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Evolving the Management of Acute Perioperative Pain Towards Opioid-Free Protocols: A Narrative Review

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ABSTRACT

Objective: Identification of pain as the fifth vital sign has resulted in over-prescription and overuse of opioids in the United States (US), with addiction reaching epidemic proportions. In Europe, and more recently in the US, a shift has occurred with the global adoption of multimodal analgesia (MMA), which seeks to minimize perioperative opioid use. Improved functional outcomes and reduced healthcare utilization costs have been demonstrated with MMA, but wide-scale use of opioids in pain management protocols continues. As a next step in the pain management evolution, opioid-free analgesia (OFA) MMA strategies have emerged as feasible in many surgical settings.
Methods: A MEDLINE search for articles published within the last 10 years was performed using the terms "opioid" and "acute pain" or "post(-)operative pain". Articles were limited to clinical studies and meta-analyses focusing on comparisons between opioid-intensive and opioid-free/opioid-sparing strategies published in English.
Results: In this review, elimination or substantial reduction in opioid use with OFA strategies for perioperative acute pain are discussed, with an emphasis on improved pain control and patient satisfaction. Improved functional outcomes and patient recovery as well as reduced healthcare utilization costs also are discussed, along with challenges facing implementation of such strategies.
Conclusions: Effective MMA strategies have paved the way for OFA approaches to postoperative pain management, with goals to reduce opioid prescriptions, improve patient recovery, and reduce overall healthcare resource utilization and costs. However, institution-wide deployment and adoption of OFA still is in early stages and will require personalization and better management of patient expectations.

1 INTRODUCTION:

Over-prescription of opioids has resulted in an opioid epidemic in the United States (US), with one death every 36 minutes considered attributable to opioids [1]. In 2015, 63.1% of deaths related to drug overdose in the US involved an opioid [2]. In 2016, the US Department of Health and Human Services reported that 116 people die each day from opioid-related drug overdose [3]. To address this issue, the recent Call to Action by the Office of the US Surgeon General highlighted an urgent need for change in current pain management strategies, with particular emphasis on reducing the prescription of opioids throughout the continuum of care [4].

Although opioids have long been the mainstay of pain management strategies in the US, their use has failed to result in incremental improvements in patients' experience of pain over the past decade. Low patient satisfaction is a common consequence of pain management strategies that rely heavily on opioids, primarily attributable to opioid-related adverse drug events (ORADEs), which can significantly lower patient quality of life and increase health-related costs [5]. ORADEs may have both short- and long-term consequences, including disruptions in normal gastrointestinal function (postoperative nausea and vomiting, postoperative ileus, constipation), respiratory depression,

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and mental confusion [5]. Opioid use also is associated with an increased risk of hyperalgesia, tolerance, and addiction [6].

Opioid use impacts a wide range of patient populations undergoing treatment for acute as well as chronic conditions. While opioid use and pain management have been studied in detail for chronic conditions, opioid exposure due to prescriptions for acute pain remains an under-recognized risk for developing chronic addiction [7]. A survey in 2013 reported that 84% of patients experience postsurgical pain after hospital discharge [8], a 2017 survey found that doctors in the US treat acute pain with opioids in 97% of cases [9]. Thus, acute care settings represent a major source of opioid prescriptions; they contribute significantly to chronic opioid use and addiction, particularly in opioid-naïve patients. Examples of such acute care settings include patient emergency department (ED) visits and hospitalizations for surgical procedures requiring intraoperative use and perioperative prescription of pain medication [10,11]. Further, patients prescribed opioids prior to surgical interventions have evident increases in postoperative opioid use [12]. Recent data show that tolerance to opioids in such patients can develop in as little as a few hours, resulting in suboptimal analgesic effects and the need to increase drug doses [13].

Leveraging an understanding of the complex humoral and neuronal response associated with surgery and pain, multimodal analgesic regimens were introduced in Europe nearly two decades ago to improve analgesia. Multimodal management protocols involve the simultaneous use of drugs with different modes of action, leading to additive or synergistic pain relief by exerting effects at different points along nociceptive pathways. Such approaches also prevent the development of adverse drug reactions associated with the use of larger doses of a single agent, specifically opioids [14]. Broadly, multimodal pain management protocols often involve the use of multiple pre-, intra- and postoperative analgesics. Currently available analgesics such as acetaminophen, gabapentin, ketamine, and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as the increased adoption of regional anesthesia techniques, have the potential to reduce or eliminate opioid use during the perioperative period.

To date, several multimodal pain management strategies have been implemented, including the use of neuraxial and peripheral nerve blocks and regional anesthesia, combinations of nonopioid medications, and, as necessary, the combination of nonopioid and opioid analgesics [15] . The use of such MMA strategies have been shown to enhance patient recovery by reducing the occurrence of ORADEs and decreasing the length of stay in hospital recovery rooms, thereby reducing the burden on healthcare resources and improving patient quality of life [16] . In the perioperative setting, most enhanced recovery after surgery (ERAS) protocols emphasize the use of such strategies [17] . The following section details several recent studies and protocols utilizing MMA opioid-sparing regimens.

Opioid-Sparing Pain Management Utilizing Multimodal Analgesia Protocols:

Several studies have been conducted on the use of multimodal opioid-sparing pain management regimens for acute surgical care Table 1. Such approaches can be used across age groups and surgery types, aiming to reduce the need for intraoperative and postoperative opioids, thereby improving patient satisfaction and recovery.

In addition, meta-analyses related to their use have also been conducted. A meta-analysis of 52 randomized trials evaluating the effect of multimodal analgesic options such as acetaminophen, NSAIDs, and selective COX-2 inhibitors in combination with morphine patient controlled analgesia (PCA) on opioid use in adults also reported a 15%-55% decrease in median 24-hour morphine consumption versus controls [28]. Similarly , a recent meta-analysis of 31 ran-domized con trolled trials evaluating the effect of NSAIDs and/or paracetamol used in combination with systemic opi-oids for pediatric periop erative pain management reported significant reductions in postoperative opioid use and superior pain relief in the multimodal analgesia group, with re- ductions in opioid use ranging from about 24% to 32% [29]. A meta-analysis of eight studies evaluating the effect of peri-operative magnesium sulfate administration on intraopera- tive fentanyl consumption reported a reduction of 53.57 g in fentanyl use in the magnesium sulfate group ($p < 0.001$) [30].

