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8

Different protocols used today to achieve total opioid-free general anesthesia without locoregional blocks

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With increasing awareness of both short- and long-term problems associated with liberal perioperative opioid administration, the need for routinely and clinically feasible alternatives is greater than ever. Opioid-free anesthesia—previously reserved for bariatric surgery—is receiving increasing attention in mainstream anesthesia.
In this review, we present the truly multimodal concept of opioid-free anesthesia, which circumvents a number of opioid-related problems. For a concrete clinical perspective, we present in depth our opioid-free protocol for bariatric surgery.
However, clinicians must be aware of potential problems related to opioid-free anesthesia.

In August 2016, the Office of the US Surgeon General issued a letter and pocket card to 2.3 million medical professionals asking them to help address America's opioid epidemic. In a perspective article entitled “Ending the Opioid Epidemic – A Call to Action,” Dr. Murthy explained the reasons behind his unprecedented move [1]. One of the worrisome facts he pointed out was that the annual number of overdose deaths involving prescription and illicit opioids nearly quadrupled since 2000, in parallel

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with marked growth in the quantity of opioid pain relievers prescribed [2,3]. Although the campaign specifically addressed opioid prescription for chronic pain, the key lines on its "Turn the Tide Rx Pocket Card" should be kept in mind for analgesia in general: assess pain and function, consider whether non-opioid therapies are appropriate, talk to patients about treatment plan, evaluate risk of harm or misuse, and check when you use or prescribe opioids, start low and go slow.

Undoubtedly, there is consensus among caregivers and patients that adequate perioperative analgesia is paramount [4,5]. Acute postoperative pain is a major risk factor for developing chronic postoperative pain with all its potentially dire consequences [1,6,7]. The incidence of inadequately treated postoperative pain is at the same high levels as it was two decades ago [4,8]. Consequently, we as anesthesiologists are also challenged to look for alternative ways. In this article, we discuss opioid-free/opioid-minimal approaches and protocols in theory and practice. A protocol for an opioid-free perioperative regimen is presented, and potential associated dangers and limitations discussed. It is not the intention of this text to review all the non-opioid treatment protocols available, which have already been reviewed in detail elsewhere [9–11]. Nonetheless, we would like to emphasize perioperative pain protocols, as proposed from key opinion leaders [12].

Opioids can provoke severe side effects

Opioids still represent the mainstay of any perioperative analgesic treatment plan. However, opioids can provoke severe side effects. Some of these side effects such as postoperative nausea and vomiting (PONV) are obvious; some are of a more clandestine nature [13–15]. For example, both hyperalgesia and postoperative respiratory depression caused by opioids are of concern yet often go unnoticed [14,16]. Postoperative desaturation episodes are far more prevalent than generally appreciated [14], especially in patient groups with specific risk factors such as morbid obesity and obstructive sleep apnea [17,18]. Furthermore, undesirable side effects such as constipation, urinary retention, and drowsiness may significantly impede an otherwise uneventful postoperative course [19]. In times of ever more ERAS® (enhanced recovery after surgery) protocols emerging [20,21], the primary reliance on analgesic agents with such suboptimal side effect profiles seems outdated. Although an opioid (side effect)-free anesthesia and analgesia regimen long seemed elusive ("the Holy Grail") [22], newer truly multimodal protocols enable opioid-free (or at least opioid-sparing) anesthesia for certain types of operations [23].

Multimodal versus one product

Following the US Congressional "decade of pain control and research" [2001–2011] and pain being upgraded to "the fifth vital sign", pain therapy continues to be exceedingly disappointing [24], as illustrated by virtually unchanged rates of postoperative pain [8]. Some 3 out of 4 patients experience moderate, severe, or extreme pain [25]. At the same time, opioid prescription has reached all-time highs [1], although new and promising medications are largely missing [26,27]. Using the currently available options, what is the role multimodal anesthesia may play in providing satisfactory analgesia?

The concept of multimodal or balanced analgesia, generally attributed to Kehlet and Dahl, is now almost 25 years old and refers to attaining adequate analgesia through additive or synergistic effects of two or more analgesics, leading to reduction in doses and lower incidence of adverse effects from any particular medication [28]. Furthermore, a multimodal approach may potentially reduce central sensitization [6], one of the most underappreciated problems in the development of chronic pain [7,29]. Current guidelines also advocate a multimodal approach [30]. Intuitively, a "multimodal" approach triggering various stages of the pain pathway seems promising. Given the multitude of types of pain (e.g., neuropathic vs. nociceptive, malignant vs. non-malignant, acute vs. chronic/persistent pain, pain at rest vs. upon movement, etc.) and the number of sites potentially modifiable along the various neurochemical pathways, ranging from transduction, transmission, modulation, and perception, it should come as no surprise that pain therapy is not a "one-size-fits-all" solution [31]. Nonetheless, the results of multimodal analgesia have been disappointing [24].

How can the results of multimodal pain management be disappointing, given the plethora of meta-analyses within the last few years indicating effective analgesia and opioid reduction from various analgesic agents? There is such a wealth of literature that there are already reviews of meta-analyses [32]. Simple NSAIDs including acetaminophen have been proven effective, in meta-analyses, at reducing pain and/or sparing opioids in single doses [32], preemptively or preventively [33,34], and even more effectively in combination with one another [35]. The use of dipyrone (metamizole) may be a powerful and safe option [36]. α_2-Agonists also decrease pain and/or opioid consumption either as intravenous agents [37,38] or when applied to nerve blocks or neuraxial anesthesia [39]. Similarly, pregabalin/gabapentin in higher doses have been shown to be effective as perioperative adjuncts in reducing acute pain and/or opioid requirements [40], for preemptive analgesia [34], and in reducing the incidence of persistent or chronic pain [40]. Ketamine also has been shown to reduce pain as an adjunct to morphine [41], to confer preemptive analgesic benefits, and to reduce persistent post-operative pain in certain situations [42]. However, data on the preventive potential of ketamine on chronic pain are conflicting [43]. Finally, both intravenous lidocaine and magnesium have shown decreased pain scores and opioid requirements in the earlier postoperative period ($\leq$24 h), particularly in abdominal surgery [9,44].

