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REVIEW ARTICLE

Morpheus and the Underworld—Interventions to Reduce the Risks of Opioid Use After Surgery: ORADEs, Dependence, Cancer Progression, and Anastomotic Leakage

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Abstract

Background Perioperative pain management is a key element of enhanced recovery after surgery (ERAS) programs. A multimodal approach to analgesia as part of a coordinated ERAS includes the reduction of opioid use. This review aims to discuss opioid-related adverse events, strategies to reduce opioid use after surgery, and the relevance to the present "opioid crisis" in North America.

Methods A literature review of the pharmacology of opioid drugs, perioperative opioid reduction strategies, and the potential public health benefit was performed. This included current ERAS guidelines on multimodal analgesia, randomized controlled trials on perioperative analgesia, and intervention studies to decrease opioid use, misuse, and diversion in North America.

Results Reduction of perioperative opioid usage has been endorsed by joint clinical practice guidelines on the management of postoperative pain from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists. Interventions as part of an "opioid bundle" that can be incorporated into ERAS protocols include multimodal analgesia, regional anesthesia, opioid sparing drugs, carbon dioxide humidification during laparoscopy, changing opioid prescription practices, patient and physician education, and proper disposal of unused opioid medications.

Conclusion There are substantial benefits in incorporating opioid reduction strategies into ERAS and clinical practice guidelines. These include faster return of function and mobility, and decreased opioid-related adverse drug events (ORADEs), postoperative morbidity and mortality, and length of hospital stay. Improved oncological outcomes after cancer surgery may be an additional benefit. Evidence-based interventions can also reduce opioid abuse and diversion in the community.

Keywords Morphine · Opioids · Analgesia · Perioperative · Dependence · ERAS

Introduction

Postoperative pain management is a key element of enhanced recovery after surgery (ERAS). The concept of a multimodal approach to analgesia in a coordinated ERAS program was first developed by the Danish surgeon Henrik Kehlet in the 1990s.[1, 2] This includes the use of multiple analgesic agents with differing modes of action, rather than reliance on single opioid agents.[3] Multimodal analgesia is effective because the perception of postoperative pain involves differing receptors, pain pathways, molecular mediators, cognitive elements, patient expectations, and premorbid states.

Postoperative pain is influenced by surgical technique and the handling of tissues, and surgical access including open, laparoscopic, or robotic approaches. Anxiety, depression, fear, sleep disturbance, pain catastrophizing, and increased circulating stress hormones (catecholamines/cortisol) can also contribute to delayed recovery from surgical pain.[4] Thus, postoperative pain may be both peripherally and centrally mediated, including nociceptive, inflammatory, neuropathic, movement evoked, allodynic, mixed, psychogenic, or idiopathic elements. There are substantial benefits in incorporating opioid reduction strategies and multimodal analgesia into ERAS programs.[3, 5] This review aims to discuss opioid-related adverse drug events (ORADEs), current and new strategies to reduce opioid use after surgery, and the relevance to the present "opioid crisis" in North America.[5]

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History of Morphine

Opium has been used to relieve pain, sleeplessness, thirst, hunger, diarrhea, and anxiety for millennia. Friedrich Wilhelm Adam Serturner, a Westphalian apothecary, originally isolated morphine salts from raw opium poppy juice in 1803–1805. Serturner initially named the new substance *Principium somniferum* and subsequently "morphium" after Morpheus, the Greek winged god of dreams. Plant alkaloids were recognized in 1818, and "morphium" was renamed "morphine." According to Greco-Roman mythology, Morpheus lived in a cave full of poppy seeds in the Underworld (Hades). This was near the River of Forgetfulness and Oblivion (Lethe), also known as Ameles potamos (the river of unmindfulness). The father of Morpheus was the god of sleep, Hypnos. Hypnos was often depicted wearing a crown of poppy flowers and carrying a horn of sleep-inducing opium, a poppy stem, or a branch dripping water from the river Lethe.[6, 7]

Opioid Drugs

The class of opioid drugs include naturally occurring opiate alkaloids (morphine, codeine, thebaine, papaverine) derived from the opium poppy (*Papaver somniferum*), semisynthetic opioids (heroin, hydrocodone, oxycodone, hydromorphone, oxymorphone, bruprenorphine), and synthetic opioids (tramadol, fentanyl, remifentanil, methadone). The semisynthetic and synthetic opioids have different potencies and half-lives compared with naturally occurring opiates. Opioid receptors are found in both the central and peripheral nervous systems, including primary afferent neurons and terminal nerve endings, the spinal cord, the midbrain, and the thalamus. These respond to both endogenous and exogenous opioids.[8]

