

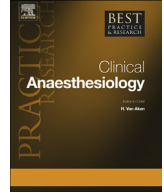


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Procedure-Specific Pain Management (PROSPECT) – An update



Brian Lee, Dr ^a, Stephan A. Schug, Professor ^{a, b, *},
Girish P. Joshi, Professor ^c, Henrik Kehlet, Professor ^d, on behalf
of the PROSPECT Working Group, Helene Beloeil,
Francis Bonnet, Patricia Lavand'Homme, Philipp Lirk,
Esther Pogatzki-Zahn, Johan Raeder, Narinder Rawal,
Marc van der Velde

^a Department of Anaesthesia and Pain Medicine, Royal Perth Hospital, Perth, Australia

^b Anaesthesiology and Pain Medicine, Medical School, University of Western Australia, Perth, Australia

^c University of Texas Southwestern Medical School, Dallas, TX, USA

^d Section for Surgical Pathophysiology, Rigshospitalet, Copenhagen University, Copenhagen, Denmark

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Post-operative pain management protocols may be optimised by examining procedure-specific evidence and outcomes. This recognition led to the formation of the PROcedure-SPECific Pain Management (PROSPECT) collaboration of anaesthesiologists and surgeons. The aim of PROSPECT is to provide practical and evidence-based recommendations to prevent and treat post-operative pain after specific surgical procedures, thereby overcoming the limitations of generic, non-specific guidelines. Updates in the methodology of PROSPECT in 2017 have placed an increased emphasis on the clinical relevance of studies, including a focus on interventions in the context of multimodal analgesia strategies and consideration of risks and benefits of interventions in specific surgical settings. Evidence-based reviews of analgesic measures, including advice on surgical techniques and adjuvants after diverse surgical procedures, have been completed by the PROSPECT collaboration and are accessible on the website (www.postoppain.org) and published in the peer-reviewed literature. These reviews continue to identify significant gaps in clinically relevant research

* Corresponding author. UWA Anaesthesiology, Royal Perth Hospital, Level 2 MRF Building, GPO Box X2213, Perth, WA, 6847, Australia. Fax: +61 8 9224 0279.

E-mail address: stephan.schug@uwa.edu.au (S.A. Schug).

on post-operative analgesia and are possibly leading to a closing of some of these gaps.

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Introduction

With the widespread adoption of multidisciplinary fast-track surgery pathways, also known as Enhanced Recovery After Surgery (ERAS), and the perioperative care required for these pathways, adequate post-operative analgesia is more important than ever to ensure expedient and optimal recovery and good outcomes with regard to patient function and complications [1]. This view is supported by more recent data, which show that poor pain relief and the experience of 'unacceptable' pain, even on the first post-operative day, are associated with more post-operative complications [2]. Furthermore, sub-optimal treatment of acute pain may increase the risk of development of chronic post-surgical pain, although this aspect is still debated [3,4]. Despite this knowledge, post-operative pain continues to be managed poorly as shown in many more recent studies, e.g. from the USA [5] and Europe [6]. One reason for these poor outcomes may be a lack of reliable and clinically relevant information to guide clinicians in the specific post-operative settings.

The PROCEDURE-SPECIFIC Pain Management (PROSPECT) collaboration was formed as a collaboration of anaesthesiologists and surgeons to fill the gap in the current pool of knowledge regarding pain management options and recommendations for specific surgical procedures [7]. In this review, we will describe the rationale for the inception of PROSPECT and its historical development, discuss the recent change in its methodology used to evaluate evidence, and examine some of the newest reviews published by the group as well as propose some future directions.

