It is recommended that appropriate pre-operative education addressing expectations of pain management should be provided to all patients where, in order to restore function, some pain is to be expected.

*Inadequate patient assessment*

The predominance of patient factors (opioid use, chronic pain and psychological co-morbidities) as predictors of persistent postoperative opioid use allows early identification of vulnerable individuals. Scoring systems have been used for patients with chronic pain to predict who may be at risk of opioid use disorder [38]. Similar tools may prove useful in the pre-assessment setting to identify patients at risk, allowing targeted mitigation of modifiable factors, such as interventions to address negative psychology or coping strategies or weaning of pre-operative opioids. There is evidence that some scoring systems have good sensitivity and specificity for persistent postoperative opioid use [39, 40]. Other tools also exist, but their utility in the peri-operative setting is uncertain [41]. A review described the evidence for psychological interventions improving postoperative recovery or reducing persistent postoperative opioid use as weak [42], but this remains a novel area delivering promising results [30, 31].

Patients at increased risk of persistent postoperative opioid use should be identified at pre-operative assessment.

**Box 1: Functional Activity Scale**

- A** No limitation: the patient is able to undertake the activity without limitation due to pain;
- B** Mild limitation: the patient is able to undertake the activity, but experiences moderate to severe pain;
- C** Significant limitation: the patient is unable to complete the activity due to pain or pain treatment-related adverse effects.

*Assumption of low-risk procedures*

It has been suggested that certain types of surgical procedures are associated with a high risk of persistent postoperative opioid use [43] (and thus, by extension, some operations that may be low risk), but this has not been consistent across studies [23]. Patients undergoing minor surgery seem to be just as vulnerable to persistent postoperative opioid use as those undergoing major procedures [32, 33]. Consequently, all patients undergoing surgery should be assumed to be at risk of developing persistent postoperative opioid use and will need interventions to mitigate that risk.

**Postoperative factors**

In addition to modifying pre-operative factors, it is necessary to amend postoperative care to reduce the risk of persistent postoperative opioid use.

*Over-reliance on unidimensional pain scoring*

The use of unidimensional pain scores, such as the numerical pain scale, may provide unrealistic expectations to patients (i.e. that the goal is to reduce a pain score to zero) and has been found to drive postoperative opioid prescribing as clinicians aspire to chase that goal [12]. Functional outcomes are now preferred to complement pain scoring and guide pharmacological pain management [12, 44]. It is, therefore, recommended that provision of immediate-release opioid analgesia for both inpatients and after discharge should be guided by functional outcomes, rather than unidimensional pain scores alone [12, 45]. An example of a functional outcome tool that is gaining acceptance is the Functional Activity Scale [12, 46–48], as shown in Box 1.

In addition, relevant functional activity may be both procedure- and time-specific. Moreover, it must be remembered that some pain is not opioid-responsive but may lead to increasing yet ineffective opioid doses, with the associated risk of opioid-induced ventilatory impairment and, later, persistent postoperative opioid use. Patients whose pain is not following an expected trajectory should be identified early as this may signify postoperative complications, neuropathic pain or psychological distress.

*Over-reliance on opioid analgesia*

Multimodal analgesia reduces opioid use in the immediate postoperative period [49], so it is likely that it will continue to be opioid-sparing once patients are discharged from the hospital. The goal remains to provide postoperative pain relief with rapid restoration of

function, rather than eliminate opioids and risk compromising patient care [3]. Even before discharge, opioid weaning strategies should be in place so that, as a patient recovers, progressively lower doses of opioids are administered before being stopped [50, 51].

#### *Long-acting opioids and compound analgesic formulations*

Long-acting opioids (also known as sustained-, modified- or extended-release formulations, as well as transdermal opioid patches) are one of the three major modifiable risk-factors for persistent postoperative opioid use [52–54]; repeat prescriptions and excess tablets on discharge being the other two [54]. In addition, they show no benefit in postoperative pain management [55] and increase the risk of opioid-induced ventilatory impairment, so should not be used for the treatment of postoperative pain in hospital or on discharge [56, 57]. Combination analgesics, such as tablets containing paracetamol (acetaminophen) combined with opioids, are not advised for postoperative pain as the fixed doses do not allow titration to patient need, nor the flexibility required for weaning [58].

Consequently, opioids should only be given as immediate-release formulations for postoperative pain management, both in hospital and on discharge. This recommendation aligns with those promulgated by a number of regulatory, advisory and professional bodies [29, 57, 59–62].