There are four opioid peptide receptor subtypes: three "classical" including μ (MOP), κ (KOP), and δ (DOP) and one "non-classical" nociceptin/orphanin FQ peptide (N/OFQ) receptor (NOP).[8] All opioid receptors are coupled to the pertussis toxin–sensitive G i/o proteins, which inhibit adenylate cyclase and voltage-gated inward calcium channels and activate channels for potassium efflux. Presynaptic opioid receptors cause inhibition of synaptic transmission of pain stimuli, whilst postsynaptic opioid receptors cause inhibition of neuronal excitation[9] (Fig. 1). Morphine has a higher affinity for μ receptors than the other opioid receptors. Activation of the NOP receptor enhances MOP receptor agonist–induced analgesia without producing side effects.[11]

Most opioids act principally as potent μ-opioid receptor (MOR) agonists, resulting in their euphoric, soporific, and analgesic effects, and also their addiction potential. κ-Opioid receptor activation is associated with dysphoria, hallucinations, sedation, and diuresis (inhibition of ADH), and δ receptors anxiolytic and antidepressant effects but increased risk of seizures.[12] It has been shown capsaicin-sensitive primary afferent neurons are involved in the peripheral anti-nociceptive

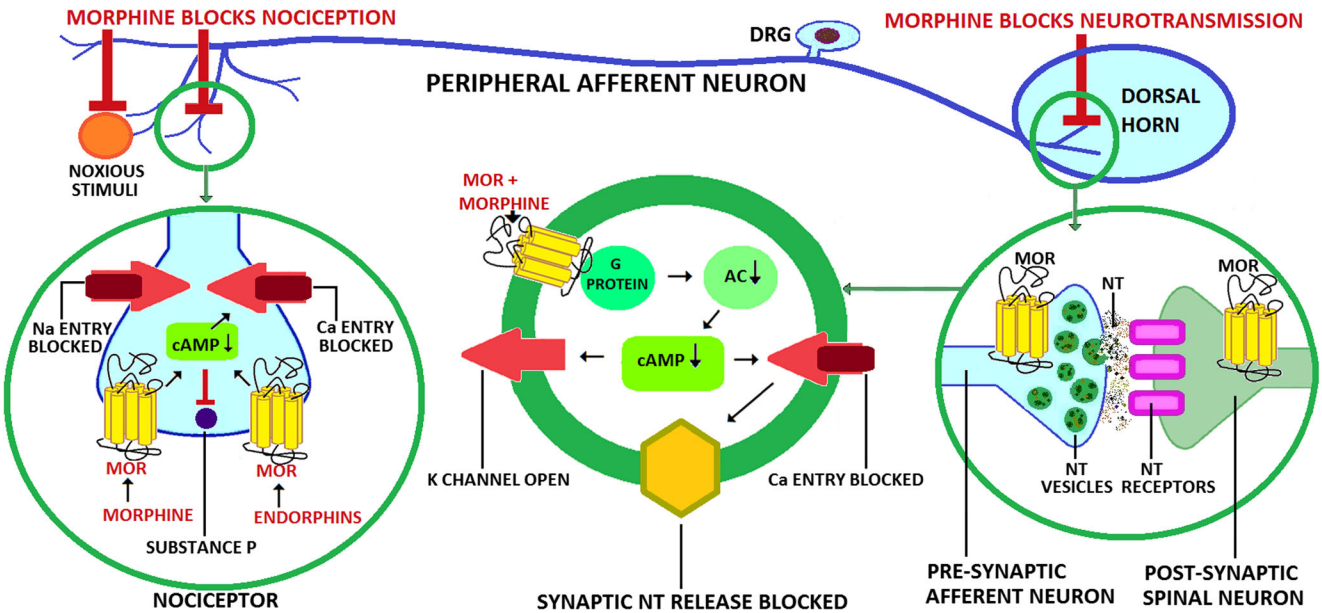

Fig. 1 MOR blockade of peripheral nociception at the afferent nerve terminal ending and neurotransmission at the presynaptic cleft. Activation of μ-opioid receptor (MOR) by exogenous opioids (morphine) or endogenous opioids (endorphins) at the terminal afferent nerve ending leads to decreased cyclic adenosine monophosphate (cAMP) via G i/o protein signaling. This leads to blockade of inward calcium and sodium channels, inhibition of substance P release, and hyperpolarization of the nerve. This inhibits the nociception of noxious chemical, mechanical, and thermal stimuli (extracellular ATP, bradykinin, H+, histamine, potassium, prostaglandins, serotonin, substance P) related to tissue injury, and the presynaptic release of neurotransmitter (NT) across the synaptic cleft to the postsynaptic spinal neuron[10]