The rationale for procedure-specific guidelines

Currently available evidence-based guidelines for post-operative pain management, such as those published by the American Pain Society (APS), the American Society of Regional Anaesthesia and Pain Medicine (ASRA) and the American Society of Anaesthesiologists (ASA) [8] and those by the Australian New Zealand College of Anaesthetists (ANZCA) and its Faculty of Pain Medicine (FPMANZCA) [9] provide an excellent overview of the evidence underlying acute pain management strategies and the available analgesic options. However, in many specific situations, these strategies are (and have to be) too broad and generalised in their approach and therefore have failed to address the medical community's need for advice that is tailored and relevant to particular surgical procedures [1,10]. These issues have likely contributed to the poor quality of post-operative pain management discussed in the introduction; the current wide variation in analgesic regimens for even some of the most common surgical procedures; and in particular, the poor utilisation of regional anaesthesia techniques despite strong supportive evidence [11]. This may also be reflected in the ongoing over-reliance on opioids in the post-operative period despite evidence for their dose-dependent adverse effects [12,13], their detrimental effects on recovery and even hospital costs [14,15] and the relevant contribution of post-operative opioid use, in particular when poorly managed upon discharge [16–18], to the 'opioid epidemic' in some Western countries (e.g. Canada, USA and Australia) [19]. The potential of opioids influencing endocrine function and causing immune suppression, which is well documented with long-term use, is a further concern, but currently not resolved for short-term use in the acute setting [20].

Similarly, the commonly used number-needed-to-treat (NNT) analgesic league tables, while a useful tool to compare the efficacy of various analgesics (e.g. [21]), are derived from multiple surgical procedures and single dose administration and thereby far removed from provision of routine clinical analgesia. They fail to consider the efficacy of each compound with repeat administration in the context of a multimodal approach and on different pain characteristics (pain intensity, site, type and duration) associated with individual procedures [22].

The benefit of these league tables is further limited by their dichotomous concept of the NNT being calculated on the basis of 50% pain relief compared to that offered by placebo; this approach does not consider the gradual effect of an analgesic (i.e. 30% pain relief would not be considered but may be clinically meaningful) and whether 50% reduction may actually correspond to a clinically relevant response [23]. In addition, the NNT calculations are primarily based on effects in minor surgical procedures such as wisdom tooth extraction and bunionectomy, and these results might not be transferable to major surgical procedures [22]. These shortcomings further reinforce a need for guidance on a procedure-specific approach that is relevant to clinical practice. The debate on this issue continues as shown in a recent discussion in the literature [24,25]; the approaches taken by league tables and procedure-specific guidelines are not mutually exclusive but can complement each other depending on the setting and questions asked.

Other arguments in favour of a procedure-specific approach stem from the different levels of importance of pain relief for post-operative outcome in specific procedures [1] and the different consequences of inadequate analgesia in specific procedures, such as pulmonary dysfunction after a thoracotomy or in particular upper abdominal laparotomy [23]. These effects would not necessarily be expected in other procedures despite the patient possibly having a similar intensity of post-operative pain. In light of such considerations, an invasive analgesic modality such as thoracic epidural analgesia would possibly be appropriate for certain major surgeries despite the potential risks, but less invasive approaches such as laparoscopic surgery may not warrant the added risk of neuraxial or regional analgesia [26]. Another example would be operations with a particularly high risk of chronic post-surgical pain, such as surgery for breast cancer, where consideration for preventive analgesia and regional blockade would be appropriate to reduce the risk of transition from acute to chronic pain [27]. Last, but not the least, certain techniques of local and regional anaesthesia are completely procedure specific, such as an adductor canal block works specifically for knee arthroplasty [28], but cannot play a role in hip arthroplasty for obvious anatomical reasons.

Similarly, adverse effects of particular analgesics or consequences of particular procedures may be more relevant in certain procedures; examples include the bleeding risk associated with NSAIDs in craniotomy [29] as well as anticoagulation complicating the use of neuraxial analgesia in major cardiovascular surgeries [30]. Careful consideration would be required in these situations considering the individual risk and benefit of each approach, and these considerations have to be procedure specific.

