

The role of multimodal analgesia in pain management after ambulatory surgery

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Purpose of review

As outpatient (day-case) surgery had continued to grow throughout the world, many more complex and potentially painful procedures are being routinely performed in the ambulatory setting. Opioid analgesics, once considered the standard approach to preventing acute postoperative pain, are being replaced by a combination of nonopioid analgesic drugs with diverse modes of action as part of a multimodal approach to preventing pain after ambulatory surgery. This review will provide an update on the topic of multimodal pain management for ambulatory (day-case) surgery.

Recent findings

Efficacy of multimodal analgesic regimens continues to improve; opioid analgesics are increasingly taking on the role of 'rescue analgesics' for acute pain after day-case surgery. The use of multimodal analgesia is rapidly becoming the 'standard of care' for preventing pain after ambulatory procedures at most surgery centers throughout the world.

Summary

This article discusses recent evidence from the peer-reviewed literature regarding the role of local anesthetics, NSAIDs, gabapentinoids, and acetaminophen, as well as alpha-2 agonists, ketamine, esmolol, and nonpharmacologic approaches (e.g., transcutaneous electrical stimulation) as parts of multimodal pain management strategies in day-case surgery.

Keywords

ambulatory surgery, multimodal analgesia, nonopioid analgesics, nonpharmacologic analgesic therapies, opioid analgesics, postoperative (acute) pain management, recovery

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Introduction

At the beginning of the new current millennium, the United States=Congress declared the 'Decade of Pain Control and Research' [1]. The USA was not alone in developing government-endorsed national guidelines for pain management. Although significant progress has been made during this decade, including advances in our knowledge of pain signaling pathways and the plasticity of the peripheral and central nervous systems leading to chronic pain, acceptance of pain as the 'fifth vital sign', and the development of standards for pain evaluation and its clinical management by the Joint Commission on Accreditation of Healthcare Organizations (JCAHCO), or The Joint Commission (TJC), many questions remain to be answered. Recently, White and Kehlet asked the question 'what are the unresolved issues?' [2].

Pain is a highly personal experience that is communicated outwardly to healthcare providers, family members,

and friends by verbal signals, as well as through body and facial expressions. Patients and their caregiver must understand how to properly assess the character and intensity of surgery-related pain and the response to the analgesic therapies. The potential negative implications of inadequate and/or overtreatment of pain with opioid and nonopioid analgesics negatively impact on recovery after ambulatory surgery [3]. Many outpatients also experience unacceptable pain when they return home after ambulatory surgery despite receiving standard analgesic drugs prescribed by their surgeons. As increasing numbers and complexity of elective operations are being performed on an ambulatory (or short-stay) basis, use of conventional opioid-based intravenous (i.v.) patient-controlled analgesia (PCA) and central neuraxial (spinal and epidural) analgesia techniques is not practical for perioperative pain management [4]. The rapidly expanding outpatient population requires an aggressive multimodal perioperative analgesic regimen that provides effective pain relief, has minimal side-effects, is

inherently safe, and can be managed by the patient and their family members away from a hospital or surgical center [5]. With the changes in healthcare dictated by economic pressures, there has been a realization that the duration of the hospital stay can be significantly reduced without compromising the quality of patient care. Advances in surgical technology and anesthetic drugs and techniques have made an impact on the way perioperative care is currently being delivered to patients undergoing ambulatory surgery.

Effective perioperative pain management poses a significant challenge for healthcare practitioners and personnel (e.g., anesthesiologists, surgeons, nurses, physiotherapists); the responsibility for inadequate pain control is multifactorial in origin. Healthcare personnel can minimize the mismanagement of pain and facilitate better postoperative pain control by implementing and applying evidence-based analgesic practices and improving communication among healthcare providers and the patients and their families. Effective communication between the patient, individual caregiver, and other healthcare personnel is crucial when it comes to improving postoperative pain management. All of these factors are of importance in improving perioperative pain management strategies as part of recently described fast-track recovery paradigms [6]. This type of multidisciplinary approach has been documented to improve the quality of the recovery process and reduce the hospital stay and postoperative morbidity, leading to a shorter period of convalescence after surgery [2].

Pain involves multiple mechanisms that ideally require treatment using a multimodal (or 'balanced') analgesic technique with the aim of improving analgesia by combining analgesics with additive or synergistic effects [2]. Multidisciplinary fast-track (or accelerated) recovery processes encompass many aspects of anesthesia and analgesic care [7], optimizing not only the preoperative preparation and prehabilitation, but also the intraoperative attenuation of surgical stress, postoperative pain control, and rehabilitation procedures [6]. Current evidence suggests that these improvements in patient outcome related to pain control can best be achieved by using a combination of preventive analgesic techniques involving both centrally and peripherally acting analgesic drugs, as well as novel approaches to administering drugs in locations remote from the hospital setting.