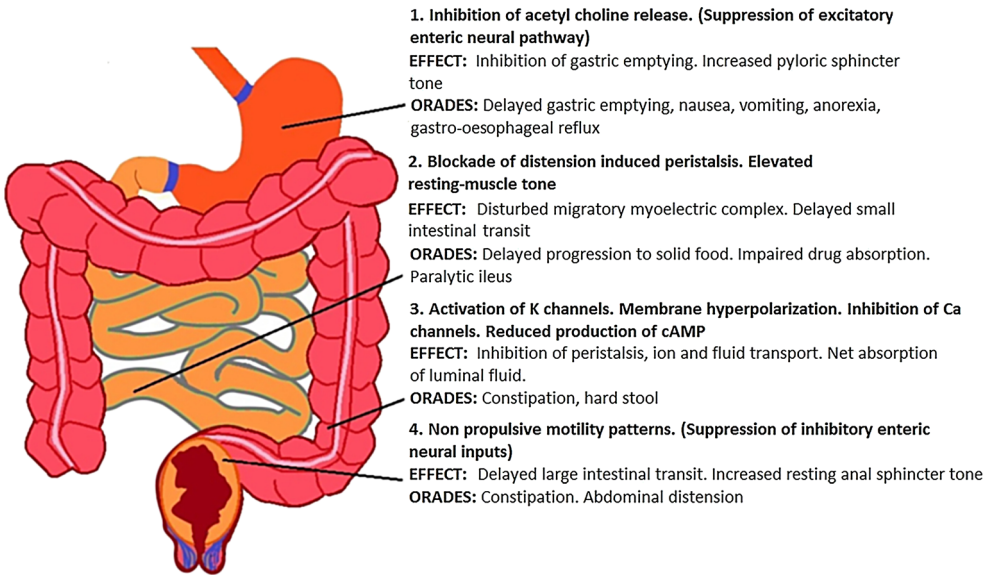

Fig. 2 Effects of human enteric MOR activation and ORADEs. Text adapted from: Holzer, P. Opioid receptors in the gastrointestinal tract. Regul Pept 2009;155(1–3):11–7[14]

effects of morphine and μ, κ, and δ selective opioid agonists. Opioid receptors are found on the terminal endings of afferent nerve fibers in the skin, peritoneum, joints, and viscera and are activated by both endogenous and exogenous opioids in the local environment. This produces hyperpolarization of the afferent nerve and inhibition of release of substance P, thereby reducing nociception[13] (Fig. 1). Opioid-related respiratory depression is caused by activation of MORs in the respiratory centers of the medulla, which decreases the sensitivity of chemoreceptors to carbon dioxide. Nausea and vomiting are common in patients given morphine, caused by stimulation of MORs in the medullary chemoreceptor trigger zone.[8]

Activation of peripheral MORs in the gastrointestinal tract results in delayed gastric emptying, reduced fluid secretion, paralytic ileus, slowing of intestinal transit, and constipation. This is mediated by opioid inhibition of nerves in the myenteric plexus that control gastrointestinal smooth muscle contraction (Fig. 2).[8, 14] Naloxone is a full MOR antagonist which, when administered intravenously, reverses all "classical" central and peripheral opioid receptors. Oral naloxone inhibits enteric MORs, but due to extensive first pass hepatic metabolism, does not have substantial systemic effects.[15] MORs are present not only on neurons but also on immune cells (granulocytes, monocytes/macrophages, lymphocytes, natural killer T cells) and cancer cells.[16]

Reduction of Opioid Use

One of the main components of multimodal analgesia in surgery as part of ERAS is the reduction of opioid usage in the perioperative period. This has been endorsed by joint clinical practice guidelines on the management of postoperative pain from the American Pain Society (APS), the American Society of Regional Anesthesia and Pain Medicine (ASRA), and the American Society of Anesthesiologists (ASA).[17]

There are numerous advantages to such an approach—these include reduction of:

1. Acute opioid-related adverse drug events including sedation, respiratory depression, and hypoxia.[18, 19]
2. Postoperative nausea, vomiting, constipation, and ileus (Fig. 2).
3. Histamine release, pruritus, hallucinations, and delirium.
4. Acute urinary retention, which occurs in 3.8–18.1% of postoperative patients.
5. Hyperalgesia, opioid tolerance, and persistence of pain.[18, 20]
6. Chronic postsurgical opioid dependence.[21]
7. Overall length of hospital stay (LOS) and treatment costs.[3, 19, 21]
8. Anastomotic leakage.[22–25]
9. Cancer progression[3, 16, 18, 26–28] (Fig. 3).
10. Illicit opioid use in the community.[31–33]

ORADEs

Opioid-related adverse drug events are associated with increased hospital LOS, costs, morbidity, and mortality.[19] ORADEs are particularly a risk in elderly or comorbid patients having major surgery. Elderly patients often have polypharmacy, chronic lung disease, renal impairment, or

hepatic dysfunction and are prone to drug interactions, hypoxia, narcosis, and delirium after surgery. For example, patients who had ORADEs following total joint replacement were eight times more likely to have a prolonged hospital stay than those who did not have adverse events.[18]

In a meta-analysis of 20,000 US patients having major gynecological, orthopedic, thoracic, or abdominal surgery using a single opioid postoperative analgesic technique, the incidence of opioid-induced respiratory depression (ORD) varied from 0.1 to 37%.[21] The most serious outcomes of ORD in a series of 357 patients between 1990 and 2009 from the US Anesthesia Closed Claims Project database were death (55%), permanent hypoxic brain damage (22%), and temporary cognitive loss (23%).[34] Most ORD events (88%) occurred within 24 h after surgery, and 13% of these occurred after the patients had been discharged to the ward. Contributing factors included concurrent administration of non-opioid sedating medications (34%), multiple prescribers (33%), inadequate nursing response (31%), obesity (66%), and obstructive sleep apnea (25%).