Enhanced recovery, outcome and multimodal analgesia

Fast-track surgery, also called ERAS and promoted by the ERAS[®] Society (<http://erassociety.org>), is a multidisciplinary multimodal perioperative care strategy that aims for improved and faster recovery after surgery by incorporating standardised care pathways and protocols [31]. Having been widely accepted by health services worldwide, it has been shown to significantly reduce post-operative complications and to improve functional recovery, leading to shorter inpatient stay and cost savings [32]. Provision of excellent analgesia alone is insufficient by itself to achieve such improved outcome and reduced hospital stay after surgery [1]. However, optimised pain relief, in particular with ambulation and for physiotherapy, is an important pre-requisite for ERAS programmes. The importance of dynamic pain control to implement ERAS programmes successfully has shifted the goals of post-operative analgesia away from low pain scores at rest to enabling early mobilisation and return of normal physical function [10]. The fact that each ERAS protocol is designed specifically for a particular surgical procedure highlights the need for high-quality, procedure-specific evidence for post-operative analgesic approaches to support this approach [10].

The development of the concept of 'balanced' or now more commonly called 'multimodal' analgesia resulted from this shift of treatment goals towards more outcome-oriented ones, when it was realized that analgesia with opioids alone, while providing good pain relief at rest (and encouraging rest by causing sedation and drowsiness), often resulted in inadequate pain relief to enable mobilisation and engagement with physiotherapy [33]. Furthermore, opioid use in higher doses is associated with significant adverse effects that often impair patients' post-surgical recovery as outlined before. Multimodal analgesia aims to overcome this by utilising a combination of different analgesic agents, each with discrete modes and sites of action, to achieve better analgesia as well as reduced opioid

consumption ('opioid-sparing effect') and thereby associated adverse effects [34]. Combining multiple analgesics takes advantage of the synergistic effects that particular combinations may provide if selected carefully; this approach can be complemented by local and regional anaesthesia techniques, which in many settings show excellent analgesic efficacy with limited adverse effects [8,9].

While multimodal analgesia itself is well accepted as an integral part of optimal post-operative care, evidence for its use, including many meta-analyses (e.g. [35]) and network meta-analyses (e.g. [36]), have not differentiated between different surgical procedures while collecting data, but collated them from multiple disparate procedures. Consequently, we may overlook benefits of specific combinations in specific settings, e.g. those procedures causing more neuropathic pain, while potentially causing adverse effects in other procedures. In conclusion, multimodal analgesia strategies have to be procedure specific to be successfully integrated into ERAS protocols [37].

Moreover, there is only very limited evidence for combinations of more than two analgesics as components of multimodal analgesia, and most of this evidence relates to the combination of one opioid with one non-opioid. Such findings are interesting, but less relevant to modern practice of multimodal analgesia, where often three or more analgesics are combined and then sometimes local and regional techniques are added for most episodes of post-surgical care. That such combinations (e.g. two non-opioids with an opioid) are leading to improved analgesia and more opioid-sparing effect has been shown only in a few settings such as for the combination of paracetamol and an NSAID [36]. The effect of the addition of a third component has been studied only very rarely; e.g. one trial showed the benefit of adding dexamethasone to paracetamol and a coxib after breast surgery [38]. Data on combinations with local and regional anaesthesia techniques are completely missing. These are vital gaps in our current knowledge, which will not be addressed as long as most randomised controlled trials (RCTs) compare one analgesic with placebo instead of assessing its role in a multimodal approach, which is now considered as 'best' practice by most researchers [39].

The procedure-specific pain management initiative PROSPECT

The PROSPECT collaboration has been formed by a panel of anaesthesiologists and surgeons with wide-ranging international representation to address the gap in the available literature of evidence-based, clinically relevant and procedure-specific pain management recommendations; the first detailed publication on this approach by the group was in 2007 [40]. It aims to provide recommendations regarding specific surgical procedures immediately applicable to the clinical decision-making process across all stages of the perioperative period. All recommendations are produced as a result of a strict protocol including rigorous systemic reviews of the available literature regarding specific procedures using the protocol of the Cochrane Collaboration; the initial methodology was published in extensive detail in 2007 [41]. These recommendations are then examined in the light of current accepted clinical practises as well as the advantages and risks of each technique. In the initial methodology, where limited procedure-specific evidence was available, supplementary 'transferable' evidence from other procedures with a comparable pain profile (derived from other systematic reviews, where possible, or identified by comprehensive literature searching) was also considered [42]. The results are presented in a flow diagram form, with grades of recommendation according to the quality and levels of evidence and are made easily accessible on the PROSPECT website (www.postoppain.org). Recommendations currently available on the website accompanied in most cases by peer-reviewed publications include a wide range of surgical procedures in the disciplines of obstetrics (C-section), gynaecology (abdominal hysterectomy), urology (radical prostatectomy [43]), general (colonic resection [26], haemorrhoid surgery [44], hernioraphy [45], laparoscopic cholecystectomy [46,47], non-cosmetic breast surgery, thoracotomy [48]) and orthopaedic surgery (total hip [49] and knee arthroplasty [50]). There is an established process to formally review these recommendations within a regular timeframe to ensure the most up-to-date advice; planned dates of the next update are published on the website.