A few case examples of opioid-sparing multimodal proto- cols pertaining to colorectal surgery are presented in Table 2.

In these patients, regional anesthetics such as bupivacaine along with ketorolac or intravenous (IV) acetaminophen were used perioperatively. Ketorolac, IV acetaminophen, methocarbamol/gabapentin, and tramadol used postoperatively in these example protocols allowed the prescription of relatively low doses of analgesics at discharge Figure 1.

Opioid-Sparing versus Opioid-Intensive Regimens: Patient Satisfaction and Cost Savings:

Patient Satisfaction and Quality of Life:

In comparison with opioid monotherapy, the use of a multimodal approach has been shown to provide several benefits for patients receiving intraoperative and perioperative pain medications. The most important among these are improved patient satisfaction and cost savings. Several studies have shown that patient satisfaction improves with the use of opioid-sparing multimodal pain management compared with standard opioid-based regimens. A pooled analysis of five methodologically similar, double-blind, randomized clinical trials evaluating patient satisfaction after surgery found that the use of perioperative regimens that included IV acetaminophen resulted in significantly higher rates of patient satisfaction than standard opioid-based regimens 32.3% of patients reported satisfaction ratings of “excel-lent” in the IV acetaminophen group versus 15.9% in the group receiving the standard opioid-based regimen [31]. In a prospective, randomized controlled trial that evalu-ated quality of recovery in patients undergoing surgery for breast cancer, patients reported significantly better pain

Table 1. Effect of Multimodal Pain Management Regimens on Opioid Use

Multimodal Approach	Opioid Monotherapy	Type of Surgery	Effect on Opioid Consumption/Prescription	Reference
Opioid Sparing				
IV acetaminophen (1000 mg every 6 hours) plus opioids	Fentanyl, morphine, hydromorphone, meperidine, or oxycodone	Hysterectomy	26% reduction in opioid use over the total perioperative period ($p = 0.001$)	Herring et al., 2014 [18]
IV acetaminophen plus MSO4 (PCA)	MSO4 PCA	Laparoscopic Roux-en-Y gastric bypass	25% reduction in narcotic demand 24 hours postoperatively ($p < 0.05$)	Saurabh et al., 2015 [19]
IV acetaminophen (1000 mg every 6 hours) postoperatively plus opioids	Only opioids	Laparoscopic sleeve gastrectomy/ laparoscopic Roux-en-Y gastric bypass	Mean reduction of 27.7 mg morphine equivalents ($p < 0.001$)	Song et al., 2014 [20]
IV paracetamol (1000 mg) OR IV dexketoprofen (50 mg) plus PCA morphine	PCA with morphine	Lumbar disk surgery	Cumulative morphine consumption increased in all groups ($p > 0.05$)	Tunali et al., 2013 [21]
Dexmedetomidine infusion + intraoperative opioids	Intraoperative opioids alone	Open and laparoscopic gynecologic surgery	15 mg vs 21 mg morphine equivalents in PACU ($p = 0.0003$)	McQueen-Shadfar et al., 2011 [22]
Ketamine + PCA	Standard intraoperative anesthesia + PCA	Open ventral hernia repair	11.6 mg vs 47.6 mg MSO4 equivalents ($p < 0.001$)	Warren et al., 2017 [23]
Opioid Free				
Gabapentin, 300 mg (1200 mg total), preoperatively and 600 mg 3 times a day postoperatively (10 total doses) OR active/inactive placebo	Previously prescribed opioids	Thoracotomy, video-assisted thoracoscopic surgery, primary or revision total hip replacement, primary or revision total knee replacement, unilateral or bilateral mastectomy, breast lumpectomy (with or without sentinel node biopsy or axillary node dissection), hand surgery, carpal tunnel surgery, knee arthroscopy, shoulder arthroplasty, and shoulder arthroscopy	24% increase in the rate of postoperative opioid cessation ($p = 0.05$)	Hah et al., 2017 [24]
Parecoxib/valdecoxib + supplemental analgesia	Placebo + supplemental analgesia	Major noncardiac surgery	31% decrease in postoperative opioid consumption vs placebo ($p < 0.0001$)	Langford et al.,2009 [25]
Ketorolac, clonidine, lidocaine, ketamine, magnesium sulfate, and methylprednisolone	Sevoflurane and fentanyl	Gastric bypass surgery	5.2 mg/h morphine PCA vs 7.8 mg/h morphine PCA in the PACU	Feld et al., 2003 [26]
IV lidocaine + epidural analgesia	Saline + epidural analgesia	Complex spine surgery	55 mg vs 74 mg morphine equivalents ($p = 0.011$)	Farag et al., 2013 [27]

IV, intravenous; MSO, morphine sulfate; PACU, post-anesthesia care unit; PCA, patient-controlled analgesia