ORADEs are also associated with prolonged recovery after gastrointestinal and colorectal surgery. Opioid-related malaise, nausea and vomiting, impaired gastric emptying, paralytic ileus, and constipation all contribute to delays in tolerance of solid food, ambulation, and recovery of bowel function[35] (Fig. 2). These side effects also impact on protein catabolism, risk of VTE, and patient satisfaction. Even in the presence of an ERAS program, 19.2% of patients undergoing laparoscopic colorectal surgery developed postoperative ileus. Factors related to this may include inadequately controlled postoperative pain (increased sympathetic tone), increased use of opioid analgesics, perioperative hypothermia, splanchnic hypoperfusion, or loss of intestinal pacemaker activity.[34] The use of combined long-acting oral opioids (oxycodone) and oral opioid antagonists (naloxone) has been shown to reduce constipation in chronic pain patients, but oxycodone/naloxone may not provide superior analgesia to oxycodone in the immediate postoperative period.[36]

Hyperalgesia and Rapid Tolerance

Opioid induced hyperalgesia is related to nociceptive hypersensitivity (increased response to painful stimuli), allodynia (painful response to normally innocuous stimuli), and intraoperative use of opioids.[18, 37] This is particularly the case with potent, ultra-short-acting opioids such as fentanyl and remifentanil. These have rapid on-off effects with abrupt cessation of analgesia, leading to high postoperative pain scores and large opioid consumption in the immediate postoperative period.[38, 39] Rapid development of tolerance particularly in opioid naïve patients can also contribute to this *opioid paradox*, where increased opioid doses are required to maintain the same analgesic effect.[21] The compensatory increase of adenyl cyclase and cAMP on morphine withdrawal is thought to contribute to opioid tolerance and dependence.[40] Administration of intraoperative propofol has an inhibitory effect on N-methyl-D-aspartate (NMDA) receptors, which is a receptor involved in remifentanil-induced hyperalgesia.[41]

Chronic Postsurgical Opioid Use

Chronic use of opioids (> 90 days) after surgery is related to prescribing practices in the perioperative period, inadequate initial pain relief, and opiate-naïve patients.[21, 42] Hyperalgesia and early rapid tolerance in opioid-naïve patients may also contribute, together with premorbid risk factors including personal or family history of substance abuse and tobacco use, history of depression or anxiety, and history of childhood trauma or abuse.[31] Prescribing practices relate to very large cumulative doses being given (≥ 700 morphine milligram equivalents), long initial opioid prescriptions (10- or 30-day supply), or a second prescription or repeat.[42] In a retrospective study of over 36,000 opioid-naïve patients having elective surgery in the USA between 2013 and 2014, the extent of surgery was not a risk factor for chronic opioid use after surgery—chronic opioid use was just as likely to occur after minor surgery as major surgery.[21] Starting on the third postoperative day, every day of opioid use increased the risk of chronic opioid dependence. This was particularly so after the fifth and 31st days of opioid therapy.[42]

Anastomotic Leakage and Morphine

Recently, it has been shown that alterations in the normal colonic microbiota can contribute to postoperative anastomotic leakage after colorectal resection. This can occur due to proliferation of commensal bacteria such as *Enterococcus faecalis* and *Pseudomonas aeruginosa*, both of which produce collagenases which degrade collagen I and activate mixed metalloprotease 9 (MMP-9), which then degrades collagen IV. The use of second- and third-generation cephalosporin prophylaxis and bowel preparation prior to colorectal surgery disrupt the dominant colonic phyla (*Bacteroidetes* and *Firmicutes*), which are known to protect the underlying colonic enterocytes from invasion by pathogenic bacteria.[22]

Exogenous morphine is concentrated in intestinal tissues and excreted into the intestinal lumen. Thus, the intestinal microbiota is exposed to both endogenous (endorphins) and exogenous morphine. Morphine is a potent chemoattractant for *Pseudomonas aeruginosa* and enhances the adhesion of *P. aeruginosa* via biofilm production. It also directly promotes adhesiveness of *E. faecalis* to anastomotic sites and increases *E. faecalis* collagenase production. The administration of morphine was significantly associated with the growth, adherence,

and collagenase activity of *E. faecalis* and the failure of colonic anastomotic healing in a murine model (morphine 56% leak rate vs placebo 3% leak rate, $p = 0.0045$). This effect of morphine on *E. faecalis* was enhanced by exposure to collagen, which occurs at anastomotic sites, and is related to an *E. faecalis*–specific collagen-binding protein, Ace.[23–25] Anastomotic leakage may also increase the risk of perianastomotic recurrence after colorectal cancer resection. The *E. faecalis* effect on increased MMP-9 activity contributes to tissue breakdown, anastomotic leakage, an inflammatory pathobiome, and cancer cell proliferation.[24] ERAS strategies to reduce *E. faecalis* and *P. aeruginosa* growth and potentially prevent anastomotic leakage include reduction of systemic and oral morphine use, using peripheral opioid antagonists, use of specific oral antibiotics with mechanical bowel preparation which do not disrupt intestinal flora, topical antibiotic wash to the rectum, and use of oral short chain fatty acids (SCFA) and nonabsorbable oral phosphates to preserve normal colonic microbiota.[24]