A number of reasons may explain the disappointment in multimodal analgesia. First, "multimodal" may be quite minimal, potentially obscuring the full extent of benefits. For example, acetaminophen and an opioid fulfill the broader definition of the term, as illustrated by the (opioid-focused) WHO analgesic ladder [45]. Modern opioid-free concepts using a number of non-opioid analgesics [www.postoppain.org] may more suitably be called "multimodal." [46] Second, benefits that are currently well-established are not implemented, and appropriate structures may be missing [47]. In a recent analysis of nearly 800,000 patients in US hospitals undergoing below-knee amputation, open lobectomy, total knee arthroplasty, and open colectomy, the authors examined pain therapy on the day of surgery and thereafter [48]. On the day of surgery, approximately 97% of patients across the board received any opioid, but only 29.8% (colectomy) to 76.5% (total knee arthroplasty) received *any* non-opioid analgesic on the day of surgery! Even worse, only 3.7% (colectomy) to 44.7% (total knee arthroplasty) received *more than one* non-opioid analgesic on the day of surgery. This is particularly disappointing given the extreme underutilization of regional and local anesthesia [regional anesthesia 2.4% (below-knee amputation) to 25.2% (lobectomy)]. Other studies confirm these low rates of "multimodal" and truly multimodal analgesia and underscore structural/institutional inadequacies [49]. Third, surgery-specific protocols that are evidence-based, incorporate anesthesiological and surgical considerations, and include a risk-benefit analysis are required; not all interventions are the same. Studies and collaborations have begun to examine study-specific multimodal regimens for postoperative pain [31,46]. For example, the PROSPECT web-page (www.postoppain.org) provides a number of recommendations on what to do (and not to do) throughout the perioperative period, i.e. , preoperatively, intraoperatively, and postoperatively. Given that the observed effects in multimodal therapy often abate after an "early period," continuation of multimodal therapy into the postoperative period may prove beneficial. These recommendations frequently included non-pharmacological methods of analgesia, paracetamol, NSAIDs, and wound infiltration, i.e., a truly multimodal approach. However, the PROSPECT working group notes that a large part of the data available comes from unimodal interventions. This highlights the fourth point: scientific research and the scientific method. In their 2010 paper (before almost all of the previously mentioned meta-analyses were published), White and Kehlet reiterated their 2007 appeal that clinicians should "return to work!" [50] and conduct trials "rather than simply performing more meta-analysis and systematic reviews of the pain management literature." [47] However, comparing a complex multimodal therapy regimen to standard care may be contrary to a classical, step-by-step, scientific approach to causally determine effect. Furthermore, decreasing effect sizes (often measured by outcomes not highly relevant to clinical outcomes [50]) by adding a third or a fourth analgesic will greatly increase sample size, will potentially lead to underpowered analyses, may result in difficult-to-place "negative" studies, and may reduce transferability (e.g., external validity) [51,52]. But what does a comparison of acetaminophen vs. placebo mean for our patients? This analysis may be scientifically sound and embody the step-by-step approach, but are those the two clinical therapy options for colectomy (or almost any other procedure)? Acetaminophen or placebo? Fortunately, with the development of enhanced recovery

after surgery [ERAS® (http://erassociety.org/guidelines)] and opioid-free anesthesia protocols [53,54], steps toward comparing regimens with one another are emerging. That being said, for simpler day clinic or ambulatory procedures, a less extensive analgesic regimen may be appropriate. However, it should be kept in mind that analgesia for these procedures is also often insufficient [55].

Problems in using opioid-free anesthesia versus opioids

Although multiple regimens for an opioid-free/opioid-minimal perioperative analgesic management are possible, potential drawbacks or dangers have to be taken into account. While we have several thousand years of experience with opioids, we have less experience with the individual drugs used in opioid-free anesthesia, let alone their combinations. As the drug that clinicians may have the least experience with, we would like to emphasize some important caveats pertaining to dexmedetomidine administration. However, we are painfully aware that other, potentially more familiar, drugs also have drawbacks: the list of NSAIDs withdrawn from the market is impressively long, and NSAIDs may *inter alia* cause serious kidney damage [56] and anastomotic leakage [57].

Dexmedetomidine should be administered cautiously as several cardiovascular effects may occur. For example, dexmedetomidine should be given over at least 10 min as hypertensive episodes may otherwise be provoked [58]. Nonetheless, a generally hypotensive effect of dexmedetomidine (as well as clonidine) may be observed later as well [59,60]. In addition, bradycardia may commonly occur [61], and even cases of asystole have been reported [62]. Importantly, the use of dexmedetomidine is contraindicated in patients with higher degree AV-blocks. While there are certainly many benefits associated with the use of dexmedetomidine in the perioperative setting, caution is required. Let us remember the impact that liberal *de novo* use of perioperative β-blockers, undoubtedly with some similar hemodynamic properties as the α_2-agonists, have on patients' outcome: reduced risk of myocardial infarction but at the cost of increased risk of death, stroke, and clinically important hypotension [63,64]. In a further study, Devereaux et al. evaluated the effects of the α_2-agonist clonidine in patients undergoing non-cardiac surgery. They found that low-dose clonidine did not reduce the rate of death or myocardial infarction but increased the risk of clinically important hypotension and non-fatal cardiac arrest [59]. A cautious approach is advised with the use of α_2-agonists, especially in patients with severe cardiovascular disease.

Ideally, a multimodal drug combination causes greater analgesic effects and lesser side effects. However, this is not always the case, as pointed out in a study by Myhre et al., in which it was shown that the combination of a gabapentinoid and remifentanil caused additive analgesia but at the same time potentiated ventilatory depression and provoked some unwanted cognitive side effects [65]. Consequently, this study and the accompanying editorial remind us that a multimodal drug approach does not necessarily *per se* always reduce side effects [65]. Generally, data on adverse events related to combinations of non-opioids are sparse, and there is an urgent need for studies looking at benefit and potential harms of multimodal pain treatment [66].

Is it worth changing to opioid-free anesthesia?

The benefits of switching to opioid-free anesthesia are largely based on the avoidance of opioid-related adverse events. These benefits include benefits for the patient, benefits for hospital resources, and societal benefits. In a 2013 analysis of 300,000 patients, 12% of surgeries had opioid-related adverse events [19]. Patients with opioid-related adverse events had nearly twice the treatment costs, twice the length of stay, and a significantly higher readmission rate. Even after adjustment for a number of factors, treatment costs and length of stay remained significantly higher in this group [19]. Although the list of side effects is long, the two most common serious side effects are respiratory depression (3.3%) and ileus (6.1%) [19,67]. Further, similar to anesthesiologists being at a higher risk of opioid dependence on account of (occupational) exposure [68], patients given opioids and leaving the hospital with opioid prescriptions appear to be at a higher risk of opioid dependence [1]. Recent estimates for the “US epidemic” are 2 million dependent users and 12 million misusers for 2015 [1], a substantial socioeconomic burden. In addition, we know that perioperatively prescribed opioids also have a risk of misuse and abuse. In the setting of low-risk day surgery, recent research suggests that

patients prescribed opioids within 7 days of discharge are almost 50% more likely to still be receiving an opioid prescription at 1 year after surgery [69].