Update in methodology

With the recent changes in perioperative care and the increasing implementation of fast-track or ERAS programmes in many hospitals as a standard of care, the PROSPECT methodology has been

updated and modified, and the refined methodology implemented in 2016 for all procedures since then. This update has enhanced the possibilities to critically analyse study designs with regard to their relevance to current practice. The previously established process to formulate the recommendations has been refined to consider not only the quality according to the protocols of the Cochrane Collaboration (see above) but also critical expert interpretation of the study design.

The new methodology addresses a number of issues, in particular with regard to meta-analyses and network meta-analyses and their applicability to clinical practice [39]. Multiple RCTs evaluating a similar topic are often pooled together to perform meta-analyses, and these meta-analyses are integral to form evidence-based recommendations for the PROSPECT initiative. The strength of conclusions, which can be derived from meta-analyses related to post-operative analgesia, has been diluted by the limitations of the original RCTs (often placebo controlled with the control group receiving only opioids, thereby making assessment of the role of the analgesic within the established 'gold standard' of multimodal analgesia impossible), as well as due to aggregation of heterogeneous RCTs examining different surgical procedures and sites [51]. Clearly, careful selection of RCTs to be included in the review is at least as important as the size of the data itself.

Network meta-analyses have been increasingly published to address the lack of direct head-to-head comparisons between healthcare interventions [52]. The previous Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement has been extended to these network meta-analyses [53], and sophisticated statistical methodology has been developed [54]. Network meta-analyses offer advantages over the traditional meta-analyses by allowing assessment of treatment effects through direct as well as indirect comparisons and thus ranking the treatments compared. Despite their relevance and value, results of network meta-analyses are susceptible to similar weaknesses as their more traditional counterparts. Again, the usefulness in, and relevance to, actual clinical decision-making is limited. Control groups are commonly receiving opioid monotherapy, and data from discrete surgical procedures are pooled together, thereby making procedure-specific assessments and recommendations difficult (e.g. [36]). Furthermore, such network meta-analyses may provide impractical and even misleading answers to clinicians seeking relevant advice in a specific situation, if they do not consider the results in contemporary clinical setting of multimodal analgesia and early ambulation (e.g. [55] recommending multiple nerve blocks as the best post-operative approach to total knee arthroplasty without consideration of effects on mobilisation or potential benefits of multimodal systemic analgesia). Therefore, network meta-analyses continue to be affected by the limitations of the parent RCTs, as well as too wide a net of inclusion criteria that dilutes the strength and specific nature of the conclusion.

In response, specific areas of change in performing a PROSPECT review relevant to a topic includes the adaptation of the PRISMA guidelines and forming clearly defined inclusion/exclusion criteria with a particular focus on grouping studies with uniformity in analgesic techniques together and avoiding bias [39]. It is of note, however, that this, along with avoiding inclusion of poor quality RCTs with significant bias, may only leave a few high-quality low-bias studies for analysis in the setting of a given procedure, thus highlighting the need for further well-designed and clinically relevant procedure-specific RCTs.