Cancer Progression and Morphine

There are multiple mechanisms by which morphine can promote cancer progression, including pro inflammatory effects, cancer cell proliferation and migration, vascular permeability, angiogenesis, and immunosuppression.[3] Activation of MORs and Toll-like receptor 4 (TLR-4) by opioids enhances the pro-inflammatory state after surgery (Fig. 3). Morphine also transactivates numerous signaling pathways involved in cellular proliferation and angiogenesis in both endothelial cells and tumor cells. These include mitogen-activated protein kinase/extracellular signal–regulated kinase (MAPK/ERK) and pro-survival Akt, vascular endothelial growth factor receptor (VEGFR-2), platelet-derived growth factor receptor β (PDGFR β), and fibroblast growth factor (FGF) receptor 1 (Fig. 3). Phosphorylation of the epidermal growth factor receptor (EGFR) occurs via opioid receptor stimulation, which can be antagonized by naloxone. After removal of the ligand (morphine), prolonged MOR activation may occur,

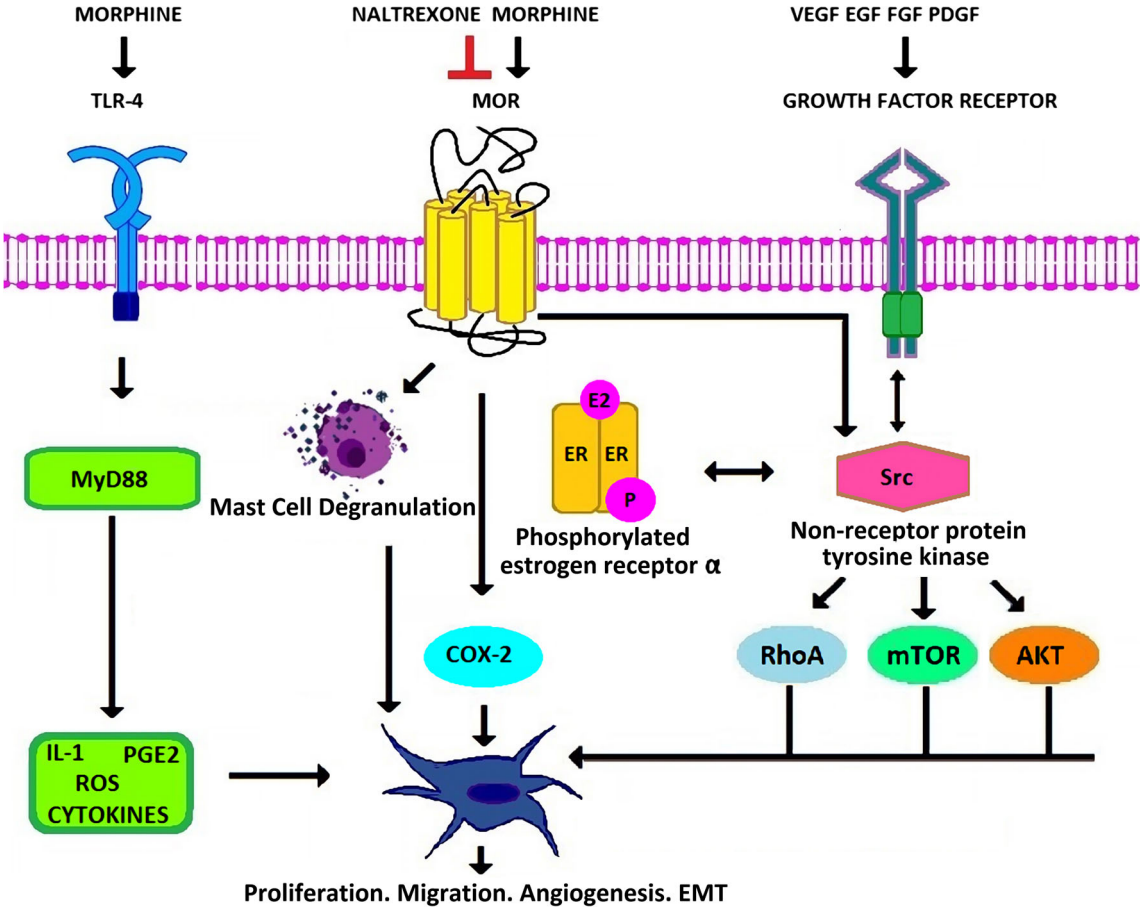

Fig. 3 Interactions between MOR, ER-α, Src, and TLR-4 in the promotion of cancer growth. Morphine activates both μ-opioid receptor (MOR) and Toll-like receptor 4 (TLR-4) on the cell membrane. MOR activation leads to phosphorylation of Src, ER-α, and growth factor receptors (VEGF, EGF, FGF, PDGF), leading to activation of downstream targets of cell survival (Akt), actin skeleton changes (RhoA), and mammalian target of rapamycin (mTOR). Activation of TLR-4 and MOR promotes inflammatory pathways via myeloid differentiation primary response 88 (MyD88) and nuclear factor kappa-B (NF-κB), mast cell degranulation, COX-2 expression, and cytokine/prostaglandin E_2 (PGE_2) release. Thus, morphine promotes cancer growth by increasing cell proliferation, migration, angiogenesis, and epithelial-mesenchymal transition (EMT). This effect is blocked by COX inhibitors or naltrexone.[29, 30]

particularly with chronic exposure. This is related to a high MOR activation versus endocytosis (RAVE) value, which contributes to super activation of adenyl cyclase. The ensuing *cAMP overshoot* promotes tumor cell survival and proliferation.[26, 40]

MOR signaling also stimulates the proto-oncogene Src, which controls resistance to anoikis, evasion of apoptosis, and many tyrosine kinase signaling pathways in carcinogenesis. Morphine induced mast cell degranulation and release of substance P enhanced the growth of pancreatic ductal cell cancer in mice and breast cancer cell lines in culture.[26, 27] Morphine induces expression of COX-2 and PGE_2, and co-treatment with morphine and the COX-2 inhibitor celecoxib reduced angiogenesis, tumor growth, metastasis, and mortality in a mouse model of breast cancer[26] (Fig. 3).

