Essential Elements of Multimodal Analgesia in Enhanced Recovery After Surgery (ERAS) Guidelines

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KEYWORDS

• Enhanced recovery • ERAS • Pharmacology • Multimodal analgesia
• Regional anesthesia • Opiate-sparing analgesia • Guidelines • Pain management

KEY POINTS

- Enhanced recovery refers to a systematic process addressing each aspect in the surgical journey that could affect recovery, from preoperative carbohydrate drinks, to surgical and anesthetic techniques or postoperative mobilization.
- The Enhanced Recovery After Surgery (ERAS) Society has published several comprehensive guidelines for different intra-abdominal surgeries, reviewing all available evidence to provide generic and specific recommendations for care of these surgical patients.
- The significant role of multimodal analgesia is emphasized in all ERAS Society guidelines. The goals are to manage pain, reduce overall neural and hormonal stress responses to surgery, and aid early mobilization, normal respiration, and oral nutrition.
- This article outlines the evidence base forming the current multimodal analgesia recommendations made by the ERAS Society for both systemic and regional analgesia or anesthesia for each procedure.
- We outline some important future directions for effective perioperative multimodal analgesia in enhanced recovery pathways. These include exploring strategies for opiate tolerant populations, chronic pain prevention, potential to modulate cancer-recurrence, and use of enhanced recovery in acute care surgery.

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INTRODUCTION

Enhanced Recovery After Surgery (ERAS) Society guidelines provide an evidence-based, multimodal approach to surgical care, to improve outcomes after major operations. The main principles of enhanced recovery are to reduce the physiologic derangement and stress response after surgery and thereby improve recovery, reduce complication rates, and shorten inpatient hospital stays. The ERAS Society guidelines (available at www.erassociety.org) comprise a series of recommendations formed after review of available evidence by working groups of experts. Each guideline addresses the evidence base for each recommendation, across approximately 20 to 22 categories, with all stages from planning surgery through to recovery included. Seven ERAS Society guidelines exist for several procedures and classes of surgery, with more guidelines currently under development. All guidelines include the perioperative management of analgesia (**Table 1**).

In keeping with Grading of Recommendations Assessment, Development, and Evaluation (GRADE), each recommendation includes an assessment of the quality of evidence used (high, moderate, low, very low) and a strength of recommendation grading (strong, weak).[11] If evidence is lacking for a specific class of surgery, it is extrapolated, usually from colorectal data, and this extrapolation is acknowledged as a limitation to the strength of the recommendation.

Reviews of evidence required for ERAS Society protocols are ambitious and comprehensive in their scope. The care recommendations cover surgical aspects, anesthesia, and nursing, as well as physiotherapy and nutrition, which all play important roles in the patient's journey. For anesthesia and pain management, it is important to incorporate all of these aspects because they interact and influence each other. Both analgesic efficacy and impact on physiologic functions and recovery are considered. Pharmacologic aspects include anesthesia mode, anxiolytics, analgesia, antiemetics, bowel motility agents, blood sugar control, anticoagulants, venous thromboembolism prophylaxis, and antibiotics. Well-managed pain, the so-called "fifth vital sign", is widely recognized as an important metric for success of surgery and recovery, quality of medical and nursing care, and even as a surrogate for patient satisfaction.[12] It also predicts complications attributed to poorly controlled pain, such as delayed oral intake and mobilization, prolonged admission, and readmissions.[13,14]

Postoperative pain is frequently underestimated and undertreated, with short-term and long-term sequelae.[14,15] This makes good pain control an important quality improvement target on an individual, institutional, and societal basis.[16] The wide range of adverse effects, including nausea, ileus, respiratory depression, hyperalgesia,

Table 1
Enhanced Recovery After Surgery Society guidelines, current and revised

Specialty	Authors
Consensus Statement: Colorectal Resection (Clinical Nutrition)	Fearon et al,[1] 2005
ERAS Colorectal Surgery	Lassen et al,[2] 2009
ERAS Colorectal Surgery Revised	Gustafsson et al,[3] 2013
ERAS Radical Cystectomy for Bladder Cancer	Cerantola et al,[4] 2013
ERAS Pancreaticoduodenectomy	Lassen et al,[5] 2013
ERAS Elective Rectal or Pelvic Surgery	Nygren et al,[6] 2013
ERAS Gastrectomy	Mortensen et al,[7] 2014
ERAS Gynecologic or Oncological Surgery	Nelson et al,[8,9] 2016
ERAS Bariatric Surgery	Thorell et al,[10] 2016

delirium, and tolerance associated with opiate analgesia demand a multimodal, opiate-sparing strategy to be advocated whenever possible.[17,18] All preoperative, intraoperative, and postoperative systemic analgesic combinations, and anesthetic or analgesic procedures, such as regional anesthesia and peripheral nerve blockade, set out by ERAS Society guidelines are reviewed and compared here.