#### **Discharge prescribing factors**

The time just before discharge provides further opportunities to mitigate the risk of harm from persistent postoperative opioid use.

#### *Over-reliance on opioids after hospital discharge*

Discharge opioid prescribing plays a crucial role in persistent postoperative opioid use and opioid diversion. Multimodal analgesia remains important after discharge to reduce the reliance on opioids. However, many patients receive a discharge prescription for opioids only [63], risking an undue emphasis on their importance and superiority over other analgesics. It should also be emphasised to patients that immediate-release opioids should only be used to promote functional recovery rather than eliminate pain [45]. There is no place for long-acting opioids on discharge.

It is, therefore, necessary that patients are educated about the use of non-pharmacological and non-opioid

analgesia to reduce the amount and duration of opioids required to restore function.

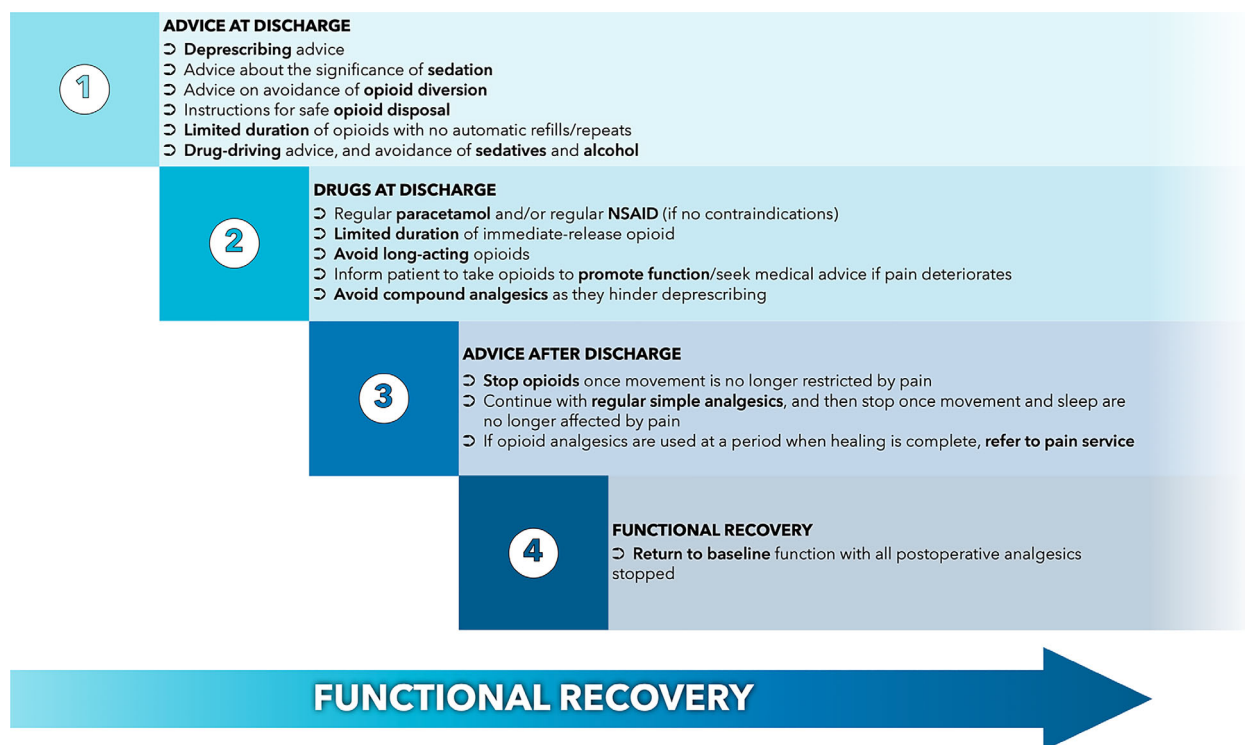
#### *Overprescribing of opioids on hospital discharge*

The number of opioid tablets prescribed at discharge often far exceeds the number used, with between 40% and 94% left untaken [64, 65]. This reservoir of unused opioids presents significant risks to the community. In the UK, oral morphine solution is commonly used for in-hospital analgesia: at low concentrations (10 mg in 5 ml), it is a schedule 5 controlled drug, requiring only one nurse to check and give it, allowing swift administration for rapid analgesia [66]. However, opioid solutions should not be used for discharge prescribing as the size of the bottles precludes safe monitoring or dose control, with a high likelihood of leftover medicine, and often unappreciated risk to the patient [67].