Many cancer cells overexpress μ-opioid receptors, including glioblastoma and colon, breast, lung, pancreatic, thyroid, endocrine, and endometrial cancers. Expression of MOR in human lung cancer is significantly increased compared with adjacent control tissues ($p = 0.0242$) and is nearly two times higher in metastatic lung cancer compared with primary disease.[16] There is an association between increased 5-year recurrence rates in resected non-small cell lung cancer (NSCLC) and higher doses of opioids in the initial 96-h postoperative period, together with poorer overall survival in resected NSCLC given intraoperative opioids.[16] Naloxone prevents the cross-talk between ER-α and MOR, suggesting that activation of MOR by opiates may contribute to E2-induced ER-α activation in breast cancers or other estrogen-sensitive cancers such as ovarian cancer[43, 44] (Fig. 3).

Opioids can modulate immune function either by acting peripherally on MOR expressed on lymphocytes and macrophages or via central MOR which activates the hypothalamic-pituitary axis.[28] Opioids may inhibit both humoral and cell-mediated immunity, as MORs are found on granulocytes, monocytes/macrophages, lymphocytes, and natural killer (NK) T cells.[16] For example, in patients receiving postoperative morphine, decreased NK cell activity has been demonstrated. In rodent models of breast cancer, morphine-related inhibition of NK cell activity resulted in tumor growth. This morphine-induced immunosuppression could be inhibited by MOR antagonism with naltrexone or naloxone.[26] Because the immunosuppressive effects of MOR activation are dose related, strategies to reduce opioid use in cancer surgery may result in improved patient outcomes.[28]

Illicit Opioid Use

North America is presently in the midst of an opioid crisis.[18, 45] Opioids are commonly overprescribed after surgery. Hasak et al. (2018) showed that on average, patients consumed only 33% of their total postoperative opioid prescription. The majority also kept their unused tablets, usually in an unsecured place in their homes.[21, 31] Unused opioids that are prescribed after surgery are a major source of illicit opioid use and also trafficking. The majority of North Americans who misuse prescription opioids obtain them from their friends or relatives who have leftover medication.[32] Two of the most commonly prescribed perioperative opioids, oxycodone and hydrocodone, are the most frequent prescription drugs associated with diversion, abuse, and overdose in the USA.[18]

Ten Interventions to Reduce Opioid Use—the Opioid Bundle

1. Multimodal analgesia
2. Regional anesthesia and analgesia
3. Avoidance of hyperalgesia
4. Systemic opioid sparing drugs
5. NSAIDs
6. TAP blocks/intrathecal morphine
7. Warmed humidified CO_2 pneumoperitoneum
8. Changing opioid prescription practices
9. Patient education/expectation
10. Proper disposal of unused opioids.