Other resources for postoperative analgesia include the PROSPECT (Procedure Specific Postoperative Pain Management) working group, originating in 2002, which provides procedure-specific recommendations for 11 different procedures, such as obstetric, orthopedic, and urologic surgery.[19,20] Additionally, comprehensive guidelines on postoperative analgesia were published in 2016 by the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia.[21] Like ERAS Society guidelines, this report highlights some gaps in the evidence-base for particular pharmacologic strategies.

As with all guidelines review of emerging evidence is periodically required for revision and with time the GRADE strength of evidence grading may need updating. However, despite significant evidence in several categories, National Inpatient Sample data suggest key components of ERAS Society, including analgesia strategy, are not widely implemented. For example, epidural use between 2002 and 2012 for elective hepatopancreatic procedures (eg, pancreaticoduodenectomy) averaged just 7.4% despite being associated with lower rates of pulmonary complications and hospital mortality.[22] This suggests that implementation of ERAS Society recommendations, such as epidural use, may require sustained and systematic change on an organizational and national basis. This may be facilitated by simultaneous data collection for audit of compliance and outcomes using programs such as ERAS Society's Interactive Audit System (EIAS). This article summarizes the ERAS Society recommendations relating to multimodal systemic and regional analgesia to date, and considers future directions for ERAS Society in the context of perioperative multimodal analgesia.

COMPONENTS OF MULTIMODAL, OPIATE-SPARING ANALGESIA

Multimodal analgesia involves use of multiple, simultaneous mechanisms of pain control acting synergistically to improve analgesic effect and reduce the doses of any single agent to minimize risks of side-effects.[23-25] This aims to avoid opiates use altogether, or at least reduce opiate doses required, and thereby reduce risk of side effects from opiates that are common and cause delays in recovery (see later discussion). There are multiple pathways and mediators involved in nociception, and targeting several mechanisms can increase analgesic efficacy, using combinations of systemic and regional anesthesia.[26]

Systemic Analgesia

Multimodal analgesia in the ERAS Society setting involves using combinations of nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol, anticonvulsant agents, and calcium channel blockers, which all target different pain receptors and pain transmission pathways peripherally and centrally. Using combinations of nonopiate medications and regional analgesia may allow clinicians to avoid or significantly reduce systemic opiate consumption altogether, reserving them as a last resort only. The goal is to optimize pain control while minimizing unpleasant and harmful drug side effects, particularly those caused by opiates. Common routes of delivery include intravenous (IV), oral, rectal, and topical; however, ERAS Society recommends that transition from the IV to oral routes should be expedited if possible to reduce risks from cannula use, cannula site thrombophlebitis, and facilitate mobility and discharge (**Table 2**).

Table 2
Systemic preoperative, intraoperative, and postoperative analgesia: the Enhanced Recovery After Surgery Society Guidelines recommendations

ERAS Society Guideline:	Drug	Recommendation and References	Other Notes
Generic Gastrointestinal[27,28]	Multimodal analgesia (MMA): comprising IV or PO acetaminophen, paracetamol & NSAIDs, or cyclooxygenase (COX inhibitor)-2 inhibitors	Routine use of paracetamol and NSAID, as part of MMA for gastrointestinal laparoscopic or open procedures, unless contraindicated[29,30] **Grade: strong**	Cardiovascular risk with COX inhibitor or NSAIDs: no evidence to avoid in low CV-risk patients[31,32] Aim: treat pain and to reduce opiate use and its dose-dependent side effects[30,33] Large randomized controlled trials (RCTs) needed to address concerns for anastomotic breakdown risk with NSAIDs, especially use >2 d[34–36] IV paracetamol reduced nausea and vomiting, possibly secondary to opiate sparing effect[37]
Colonic[3] (excluding rectal)	Anxiolytics	Avoid routine use due to delayed immediate postoperative recovery[38] **Evidence: high, grade: strong**	Short-acting agents (fentanyl, midazolam, propofol) to facilitate neuraxial analgesia or line placement if required Administer under monitored conditions, titrated by anesthesiologist
	MMA	Paracetamol 1g IV QDS, tramadol +/– NSAIDs **Evidence: moderate** (inconsistency or few studies), **grade: strong** Laparoscopic: morphine PCA may be equivalent to spinal or epidural.[39] **Evidence: moderate**	Systemic opioids compared with epidural anesthesia are associated with ileus[40,41]
	Morphine or other opiate	Open: If systemic opiates are required, titrate, to minimize dose **Evidence: high, grade: strong**	