The final verdict is not in. However, the feasibility of opioid-free anesthesia has been demonstrated by a number of authors and protocols [23].

Low opioid dosing

Although it is possible to block autonomic hemodynamic reactions with high doses of opioids, this is a side effect-laden approach. Note that opioids are strong and rapidly acting autonomic blocking agents. However, they act so at a higher dose than required for analgesia. Thus, combining hypnotics (for anesthesia) and any of a number of autonomic blocking agents such as α_2-agonists [70], β-blockers [71], calcium antagonists [72], lidocaine [73], magnesium, or ketamine [74] could be an effective way of reducing or eliminating opioids [23]. From a philosophical perspective, it is uncertain what nociceptive firing during anesthesia really means for the patient and to what extent analgesics should be administered during anesthesia. Ethically, this is difficult to examine with the current standard of care, which explains a lack of studies in this area. Certainly adequate analgesia—through a multimodal approach—should be ensured during emergence from anesthesia. Preemptive or preventive analgesia with non-opioids [33,34], reduced surgical trauma through minimally invasive techniques, local wound infiltration, and non-opioid postoperative analgesia often suffice [23]. Furthermore, the hyperalgesic effect of opioids [15] and the role of secondary hyperalgesia on the development of chronic or persisting pain is one of the most underappreciated problems of (liberal) opioid administration [1,29,75].

Nonetheless, there may be situations in which some clinicians would generally administer some dose of opioid for immediate analgesic purposes (e.g., spinal anesthesia for Caesarian section) [76]. Although a number of other agents have been successfully used [77,78], their side effects, especially on the mother and child, may be limiting. However, even in these situations, an opioid reduction will probably be of benefit for the patient as the majority of opioid-induced side effects occur in a dose-dependent manner, and even single doses of opioids may cause hyperalgesia [23]. Interestingly, very low-dose fentanyl in rats has been shown to induce hyperalgesia but not analgesia [79].

In human studies, finding data with truly convincing clinical endpoints is challenging as postoperative opioid administration is often influenced by external factors, and the real clinical relevance of small differences in pain scores in the early postoperative period is uncertain. Furthermore, central sensitization such as secondary hyperalgesia is very rarely measured even in the experimental setting [7], and the antihyperalgesic properties of non-opioid analgesics is underexplored [78]. Finally, data on postoperative persistent/chronic pain associated with perioperative opioid dosing is rare [80,81] and potentially influenced by postoperative pain levels. Unfortunately, even factors such as clinical experience may be misguided in the context of the development of chronic pain as treating clinicians rarely follow-up on patient pain beyond the first few days [6]; this may be one of our collective "blind spots."

Nonetheless, a few general comments pertaining to perioperative opioid administration may be made. First, there seems little benefit to higher dose continuous remifentanil infusion (other than favorable pharmacokinetics and dynamics for the clinician) as it is fairly evident that hyperalgesia can result [15]. Reduction or avoidance of a longer acting μ-agonist may be more difficult. Higher doses of intrathecal and epidural fentanyl have also been shown to increase postoperative opioid requirements and/or have been associated with higher pain scores [76,82]. However, neither of these outcomes truly indicate central sensitization (e.g., hyperalgesia) [83] as commonly misconceived. In a cross-over experiment of experimental pain, we administered a high dose (10 μg/kg) and a low dose (1 μg/kg) of fentanyl to healthy volunteers and measured acute pain by the numeric rating scale (NRS) and hyperalgesia by pinprick test [13]. The higher dose showed a 30% greater area of hyperalgesia but also lower pain scores (0.8 units) some 5 h after fentanyl administration. This apparent dissonance of increased hyperalgesia (+30%) but better analgesia (−0.8 units) may be common to longer lasting μ-agonists (but not remifentanil). This solicits the question of the clinical relevance of hyperalgesia *per se*. It seems possible that persistent or chronic pain may ensue [29,75,80,81].

While remifentanil is relatively easy to avoid in most situations, hyperalgesia resulting from longer-lasting μ-agonists poses a potential problem. Which opioid should we use, if one is really required?