Multimodality Analgesia and ERAS

Henrik Kehlet advocated a multimodal approach to reduce perioperative opioid use in enhanced recovery after surgery, which has now been widely implemented in modern ERAS programs.[3, 5, 46–50] This includes the use of regional anesthesia and analgesia in conjunction with systemic opioid–sparing drugs, such as dexamethasone, ketamine, clonidine/dexmedetomidine, lidocaine, gabapentinoids, acetaminophen, or cyclooxygenase inhibitors.[18, 51] For example, using combined general-epidural anesthesia together with oral celecoxib, tramadol, and pregabalin and the systemic infusion of lidocaine, dexmedetomidine, and/or ketamine could reduce the use of postoperative opioids by up to 84% in patients undergoing HIPEC/cytoreductive surgery, hepatobiliary surgery, or gynecological surgery.[18] Randomized controlled trials of regional anesthesia versus systemic opioid analgesia have shown improved oncological outcomes in human colorectal, prostate, ovarian, and breast cancer surgery.[3]

Total intravenous anesthesia (TIVA) with propofol/remifentanil infusion versus inhalational sevoflurane/remifentanil infusion was associated with a significantly reduced total postoperative PCA morphine consumption (16.64 mg vs 24.07 mg, $p < 0.001$) after colorectal surgery. A meta-analysis of 14 clinical trials showed intraoperative propofol resulted in lower postoperative pain scores at

24 h.[41] Co-administration of subcutaneous gabapentin with morphine has been shown to decrease morphine hyperalgesia. The antihyperalgesic effects of intrathecal gabapentin were augmented by small doses of intrathecal diclofenac (which alone were insufficient to normally affect nociception).[20] In a placebo-controlled RCT of gabapentin administration for 72 h after a variety of surgical procedures (general, orthopedic, thoracic), a 24% increase in the rate of opioid cessation was shown.[52]

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) include non-selective and selective cyclooxygenase (COX)-2-specific inhibitors (coxibs). These have been shown to significantly reduce PCA opioid consumption, vomiting, and sedation after major surgery respectively by 30%, 32%, and 29%. This is associated with improvements in the quality of recovery and patient satisfaction.[53] When used in scheduled doses and in correctly selected patients, NSAIDs can be a powerful adjunct to multimodal analgesia.[21] Wick et al. (2017) found 600 mg of oral ibuprofen was as efficacious as 15 mg of oxycodone hydrochloride.[54] Perioperative NSAIDs are considered to have a good safety profile, but there are some contraindications. In a study comparing the use of non-selective NSAIDs in abdominal, orthopedic, gynecological, or urological surgery in a total of 11,245 patients, 155 patients (1.38%) had a serious adverse outcome. These included 19 deaths, 117 patients who had surgical site bleeding, 12 allergic reactions, 10 patients who had acute renal failure, and 4 patients who had gastrointestinal bleeding. The safety profiles of ketorolac, ketoprofen, or diclofenac were found to be similar.[55]

In animal studies, use of NSAIDs has been shown to decrease hydroxyproline levels, angiogenesis, cell migration, tensile strength, and the bursting pressure of colonic anastomoses. However, the evidence in human trials of colorectal anastomotic surgery is conflicting. Early perioperative administration (within 48 h) and large doses of diclofenac (> 100 mg) and celecoxib (> 200 mg) appear to promote colorectal anastomotic leakage, rather than later administration and smaller doses. Other contributing risk factors include malnourished or diabetic patients, emergency surgery, or rectal resections.[56] Because of the lack of consensus regarding the use of NSAIDs and anastomotic leakage in colorectal surgery, a recent Canadian ERAS protocol suggested "celecoxib 400 mg as a loading dose should be considered in all open and laparoscopic colorectal procedures after discussion between the surgeon and anesthesiologist regarding the potential risks and benefits."[49]

TAP blocks

Regional analgesia with transversus abdominis plane (TAP) block using local anesthetic has been shown to be safe and effective in reducing postoperative opioid use. In a meta-analysis of TAP block versus placebo in abdominal surgery, a significant reduction was shown in pain scores and morphine consumption (− 14.7 mg morphine, 95% CI, − 18.4 to − 11.0 mg; $p < 0.001$) in the TAP block group at 24 h after appendicectomy and gynecological, inguinal hernia, bariatric, and urological surgery. Decrease in morphine use with TAP block versus local infiltration ranged from 4.9 to 10.1 mg in Cesarean section and up to 20.4 mg in appendicectomy and inguinal surgery. When TAP blocks and intrathecal morphine were compared, VAS scores at 24 h showed no statistical difference; however, intrathecal morphine showed significantly reduced opioid consumption (− 7.7 mg morphine, 95% CI, − 1.9 to − 13.5; $p = 0.009$) in comparison with TAP block.[57]

In a meta-analysis of 7 RCTs involving 511 patients undergoing laparoscopic or open colorectal surgery for benign or malignant conditions, Liu et al. (2018) found TAP block resulted in significantly less patient pain and opioid use in the first 24 h after surgery when compared with controls.[58] TAP block was easy to perform and cost-effective with no adverse events related to the TAP block procedure or anesthetic-related toxicity reported. Other studies found TAP blocks were not so effective after colorectal surgery, particularly for upper abdominal incisions for right hemicolectomy. TAP blocks effectively anesthetize sensory dermatomes from T10 to L1, but not the upper abdomen above the umbilicus. They provide relief of pain related to the incision and parietal peritoneum, but not visceral pain or diaphragmatic pain.[58]