Rectal or Pelvic[6] (last 12–15 cm of large bowel above or below pelvic reflection)	Anxiolytic	As for colorectal	
	MMA	As above Additionally, rectal stump excision or previous radiotherapy sites can develop neuropathic pain requiring additional multimodal approach	No ERAS Society guidance on whether ketamine, gabapentin, or tramadol postoperatively affects outcomes
	Opioids	Remifentanil attenuates intraoperative stress response[42] **Evidence: low** (from gynecological laparoscopy), **grade: strong** Breakthrough or as required opioid for perineal pain if not covered by thoracic epidural anesthesia (TEA)	No evidence for prevention of remifentanil induced acute hyperalgesia with NDMA antagonists, magnesium, or ketamine[43]
	IV local anesthetic	Continuous IV lidocaine infusion (1.5 mg/kg induction, 2 mg/kg/h intraoperative) may reduce opiate use and inflammatory response[44] if TEA is not feasible. **Evidence: low, grade: weak**	No ERAS Society data or statement comparing IV lidocaine and TEA for open rectal procedures May be comparable to TEA for laparoscopic procedures[45]
Pancreaticoduodenectomy (PD)[5]	Anxiolytics	No long-acting sedatives, as for colorectal Short-acting agents for procedures (eg, line placement or epidural) **Evidence: moderate, grade: weak** (abdominal surgery studies)	Avoiding prolonged starvation may also reduce anxiety[46]
	MMA	Regular paracetamol, NSAIDs/COX-2 inhibitors with oral opioids as required post-TEA	PD patients have prolonged recovery compared with other laparotomies but extended bed rest has adverse effects Analgesia must be sufficient for early mobilization[47]
	Opioids	If TEA not possible, consider opiate PCA **Evidence: very low**	Sparse evidence for PD-specific recommendations compared with other gastrointestinal surgery
	IV local anesthetic	Continuous IV lidocaine infusion may outperform, or have fewer side effects vs PCA[44] but not vs TEA[45] **Evidence: moderate, grade: weak**	

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Table 2
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ERAS Society Guideline:	Drug	Recommendation and References	Other	Notes
Gastrectomy[7] (no recommendations for systemic analgesia use gastrectomy specific evidence)	Anxiolytics MMA Opioids IV local anesthetic	As for PD	For gastrectomy for cancer, PCA IV inferior for pain relief and stress response compared with patient-controlled epidural[48] RCT in subjects undergoing laparoscopic gastrectomy showed a reduction in postoperative fentanyl consumption and pain with preoperative and intraoperative injection of lidocaine by PCA[49]	
Bariatric[10]	Anxiolytics	As for colorectal	Evidence for efficacy of pregabalin awaited[50] Dexmedetomidine: not routinely recommended[51] Obesity induces severe restrictive syndrome, lying flat induces atelectasis Avoid respiratory depressants	
	MMA	As above Multimodal systemically[52,53] and local anesthetic infiltration to reduce opiate use **Evidence: high, grade: strong**	Dose adaptation for body weight	
	Opioids	If opiate required, PCA with increased refractory period vs continuous infusion, particularly for patients with OSA[54,55]	Continuous respiratory surveillance postoperatively and use enteral route as soon as possible[56]	
	IV local anesthetic	Not addressed		

Radical Cystectomy for Bladder Cancer[4] (no recommendations for systemic analgesia use cystectomy specific evidence)	Anxiolytics MMA Opioids IV local anesthetic	As for colorectal[3]	Limited data suggest opioid sparing MMA concepts can be adopted in major urologic surgery[57,58]
Gynecological[8,9]	Anxiolytics	As for colorectal	Gynecologic patients prefer to be well informed and should receive dedicated preoperative counseling to reduce anxiety. Nurse presence at diagnosis reduces patient stress levels at up to 6 mo[59]
	MMA	Paracetamol & NSAIDs[60,61] **Evidence: high** Gabapentin[62,63] **Evidence: moderate** Dexamethasone.[64] **Evidence: low, grade: strong**	Higher risk for developing chronic pain[65]
	Opioids	For major oncological surgery, patients frequently require IV opioids as well as TEA **Evidence: low, grade: weak** Oral route as soon as possible, otherwise PCA IV opioid For laparoscopic surgery, lack of evidence with which to recommend analgesia plan; however, MMA recommended. **Evidence: low, grade: weak**	Optimal gabapentin dose unknown
	IV local anesthetic	No specific evidence for gynecology	

Abbreviations: COX, cyclo-oxygenase inhibitor; MMA, multimodal analgesia; NSAIDs, non-steroidal anti inflammatory; PCA, patient controlled analgesia; QDS, four times daily (quater die sumendus).

Nonsteroidal anti-inflammatory drugs

NSAIDs block the enzymatic action of cyclooxygenase (COX inhibitor)-1 and COX inhibitor-2 that reduces prostaglandin synthesis, thereby reducing the peripheral nociception and swelling associated with tissue damage. Routes include oral, IV, topical, and rectal. NSAIDs include nonselective agents, such as aspirin, ibuprofen, ketorolac, and diclofenac, as well as newer COX inhibitor-2 selective agents, such as parecoxib and celecoxib. COX inhibitor-2 inhibitors allow ongoing prostaglandin synthesis in the stomach via COX inhibitor-1, maintaining gastric mucus production and thus reducing the risk of peptic ulceration associated with NSAIDs. Some COX inhibitor-2 selective agents carry an increased cardiovascular risk profile with prolonged use but this has not been demonstrated with shorter term use. Recently, potential links between postoperative NSAID use and anastomotic breakdown have been suggested by observational studies.[66] However, the evidence is inconclusive, with other studies reporting no statistically significant associations.[67] Predictive factors for anastomotic leakage after colorectal Surgery: study protocol for a prospective observational study (REVEAL Study) is a large prospective observational study that is currently enrolling subjects, with completion due in 2018 and may answer this question more definitively.[68] At the present time, evidence supports regular doses of NSAIDs in the postoperative period as an effective component of a multimodal, opioid-sparing regime to manage acute pain and, as such, is recommended in all ERAS Society guidelines.[1–9]