When dispensing discharge opioids, four factors need to be considered. The first is that the quantity of opioids dispensed at discharge directly impacts patient-reported opioid consumption after surgery [68], with patients given more tablets at discharge likely to take more opioids than those given a small number. This also increases the risk of persistent postoperative opioid use [69]. The second factor is the type of surgery [45, 70], modified by the third factor, a patient-centred approach, which takes into account the patient's opioid requirements the day before discharge [71, 72], and which should be used to limit both the duration and the number of opioid tablets in discharge opioid prescriptions. Finally, the duration of discharge opioid prescription should usually be limited to 3–5 days [73], but extended to 7 days in some circumstances [45]. As the patient recovers, their opioid requirements will decrease. The opioid dose must be weaned accordingly, so patients and carers must be educated on how to reduce and deprescribe their opioids (Fig. 3). Crucially, patients should be advised on how to store and dispose unused opioids safely and not to share opioids with friends or family.

#### *Inexperienced prescribers*

Commonly, it is the most junior hospital doctors who are tasked with prescribing discharge analgesia [55]. Stepwise interventions have been shown to be of benefit in improving the safety and appropriateness of their opioid prescribing, including targeted education; lowered prescription defaults on automated prescribing systems; and clinician dashboards to allow peer-to-peer comparison in adherence to protocols [55]. Junior hospital staff need support and



**Figure 3** Reverse pain ladder to promote postoperative analgesic deprescribing. NSAID, non-steroidal anti-inflammatory drugs.

teaching for appropriate and safe discharge opioid prescribing.

### Post-discharge factors

Once the patient has been discharged, there are necessary interventions to reduce the risk of persistent postoperative opioid use.

#### Repeat opioid prescriptions

As repeat and refill prescriptions of opioids are one of the major modifiable risk-factors for persistent postoperative opioid use [54], repeat prescriptions for opioids should be avoided. Each additional refill has been found to increase the risk of opioid misuse (encompassing diagnoses of opioid dependence; abuse; or overdose) by 40%, with each additional week of opioids taken raising the risk of misuse by 20% [69].

It must be communicated to primary care teams that a request for more opioids should initiate a patient review rather than an automated repeat prescription. If the patient is still requiring postoperative opioids beyond the normal healing period for that surgery, or they are taking opioids 90 days after surgery, they should be referred to pain

specialists for opioid weaning or assessment for chronic postsurgical pain.

#### Lack of safe storage and disposal

Up to 90% of patients fail to dispose excess opioids after surgery [74] and approximately 75% of patients report that their prescription opioids are not stored in locked containers [64], increasing the risk of accidental poisoning and drug diversion. Paediatric mortality from unintentional opioid overdose has increased three-fold in the last 20 years and has followed a similar temporal course to adult overdose deaths [75].

Patients and carers must be educated on the need to store opioids securely and dispose excess medicines safely to reduce the likelihood of patients keeping leftover opioids [76] and to reduce community harm.

### Opioid-induced ventilatory impairment

Opioid-induced ventilatory impairment can be defined as type-2 respiratory failure associated with opioid administration and high arterial partial pressures of carbon dioxide with or without hypoxaemia. It is caused by one or more of the following three factors:

- 1 Depression of the respiratory centre in the brainstem, leading to a reduction in alveolar ventilation (reduced respiratory rate and/or tidal volume).
- 2 Reduced oropharyngeal muscle tone, which can result in upper airway obstruction [77].
- 3 Depression of the hypothalamus leading to increased arousal thresholds and reduced wakefulness (sedation) [77].

These processes, alone or in combination, can lead to severe opioid-induced ventilatory impairment which, if unrecognised and untreated, may result in brain injury or death [78]. As depression of the respiratory centre is only one component of this triad, opioid-induced ventilatory impairment is a more appropriate term than opioid-induced respiratory depression [18].

As routine measurement of arterial partial pressures of carbon dioxide is not possible, investigators usually define opioid-induced ventilatory impairment using surrogate measures that include respiratory rate (often arbitrarily defined as  $< 8$  or  $10 \text{ breaths.min}^{-1}$ ); peripheral oxygen saturation; level of sedation; and rates of naloxone administration. Unfortunately, good evidence showing a reliable correlation between these measures and arterial partial pressures of carbon dioxide is lacking [18].