Table 2. Multimodal Pain Management Protocols for Colorectal Surgery

Age (years)	Sex	Diagnosis	Procedure	Preoperative Medications	Perioperative Medications	Postoperative Medications	Discharge Medications	Discharge day (POD)
78	M	Transverse colon adenocarcinoma	Laparoscopic extended right hemicolectomy	None	Fentanyl 100 g (once) Bupivacaine 40 cc Acetaminophen 1000 mg (once)	Ketorolac 15 mg IV q6h (8 doses) Gabapentin 300 mg PO TID (5 doses) Acetaminophen 1000 mg IV q6h (3 doses)	Gabapentin 300 mg PO TID	3 in days
69	M	Abnormal appendiceal orifice and abnormal cecum on CT	Laparoscopic right hemicolectomy	None	Fentanyl 100 g (once) Acetaminophen 1000 mg (once) Bupivacaine 40 cc	Acetaminophen 1000 mg IV q6h (2 doses) Ketorolac 15 mg IV q6h (2 doses)	Tramadol 50 mg TID	2
27	F	Recurrent neoterminal ileal Crohn disease	Laparoscopic Redo-ileocolic resection	Celecoxib 200 mg PO (once) Gabapentin 600 mg PO (once)	Fentanyl 100 g (once) Ketorolac 30 mg (once) Bupivacaine 20 cc	Acetaminophen 1000 mg IV q6h (4 doses) Ketorolac 30 mg IV q6h (5 doses) Methocarbamol 500 mg PO (once) Tramadol 50 mg q4h (3 doses) Acetaminophen	Tramadol 50 mg q6h	2
33	F	Familial adenomatous polyposis	Laparoscopic total proctocolectomy, ileoanal J-pouch to diverting ileostomy, transanal TME	Celecoxib 200 mg PO (once) Gabapentin 600 mg PO (once)	Fentanyl 100 g (once) Acetaminophen 1000 mg (once)	1000 mg IV q6h (5 doses) Gabapentin 300 mg PO TID (6 doses) Ketorolac 30 mg IV q6h (7 doses) Tramadol 50 mg q4h (4 doses)	None	2

c

c, cubic centimeters; CT, computed tomography; IV, intravenous; PO, oral; POD, postoperative day; q4h, every 4 hours; q6h, every 6 hours; TID, three times a day; TME, total mesorectal excision.

scores and equal levels of comfort when multimodal opioid free anesthesia was used (ketamine, lidocaine, and clonidine) versus an opioid-based regimen [32]. A retrospective study of inpatients undergoing colorectal surgery reported a negative correlation between increased opioid doses and pain scores or levels of patient satisfaction. This study, which assessed 943 adult patients who underwent nonemergent colorectal surgery, reported an inverse association between opioid dose and pain-related patient satisfaction scores ($p < 0.001$) [33]. Similarly, a retrospective cohort study con-ducted on survey responses received from 2107 adult ED patients failed to find an association between opioid pre-scriptions, increasing morphine equivalents, and patient sat-isfaction scores [34].

Cost-Related Outcomes:

In addition to outcomes related to patient satisfaction and recovery, multimodal pain management approaches provide benefits in terms of healthcare resource utilization and associated costs Figure 2, with factors such as re-duced occurrence of adverse events (AEs) and improved patient recovery and function being important contributors. Specifically, ORADEs such as postoperative ileus and respiratory depression contribute to increased costs, morbidity, and mortality, extended length of hospital stay, and higher rates of hospital readmissions [35, 36].

Maiese 2017 [37] and Apfel 2015 [38] compared costs between MMA regimens that included IV APAP and MMA regimens without IV APAP or opioid based monotherapy. Xie 2013 [39] included patients who received opioid prescriptions in ED or inpatient settings. Comorbidities such as arthritis, lower back pain, and other back/neck disorders were common at baseline. Duncan 2009 [40] compared costs for patients undergoing lower-extremity joint replacement receiving the Mayo Clinic total joint regional anesthesia multimodal protocol versus those receiving standard-of-care pain management. Gold 2016 [41] compared costs over a period of 12 months for patients who were prescribed LAOs after joint replace-ment surgery versus those who were not. $p < 0.001$ when IV APAP/MMA is compared to controls for all pain man-agement regimens.

Emergency department; IV APAP, intravenous acetaminophen; LAO, long-acting opioid; MMA, multimodal analgesia; TJRA, total joint regional anesthesia.

A recent study assessing the incidence of postoperative ileus in patients undergoing gastric surgery reported that those who received higher morphine equivalent doses (MED; median MED 285 mg versus 95 mg, $p < 0.0001$) were twice as likely to develop ileus. The study also reported that patients who received opioids and developed ileus had readmission rates 2.3%-5.3% higher than those who did not [42]. Similarly, an analysis of the MarketScan databases including patients prescribed opioids during ED or inpatient visits revealed that patients prescribed opioids incurred significantly higher overall healthcare resource utilization costs than those who were not prescribed opioids ($49,766 versus $19,875) [39].