Acetaminophen

Acetaminophen (paracetamol) is also recommended by ERAS Society guidelines, on a regular schedule, 15 mg/kg, up to 1 g, 4 times daily, either orally or by IV.[1–9] It is well tolerated, with a minimal side effect profile but is hepatotoxic in overdose. Its mechanism of action is still incompletely understood; however, there are some similarities to NSAIDs, in that it inhibits COX inhibitor, particularly COX inhibitor-3, an isoenzyme of COX inhibitor-1.[69] Its impact on COX inhibitor may be predominantly in the central nervous system where it may also modulate the endogenous cannabinoid system. When used in combination with NSAIDs or opioids it provides superior analgesia to single-agent NSAIDs or opiate regimes.[33,52,53,60]

Opiates

Opiates, morphine and diamorphine, and synthetic opioids, including fentanyl, alfentanil, remifentanil, are used for intraoperative analgesia. Delivery routes include IV, intrathecal, and epidural. ERAS Society recommends that short-acting (fentanyl and alfentanil) and ultrashort-acting (remifentanil via infusion) opioids are used if required intraoperatively, instead of morphine, because they are less likely to cause side effects, such as respiratory depression and nausea during recovery, due to their shorter half-life. Some opiates have been used as adjuncts with local anesthesia in field blocks, such as transversus abdominis plane (TAP) blocks and in low doses in epidural or spinal anesthesia.

For postoperative pain management, if possible, ERAS Society generally recommends avoidance of opioids, which should be used as a last resort. Dosage response to opiates can vary greatly between individuals and must also be tailored in renal and hepatic impairment, depending on the metabolism and elimination of the particular drug.[70] Susceptibility to side effects also varies between individuals but include itching, nausea, bowel ileus, constipation, urinary retention, hypotension, respiratory depression, confusion and hallucinations, and tolerance. For these reasons, multimodal analgesia aims to avoid or reduce opiate consumption by introducing other synergistic systemic agents and by using regional or neuraxial blockade. If pain is

not adequately controlled with these methods, postoperative opiates, such as morphine, can be delivered via patient-controlled infusion; or oxycodone, tramadol, or codeine can be delivered via IV bolus doses or orally. ERAS Society recommends the use of patient-controlled delivery systems, if possible, so that dosage is individualized rather than standardized. Patches are used predominantly in chronic pain because the transdermal route is less suitable for acute pain of fluctuating severity. In addition, alvimopan, a peripherally acting μ-opiate antagonist, has also been recommended by ERAS Society guidelines to avoid gastrointestinal side-effects, due to associated reduced length of stay and cost.[71,72]

N-Methyl D-Aspartate receptor antagonists

N-Methyl D-Aspartate (NMDA) receptor antagonists include ketamine, memantine, and magnesium sulfate. Ketamine modulates nociception by noncompetitive binding and allosteric inhibition of NMDA channel's excitatory glutamate receptor site. At anesthetic doses, ketamine produces a dissociative state. However, smaller analgesic doses of ketamine have been demonstrated to reduce postoperative pain and opiate requirements, both when administered as an IV bolus at induction and as ketamine-bupivacaine epidural compared with a fentanyl-bupivacaine epidural.[73–76] Evidence for the role of ketamine in elective surgery is limited and ERAS Society guidelines do not recommend its routine use at present, though it may be considered if other recommended strategies are contraindicated. The literature on ketamine anesthesia and analgesia is predominantly from patients with cardiovascular instability (eg, sepsis and civilian or military trauma) undergoing surgery because ketamine, unlike many induction agents, does not cause hypotension or bradycardia so may be the agent of choice in these cases. Side effects, including hallucination, may be reduced by enantiomer-pure preparations.

Gabapentin and pregabalin

Gabapentin and pregabalin have both been demonstrated to reduce postoperative opiate requirements as part of a multimodal analgesia regime. However, neither agent has sufficient evidence to warrant inclusion for routine recommendation in ERAS Society guidelines to date. γ-Aminobutyric acid (GABA) analogues seem to interact not only at voltage-gated calcium channels but also at NMDA receptors, and with protein kinase C, rather than at GABA receptors. Side effects include dizziness, drowsiness, and fatigue.