Thus, the reported incidence of postoperative opioid-induced ventilatory impairment is difficult to determine. Reported rates range from 0.04% to 41%, depending on the measure used [79].

## Detection of opioid-induced ventilatory impairment

Harm from opioid-induced ventilatory impairment is preventable in the majority of cases if detected and managed at an early stage [80]. Routine use of continuous pulse oximetry has been recommended [51]. However, hypoxaemia may be a very late sign of hypoventilation [77, 81], especially if the patient is receiving supplemental oxygen [77, 81–83]. In addition, reduced oxygen saturations may result from causes other than opioid-induced ventilatory impairment.

Continuous monitoring of carbon dioxide partial pressures, for example, using capnography, as a measure of ventilation has also been recommended in selected patients [51], but is commonly limited to higher-acuity settings. However, carbon dioxide partial pressures obtained using capnography may not always correlate well with arterial partial pressures of carbon dioxide [81].

The lack of reliability of respiratory rate as a measure of opioid-induced ventilatory impairment is also well recognised. In 1988, a small case series demonstrated that neither respiratory rate nor oxygen saturation correlated with arterial partial pressures of carbon dioxide, while sedation levels did [82]. Subsequently, the authors developed a five-point sedation scale to add to routine monitoring practices [84]. Since that time other variations of this sedation scoring system have been published [18].

The significance of sedation as a better clinical indicator of opioid-induced ventilatory impairment than respiratory rate was highlighted in a study in which immediate-release opioids were given 'as needed' to reduce pain scores to four or less after the introduction of the 'Pain as the 5th Vital Sign' policy [85]. As well as demonstrating that titration of opioids to unidimensional pain scores doubled the risk of opioid-induced ventilatory impairment, this study showed that reduced levels of consciousness were a more reliable marker of opioid-induced ventilatory impairment than reduced respiratory rates [85]. A closed-claims analysis of patients who developed severe postoperative opioid-induced ventilatory impairment further confirmed the importance of monitoring sedation levels [80].












## Fixed risk-factors for opioid-induced ventilatory impairment

Reported risk-factors for opioid-induced ventilatory impairment include older age; sleep-disordered breathing; obesity; renal impairment; respiratory, cardiac and neurological diseases; diabetes mellitus; tolerance to opioids; and genetic variations in opioid metabolism [51, 81, 83, 86]. The higher risk in opioid-tolerant patients likely relates to differential tolerance to opioids [87–89].

However, many patients who develop opioid-induced ventilatory impairment have no identifiable risk-factors [51, 78, 80]. Therefore, all patients given opioids postoperatively must be considered to be at risk [51, 83, 86, 90].

## Reducing the risk: recommendations and rationale

Modifiable risk-factors for opioid-induced ventilatory impairment that have been identified are summarised in Fig. 4 [51, 79, 80, 83, 86, 91–94]. Recommendations are based on the avoidance of these risk-factors.

SETTING	MODIFIABLE RISK FACTORS	RECOMMENDATIONS OR RATIONALE
Postoperative period in hospital	 Not modifying opioid dose according to age	Opioid sensitivity increases with age: use age-adjusted opioid doses initially
	 Continuous infusions or use of more than one opioid or formulation	Avoid where possible
	 Initiation of long-acting opioids	Use immediate-release opioids
	 Co-administration of sedatives	Avoid gabapentinoids and benzodiazepines where possible
	 Reliance on unidimensional pain scores alone	Titrate immediate-release opioids to functional outcomes
	 Inadequate monitoring and 'track and trigger' responses	Measure sedation scores in all patients and respond appropriately
	 Inadequate education of healthcare professionals	Education to recognise OIVI at an early stage and institute appropriate interventions
	 Using opioids for minimally or non-opioid-responsive pain	Some pain is not opioid-responsive and continuation of opioids may lead to OIVI
Preparation for hospital discharge and post-discharge	 Over-emphasis on opioids for discharge medication	Educate patients and carers about multimodal analgesia and non-pharmacological techniques for pain relief
	 Lack of deprescribing advice and risks of concurrent sedative use	Educate patients and carers about reducing opioids and avoiding sedatives and alcohol
	 Lack of recognition that increasing sedation is a marker of OIVI	Educate patients and carers to stop opioids if sleepy and seek medical advice if having difficulty staying awake. Call emergency services if unrousable

**Figure 4** Modifiable risk-factors and suggested recommendations or rationale for opioid-induced ventilatory impairment (OIVI).