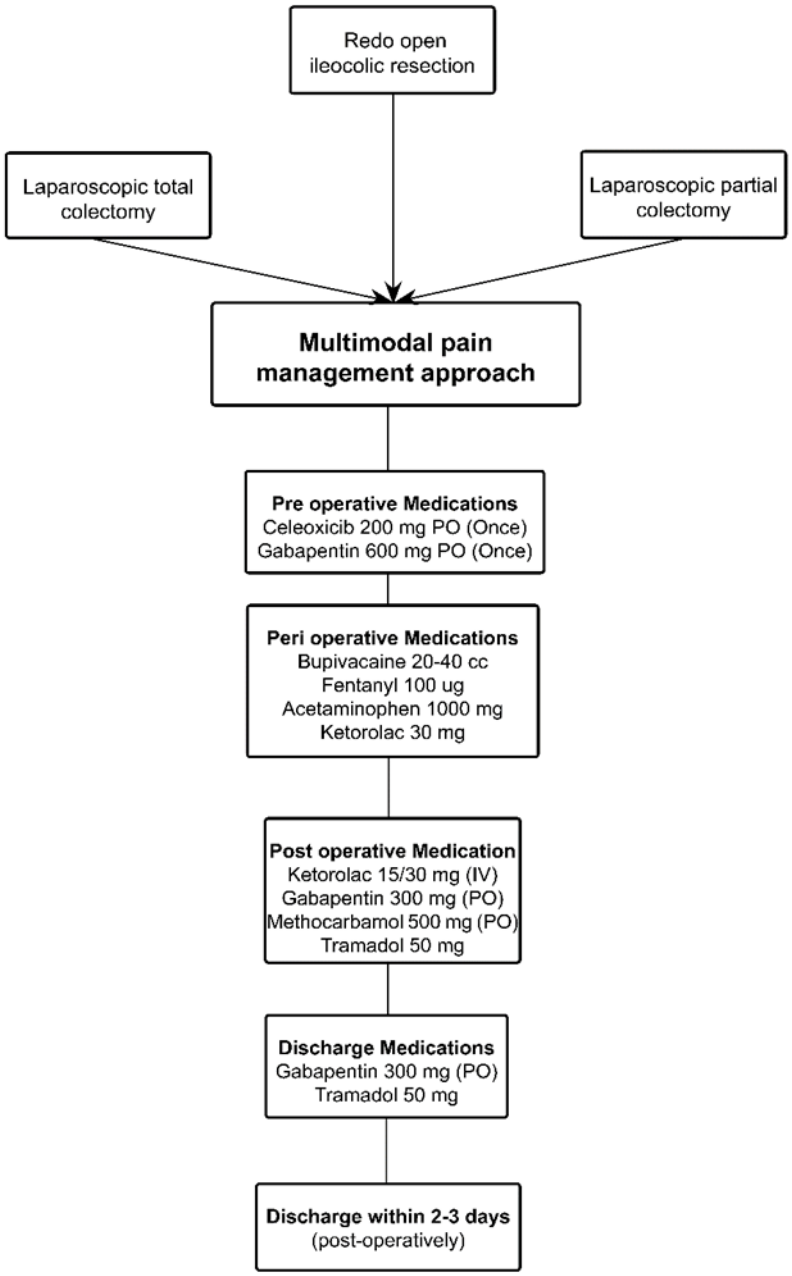

Figure 1. Multimodal pain management approach used in colorectal surgery cases at AdventHealth Center of Colon and Rectal Surgery. IV, intravenous; PO, oral.

A retrospective analysis of postoperative pain management data from more than 140,000 patients undergoing hip or knee surgery showed significant reductions in total hospitalization costs in the group receiving IV acetaminophen-based multimodal analgesia versus the group receiving IV opioid monotherapy ($p < 0.0001$) [37]. These findings were consistent with the results of a matched-pairs analysis of adult in-patients undergoing elective total hip arthroplasty or total knee arthroplasty, which showed that reductions in hospital costs may be due to a reduced length of hospital stay and a decreased occurrence of AEs [38]. Similarly, results from a comparison of a prospective cohort with retrospective historical controls in patients undergoing open abdominal hysterectomy showed that the length of hospital stay for patients receiving multimodal analgesia, including gabapentin, ketorolac, and IV acetaminophen, was significantly reduced compared with those receiving postoperative morphine alone (1.6 days versus 3.3 days; $p< 0.001$) [43]. In a retrospective cohort study of more than 225,000 obstetrics and gynecology patients undergoing surgery, a significant reduction in hospitalization costs and opioid

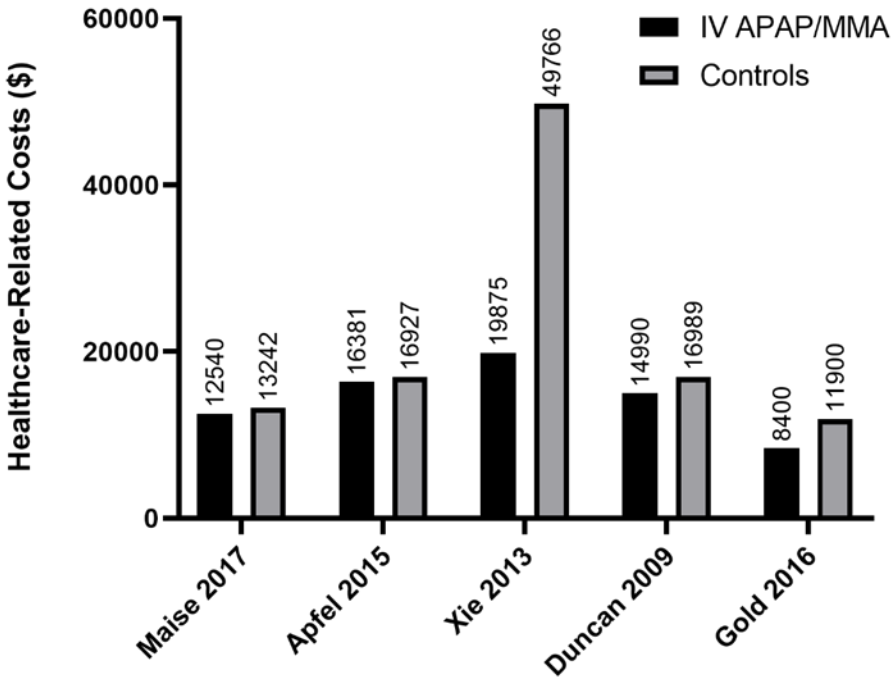

Figure 2. : Comparison of healthcare-related costs between multimodal and standard opioid-based pain management regimens. IV APAP, intravenous acetaminophen; MMA, multimodal analgesia.

use was observed among patients receiving mul- timodal IV acetaminophen-based analgesia compared with those receiving IV opioid analgesia alone (p= 0.0006; p<0.0001). However, the difference in length of hospital stay between the two groups was not significantly different [44]. A study of patients who underwent joint replacement surgery also demonstrated long-term cost savings in patients who did not receive long-acting opioids (LAOs) versus those who did. The authors reported that postsurgical costs for up to 12 months differed significantly between the two groups, with the non-LAO group accruing median costs of $8,400 versus $11,900 in the LAO group ($p < 0.0001$) [41].

Evolving from Opioid-Sparing to Opioid-Free Pain Management:

While multimodal opioid sparing approaches are now widely recommended, recognized, and used as part of ERAS protocols, opioid-free anesthesia appears to be feasible and may offer a dditional b enefits fo r so me pa tients an d caregivers. A recent retrospective analysis of patients receiving analgesics for different t ypes o f s urgery r eported that patients and surgeons were equally satisfied w ith opioid-sparing and opioid free analgesia regimens. Of greater clinical importance, this analysis revealed that patient opioid use in both the post-anesthesia care unit (PACU) and the surgical postoperative unit doubled when an opioid-based/opioid-sparing regimen was used versus an opioid-free regimen ($p < 0.007$). Additionally, the authors reported that 73% of patients receiving opioid-free analgesia required no postoperative use of opioids versus approximately 35%-55% of patients in the other two groups [45].