Furthermore, to ensure clinical relevance of the recommendations given by PROSPECT, the focus of assessment has to be on the benefit of adding the analgesic intervention in question to an already accepted 'best practice' multimodal regimen, rather than focussing on the single intervention versus the standard control of opioid monotherapy or even less useful placebo therapy [39]. For the same reasons, the concept of 'transferable evidence' from similar other surgical interventions has been excluded from the new methodology. Increased emphasis is also placed on assessing the benefits versus the risks of the analgesic intervention. With regard to benefits, impact on rehabilitation as well as analgesic efficacy and the consequences of inadequate analgesia after the particular surgical procedure (e.g. physiological impact such as hypoventilation after a thoracotomy, and the risk of acute-to-chronic transition) are to be considered, while the risks include adverse effects and invasiveness of the approach [56].

A detailed step-wise description of the methodology is currently available on the website of PROSPECT (www.postoppain.org).

The following is a very brief summary of the processes leading from the selection of a specific procedure to the final PROSPECT recommendations: For each selected procedure, a subgroup of the PROSPECT members is formed (at least two members and external members are invited to join this

subgroup if deemed necessary (e.g. with specific expertise in the surgical procedure to be reviewed). Specialists in literature searches and/or data analysis, and research fellows may also be invited to join the subgroup for a particular procedure. The subgroup is responsible for the initial literature search, which is done using broad search terms and standard search strategies in several electronic databases (e.g., Ovid Medline, Medline In Process, other non-indexed citations, Medline Epub ahead of print, Embase, and Cochrane controlled trials register published by the Cochrane Library). The subgroup then reviews all manuscripts to identify relevant studies for inclusion, assesses the quality and level of evidence of included studies and creates standardised data tables using the selected references. On the basis of these data tables, qualitative and quantitative analyses are carried out. The design of the included study with regard to their relevance in current perioperative care practice is analysed. The result of the subgroup work is a summary document for presentation to the full PROSPECT group. It subsequently examines, in detail, each analgesic, anaesthetic or surgical intervention recommended and not recommended by the subgroup, refines them as necessary, and comes to a consensus agreement on all the recommendations, which are subsequently presented on the website. Recommendations for or against a certain analgesic approach are given even for approach with poor or sparse evidence with clear identification of the limitations these recommendations are based on. The relationship between quality and source of evidence, levels of evidence and grade of recommendation are presented in [Table 1](#).

Latest reviews

The latest review completed by the PROSPECT group applying the new methodology is for the management of pain after excisional haemorrhoidectomy; the peer-reviewed paper is published, and the procedure is currently updated on the PROSPECT website [\[57\]](#). A total of 464 further reviews of new RCTs and systemic reviews published since the previous initial review in 2006 were identified and 74

Table 1
Relationship between quality and source of evidence, levels of evidence and recommendation grade.

Study type	Study quality assessments					Level of Evidence (LoE)	Grade of recommendation (based on overall LoE, considering balance of clinical practice information and evidence)
	Statistical analyses and patient follow up assessment	Allocation concealment		Jadad scores	Additional assessment of overall study quality required to judge LoE		
Systematic review with homogeneous results	N/A	N/A		N/A	N/A	1	A
Randomised controlled trial (RCT)	Statistics reported and >80% follow-up	AND	A OR B OR B	(1–5) (3–5)	N/A N/A	1	A (based on two or more studies or a single large, well-designed study)
Randomised controlled trial (RCT)	Statistics not reported or questionable or <80% follow-up	AND/OR	B OR C OR D	(1–2) (1–2) (1–5) (1–5)	Yes Yes N/A N/A	2	
Non-systematic review, cohort study, case study; (e.g. adverse effects)	N/A	N/A				3	C
Clinical practice information (expert opinion); inconsistent evidence	N/A	N/A				4	D

selected as meeting the inclusion criteria, of which 48 were RCTs. Quantitative analysis was not performed due to limited number of trials with homogenous designs, and further limitations of the data including the lack of studies examining multimodal analgesic interventions. Recommendations were divided into areas of conventional analgesics, topical agents, analgesic adjuncts, regional anaesthesia, anaesthetic interventions, and operative interventions. In comparison to the previous recommendations from 2006, changes of note include specific recommendation for pudendal nerve block with or without general anaesthesia over local infiltration or spinal anaesthesia (previously recommended local/regional techniques in general without specification) and recommendation of certain post-operative topical agents such as glyceryl tri-nitrate (GTN)/lignocaine or cholestyramine. Specific recommendations were also made for surgical technique of either closed haemorrhoidectomy or open haemorrhoidectomy with electrocoagulation of the pedicle, but with the proviso that the choice should not solely be based on the level of post-operative pain, but also on other factors including patient and surgeon preference. Fig. 1 shows the perioperative analgesic recommendations.