### Age-adjusted opioid dosing

It is known that age is a better predictor of opioid requirements than patient weight, with requirements decreasing as age increases [18, 95]. This appears to be primarily a result of increased brain sensitivity to opioids rather than age-related changes in pharmacokinetics, which are usually not of the magnitude needed to account for the up to four-fold difference between younger and older patient groups [96]. Initial opioid doses should, therefore, be based on patient age and not weight, as older patients require lower doses to achieve analgesia and also to develop opioid-induced ventilatory impairment [18].

### Titration of opioid dose to patient function

As noted above, reliance on unidimensional pain scores alone to guide titration of opioids increases the risk of opioid-induced ventilatory impairment [85]. Measures of effectiveness of analgesia should not rely on these scores alone. The focus should change to an assessment of patient function [18, 44, 97].

### Avoidance of long-acting opioid formulations and sedatives

The slow onset times of modified-release oral and transdermal opioids make safe and rapid titration of opioids

(both upwards and downwards) impossible. The use of these formulations increases the risk of opioid-induced ventilatory impairment [90] and they are not recommended for the management of postoperative pain [57, 86, 91, 98].

Concurrent use of opioids and other sedating medicines (including benzodiazepines and gabapentinoids) increases the risk of opioid-induced ventilatory impairment [18, 51, 79, 80, 92, 99]. Thus, regulatory agencies recommend caution when combinations of gabapentinoids and opioids are used [93, 94].

### Opioid-sparing or opioid-free techniques

Opioid-sparing or opioid-free techniques are sometimes recommended to minimise or avoid the need for postoperative opioids. Currently, there is no good evidence to show that such regimens reduce the risk of opioid-induced ventilatory impairment.

### Non-opioid-responsive pain

A less recognised risk is the use of opioids in patients with non-opioid-responsive pain [90]. If the patient's pain does not seem to be responding to escalating doses of opioids, and especially if the patient is becoming sedated, non-opioid-responsive pain must be considered and alternative analgesic options employed. Continued

**Table 1** Comparison of three commonly used sedation scores.

Sedation scores [84]	Pasero opioid-induced sedation scale [100]	Sedation score recommended by ANZCA [90]
0 (none) – alert	S – Sleep, easily aroused	0 – Wide awake
1 (mild) – occasionally drowsy, easy to arouse	1 – Awake and alert	1 – Easy to rouse (and can stay awake)
2 (moderate) – frequently drowsy, easy to arouse	2 – Occasionally drowsy	2 – Easy to rouse but unable to remain awake
3 (severe) – somnolent, difficult to arouse	3 – Frequently drowsy, arousable, drifts off to sleep during conversation	3 – Difficult to rouse
S (sleeping) – normal sleep, easy to arouse	4 – Somnolent, minimal or no response to stimulation	A score of 2 is taken to indicate early OVI and, therefore, the aim should be to titrate an opioid so that a patient's sedation score is always less than 2
	This scale was subsequently updated, and each score is now accompanied by instructions outlining the appropriate actions to be taken [51, 86]	

Reproduced from Bowen et al. [18], with permission.

OVI, opioid-induced ventilatory impairment; ANZCA, Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine.

use of opioids can lead to opioid-induced ventilatory impairment.

### Use of sedation scores

As sedation is currently the most reliable clinical marker of opioid-induced ventilatory impairment, all patients given an opioid for management of their acute pain must have their level of sedation assessed at appropriate and repeated intervals to allow detection and treatment of opioid-induced ventilatory impairment [18, 51, 83]. Examples of sedation scores are summarised in Table 1 [84, 90, 100]. It is recommended that a sedation scoring system containing 'S' is not used as the patient may not be woken properly to have their level of sedation assessed more accurately. They may wake easily, but then either stay awake or have difficulty staying awake [18, 90]. If the latter is the case, the opportunity to recognise and treat opioid-induced ventilatory impairment before significant patient harm has occurred may be lost.

### Standard orders

Standard orders, often used with techniques such as patient-controlled, epidural or regional analgesia, aim to maximise analgesia as well as patient safety. Hospitals should have standardised order sets automatically linking all opioid prescribing and monitoring. At a minimum, these must include instructions outlining appropriate actions to be taken if over-sedation occurs [18, 83, 90].