In this section, we summarize studies that have employed different types of opioid-free pain management protocols and comparisons with standard opioid-based regimens. As part of the search strategy, the MEDLINE database was searched using the terms “opioid” and “acute pain” or “postoperative pain.” English language articles published within the last 10 years focusing on comparisons between opioid-free pain management strategies and standard opioid-based strategies were retrieved. The abstracts of these articles were reviewed for relevance. Relevant clinical trials, retrospective analyses, and meta-analyses have been included below. Specifically, articles pertaining to opioid-free analgesia and patient outcomes (AE occurrence and recovery, patient satisfaction, and hospital discharge times) are discussed.

Several prospective studies have shown advantages of opioid-free pain management across different s urgery types and patient populations. A randomized, controlled trial that included 80 patients undergoing laparoscopic cholecystectomy showed that opioid-free IV analgesia (dexmedetomidine, lidocaine, and propofol infusions) was significantly superior to standard opioid-based analgesia (remifentanil and propofol infusions) in terms of postoperative fentanyl use delivered via a PCA pump (at 2 hours post-surgery; $p = 0.04$), rescue analgesic need ($p = 0.034$), and pain scores measured on a 11-point numerical rating scale (NRS; $p = 0.028$) [46]. In another study, patients undergoing bariatric surgery were randomized to one of two anesthetic

regimens, an opioid dependent one (OA; sufentanil) and an OFA group (dexmedetomidine, ketamine, lidocaine). Postoperative analgesia included paracetamol and morphine (delivered via a PCA pump). The OFA regimen was found to be significantly superior to the OA regimen in terms of AEs such as PONV, hypertension and bleeding, opioid consumption in the PACU and quality of recovery on the day after surgery (measured by the QoR40 scale) [47]. Similar differences were observed in another trial which included patients undergoing bariatric surgery at high risk for PONV. Patients were randomized to an opioid free TIVA regimen of propofol, ketamine, and dexmedetomidine or to a classic opioid containing regimen of fentanyl, sevoflurane and morphine/hydromorphone. In both groups, postoperative pain was treated with acetaminophen and ketorolac and breakthrough pain was treated with oxycodone or hydromorphone. The absolute risk of developing PONV was reduced by 17.3% in the opioid free group compared to the group receiving the classical opioid based regimen [48].

In a cohort of 48 breast cancer patients undergoing modified radical m astectomy, an opioid free anesthetic regimen (including lidocaine, bupivacaine and dexmedetomi-dine along with propofol induction and isoflurane mainte-nance) was compared with a standard opioid based anes-thetic regimen (including injectable morphine and vecuro-nium along with propofol induction and isoflurane mainte-nance). The incidence of PONV, length of stay in the PACU, postoperative analgesic requirements, pain scores on a VAS scale and QoL scores on the Euro QoL-5D questionnaire were compared between groups. The opioid free regimen was associated with better outcomes on all parameters, along with significantly better patient satisfaction and hospital discharge times [49].

Similarly, studies on pediatric patients have also demonstrated significant benefits of opioid free anesthetic regimens. In a randomized study conducted on children undergoing distal hand surgery, the use of an opioid free regimen including peripheral nerve blocks was compared to an IV-opioid based anesthetic regimen. The incidence of PONV, time to oral intake and time to meet discharge criteria were all reduced in the opioid free group [50] . Another trial conducted on 101 pediatric patients undergoing tonsillectomy compared outcomes between a fentanyl-based anesthetic regimen and a dexmedetomidine based one. Outcomes including rescue medication use (morphine sulfate), and incidence of PONV were assessed between groups. While the incidence of PONV and the proportion of patients requiring morphine rescue was lower in the group of patients receiving opioid free anesthesia, the length of stay in the PACU was significantly longer, in contrast to what was reported in previous studies [51].

Apart from being assessed in prospective studies, opioid free approaches to surgical pain management have also been shown to be beneficial in cases of patients presenting with complications or in patients in whom the use of an opioid-based regimen was shown to be infeasible. For example, morbidly obese patients prone to respiratory depression [52, 53] patients with a high risk of opioid induced PONV [54] post-partum patients [55] or those with opioid-induced delirium [56] have been shown to benefit from such approaches. Additionally, the use of opioid free regimens also has specifically benefited patients with comorbidities such as diabetes, hypertension, and obesity, by preventing the occurrence of ORADEs (particularly respiratory depression) in high-risk patients [57, 58].

Challenges in Implementing Opioid Free Multi-modal Pain Management:

Despite the potential advantages of opioid free multimodal pain management strategies, there exist numerous challenges that prevent their widespread use. Patient expectations pertaining to pain relief, the requirement for an interdisciplinary approach to pain management, and short-term versus long-term cost and value estimations represent some of the major hurdles. Patient expectations with respect to pain levels often dictate the intensity/type of pain management regimen used and contribute to overall patient satisfaction. Thus, goals for acute pain management should not aim for zero pain, but rather focus on achieving a manageable level of pain. A survey of 522 ED patients concluded that many patients expect complete analgesia, and patient expectations with respect to pain relief do not vary based on the initial intensity of the pain they experienced [59]

Postoperative addiction to opioids also is linked to several patient- and caregiver-related factors. Patient anxiety regarding impending pain and a heightened perception of pain can make it more difficult for an opioid free technique to be successful. Challenges in the management of patient dependence and withdrawal symptoms, and in the identification of appropriate personalized care on the part of caregivers also are important determinants for opioid addiction [60]. A recent analysis of perspectives of patients discharged from an urban ED after receiving pain medication revealed that approximately one of four (24.1%) patients were unaware that opioids could be addictive and approximately two of three patients (64.4%) did not discuss their personal experience with pain medication with their caregivers. Conversely, the analysis also identified that certain patients feared addiction to opioids and therefore risked inadequate pain control [61].