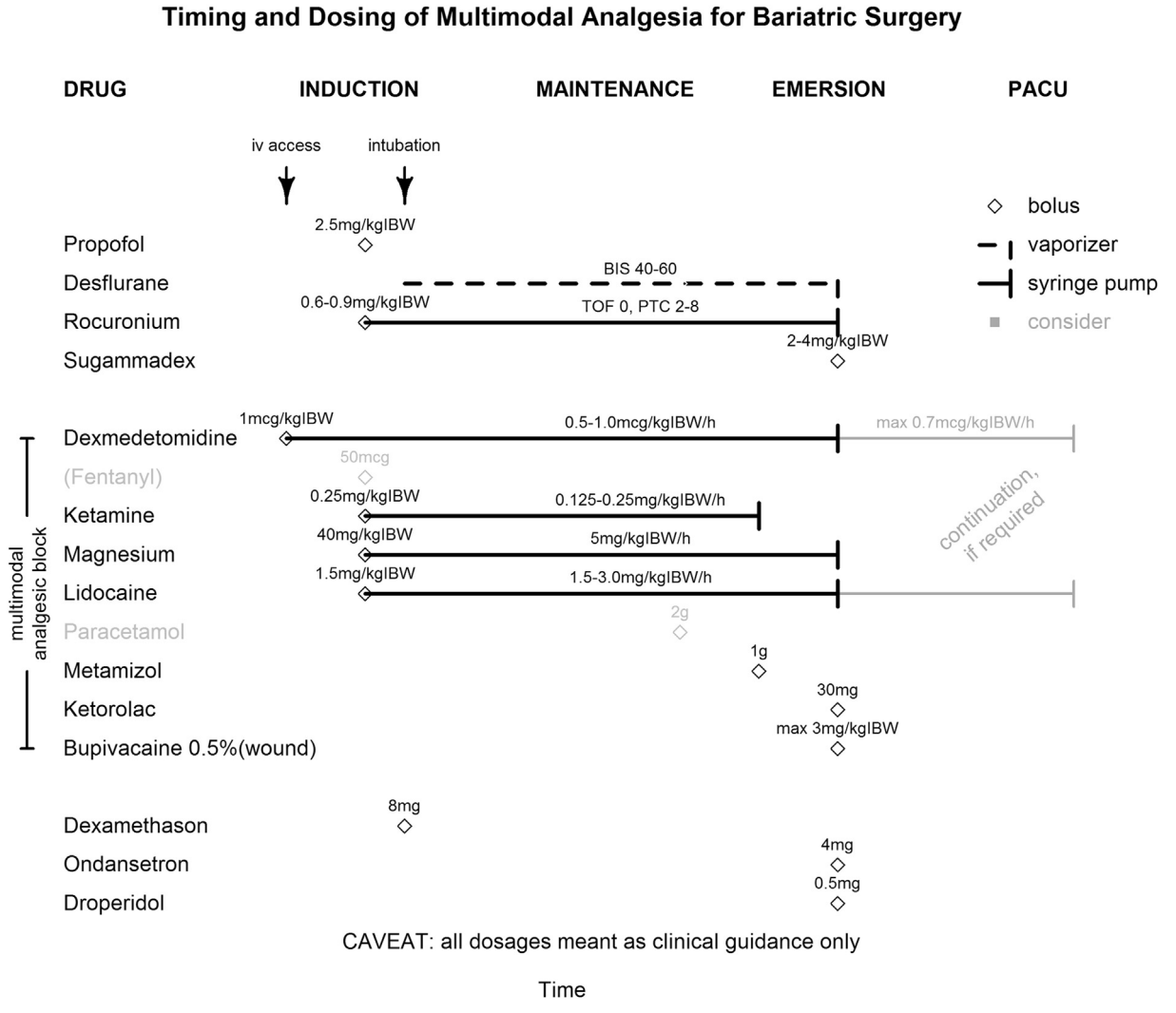

Fig. 1. Timing and dosing of multimodal analgesia for bariatric surgery.

Three things should be considered. First, the old adage "use as little as possible, but as much as necessary" will limit general use. Second, opioid selection is procedure specific and depends on the timing of nociception (e.g., remifentanil for short intense peaks, such as during craniotomy and pin placement). Third, clinician familiarity is important for patient safety. Hyperalgesia is probably a class effect, with the possible exceptions of racemic methadone [84,85] and μ-agonists-antagonists [86].

In summary, while completely opioid-free analgesia may not be (or may not be perceived to be) an option in all situations, a critical evaluation of opioid dosing and a full-fledged consideration of alternatives/adjuncts can and should take place in every patient.

Multimodal analgesia concept for bariatric surgery

Patients scheduled for gastric bypass surgery or sleeve gastrectomy often are enrolled in an opioid-free regimen at our institution. In this multimodal analgesic concept, several known and established non-opioid analgesic treatments are combined to eliminate (or at least minimize) opioid dosing [23]. In the case of laparoscopic bariatric surgery, this works remarkably well. Often it is even possible to totally abstain from opioids and still sufficiently block the autonomic nervous system reaction to painful stimuli. Several non-opioid drugs known for a (mild) analgesic effect are used [87]. These are, among others, dexmedetomidine, ketamine, lidocaine, and magnesium [9,73,88,89]. All these different agents are given as bolus doses at the start of anesthesia and are then continued at predefined rates (Fig. 1 schematically shows our perioperative protocol). Dexmedetomidine is best started as soon as an intravenous line is established and at least 10 min prior to induction (the bolus infusion is administered over the course of 10 min). As a result, by the time of induction, a good sedative effect and autonomic block is present, and any intubation stimulus is sufficiently blunted. Of note, this effect is somewhat slower with dexmedetomidine than with opioids. After preoxygenation, an induction dose of propofol is given (propofol 2.5 mg/kg IBW with additional bolus until loss of consciousness). As soon as the patient is unconscious, a bolus dose of ketamine is administered and neuromuscular blockade with rocuronium initiated. Importantly, given even the smallest suspicion of a difficult intubation, an awake fiberoptic intubation should be chosen. Once the patient is intubated, desflurane anesthesia is started, aiming for a Bispectral Index Scale (BIS®) value of 40–60. Dexmedetomidine and ketamine infusions are continued at predefined rates, and lidocaine and magnesium infusions are begun. Administering lidocaine prior to surgery as a bolus (1.5 mg/kg IBW) is also an option and may help further reduce a reaction to intubation. All infusions are then continued at predefined rates (or ranges) until the end of the intervention (or even beyond). The only exception is ketamine, which is stopped 30 min prior to the end to minimize any potential psychotomimetic side effects. PONV prophylaxis with dexamethasone (after induction) and ondansetron (prior to emersion) is given. Both these substance classes are known for some mild analgesia apart of their primary antiemetic action [90,91]. Dexamethasone has been shown to provoke hyperglycemia in obese patients with diminished glucose tolerance, so it is prudent to check glucose levels perioperatively [92]. In addition, classic analgesic medication such as acetaminophen and NSAIDs are administered at the end of the intervention. In this regimen, the use of acetaminophen may be limited as some studies have shown a loss of analgesic efficacy when acetaminophen and serotonin receptor antagonists were combined [90,93]. However, there are conflicting data on this, and larger trials are still needed to confirm a clinically meaningful interaction [94]. In sum, the analgesic protocol outlined above allows for opioid-free/opioid-minimal anesthesia in routine laparoscopic bariatric interventions. In our experience, patients treated according to this protocol have an astonishingly smooth recovery from surgery.

Dexmedetomidine for bariatric surgery

Dexmedetomidine is a highly selective α_2-agonist. It is approximately 8 times more specific to $\alpha 2$ adrenergic receptors than clonidine, and its elimination half-life is much shorter (2 h vs. 11.4 h) [95]. As early as 2002, Ramsay et al. presented the results of a study in morbidly obese patients testing the hypothesis that dexmedetomidine would improve postoperative pain management [58]. The authors had initially planned to include 80 patients in their study yet decided to stop the trial after the inclusion of only 25 patients because of the clear benefits of dexmedetomidine treatment. In addition to standard

care, the patients in this study randomly received an infusion of dexmedetomidine or saline 1 h prior to the end of the surgery. The study infusion was started at 0.5–0.7 μg/kg/h and adjusted intraoperatively according to the involved anesthesiologist. The study medication was continued postoperatively in the recovery room to keep the patient comfortable (maximal dose of 0.7 μg/kg/h dexmedetomidine). Additional analgesia was provided with 1- to 2-mg morphine boli. While there were no differences between the two groups in the time to extubation, the patients in the placebo group had significantly higher blood pressures and heart rates in the recovery room. At the same time, dexmedetomidine-treated patients received significantly less morphine. Further analysis revealed that all the patients in the placebo group required an airway intervention: all needed chin-lift post extubation, 62% needed a nasopharyngeal airway inserted, all had at least one episode of hypoxia (O_2 saturation below 90%), and 23% even needed reintubation. On the contrary, in the dexmedetomidine-treated group, none of the 12 patients required an airway intervention [58]. In 2006, this same bariatric surgery center had already treated over 2000 bariatric surgery patients. According to their experience, dexmedetomidine has been a significant factor in enabling over 85% of their patients to be discharged within 24 h of admission [96]. Furthermore, Ramsay concludes that dexmedetomidine seems to be ideal for the morbidly obese patient group because of its quality of analgesia and sedation while at the same time enhancing patient safety through lack of airway and ventilation compromise [58].