Local anesthetics

Local anesthetics are widely used for subcutaneous infiltration and regional anesthesia. However, there is growing evidence for local anesthetic use systemically via the IV route and not only in limited regions under tourniquet (eg, a Bier limb block). Clinically significant reductions in opiate requirements have been demonstrated during and after abdominal surgery in which systemic IV lidocaine infusions were used (available at http://www.medscape.com/viewarticle/811736_6). IV lidocaine is featured in several ERAS Society guidelines, predominantly for hysterectomy in place of intraperitoneal lidocaine, and for laparoscopic colorectal or rectal surgery in place of an epidural.[44,45,77] Benefits may include analgesia, antihyperalgesia, and anti-inflammatory properties via multiple mechanisms, including suppression of signal transmission through the dorsal root ganglion from damaged peripheral nerves, attenuation of neurogenic inflammation peripherally, suppression of granulocyte and lysosomal activity, reduced cytokine activity, and suppression of central sensitization.[78] However, caution is needed with bolus and infusion doses to avoid toxicity.

Nonsystemic Anesthesia or Analgesia

Systemic analgesia is complemented by the use of local anesthetic injections or infusions around specific peripheral nerves or nerve plexus, into tissue at the site of incision, into joint spaces, peritoneal spaces, tissue planes, and via epidural or intrathecal routes. Local anesthetic agents, such as lidocaine and bupivacaine, can be used in varying concentrations and volumes to reduce or block nerve transmission. Although sensory transmission is the true target, motor and autonomic nervous systems may also be affected, depending on dosage, and autonomic blockade may enhance analgesic properties.

Thoracic Epidural Anesthesia or Analgesia and Spinal Anesthesia

Local anesthetic infusion (plus or minus opiate additives) via midthoracic epidural (thoracic epidural anesthesia [TEA]) is recommended with the highest strength and quality of evidence possible for open colorectal and open rectal surgery, open radical cystectomy, and open general gynecologic surgery. However, the recommendation for TEA is weaker in laparoscopic surgery, in which spinal injection is an adequate alternative, and in bariatric surgery, due to higher reported complication rates of TEA in this population. There is conflicting evidence as to whether TEA causes hypotension or splanchnic hypoperfusion, or whether they provide some degree of microcirculatory protection. It is likely that the patient's volume and hemodynamic status and extent of blockade are all important. ERAS Society guidelines recommend hypotension with epidural anesthesia is managed with vasopressors, rather than fluid challenges alone, to avoid inadvertent fluid overload.[1] Intrathecal and epidural additives, such as fentanyl, improve analgesia but increase side effects such as itching, nausea, and hypotension.

Transversus Abdominis Plane Blocks and Continuous Wound Infiltration

TAP blocks and continuous wound infiltration both feature in ERAS Society guidelines, particularly for open abdominal surgery or in cases in which TEA is not used. Intraoperative aerosol administration of intraperitoneal local anesthetic is not presently recommended by ERAS Society guidelines though there is some evidence of reduced pain and opiate consumption when used in colorectal surgery, laparoscopic gastric surgery, and laparoscopic and abdominal hysterectomy (**Table 3**).[77,100,101,127]

FUTURE DIRECTIONS FOR ENHANCED RECOVERY AFTER SURGERY SOCIETY GUIDELINES AND BUNDLED CARE IN DELIVERING MULTIMODAL ANALGESIA

There are various other systems of bundled care, such as Enhanced Recovery Programs in the United Kingdom, Perioperative Surgical Home in the United States, and other local systems that have been implemented successfully worldwide. However, ERAS Society guidelines are emerging as a predominant international resource in the amalgamation of high-quality, evidence-based, perioperative care into standardized clinical guidance. Many single center and multicenter studies have reported some improvements in outcomes or cost-effectiveness after implementation of ERAS Society guidelines, in cohort comparisons, randomized controlled trials, and systematic reviews.[131–142] Randomized studies comparing ERAS Society guideline-compliant care and traditional care have heterogeneous study protocols, complicating meta-analyses; however, 2 studies demonstrated that for colorectal surgery, the more individual ERAS Society recommended elements adhered to, the better the associated outcomes.[143,144]

PROCEDURE-SPECIFIC MULTIMODAL ANALGESIA

Enhanced recovery protocols and the aggregation of marginal gains are now being considered on the wider elective surgery stage, with expert consensus statements and pilot studies in fields including cardiac surgery, neurosurgery, breast surgery, head and neck surgery, and orthopedics.[145–150] Future ERAS Society protocols for nonabdominal surgery cannot use extrapolated data from abdominal surgery in same the way that colorectal data has laid foundations for gastrectomy guidelines. With respect to multimodal analgesia, recent breast, orthopedic, and spinal surgery literature describe success with a range of procedures, including epidurals, spinals paravertebral blocks, pectoralis 1 and 2 blocks, and field blocks, providing procedure-specific evidence for future ERAS Society guidelines.[151–160] Although some aspects of ERAS Society guidelines, such as bowel preparation, may have less impact than in, for example, breast versus abdominal surgery, standardization of other aspects, such as carbohydrate preload drinks; warming; prehabilitation and rehabilitation; and, especially, multimodal analgesia may translate to improved outcomes in other specialties.