In addition, the implementation of multimodal analgesic approaches is not always straightforward and often involves collaboration between different stakeholders, viz., surgeons, anesthesia providers, patients and their families. Discussions between patients and caregivers on expectations and long-term consequences of different a nalgesic approaches can help tailor the pain management regimen to the patients' needs, and frequent communication between physicians and patients forms the cornerstone of effective patient-centered pain management [62]. Moreover, unanticipated patient-specific AEs and drug interactions may a rise from the use of multiple analgesics (as recommended by multimodal pain management protocols) and hence, individualization of such regimens is required [63]. Thus, the implementation of opioid-free multimodal pain management strategies requires more planning and personalization and may be more time consuming at the outset. However, the

positive long-term benefits of such an approach in terms of overall healthcare resource utilization, total time spent, and costs are currently under-recognized, and institution-wide measures are required to tackle this issue. Recent examples of such measures include the presence of a dedicated acute pain service team comprising physicians and nurses across disciplines that enables rigorous surveillance of patient pain levels [64].

Another major issue in implementing opioid-free multimodal pain management protocols is the perception value and cost estimation due to higher drug acquisition costs of multimodal pain medications when compared to opioids. Whereas lower direct costs (including drug acquisition costs, hospitalization costs, and costs related to AE management when accounted for together) are associated with multimodal approaches, drug acquisition costs alone may be lower for opioid-based analgesia [65].

As the biology of pain is further elucidated, new challenges will be presented. Recent research has shown that sensitivity to pain medication is dependent on and the result of the genetic constitution of the patient. The use of pharmacogenomics to predict patient response to individual analgesics and to optimize opioid-free analgesic regimens is therefore likely to emerge as an important area of investigation and clinical practice.

2 CONCLUSION:

Several opioid sparing multimodal pain management protocols have been developed for the treatment of acute postsurgical pain, and a number of nonopioid treatment options such as long-acting anesthetics, NSAIDs, anticonvulsants, and IV acetaminophen are available. The adoption of MMA approaches has been shown to reduce the quantity of opioids used perioperatively without compromising the quality of pain control. The implementation of such protocols has many advantages including improved analgesia, reduced incidence of AEs, enhanced recovery, earlier restored function, better patient satisfaction, lower overall treatment costs, and reduced utilization of healthcare resources. This approach can also lower the risk of developing sustained chronic pain as well as opioid addiction. However, current rates of opioid prescription at discharge post-surgery still remain high despite the implementation of MMA regimens and ERAS protocols [66, 67]. Now it is possible to have a postsurgical acute-pain management regimen that is completely devoid of opioids without resulting in suboptimal pain management. Effective m ultimodal p ain management strategies have paved the way for an OFA approach to treating postoperative pain, with the goal of reducing opioid prescriptions, improving patient recovery, and reducing overall healthcare resource utilization and costs. However, institution-wide deployment and adoption of OFA is still in the early stages and will require extensive personalization and better management of patient expectations.

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REFERENCES

[1] L. Manchikanti, S. Helm, 2nd, B. Fellows, et al., Opioid epidemic in the United States, Pain Physician. 15(3 Suppl) (2012) ES9-38.

[2] R.A. Rudd, P. Seth, F. David, et al., Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015, MMWR Morb Mortal Wkly Rep. 65(5051) (2016) 1445-1452.

[3] U.S.D.o.H.a.H. Services. The opioid epidemic: by the numbers. Washington, DC 2016. Available from: https://www.hhs.gov/opioids/sites/default/files/2018-01/opioids-infographic.pdf

[4] V.H. Murthy, Ending the Opioid Epidemic - A Call to Action, N Engl J Med. 375(25) (2016) 2413-2415.

[5] J. Savarese, N.G. Tabler, Jr., Multimodal analgesia as an alternative to the risks of opioid monotherapy in surgical pain management, J Healthc Risk Manag. 37(1) (2017) 24-30.

[6] T. Trang, R. Al-Hasani, D. Salvemini, et al., Pain and Poppies: The Good, the Bad, and the Ugly of Opioid Analgesics, J Neurosci. 35(41) (2015) 13879-88.

[7] E.C. Sun, B.D. Darnall, L.C. Baker, et al., Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period, JAMA Intern Med. 176(9) (2016) 1286-93.

[8] T.J. Gan, A.S. Habib, T.E. Miller, et al., Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey, Current medical research and opinion. 30(1) (2014) 149-60.

[9] E. Onishi, T. Kobayashi, E. Dexter, et al., Comparison of Opioid Prescribing Patterns in the United States and Japan: Primary Care Physicians' Attitudes and Perceptions, J Am Board Fam Med. 30(2) (2017) 248-254.

[10] C.M. Brummett, J.F. Waljee, J. Goesling, et al., New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults, JAMA surgery. 152(6) (2017) e170504.

[11] J.A. Hoppe, H. Kim, K. Heard, Association of emergency department opioid initiation with recurrent opioid use, Ann Emerg Med. 65(5) (2015) 493-499 e4.

[12] E.K. Aasvang, T.H. Lunn, T.B. Hansen, et al., Chronic pre-operative opioid use and acute pain after fast-track total knee arthroplasty, Acta Anaesthesiol Scand. 60(4) (2016) 529-36.

[13] C.J. Hayhurst, M.E. Durieux, Differential Opioid Tolerance and Opioid-induced Hyperalgesia: A Clinical Reality, Anesthesiology. 124(2) (2016) 483-8.

[14] K. Gritsenko, Y. Khelemsky, A.D. Kaye, et al., Multimodal therapy in perioperative analgesia, Best Pract Res Clin Anaesthesiol. 28(1) (2014) 59-79.

[15] E.C. Wick, M.C. Grant, C.L. Wu, Postoperative Multimodal Analgesia Pain Management With Nonopioid Analgesics and Techniques: A Review JAMA Surg. 152(7) (2017) 691 697

[16] E.E. Shaffer, A. Pham, R.L. Woldman, et al., Estimating the Effect of Intravenous Acetaminophen for Postoperative Pain Management on Length of Stay and Inpatient Hospital Costs, Adv Ther. 33(12) (2017) 2211-2228.