Another topic that was recently reviewed by the PROSPECT collaboration was radical prostatectomy [43]. This review highlights some of the issues touched upon above. Despite patients experiencing moderate dynamic pain after radical prostatectomy [58], and the surgical technique undergoing significant changes with increased uptake of robotic and laparoscopic methods, analgesic options for radical prostatectomy were not reviewed up to that point and no evidence-based recommendation existed. A literature search was conducted twice, in October 2012 and updated in June 2015, which yielded 38 studies examining a wide array of analgesic interventions satisfying the inclusion criteria. Significant heterogeneity prevented a quantitative analysis from being performed. Unfortunately, the review was marred by the limitations of included studies, in particular the poor study design, lack of

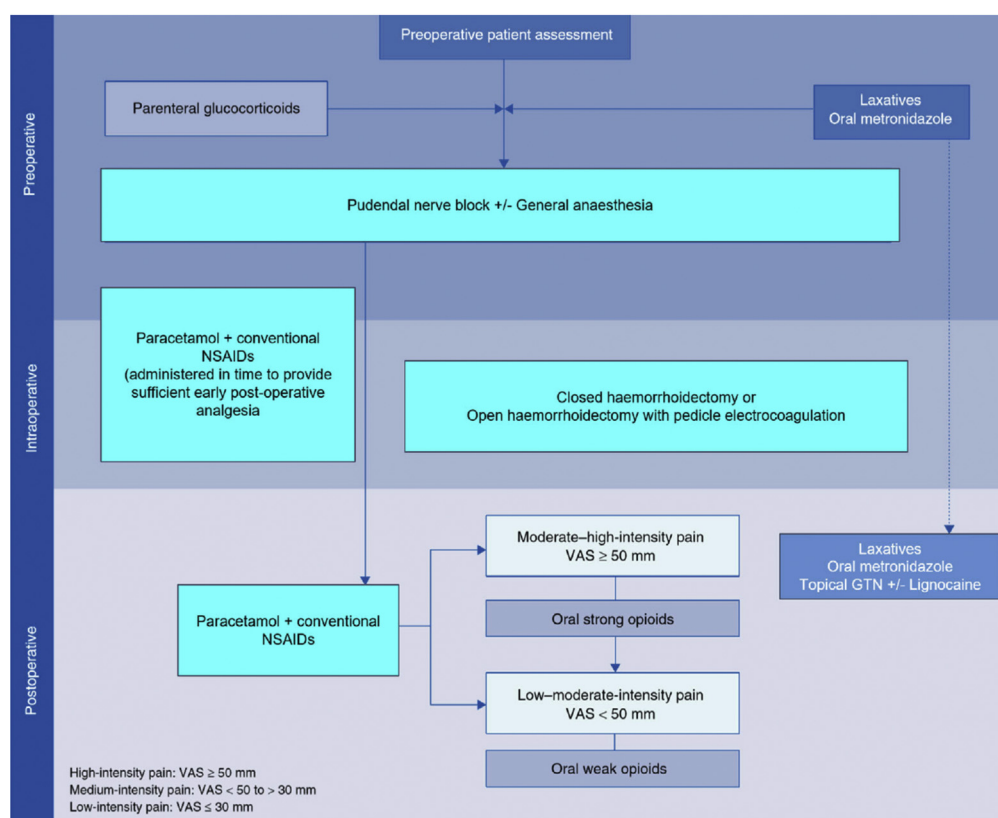


Fig. 1. Updated PROSPECT recommendations for pain management after haemorrhoidectomy (used with permission from [57]).

studies examining simple non-opioid analgesics (e.g. paracetamol and NSAID/COX-2 inhibitor) and other simple techniques such as wound infiltration. Other limitations of the review include a lack of studies examining analgesic interventions as a part of multimodal analgesia, with the vast majority of studies comparing pharmacological intervention to a control group receiving opioid alone. Despite rapid uptake of laparoscopic robotic surgical techniques and its apparent decreased postoperative pain [58], minimal research has been conducted in this area. As such, simply because of lack of evidence, the review did not result in an evidence-based analgesic guideline specific to radical prostatectomy; a basic analgesic guideline could only be provided, and the need for more procedure-specific studies in this field has been identified.