Hofer et al. reported similar experiences with the use of dexmedetomidine in a 433-kg morbidly obese patient with obstructive sleep apnea and pulmonary hypertension scheduled for Roux-en-Y gastric bypass [70]. The patient refused preoperative epidural placement. Thus, dexmedetomidine was chosen as primary analgesic for the intervention as the authors feared opioid associated perioperative respiratory depression. Immediately after anesthesia induction, a loading dose of intravenous dexmedetomidine 1.4 μg/kg (dosing weight based on an estimated lean body mass of 175 kg) was administered over 10 min, followed by a continuous infusion of 0.7 μg/kg/h. This rate was continued without cessation until the end of the first postoperative day. The authors describe an uneventful intraoperative course (low anesthetic requirements of isoflurane, 0.5 minimum alveolar concentration). No opioids were given prior to emergence. Upon awakening, the patient denied any pain and only complained of the endotracheal tube. Because of inadequate breathing patterns and the extreme obesity, the patient was transferred to the intensive care unit (ICU) for gradual weaning from mechanical ventilation, with uneventful extubation on the next morning. Interestingly, the patient exhibited lower opioid requirements during the first postoperative day while receiving dexmedetomidine (48 mg of morphine by PCA) as compared to the second postoperative day (148 mg of morphine by PCA) with similar pain scores.

In 2014, a further study on dexmedetomidine in bariatric surgery was published [97]. In this study, the authors compared a conventional arm (volatile anesthesia and opioids) with an opioid-free total intravenous anesthesia (TIVA) using propofol, ketamine, and dexmedetomidine. Patients in the TIVA group received propofol titrated to a BIS® level between 40 and 60, dexmedetomidine in a loading dose (0.5 μg/kg iv over 10 min), and with a continuous perfusion syringe thereafter (0.1–0.3 μg/kg/h). Additionally, prior to skin incision, 0.5 mg/kg ketamine was given. This study again proved the feasibility of an opioid-free anesthesia/analgesia concept in bariatric surgery. Furthermore, while the study team did not detect any difference between the two groups regarding pain levels and hydromorphone consumption during the recovery room period, both frequency and severity of PONV events were clearly reduced in the opioid-free TIVA arm (absolute risk reduction of 17.3%; number-needed-to-treat (NNT) = 6).

Use of dexmedetomidine in other situations and comparison with clonidine

The benefits of a dexmedetomidine infusion are not uniquely reserved for bariatric surgery. In various types of other procedures and patients, it has been shown that adding dexmedetomidine to a perioperative analgesic regimen can be advantageous [98]. A recent meta-analysis on the intraoperative use of dexmedetomidine also concluded that there is ample evidence for a postoperative analgesic effect [10]. Arain et al. found that the administration of dexmedetomidine before the end of a major inpatient surgery (initial loading dose of 1 μg/kg over 10 min, followed by 0.4 μg/kg/h for 4 h) reduced the early postoperative need for morphine by 66% [99]. Obviously, in a patient group in which

we particularly fear the side effects of opioids (i.e., postoperative hypoventilation, PONV), like in the morbidly obese or OSAS patients, this finding is especially relevant. Apart from its analgesic effect, dexmedetomidine also provides sedation, hypnosis, anxiolysis, and sympatholysis [11,37]. Most of the literature concerning dexmedetomidine addresses its sedative properties, particularly in the ICU setting [100]. It is possible that these sedative and anxiolytic properties contributed to the subjective better postoperative experience in some patients in the study by Arain et al. [99]. Because of the significant pharmacodynamic and pharmacokinetic differences of the α_2-agonists, the authors of a recent meta-analysis analyzed the influence of dexmedetomidine and clonidine on postoperative opioid consumption and pain intensity separately [37]. They found that both drugs given intraoperatively reduced postoperative morphine consumption. While dexmedetomidine treatment led to a significant decrease in opioid consumption from the 2nd postoperative hour until the 24th postoperative hour, clonidine had opioid-decreasing effects from the 12th until the 24th postoperative hour. In their analysis, morphine-sparing was more pronounced with dexmedetomidine than with clonidine: on average, 15 mg less morphine in the dexmedetomidine trials vs. only 4 mg morphine spared in the clonidine trials [37]. Both agents led to decreased pain intensity at 24 h (0.7 cm on the 10-cm VAS scale); however, at 48 h postoperatively, this pain-relieving effect was gone [37]. The authors could further show that the α_2-agonists reduced the incidence of early postoperative nausea: the NNT to prevent nausea with these agents was approximately 9. At the same time, they found no evidence that the treatment with α_2-agonists would delay recovery times.

Use of low opioid dose postoperatively as escape

Acute, insufficiently treated postoperative pain is not only traumatic for patients and frustrating for physicians but also a risk factor for the development of chronic pain and can increase postoperative morbidity [1,6]. As such, any discussion of chronic pain should also address acute postoperative pain. Severe postoperative pain may indicate the *temporary* need for an opioid, but it certainly indicates the need to reappraise the multimodal pain therapy. An underappreciated, effective, and quick-acting option is the use of local anesthetics [24]. The administration of an opioid and ketamine will buy time to optimize therapy (both pharmaceutical and non-pharmaceutical factors) and improve analgesia [41] and may reduce hyperalgesia [101]. Non-pharmaceutical options may be as simple as ensuring a warm environment (with facial warming) in slightly hypothermic patients. This has been shown to lead to significantly increased comfort scores and reduce self-administered analgesic agents [102].

If long-term opioid analgesia is perceived to be required, a combination of an opioid and NMDA-antagonist may be beneficial for the same reasons and should be administered with an antiemetic such as a serotonin 5-HT3 receptor antagonist, which also has some analgesic properties. An alternative in the absence of contraindications and provided that sufficient surveillance is available may be racemic methadone (the D-isomer is an NMDA-antagonist) [84].