### Institutional factors

Education is a necessary component of good opioid stewardship but may not by itself reduce the risk of

postoperative opioid-induced ventilatory impairment [101]. However, implementation of a 'solutions bundle' which includes the introduction of all of the aforementioned recommendations has been demonstrated to be effective in reducing the incidence of opioid-induced ventilatory impairment [86].

### Post-discharge factors

Information on the risk of opioid-induced ventilatory impairment after surgical discharge is limited. While uncommon, it is more likely to occur within the first 30 days after discharge and with higher opioid doses [102, 103]. It is, therefore, sensible to apply many of the strategies summarised in Fig. 2.

Patients and carers must know about the risks, signs and management of opioid-induced ventilatory impairment; that they must avoid concurrent use of medicines with sedative effects and alcohol while taking opioids; and when to call for emergency assistance.

## Non-medical use of opioids and opioid diversion

Non-medical opioid use is use without a prescription or use for reasons other than that for which the opioid was prescribed. Opioid diversion is the transfer by any means of a legitimately prescribed opioid(s) to a party other than the individual for whom it was originally prescribed [17].

Diversion is an important source of opioids, with addiction surveys finding that around 50% of adults who misuse opioids obtain them from friends and family [104, 105]. Furthermore, 55% of adolescents and young adults who have developed opioid addiction obtained their opioids through similar sources [106].

The causes of opioid diversion are multifactorial but include overprescribing of discharge opioids and creating a pool of opioids in the community that can then be diverted [107, 108]; unsecured storage of opioids; and inadequate safe disposal of unused opioids [74].

As unused opioids are a reservoir for opioid diversion, prescribers should limit the amount of discharge opioids prescribed [109]. Patients should be informed to safely dispose unused opioids and not to share opioids with friends or family. Education on the need to store opioids securely and dispose excess medicines safely decreases the likelihood of patients keeping leftover opioids [76, 110] and reduces the amount of opioids available for community harm.

## Driving under the influence of prescription opioids

Prescribed opioids impair driving skills and cognitive reasoning in a similar manner to alcohol. Driving under the influence of drugs, including prescribed opioids, is now recognised to be a major cause of motor vehicle collisions and subsequent fatalities [19, 20, 111], particularly if the person commenced the opioid within the previous 30 days [112].

In response to the increasing public health and traffic safety concerns of drug-driving, many countries have now introduced legislation to either make drug-driving illegal or to prosecute drivers whose driving is impaired and are found to have blood drug levels of certain prescribed medicines, including opioids, that exceed predefined thresholds [113].

Consequently, patients should be advised of the dangers and the legal implications of driving while taking opioids prescribed for postoperative pain and that they should not drive until they have stopped the opioids.

## Opioid stewardship

Opioid stewardship has been described as co-ordinated interventions designed to improve, monitor, and evaluate the use of opioids in order to support and protect human health [114]. Opioids remain a core component of peri-operative multimodal analgesia to promote optimal functional recovery in many surgical patients. Effective opioid stewardship is important to minimise the risk of opioid-related harm.

## Implementing opioid stewardship

It has been suggested that opioid stewardship is composed of six components: recognising the risk of opioid-related harms; educating patients (and healthcare providers); creating realistic patient expectations; the use of multimodal analgesia; controlled prescribing; and early

referral to pain specialists [115]. However, for safe and effective opioid stewardship a full package of interventions needs implementation and, while individual practitioners play a role, a transformation of services needs to happen at local and national levels (Table 2). While these include increasing the knowledge of healthcare professionals, patients and their carers, education should only be one component of an institution's strategy to improve opioid-related safety [116]. Education alone has been found to be one of the least effective interventions in the hierarchy of medicine safety risk-reduction strategies. It, therefore, needs to be supplemented by more effective but harder to implement system-focused strategies such as the use of forcing functions; barriers and fail-safes; automation; standardisation; and protocols, together with warnings; alerts; checklists; and reminders [116].

## Research and quality improvement

Currently, most of the research in opioid stewardship and opioid-related adverse drug events originates from the USA. However, use and misuse of prescribed opioids is not restricted to the USA. Therefore, more country-specific research is needed to address national and cultural issues around persistent postoperative opioid use and opioid-induced ventilatory impairment, with further research to define the optimal strategies required to implement safe opioid stewardship practices.