EMERGENCY SURGERY

The attention for enhanced recovery next turns to emergency surgery. Indeed, because work from Pearse and colleagues[161] in the EuSOS (European Surgical Outcomes Study) cohort demonstrated the highest postoperative morbidity and mortality were associated with urgent and emergency surgery, this group may benefit the most from an ERAS Society framework, particularly adequate analgesia.[162–166] Multimodal analgesic regiments and evidence-based recommendations have been more comprehensively addressed in elective cohorts but barely addressed in emergent cohorts and, although translation is lagging, it is rightly starting to be addressed.[162] Studies have already demonstrated translatable benefit of bundled enhanced recovery interventions in emergency surgery, modeled on ERAS Society guidelines.[164]

SPECIFIC PATIENT GROUPS

ERAS Society guidelines presently make recommendations based by surgery and do not make recommendations for specific patient groups separately, or within that surgery. Examples of clinically challenging patient groups for which additional specific guidelines might be beneficial include those with extreme advanced age or morbid obesity. Although bariatric surgery guideline exists,[10] there is no specific advice in other ERAS Society statements addressing obese patients. Patients with chronic opiate use or overuse present an additional challenge, both from opiate induced tolerance and opiate induced hyperalgesia.[167] Important steps include preoperative identification and dose verification, nonjudgmental discussion of analgesia options, use of regional anesthesia, consideration of opiate maintenance dosing requirements, attentive titration to adequately manage acute pain, and collaboration with pain teams if available.[168,169]

CANCER RECURRENCE TO MEASURE IMPACT OF ENHANCED RECOVERY OR MULTIMODAL STRATEGY

It is possible that the role of different drugs and techniques on immune modulation, cancer recurrence, and long-term survival will have more emphasis in future revisions of ERAS Society guidelines, depending on the evidence to emerge. A Cochrane database systematic review in 2014 concluded there was currently inconclusive evidence

Table 3
Regional anesthesia or analgesia: the Enhanced Recovery After Surgery Society Guidelines recommendations

ERAS Society Guidelines:	Route & Drug	Recommendation	Exceptions or Caution	Other
General Considerations: Gastrointestinal (GI)[27,28]	TEA (eg, bupivacaine 0.1 mg/ml +/− opioid)	Open: TEA remains gold standard in open abdominal surgery[79] TEA, **grade: strong**, TAP block, grade: moderate Continuous wound infiltration (CWI), **grade: weak**	Increasing role for laparoscopic surgery if possible under spinal + TAP block vs open surgery with TEA + NSAIDs[28]	Epidural anesthesia reduces stress response and insulin resistance to surgery[80,81] and reduces time for gastrointestinal recovery[82] compared with IV opiates
	Intrathecal Local anesthetic +/− opioid	Laparoscopic TEA, **grade: weak** TAP block, **grade: moderate** Intrathecal, **grade: weak**[83]	Epidural clonidine: inconclusive evidence, may cause hypotension and sedation[91]	Manage epidural related hypotension in normovolemic patients with vasopressors to avoid splanchnic hypoperfusion and anastomotic compromise[92]
		Epidural additives: Lipophilic (eg, fentanyl) 3 μg/ml may have fewer side effects[84] Hydrophilic (eg, morphine) 0.02 mg/mL may increase segmental spread, useful for long midline incisions[85] Adrenaline (epinephrine) 1.5–2 μg/ml may improve analgesia, reduce pruritus and nausea[86–89] Intrathecal additives: Morphine provides excellent analgesia and may reduce length of stay for colorectal laparoscopic surgery according to ERAS Society guidelines[83,90]		Epidural does not increase length of stay vs PCA morphine[41] Pruritus, urinary retention[93] and respiratory depression (rare) increased with epidural and intrathecal opiates,[86] though these improve analgesia[86]
	Continuous wound infusion (CWI)	CWI: preperitoneal (eg, continuous infusion of ropivacaine 0.2%, 10 mL/h for 48–72 h for laparotomy)	CWI & TAP still require systemic opiates to control visceral pain	CWI: inconclusive evidence, optimal anatomic location undetermined Somatic pain relief only[94–96]

	TAP block	TAP: single shot- (>15 ml bilaterally) significant reduction in systemic opiate use in first 24 h postoperatively[97–99] TAP: catheter not inferior to epidural if functioning well[97]	Failure or replacement rates of both epidural (22%) and TAP catheters (nearly 50) are high[97]
	Intraperitoneal local anesthesia	RCT demonstrates intraperitoneal local anesthetic (IPLA) in addition to TEA reduces pain and opioid consumption with improved recovery after open colectomy[100] and reduces opioid use and shoulder pain after laparoscopic procedures[101] No IPLA recommendations made	
Colonic[3] (excluding rectal)	Midthoracic epidural	Open: midthoracic epidural with local anesthetic and low-dose opioids for open surgery, to attenuate stress response and facilitate rapid awakening anesthesia **Evidence: high, grade: strong**	Note: laparoscopic vs open preferable if expertise is available Potentially suitable for >90% of elective colorectal cancer cases, with <10% conversion[102] **Grade: strong**
	Spinal ± TAP	Laparoscopic: spinal analgesia or morphine PCA alternative to epidural **Evidence: moderate, grade: strong**	Epidural vs IV opiates for the prevention of postoperative ileus **Evidence: high, grade: strong**