As a concluding note, although not in the focus of this review, it is very important to be aware that psychological influences are an important outcome parameter on pain and especially the development of chronic postoperative pain. In our experience, it is crucial to be aware of psychological features and involve them in the therapeutic plan as well.

Summary

We would like to reiterate both the feasibility and necessity of truly multimodal, opioid-free analgesia in the perioperative period. For an increasing number of surgical procedures, total opioid-free or at least low-opioid anesthesia is possible and advisable. Several different protocols are available, should be employed, and will continue to be refined and applied to various interventions. The protocol we use in our center for bariatric surgery has been presented in detail.

Dr. Murthy's call – issued in August of 2016 – cannot be loud enough. A 2017 article in the New York Times stated that 2016 had the largest annual jump in drug-related deaths; fueled by the opioid crisis, drug-related deaths are now the leading cause of death among Americans under the age of 50 [103]. Recent studies have illustrated the skyrocketing prescription of opioids in the perioperative period in

the US [104,105]. In low-risk, opioid-naïve patients, approximately 70%–80% of patients filled prescriptions for an opioid postoperatively [104,105], and 13% of these continued to fill opioid prescriptions some 90–180 days later [104]. In another study in over 64,000 patients undergoing a mix of general surgical procedures, opioid-naïve patients required a median 15 days to discontinue postoperative opioid use [105]. It appears that the current opioid epidemic is in part based on the perioperative period and our indiscriminate administration of opioids. This is simply not acceptable.

Practice points

- Opioid-free anesthesia is feasible and confers many benefits.
- A truly multimodal approach using several analgesic agents may improve both short- and long-term outcomes.
- We, as perioperative physicians, should take on a leading role in halting the opioid epidemic.

Research agenda

- More and larger clinical trials exploring the efficacy of multimodal, opioid-free analgesic regimens are required.
- A better understanding of potential interactions among non-opioid analgesics is needed.
- Further research is warranted on understanding how analgesic drugs may affect hyperalgesia and persisting pain.

Conflicts of interest

None.

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References

*[1] Murthy VH. Ending the opioid epidemic - a call to action. N Engl J Med 2016;375(25):2413–5.
[2] Rudd RA, Aleshire N, Zibbell JE, et al. Increases in drug and opioid overdose deaths–United States, 2000-2014. MMWR Morb Mortal Wkly Rep 2016;64(50–51):1378–82.
[3] Rudd RA, Seth P, David F, et al. Increases in drug and opioid-involved overdose deaths - United States, 2010-2015. MMWR Morb Mortal Wkly Rep 2016;65(5051):1445–52.
[4] Kharasch ED, Brunt LM. Perioperative opioids and public health. Anesthesiology 2016;124(4):960–5.
[5] Hughes M, Coolsen MM, Aahlin EK, et al. Attitudes of patients and care providers to enhanced recovery after surgery programs after major abdominal surgery. J Surg Res 2015;193(1):102–10.
*[6] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367(9522):1618–25.
[7] Steyaert A, De Kock M. Chronic postsurgical pain. Curr Opin Anaesthesiol 2012;25(5):584–8.
*[8] Gan TJ, Habib AS, Miller TE, et al. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Curr Med Res Opin 2014;30(1):149–60.
[9] Albrecht E, Kirkham KR, Liu SS, et al. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. Anaesthesia 2013;68(1):79–90.
[10] Schnabel A, Meyer-Friessem CH, Reichl SU, et al. Is intraoperative dexmedetomidine a new option for postoperative pain treatment? A meta-analysis of randomized controlled trials. Pain 2013;154(7):1140–9.
[11] Chan AK, Cheung CW, Chong YK. Alpha-2 agonists in acute pain management. Expert Opin Pharmacother 2010;11(17):2849–68.
*[12] Joshi GP, Kehlet H. Procedure-specific pain management: the road to improve postsurgical pain management? Anesthesiology 2013;118(4):780–2.
*[13] Mauermann E, Filitz J, Dolder P, et al. Does fentanyl lead to opioid-induced hyperalgesia in healthy Volunteers?: a double-blind, randomized, crossover trial. Anesthesiology 2016;124(2):453–63.