[17] M. Melnyk, R.G. Casey, P. Black, et al., Enhanced recovery after surgery (ERAS) protocols: Time to change practice?, Can Urol Assoc J. 5(5) (2011) 342-8.

[18] B.O. Herring, S. Ader, A. Maldonado, et al., Impact of intravenous acetaminophen on reducing opioid use after hysterectomy, Pharmacotherapy. 34 Suppl 1 (2014) 27S-33S.

[19] S. Saurabh, J.K. Smith, M. Pedersen, et al., Scheduled intravenous acetaminophen reduces postoperative narcotic analgesic demand and requirement after laparoscopic Roux-en-Y gastric bypass, Surg Obes Relat Dis. 11(2) (2015) 424-30.

[20] K. Song, M.J. Melroy, O.C. Whipple, Optimizing multimodal analgesia with intravenous acetaminophen and opioids in postoperative bariatric patients, Pharmacotherapy. 34 Suppl 1 (2014) 14S-21S.
[21] Y. Tunali, E.F. Akcil, O.K. Dilmen, et al., Efficacy of intravenous paracetamol and dexketoprofen on postoperative pain and morphine consumption after a lumbar disk surgery, J Neurosurg Anesthesiol. 25(2) (2013) 143-7.
[22] L.A. McQueen-Shadfar, S.A. Megalla, W.D. White, et al., Impact of intraoperative dexmedetomidine on postoperative analgesia following gynecologic surgery, Curr Med Res Opin. 27(11) (2011) 2091-7.
[23] J.A. Warren, C. Stoddard, A.L. Hunter, et al., Effect of Multimodal Analgesia on Opioid Use After Open Ventral Hernia Repair, J Gastrointest Surg. 21(10) (2017) 1692-1699.
[24] J. Hah, S.C. Mackey, P. Schmidt, et al., Effect of Perioperative Gabapentin on Postoperative Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort: A Randomized Clinical Trial, JAMA Surg. (2017).
[25] R.M. Langford, G.P. Joshi, T.J. Gan, et al., Reduction in opioid-related adverse events and improvement in function with parecoxib followed by valdecoxib treatment after non-cardiac surgery: a randomized, double-blind, placebo-controlled, parallel-group trial, Clin Drug Investig. 29(9) (2009) 577-90.
[26] J.M. Feld, C.E. Laurito, M. Beckerman, et al., Non-opioid analgesia improves pain relief and decreases sedation after gastric bypass surgery, Can J Anaesth. 50(4) (2003) 336-41.
[27] E. Farag, M. Ghobrial, D.I. Sessler, et al., Effect of perioperative intravenous lidocaine administration on pain, opioid consumption, and quality of life after complex spine surgery, Anesthesiology. 119(4) (2013) 932-40.
[28] N. Elia, C. Lysakowski, M.R. Tramer, Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient controlled analgesia morphine offer advantages over morphine alone? Meta analyses of randomized trials, Anesthesiology. 103(6) (2005) 1296-304.
[29] I. Wong, C. St John-Green, S.M. Walker, Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children, Paediatric anaesthesia. 23(6) (2013) 475-95.
[30] L. Rodriguez-Rubio, E. Nava, J.S.G. Del Pozo, et al., Influence of the perioperative administration of magnesium sulfate on the total dose of anesthetics during general anesthesia. A systematic review and meta-analysis, J Clin Anesth. 39 (2017) 129-138.
[31] C.C. Apfel, K. Souza, J. Portillo, et al., Patient satisfaction with intravenous acetaminophen: a pooled analysis of five randomized, placebo-controlled studies in the acute postoperative setting, J Healthc Qual. 37(3) (2015) 155-62.
[32] S. S. Hontoir, P. Saxena, M.K. Gatto, et al., Opioid-free anesthesia: what about patient comfort? A prospective, randomized, controlled trial, Acta Anaesth. Belg. 67 183-190.
[33] K. Maheshwari, K.C. Cummings, 3rd, E. Farag, et al., A temporal analysis of opioid use, patient satisfaction, and pain scores in colorectal surgery patients, J Clin Anesth. 34 (2016) 661-7.
[34] H.S. Kim, P.M. Lank, P.S. Pang, et al., ED opioid prescribing is not associated with higher patient satisfaction scores, Am J Emerg Med. 34(10) (2016) 2032-2034.
[35] J.F. Barletta, Clinical and economic burden of opioid use for postsurgical pain: focus on ventilatory impairment and ileus, Pharmacotherapy. 32(9 Suppl) (2012) 12s-8s.
[36] E.R. Kessler, M. Shah, S.K. Gruschkus, et al., Cost and quality implications of opioid based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes, Pharmacotherapy. 33(4) (2013) 383-91
[37] B.A. Maiese, A.T. Pham, M.V. Shah, et al., Hospitalization Costs for Patients Undergoing Orthopedic Surgery Treated With Intravenous Acetaminophen (IV-APAP) Plus Other IV Analgesics or IV Opioid Monotherapy for Postoperative Pain, Adv Ther. 34(2) (2017) 421 435.
[38] C. Apfel, J.R. Jahr, C.L. Kelly, et al., Effect of i.v. acetaminophen on total hip or knee replacement surgery: a case-matched evaluation of a national patient database, Am J Health Syst Pharm. 72(22) (2015) 1961-8.
[39] L. Xie, A.V. Joshi, D. Schaaf, et al., Differences in healthcare utilization and associated costs between patients prescribed vs. nonprescribed opioids during an inpatient or emergency department visit, Pain Pract. 14(5) (2014) 446-56.
[40] C.M. Duncan, K. Hall Long, D.O. Warner, et al., The economic implications of a multimodal analgesic regimen for patients undergoing major orthopedic surgery: a comparative study of direct costs, Reg Anesth Pain Med. 34(4) (2009) 301-7.
[41] L.S. Gold, S.A. Strassels, R.N. Hansen, Health Care Costs and Utilization in Patients Receiving Prescriptions for Long-acting Opioids for Acute Postsurgical Pain, Clin J Pain. 32(9) (2016) 747-54.
[42] T.J. Gan, S.B. Robinson, G.M. Oderda, et al., Impact of postsurgical opioid use and ileus on economic outcomes in gastrointestinal surgeries, Curr Med Res Opin. 31(4) (2015) 677 86.
[43] J.T. Santoso, M.A. Ulm, P.W. Jennings, et al., Multimodal pain control is associated with reduced hospital stay following open abdominal hysterectomy, Eur J Obstet Gynecol Reprod Biol. 183 (2014) 48-51.
[44] R.N. Hansen, A.T. Pham, B. Lovelace, et al., Comparative Analysis of Inpatient Costs for Obstetrics and Gynecology Surgery Patients Treated With IV Acetaminophen and IV Opioids Versus IV Opioid-only Analgesia for Postoperative Pain, Ann Pharmacother. 51(10) (2017) 834-839.
[45] A. Buvanendran, Opioid-free Anesthesia Results in Reduced Post-operative Opioid Consumption, edition, J Clin Anesth Pain Med. 2017;2(1):1-3, 2017.
[46] M. Bakan, T. Umutoglu, U. Topuz, et al., Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study, Braz J Anesthesiol. 65(3) (2015) 191-9.
[47] J.P. Mulier, R. Wouters, B. Dilleman, et al., A Randomized Controlled, Double-Blind Trial Evaluating the Effect of Opioid-Free Versus Opioid General Anaesthesia on Postoperative Pain and Discomfort Measured by the QoR-40, Journal of Clinical Anesthesia and Pain Medicine. 2(1) (2018) 1-6.
[48] P. Ziemann-Gimmel, A.A. Goldfarb, J. Koppman, et al., Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis, Br J Anaesth. 112(5) (2014) 906-11.
[49] S. Tripathy, S. Rath, S. Agrawal, et al., Opioid-free anesthesia for breast cancer surgery: An observational study, J Anaesthesiol Clin Pharmacol. 34(1) (2018) 35-40.
[50] A.C. De Windt, K. Asehnoune, A. Roquilly, et al., An opioid-free anaesthetic using nerve blocks enhances rapid recovery after minor hand surgery in children, Eur J Anaesthesiol. 27(6) (2010) 521-5.
[51] S.R. Pestieau, Z.M. Quezado, Y.J. Johnson, et al., High-dose dexmedetomidine increases the opioid-free interval and decreases opioid requirement after tonsillectomy in children, Can J Anaesth. 58(6) (2011) 540-50.
[52] T. Gaszynski, E. Gaszynska, T. Szewczyk, Dexmedetomidine for awake intubation and an opioid-free general anesthesia in a superobese patient with suspected difficult intubation, Drug Des Devel Ther. 8 (2014) 909-12.
[53] K.K. Lam, W.L. Mui, Multimodal analgesia model to achieve low postoperative opioid requirement following bariatric surgery, Hong Kong Med J. 22(5) (2016) 428-34.
[54] T.T. Horlocker, J.R. Hebl, M.A. Kinney, et al., Opioid-free analgesia following total knee arthroplasty--a multimodal approach using continuous lumbar plexus (psoas compartment) block, acetaminophen, and ketorolac, Reg Anesth Pain Med. 27(1) (2002) 105-8.
[55] K. Matthes, M.A. Gromski, B.E. Schneider, et al., Opioid-free single-incision laparoscopic (SIL) cholecystectomy using bilateral TAP blocks, J Clin Anesth. 24(1) (2012) 65-7.
[56] S.K. Patil, M. Anitescu, Opioid-free perioperative analgesia for hemicolectomy in a patient with opioid-induced delirium: a case report and review of the analgesic efficacy of the alpha-2 agonist agents, Pain Pract. 12(8) (2012) 656-62.
[57] G. Oderda, Challenges in the management of acute postsurgical pain, Pharmacotherapy. 32(9 Suppl) (2012) 6S-11S.
[58] K. Gupta, A. Prasad, M. Nagappa, et al., Risk factors for opioid-induced respiratory depression and failure to rescue: a review, Curr Opin Anaesthesiol. 31(1) (2018) 110-119.
[59] D.E. Fosnocht, N.D. Heaps, E.R. Swanson, Patient expectations for pain relief in the ED, Am J Emerg Med. 22(4) (2004) 286-8.
[60] R.J. Smith, K. Rhodes, B. Paciotti, et al., Patient Perspectives of Acute Pain Management in the Era of the Opioid Epidemic, Ann Emerg Med. 66(3) (2015) 246-252 e1.