Future directions

The PROSPECT collaboration, now affiliated with the European Society of Regional Anaesthesia & Pain Therapy (ESRA), will continue to provide evidence-based procedure-specific recommendations for the treatment of post-operative pain, which now uses an updated and improved methodology. Further new procedures in advanced stages of development are laparoscopic hysterectomy (review paper submitted for publication) and tonsillectomy (currently in the review process) and in preparation are laparoscopic colonic resection, sleeve gastrectomy and shoulder arthroplasty. Updates are imminent on open abdominal hysterectomy and laparoscopic cholecystectomy (publication in preparation) with most other updates aiming for 2019 and 2020.

As evident from existing reviews, perhaps the biggest obstacle to perform an effective review and produce procedure-specific guidelines is the lack of evidence in the respective areas, namely the absence of high-quality and procedure-specific studies examining analgesic modalities as a component of a multimodal regimen. Furthermore, studies are needed with assessment for outcomes with importance for post-operative recovery such as dynamic pain control and improved mobilisation. It is hoped that the repeated identification of these gaps in the current literature will steer future research towards these clinically relevant areas and help to shed further light onto the field of procedure-specific pain management. A recent approach to assess perioperative efficacy of adjuvant analgesics by meta-regression to basic opioid requirements has been published [59,60]. This alternative approach using sophisticated statistical methodology identifies these baseline opioid requirements as the main cause of heterogeneity in meta-analyses, thereby challenging some of the procedure-specific concepts, but it awaits further confirmation and analysis.

Practice points

- Post-operative pain continues to be poorly managed in many settings, resulting in human suffering and poor post-operative outcomes
- One reason for this poor post-operative pain management is over-reliance on opioid analgesia, resulting in adverse effects and poor recovery, while also contributing to the 'opioid epidemic' by unnecessary discharge of patients on high doses of opioids supplied in large quantities
- Multimodal analgesia could address these issues, but is currently poorly researched due to studies primarily comparing the effect of one added analgesic to opioids instead of to a multimodal strategy as the current best 'practice'
- Appropriate post-operative pain relief needs to address dynamic pain to enable ambulation and mobilisation of patients and thereby contribute to 'fast-track' clinical pathways in line with the multimodal and multidisciplinary approach of enhanced recovery after surgery (ERAS)
- Pain management contributing to ERAS needs to be procedure specific to address the specific pain states, analgesic requirements and risk-benefit assessments for a specific surgical procedure
- The PROcedure-SPECific Pain Management (PROSPECT) collaboration provides evidence-based, clinically relevant guidelines for procedure-specific post-operative pain management in their publications and on their website (www.postoppain.org)

Research agenda

- The activities of PROSPECT have identified a number of important topics for future research activities in the area of post-operative pain management, which need to be addressed
- Research is needed in the area of multimodal analgesia, to identify the role of non-opioids and adjuvants combined with opioids not only against opioids alone, but more importantly against established regimens of multimodal analgesia as standard of care (including regional techniques)
- Studies on the addition of a further medication or modality on top of a multimodal regimen need to be performed in a sufficient number of patients undergoing a specific procedure to achieve statistical power and permit conclusions on such additions.
- It was further identified that in many settings of moderately to severe painful surgeries, there are nearly no or only very limited and often poorly designed clinical trials, making the development of procedure-specific guidelines nearly impossible without more targeted research
- Future research activities in the area of post-operative pain management need also to focus on dynamic pain relief and outcome benefits, to permit integration of evidence-based analgesic recommendations into guidelines for enhanced recovery after surgery (ERAS), which are intrinsically procedure specific.

Conflict of interest statement

B.L. has no conflict to declare.

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