[14] Sun Z, Sessler DI, Dalton JE, et al. Postoperative hypoxemia is common and persistent: a prospective blinded observational study. Anesth Analg 2015;121(3):709–15.
*[15] Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth 2014;112(6):991–1004.
[16] Belcher AW, Khanna AK, Leung S, et al. Long-acting patient-controlled opioids are not associated with more postoperative hypoxemia than short-acting patient-controlled opioids after noncardiac surgery: a cohort analysis. Anesth Analg 2016;123(6):1471–9.
[17] Kabon B, Nagele A, Reddy D, et al. Obesity decreases perioperative tissue oxygenation. Anesthesiology 2004;100(2):274–80.
[18] Weingarten TN, Jacob AK, Njathi CW, et al. Multimodal analgesic protocol and postanesthesia respiratory depression during phase I recovery after total joint arthroplasty. Reg Anesth Pain Med 2015;40(4):330–6.
[19] Oderda GM, Gan TJ, Johnson BH, et al. Effect of opioid-related adverse events on outcomes in selected surgical patients. J Pain Palliat Care Pharmacother 2013;27(1):62–70.
[20] Melloul E, Hubner M, Scott M, et al. Guidelines for perioperative care for liver surgery: enhanced recovery after surgery (ERAS) society recommendations. World J Surg 2016;40(10):2425–40.
[21] Thorell A, MacCormick AD, Awad S, et al. Guidelines for perioperative care in bariatric surgery: enhanced recovery after surgery (ERAS) society recommendations. World J Surg 2016;40(9):2065–83.
[22] Corbett AD, Henderson G, McKnight AT, et al. 75 years of opioid research: the exciting but vain quest for the Holy Grail. Br J Pharmacol 2006;147(Suppl. 1):S153–62.
[23] Mulier JP. Perioperative opioids aggravate obstructive breathing in sleep apnea syndrome: mechanisms and alternative anesthesia strategies. Curr Opin Anaesthesiol 2016;29(1):129–33.
[24] Rawal N. Current issues in postoperative pain management. Eur J Anaesthesiol 2016;33(3):160–71.
[25] Centers for Disease C. 2017 http://www.cdc.gov/nchs/nhds.htm. [Accessed 03 January 2017]. Available from: http://www.cdc.gov/nchs/nhds.htm.
[26] Sitbon P, Van Elstraete A, Hamdi L, et al. STR-324, a stable analog of opiorphin, causes analgesia in postoperative pain by activating endogenous opioid receptor-dependent pathways. Anesthesiology 2016;125(5):1017–29.
[27] Dahan A. Potent opioid analgesia without respiratory depression: could it be possible? Anesthesiology 2016;125(5):841–3.
[28] Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 1993;77(5):1048–56.
[29] De Kock M. Expanding our horizons: transition of acute postoperative pain to persistent pain and establishment of chronic postsurgical pain services. Anesthesiology 2009;111(3):461–3.
*[30] Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116(2):248–73.
[31] Gritsenko K, Khelemsky Y, Kaye AD, et al. Multimodal therapy in perioperative analgesia. Best Pract Res Clin Anaesthesiol 2014;28(1):59–79.
[32] Moore RA, Derry S, Aldington D, et al. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database Syst Rev 2015;(9):1–37. CD008659.
[33] Doleman B, Read D, Lund JN, et al. Preventive acetaminophen reduces postoperative opioid consumption, vomiting, and pain scores after surgery: systematic review and meta-analysis. Reg Anesth Pain Med 2015;40(6):706–12.
[34] Nir RR, Nahman-Averbuch H, Moont R, et al. Preoperative preemptive drug administration for acute postoperative pain: a systematic review and meta-analysis. Eur J Pain 2016;20(7):1025–43.
[35] Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. Cochrane Database Syst Rev 2013;(6):1–40. CD010210.
[36] Hearn L, Derry S, Moore RA. Single dose dipyrone (metamizole) for acute postoperative pain in adults. Cochrane Database Syst Rev 2016;4, CD011421.
[37] Blaudszun G, Lysakowski C, Elia N, et al. Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. Anesthesiology 2012;116(6):1312–22.
[38] Jessen Lundorf L, Korvenius Nedergaard H, Moller AM. Perioperative dexmedetomidine for acute pain after abdominal surgery in adults. Cochrane Database Syst Rev 2016;2, CD010358.
[39] Abdallah FW, Brull R. Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth 2013;110(6):915–25.
[40] Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. Br J Anaesth 2015;114(1):10–31.
[41] Wang L, Johnston B, Kaushal A, et al. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials. Can J Anaesth 2016;63(3):311–25.
[42] McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. Acta Anaesthesiol Scand 2014;58(10):1199–213.
[43] Klatt E, Zumbrunn T, Bandschapp O, et al. Intra- and postoperative intravenous ketamine does not prevent chronic pain: a systematic review and meta-analysis. Scand J Pain 2015;7:42–54.
[44] Kranke P, Jokinen J, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Database Syst Rev 2015;(7):1–222. CD009642.
[45] Ventafridda V, Tamburini M, Caraceni A, et al. A validation study of the WHO method for cancer pain relief. Cancer 1987;59(4):850–6.
*[46] Management Ppspp. 2017 www.postoppain.org. [Accessed 03 March 2017].
[47] White PF, Kehlet H. Improving postoperative pain management: what are the unresolved issues? Anesthesiology 2010;112(1):220–5.
[48] Ladha KS, Patorno E, Huybrechts KF, et al. Variations in the use of perioperative multimodal analgesic therapy. Anesthesiology 2016;124(4):837–45.

[49] Benhamou D, Berti M, Brodner G, et al. Postoperative analgesic therapy observational survey (PATHOS): a practice pattern study in 7 central/southern European countries. Pain 2008;136(1–2):134–41.
[50] White PF, Kehlet H. Postoperative pain management and patient outcome: time to return to work! Anesth Analg 2007;104(3):487–9.
[51] Dahl JB. Pitfalls in trials of "multimodal analgesia". Pain 2016;157(1):280–1.
[52] Lunn TH, Husted H, Laursen MB, et al. Analgesic and sedative effects of perioperative gabapentin in total knee arthroplasty: a randomized, double-blind, placebo-controlled dose-finding study. Pain 2015;156(12):2438–48.
[53] Santoso JT, Ulm MA, Jennings PW, et al. Multimodal pain control is associated with reduced hospital stay following open abdominal hysterectomy. Eur J Obstet Gynecol Reprod Biol 2014;183:48–51.
[54] Mathiesen O, Dahl B, Thomsen BA, et al. A comprehensive multimodal pain treatment reduces opioid consumption after multilevel spine surgery. Eur Spine J 2013;22(9):2089–96.
[55] Gerbershagen HJ, Aduckathil S, van Wijck AJ, et al. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology 2013;118(4):934–44.
[56] Ungprasert P, Cheungpasitporn W, Crowson CS, et al. Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: a systematic review and meta-analysis of observational studies. Eur J Intern Med 2015;26(4):285–91.
[57] Bhangu A, Singh P, Fitzgerald JE, et al. Postoperative nonsteroidal anti-inflammatory drugs and risk of anastomotic leak: meta-analysis of clinical and experimental studies. World J Surg 2014;38(9):2247–57.
[58] Ramsay M. Bariatric surgery: the role of dexmedetomidine. Semin Anesth Perioperat Med Pain 2006;25(2):51–6.
[59] Devereaux PJ, Sessler DI, Leslie K, et al. Clonidine in patients undergoing noncardiac surgery. N Engl J Med 2014;370(16):1504–13.
[60] Precedex (package insert). North Chicago, IL: Abbott Laboratories; 2001.
[61] Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298(22):2644–53.
[62] Ingersoll-Weng E, Manecke Jr GR, Thistlethwaite PA. Dexmedetomidine and cardiac arrest. Anesthesiology 2004;100(3):738–9.
[63] Group PS, Devereaux PJ, Yang H, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371(9627):1839–47.
[64] Wijeysundera DN, Duncan D, Nkonde-Price C, et al. Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2014;64(22):2406–25.
[65] Myhre M, Diep LM, Stubhaug A. Pregabalin has analgesic, ventilatory, and cognitive effects in combination with remifentanil. Anesthesiology 2016;124(1):141–9.
[66] Mathiesen O, Wetterslev J, Kontinen VK, et al. Adverse effects of perioperative paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. Acta Anaesthesiol Scand 2014;58(10):1182–98.
[67] Barletta JF. Clinical and economic burden of opioid use for postsurgical pain: focus on ventilatory impairment and ileus. Pharmacotherapy 2012;32(9 Suppl):12s–8s.
[68] Bryson EO, Silverstein JH. Addiction and substance abuse in anesthesiology. Anesthesiology 2008;109(5):905–17.
[69] Alam A, Gomes T, Zheng H, et al. Long-term analgesic use after low-risk surgery: a retrospective cohort study. Arch Intern Med 2012;172(5):425–30.
[70] Hofer RE, Sprung J, Sarr MG, et al. Anesthesia for a patient with morbid obesity using dexmedetomidine without narcotics. Can J Anaesth 2005;52(2):176–80.
[71] Collard V, Mistraletti G, Taqi A, et al. Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy. Anesth Analg 2007;105(5):1255–62.
[72] White PF, Wang B, Tang J, et al. The effect of intraoperative use of esmolol and nicardipine on recovery after ambulatory surgery. Anesth Analg 2003;97(6):1633–8.
[73] De Oliveira Jr GS, Duncan K, Fitzgerald P, et al. Systemic lidocaine to improve quality of recovery after laparoscopic bariatric surgery: a randomized double-blinded placebo-controlled trial. Obes Surg 2014;24(2):212–8.
[74] Kaur S, Saroa R, Aggarwal S. Effect of intraoperative infusion of low-dose ketamine on management of postoperative analgesia. J Nat Sci Biol Med 2015;6(2):378–82.
[75] Eisenach JC. Preventing chronic pain after surgery: who, how, and when? Reg Anesth Pain Med 2006;31(1):1–3.
[76] Carvalho B, Drover DR, Ginosar Y, et al. Intrathecal fentanyl added to bupivacaine and morphine for cesarean delivery may induce a subtle acute opioid tolerance. Int J Obstet Anesth 2012;21(1):29–34.
[77] Morrison AP, Hunter JM, Halpern SH, et al. Effect of intrathecal magnesium in the presence or absence of local anaesthetic with and without lipophilic opioids: a systematic review and meta-analysis. Br J Anaesth 2013;110(5):702–12.
[78] Lavand'homme PM, Roelants F, Waterloos H, et al. An evaluation of the postoperative antihyperalgesic and analgesic effects of intrathecal clonidine administered during elective cesarean delivery. Anesth Analg 2008;107(3):948–55.
[79] Rivat C, Laulin JP, Corcuff JB, et al. Fentanyl enhancement of carrageenan-induced long-lasting hyperalgesia in rats: prevention by the N-methyl-D-aspartate receptor antagonist ketamine. Anesthesiology 2002;96(2):381–91.
[80] Steyaert A, Forget P, Dubois V, et al. Does the perioperative analgesic/anesthetic regimen influence the prevalence of long-term chronic pain after mastectomy? J Clin Anesth 2016;33:20–5.
[81] van Gulik L, Ahlers SJ, van de Garde EM, et al. Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. Br J Anaesth 2012;109(4):616–22.
[82] Chia YY, Liu K, Wang JJ, et al. Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. Can J Anaesth 1999;46(9):872–7.
*[83] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011;152(3 Suppl):S2–15.
[84] Davis AM, Inturrisi CE. d-Methadone blocks morphine tolerance and N-methyl-D-aspartate-induced hyperalgesia. J Pharmacol Exp Ther 1999;289(2):1048–53.