.

[61] M. Conrardy, P. Lank, K.A. Cameron, et al., Emergency Department Patient Perspectives on the Risk of Addiction to Prescription Opioids, Pain Med. 17(1) (2016) 114-21.
[62] L. Le-Wendling, W. Glick, P. Tighe, Goals and Objectives to Optimize the Value of an Acute Pain Service in Perioperative Pain Management, Tech Orthop. 32(4) (2017) 200 208.
[63] A. Buvanendran, Multimodal Analgesia for Perioperative Pain Management, International Anesthesia Research Society. 58-62.
[64] W. Meissner, F. Coluzzi, D. Fletcher, et al., Improving the management of post-operative acute pain: priorities for change, Curr Med Res Opin. 31(11) (2015) 2131-43.
[65] M.L. Gora-Harper, K.E. Record, T. Darkow, et al., Opioid analgesics versus ketorolac in spine and joint procedures: impact on healthcare resources, Ann Pharmacother. 35(11) (2001) 1320-6.
[66] D. Brandal, M.S. Keller, C. Lee, et al., Impact of Enhanced Recovery After Surgery and Opioid-Free Anesthesia on Opioid Prescriptions at Discharge From the Hospital: A Historical-Prospective Study, Anesth Analg. 125(5) (2017) 1784-1792.