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Table 3
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ERAS Society Guidelines:	Route & Drug	Recommendation	Exceptions or Caution	Other
Rectal or Pelvic[6] (last 12–15 cm of large bowel above or below pelvic reflection)	TEA	As for, or derived from gastrointestinal or colonic guidelines	Thoracic epidural may need siting more caudally to cover perineal wound pain Consider lower site for APR	Multimodal approach required to reduce rectal neuropathic or chronic pain
	Spinal	TEA recommended for open and assisted laparoscopic surgery (specimen delivery incision 5–7 cm) Fewer rectal vs colorectal cancer cases are achievable entirely laparoscopically Epidural attenuates surgical stress response **Evidence: moderate, grade: strong** Open: TEA **Evidence: high, grade: strong** Laparoscopic: TEA. **Evidence: low, grade: weak**		Urinary retention more common due to surgical reasons (eg, bladder retraction)
	CWI & TAP as above	Abdominoperineal resection may require additional lower epidural L3-4 Limited evidence for wound catheters or continuous TAP catheters specifically in rectal surgery		Treat epidural-associated hypotension (as above) to reduce gut hypoperfusion and anastomotic breakdown
Pancreaticoduodenectomy (PD)[5]	TEA	As per, or derived from colorectal guideline Mid thoracic epidural- **Grade: Weak** Improved analgesia- **Evidence: High** Fewer respiratory complications- **Evidence: Moderate** Better outcomes- **Evidence: Low**	Epidural-induced hypotension causing anastomotic compromise may be related to sparse evidence and increased morbidity	
	CWI & TAP	Some but variable and conflicting evidence for TAP and CWI, from gastrointestinal surgery data		

Gastrectomy[7]	TEA CWI & TAP as for PD or GI surgery	Gastrectomy recommendations are as for PD (see above) RCT specific to gastrectomy for gastric cancer demonstrated TEA superior to PCA, both superior pain relief AND lower stress response[48]		No recommendations made specific to laparoscopic gastrectomy
Bariatric[10]	TEA	Consider TEA for laparotomy **Evidence: very low, grade: weak**	One study suggests TEA in obese patients associated with increased complication rate (wound infection), therefore, IV PCA is acceptable for gastric bypass[103]	Data comparing TAP and local infiltration in bariatrics lacking, despite evidence for feasibility and safety[104]
	CWI & TAP as for GI LA aerosol (laparoscopic)	Local anesthetic infiltration techniques should be considered **Evidence: high, grade: strong**		Evidence for local anesthetic aerosolizing techniques in laparoscopic bariatric surgery[105,106]
Radical Cystectomy for Bladder Cancer[4]	TEA CWI & TAP, as for GI	Thoracic epidural analgesia superior to systemic opioids, continue for 72 h **Evidence: high, grade: strong**	Techniques for minimally invasive (robotic or laparoscopic) surgery not addressed in ERAS Society guidelines due to limited use as of 2013	Evidence taken from colorectal and urologic studies

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Table 3
(*continued*)

ERAS Society Guidelines:	Route & Drug	Recommendation	Exceptions or Caution	Other
Gynecological[8,9]	Procedure-specific	Vaginal hysterectomy paracervical nerve block or intrathecal morphine to reduce pain and opioid requirements **Evidence: low, grade: weak**	Cochrane review: little benefit from paracervical block for cervical dilation[107] although successfully used in enhanced recovery programs for vaginal hysterectomy together with spinal morphine[108,109]	
		Open general gynecologic surgery Low concentration local anesthetic plus opiate TEA for 24–48 h **Evidence: high, grade: strong** Or, spinal anesthesia with intrathecal morphine **Evidence: moderate, grade: strong** TAP or ilioinguinal block or CWI if GA undertaken without neuraxial analgesia **Evidence: moderate, grade: strong**		TEA: benefits for open gynecologic as for open abdominal surgery; however, issues include failure (requiring supplemental opiates), hypotension requiring vasopressors, and may hinder other enhanced recovery goals (eg, mobilization[110]) and may delay discharge (ERAS Society hysterectomy target is 1–2 d admission) in oncological surgery[111] Open abdominal hysterectomy specific evidence for intrathecal LA + low-dose opioids[112–115]