[85] Salpeter SR, Buckley JS, Bruera E. The use of very-low-dose methadone for palliative pain control and the prevention of opioid hyperalgesia. J Palliat Med 2013;16(6):616–22.
[86] Koppert W, Ihmsen H, Korber N, et al. Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. Pain 2005;118(1–2):15–22.
[87] White PF. The role of non-opioid analgesic techniques in the management of pain after ambulatory surgery. Anesth Analg 2002;94(3):577–85.
[88] Guignard B, Coste C, Costes H, et al. Supplementing desflurane-remifentanil anesthesia with small-dose ketamine reduces perioperative opioid analgesic requirements. Anesth Analg 2002;95(1):103–8 [table of contents].
[89] Feld JM, Hoffman WE, Stechert MM, et al. Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery. J Clin Anesth 2006;18(1):24–8.
[90] Bandschapp O, Filitz J, Urwyler A, et al. Tropisetron blocks analgesic action of acetaminophen: a human pain model study. Pain 2011;152(6):1304–10.
[91] De Oliveira Jr GS, Almeida MD, Benzon HT, et al. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology 2011;115(3):575–88.
[92] Nazar CE, Lacassie HJ, Lopez RA, et al. Dexamethasone for postoperative nausea and vomiting prophylaxis: effect on glycaemia in obese patients with impaired glucose tolerance. Eur J Anaesthesiol 2009;26(4):318–21.
[93] Ramirez L, Cros J, Marin B, et al. Analgesic interaction between ondansetron and acetaminophen after tonsillectomy in children: the Paratron randomized, controlled trial. Eur J Pain 2015;19(5):661–8.
[94] Tiippana E, Hamunen K, Kontinen V, et al. The effect of paracetamol and tropisetron on pain: experimental studies and a review of published data. Basic Clin Pharmacol Toxicol 2013;112(2):124–31.
[95] Paris A, Tonner PH. Dexmedetomidine in anaesthesia. Curr Opin Anaesthesiol 2005;18(4):412–8.
[96] McCarty TM, Arnold DT, Lamont JP, et al. Optimizing outcomes in bariatric surgery: outpatient laparoscopic gastric bypass. Ann Surg 2005;242(4):494–8. discussion 8–501.
*[97] Ziemann-Gimmel P, Goldfarb AA, Koppman J, et al. Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. Br J Anaesth 2014;112(5):906–11.
[98] Gurbet A, Basagan-Mogol E, Turker G, et al. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anaesth 2006;53(7):646–52.
[99] Arain SR, Ruehlow RM, Uhrich TD, et al. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg 2004;98(1):153–8 [table of contents].
[100] Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301(5):489–99.
[101] Hayhurst CJ, Durieux ME. Differential opioid tolerance and opioid-induced hyperalgesia: a clinical reality. Anesthesiology 2016;124(2):483–8.
[102] Iaizzo PA, Jeon YM, Sigg DC. Facial warming increases the threshold for shivering. J Neurosurg Anesthesiol 1999;11(4):231–9.
[103] Katz J. Drug deaths in America are rising faster than ever. N Y Times June 5 2017.
[104] Johnson SP, Chung KC, Zhong L, et al. Risk of prolonged opioid use among opioid-naive patients following common hand surgery procedures. J Hand Surg Am 2016;(10):947–57.
[105] Wunsch H, Wijeysundera DN, Passarella MA, et al. Opioids prescribed after low-risk surgical procedures in the United States, 2004-2012. JAMA 2016;315(15):1654–7.