## Limitations

Many of the recommendations in this guideline are supported by a limited evidence base and are dependent on expert opinion. The limited evidence and heterogeneity of the nature of the questions asked precluded a systematic review and objective grading of recommendations. A further limitation of this guideline was the inability to include authors from more countries and additional subspecialties. The scope of this guideline did not extend to short-term side-effects of opioids such as constipation, confusion, itching, nausea and vomiting. Nevertheless, this guideline should inform future research and help strengthen the evidence base.

## Conclusion

While the peri-operative use of opioids has the capacity to promote recovery after life-saving or life-enhancing surgery, their use can be associated with harm from persistent postoperative opioid use; opioid-induced ventilatory impairment; opioid diversion; and driving under the influence of prescription opioids. Institutional opioid stewardship is required to minimise the risk of opioid-related harm. This will

**Table 2** Strategies to promote opioid stewardship within hospitals and the community.

Domain	Modifiable risk	Recommendation
Knowledge	Insufficient understanding of the importance of opioid stewardship among healthcare professionals	<ul style="list-style-type: none"> <li>Opioid stewardship should be embedded in the undergraduate, postgraduate and in-hospital curricula of healthcare professionals</li> <li>Staff need formal support and teaching for safe administration of opioids</li> </ul>
	Insufficient understanding of opioid stewardship in patients and carers	<ul style="list-style-type: none"> <li>The peri-operative team should provide education to patients and carers regarding expectations of pain and opioid stewardship</li> <li>Clearly written patient information about the safe use of opioids should be available as leaflets or on websites</li> <li>Patients and carers should be advised about the dangers and the legal implications of driving while taking opioids for postoperative pain</li> </ul>
Policies and guidelines	Lack of institutional guidance on prevention and management of PPOU and OIVI	<ul style="list-style-type: none"> <li>Multidisciplinary involvement of anaesthetists, surgeons, pain specialists, pharmacists, nursing staff, physiotherapists, primary care clinicians, hospital management, patients and carers is necessary to translate the recommendations from this consensus statement to local practice</li> <li>Hospitals should have strategies to mitigate the occurrence of OIVI and standardised order sets automatically linking prescribing, monitoring and interventions</li> </ul>
	Pharmaceutical companies influencing guidelines	<ul style="list-style-type: none"> <li>There should be clear separation between opioid manufacturers and the formulation of prescription practice guidelines</li> </ul>
	Adherence to the 'Pain is the 5th Vital Sign' recommendations	<ul style="list-style-type: none"> <li>Opioid analgesia provision should be guided by functional outcomes, rather than unidimensional pain scores alone</li> </ul>
	Inadequate safe opioid disposal	<ul style="list-style-type: none"> <li>Patients and carers should be advised on safe storage and disposal of unused opioids, and directed to avoid opioid diversion (e.g. sharing with friends and family)</li> </ul>
Research and audit	Inadequate recognition and management of patients developing PPOU	<ul style="list-style-type: none"> <li>Refer surgical patients to pain specialists if still taking postoperative opioids beyond the normal healing period for that surgery and certainly if still taking opioids 90 days after surgery</li> </ul>
	Lack of acknowledgement of regional and national differences in opioid prescribing	<ul style="list-style-type: none"> <li>More country-specific research is needed to address national and cultural issues around PPOU and OIVI</li> </ul>
	Insufficient knowledge of optimal methods of implementing opioid stewardship	<ul style="list-style-type: none"> <li>Research should be undertaken into the optimal strategies required to implement safe opioid stewardship practices</li> </ul>
	Insufficient appreciation of the prevalence of PPOU and incidence of OIVI	<ul style="list-style-type: none"> <li>Opioid-related serious adverse events should be routinely audited and investigated</li> </ul>

PPOU, persistent postoperative opioid use; OIVI, opioid-induced ventilatory impairment.

require the multidisciplinary involvement of anaesthetists; surgeons; pain specialists; pharmacists; nursing staff; physiotherapists; primary care clinicians; hospital management; and patients to adopt the recommendations from this consensus statement to local practice.

In addition to local changes, there is the requirement to ensure that all healthcare professionals are aware of the risks and benefits of peri-operative opioid use and can apply and discuss these with their patients. Therefore, the principles of safe opioid stewardship should be embedded in the undergraduate, postgraduate and in-hospital

curricula of all healthcare professionals. Furthermore, all opioid-related serious adverse events should be audited and investigated to facilitate learning and reflection to prevent re-occurrence. With the implementation of these strategies the accidental risk of iatrogenic harm from the use of peri-operative opioid use in adults could be minimised.

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