		For TAP (24 h) if neuraxial not feasible [116,117] but CWI shows only very early benefit[117] or none[118–120] IPLA: very short-lived reduced pain[121] and opiate consumption[122,123]
Major oncologic surgery TEA (though patients frequently require additional IV PCA opioids) **Evidence: low, grade: weak**	Patients undergoing heated intraperitoneal chemotherapy may develop coagulopathy (0.05% incidence) complicating TEA removal[124,125]	Major oncological surgery TEA or PCA are both suitable options[110]
Laparoscopic gynecologic or oncology surgery Often severe postoperative pain Multimodal, otherwise no specific recommendations **Evidence: low, grade: weak**		TAP of benefit in laparoscopic hysterectomy for rest pain only[126] IPLA seems effective for minor not major laparoscopic gynecologic procedures[127–129] Spinal + GA vs GA alone seems superior in robotic urologic surgery[130]

to advocate particular anesthetic and analgesic techniques as a way to reduce cancer recurrence.[170] However, in animal models, a systematic review in 2016 demonstrated that volatile anesthetics seemed to increase and local anesthesia infiltration seemed to decrease the likelihood of distant metastasis.[171] Conflicting data for regional anesthesia and analgesia also exist, suggesting regional anesthesia improves survival but not recurrence in oncological surgery.[172] Recent investigations have identified that opioids inhibit cell-mediated and humoral immunity; promote tumor cell migration, proliferation, and cancer gene expression in human cells in vitro; and facilitate angiogenesis.[173] Conversely, a postoperative NSAID (eg, ketorolac) has been associated with decreased recurrence after breast cancer surgery, possibly via prostaglandin-mediated effects on cancer immunity.[174] However, a recent report showed that better compliance with ERAS Society protocols was associated with improved 5-year cancer survival.[175]

CHRONIC POSTSURGICAL PAIN PREVENTION WITH ADEQUATE ACUTE PAIN MANAGEMENT?

Chronic postsurgical pain is a common and serious complication involving postoperative pain lasting at least 2 months that is not related to a new or pre-existing pathologic condition.[65] As with cancer recurrence, although some mechanisms and associations have been demonstrated, the impact of acute pain management on chronic pain pathophysiology has not been fully described.[176] It is, however, an important area in which to monitor development and understanding could be enhanced by longitudinal health database technology facilitating longer-term population studies, as well as by conventional randomized controlled trial methodologies. A 2015 systematic review of chronic postsurgical pain after thoracotomy, amputation, and mastectomy demonstrated that appropriate dose regimes of gabapentinoids, antidepressants, local anesthetics, and regional anesthesia all potentially reduced the severity of both acute and chronic pain.[177] ERAS Society guidelines make reference to chronic and neuropathic pain for rectal or pelvic surgery only; however, there is insufficient evidence base for any of the ERAS Society guidelines to advocate a specific chronic pain prevention regime at this time, beyond optimizing acute pain management. This may be a more prominent feature of future ERAS Society guidelines and revisions.

AUDIT, EVALUATION OF OUTCOMES, AND LONG-TERM FOLLOW-UP OF PATIENTS ON ENHANCED RECOVERY AFTER SURGERY SOCIETY GUIDELINE–COMPLIANT PATHWAYS

Research on perioperative outcomes, including analgesia efficacy and the sequelae of pain, is hampered by a lack of an international standardized reporting system for postoperative outcomes over an adequate follow-up time. The use of large national data registries (eg, the American College of Surgeons' National Surgical Inpatient Quality Improvement Project) brings some standardization regarding postoperative complications to datasets, though these do not report on postoperative pain as a symptom or on pharmacologic management in any detail. The EIAS may help fill this role as a complement to existing administrative and academic health care registries and as a basis for research.[178] New perioperative outcome research registries include the Multicenter Perioperative Outcomes Group, a consortium of 56 medical centers across the United States and Europe. Although randomized controlled studies are considered a superior quality of evidence to case controlled studies, these very large registries of data are increasingly being used to analyze outcomes of diverse patient subpopulations on national and international bases, avoiding some cost and enrollment issues associated with clinical trials.

Patient's self-assessment of their care (broadly divided into patient-reported experience measures and patient-reported outcome measures)[179–181] may be integrated further, with effective pain management a dominant component in patient's assessment. Increasingly, patient satisfaction is recognized as a valid outcome measure due to its sensitivity in reporting unmet analgesic requirements, appropriateness in surgical candidate selection, and the impact of surgery on longer term quality of life.

SUMMARY

The ERAS Society has provided recommendations, which include optimal multimodal analgesia, as part of an evidence-based perioperative care pathway. Major challenges for pain management with multimodal analgesia are now 3-fold. First, there is a more general challenge to disseminate current best practice standards and procedural training to deliver multimodal analgesia to more patients globally. This is important because many other treatments influence pain and its management. Second, there is a need to consistently quantify adherence to ERAS Society guidelines for multimodal analgesia and quality of care according to standardized, carefully selected outcome measures in accessibly registries. Finally, we must develop and expand ERAS Society Guidelines in the future, with continuing review of new evidence in multimodal analgesia, ranging from trials of new drugs (eg, liposomal long-acting local anesthetics), trials of bundled care in emergency surgery or trauma, and studies into the role of analgesic pharmacotherapy in cancer recurrence and chronic pain.

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