Humidified Warmed Carbon Dioxide Pneumoperitoneum

Cold dry or warm dry pneumoperitoneum during laparoscopic surgery can contribute to postoperative pain and opioid use. This is related to desiccation of the visceral and parietal peritoneum due to evaporation and thermodynamic losses associated with humidifying the dry gas. Such damage is increased by high CO_2 insufflation pressures and gas velocities and prolonged laparoscopic procedures.[59] Shoulder tip pain after laparoscopy is thought to be related to peritoneal desiccation and inflammation and activation of phrenic nerve nociceptors, rather than mechanical stretching of the diaphragm.[60] This is actually *worsened* by warmed dry CO_2 compared with standard cold dry CO_2 insufflation after procedures such as laparoscopic fundoplication/hiatus hernia repair.[61] Shoulder tip pain is poorly relieved by systemic opioids. Humidification and warming of insufflated CO_2 to body temperature have been shown in a RCT of laparoscopic hysterectomy to improve shoulder tip pain and

decrease total morphine consumption (− 7.5 mg, $p = 0.025$) and the number of rejected PCA boli.[62]

A recent meta-analysis of 16 RCTs compared cold dry CO_2 with warm humidified CO_2 insufflation during human laparoscopic surgery. Procedures included laparoscopic appendicectomy, cholecystectomy, gastric band surgery, Nissen fundoplication, Roux-en-Y gastric bypass, hysterectomy, colonic resection, and gynecological laparoscopy. Pain was measured using a visual analogue score (VAS), verbal rating scale (VRS), morphine equivalent daily dose (MEDD), and total analgesia requirement. Nine studies (602 patients) found no difference in postoperative pain whilst seven studies (621 patients) found that pain was significantly lower with the use of humidified, warmed CO_2 pneumoperitoneum. The authors noted that comparing shorter procedures such as laparoscopic appendicectomy to longer, complex procedures may be a confounding factor, particularly when the largest included trial did not show any difference in postoperative pain and involved a total of 195 laparoscopic appendicectomies. Other benefits of CO_2 humidification include avoidance of hypothermia and improved splanchnic circulation.[14, 63, 64]

Changing Post Surgery Opioid Prescribing

The use of clinician-mediated and organizational-level interventions has been shown to change postsurgical opioid prescribing. Organizational interventions include changes to electronic health records order sets and workflow. The development of guidelines based on actual postoperative opioid use by patients and the dissemination of guidelines to clinicians resulted in a 53% reduction in the opioid quantity prescribed. This did not result in increased emergency department visits or prescription refill requests by patients.[33]

Howard et al. (2018) implemented a program of evidence-based opioid prescribing recommendations after laparoscopic cholecystectomy. This resulted in a 63% post intervention reduction in opioid prescription size.[32] Multimodal analgesia including acetaminophen or ibuprofen was encouraged. Patients were educated about postoperative pain and multimodal analgesia and expectations were set regarding patients' use of perioperative opioids. The flow on effect of this intervention in laparoscopic cholecystectomy was then studied in 4 other commonly performed general surgery procedures in the same institution. These included laparoscopic appendicectomy, laparoscopic sleeve gastrectomy, laparoscopic inguinal hernia repair, and thyroidectomy/parathyroidectomy.[32]

Mean size of opioid prescription (oral morphine equivalents) was significantly reduced for all 4 procedures ($p < 0.001$), with only laparoscopic appendicectomy showing an increase for prescription refills. An estimated 10,000 opioid tablets were prevented from entering Michigan communities over a 10-month period, due to the post intervention prescription changes in these 4 procedures. A potential confounding factor in the change in prescribing practices was increased publicity during the study period about the relationship between postoperative opioid prescribing and the North American opioid epidemic.[32]

Disposal of Unused Opioids

Failure of disposal of unused or expired opioids after surgery is a major public health problem due to opioid diversion or abuse. Educating patients regarding safe disposal and the risk of keeping excess opioids can be effective. A simple educational pamphlet was shown to significantly improve safe opioid disposal from 11 to 22%. Methods of unused opioid disposal ranged from flushing down the toilet, placing in the garbage mixed with an unpalatable substance (e.g., soap/detergent), returning to a pharmacy, DEA, or police station. Barriers to disposal included discrepancies in disposal recommendations between the US EPA and the FDA. Some pharmacies are not registered with the DEA as designated opioid return centers, or only have specific return days.[31]

Conclusions

There are substantial benefits in incorporating opioid reduction strategies into ERAS programs. These include decreased ORADEs, faster return of function and mobility, minimization of perioperative morbidity and mortality, and shorter length of hospital stay. There is some emerging evidence that opioids promote anastomotic leaks after colorectal surgery and cancer recurrence after oncology surgery. Interventions to reduce opioids include multimodal analgesia, regional anesthesia/analgesia, opioid-sparing drugs, and CO_2 humidification during more prolonged laparoscopic procedures.

Evidence-based opioid prescription practices, physician and patient education, and promotion of safe disposal of unused opioids can all contribute to minimizing opioid abuse and diversion in the community.

Author Contribution Robert B. Wilson conceived, researched, wrote, and prepared the review, manuscript, and references.

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