This decade has witnessed important advances in our understanding of the pathophysiologic basis of acute pain, the development of new opioid and nonopioid analgesics and novel methods of drug delivery, and more widespread use of pain-reducing minimally invasive surgical techniques. Still the management of pain after surgery remains a challenge for many practitioners [4].

The increasing implementation of standardized pain evaluation, treatment protocols, and the more routine use of multimodal analgesic techniques are hopeful signs that improvements in pain management are likely to continue in the years ahead [2]. Multimodal analgesia is an approach to preventing postoperative pain that involves administering a combination of opioid and non-opioid analgesics that act at different sites within the central and peripheral nervous systems in an effort to improve pain control while eliminating opioid-related side-effects. Use of multimodal analgesia for the prevention of pain in the ambulatory setting is one of the keys to improving the recovery process, reducing delayed discharges from hospital and surgery centers, and most importantly, facilitating the ability of patients to resume their activities of daily living after day surgery [3,7–10].

Implementation of evidence-based multimodal analgesic regimens in the perioperative period can maximize the short-term and long-term benefits of the therapy. A deficiency in the design of many of the published studies involving multimodal analgesic therapies is that the drug regimens were not continued into the postdischarge period [11]. Although many of the recent studies have utilized perioperative multimodal analgesic regimens, this approach does not seem to offer any clinically significant advantages over so-called preventive multimodal analgesic regimens when an effective proactive approach to pain management is initiated in the early postoperative period and extended into the postdischarge period for 3–7 days depending on the extent of the ambulatory surgical procedure [12]. Bisgaard [13] concluded that a multimodal analgesic regimen consisting of a preoperative single dose of dexamethasone, incisional local anesthetics (at the beginning and/or end of surgery), and continuous treatment with NSAIDs or COX-2 inhibitors during the first 3–4 postoperative days produced the best clinical outcome. Moreover, recent clinical studies suggest that when classical NSAIDs or more selective COX-2 inhibiting drugs were administered for 3–5 days after ambulatory surgery, a significant benefit was achieved with respect to clinically relevant patient outcomes (e.g., resumption of normal activities) and improvements in short-term pain control [14,15].

Opioid analgesics continue to play an important role in the acute treatment of moderate-to-severe pain in the early postoperative period. However, nonopioid analgesics are increasingly being used as adjuvant before, during, and after surgery to facilitate the recovery process after ambulatory surgery because of their anesthetic and analgesic-sparing effects, their ability to reduce postoperative pain (with movement), and their opioid-related side-effects (e.g., gastrointestinal and bladder dysfunction), thereby shortening the duration of the hospital stay and the convalescence period.

Table 1 Effect of postoperative celecoxib administration (400 mg/day) on recovery after outpatient laparoscopy surgery procedures as part of a multimodal analgesic regimen

	Control	Celecoxib
Age (years)	39 ± 11	36 ± 10
Weight (kg)	80 ± 16	83 ± 16
Surgery time (min)	100 ± 56	97 ± 51
Pain scores (0–10)	4 (3–6)	2 (2–5) ^a
Rescue analgesic use (n, %)	32, 80	18, 44
Quality of recovery scores (0–18)	16 (15–18)	18 (17–18) ^a
Patient satisfaction with pain management (0–100)	76 ± 26	92 ± 11 ^a
Recovery outcome variables		
Normal diet (days)	3 (2–4)	2 (1–3) ^a
Normal bowel function (days)	2 (2–4)	1 (1–2) ^a
Resume normal activities (days)	6 (3–7)	4 (1–5)

Data from [14].

^aSignificant differences between groups, $P < 0.05$.

Nonopioid analgesics will likely assume a greater role as preventive analgesics in the future as the number of minimally invasive (keyhole) surgery cases continues to expand. The use of traditional nonselective NSAIDs or the more selective COX-2 inhibitors during the first 3–4 days provides the best clinical outcome. As described in a prospective, placebo-controlled study involving outpatients undergoing laparoscopic surgery by White *et al.* [14], the administration of celecoxib prior to discharge home and subsequently for 3 days after discharge as part of a multimodal analgesic regimen not only experienced less pain and reduced need for opioid-containing oral analgesics, but also more importantly allowed patients to resume normal activities of daily living 1–2 days earlier (Table 1).

Other nonopioid analgesics including ketamine [16,17], dexmedetomidine [18,19[•]], dextromethorphan, alpha-2agonists, beta-blockers [20–24], local anesthetics, and acetaminophen [25–28] can help to improve the pain management and perioperative outcome. For example, the administration of i.v. acetaminophen (1 g) preoperatively reduced the total dose requirement of opioid analgesic medications and facilitated recovery in patients undergoing laparoscopic hysterectomy [29[•]] and laparoscopic cholecystectomy procedure [30]. The addition of either acetaminophen (300 mg) or ketorolac (10 mg) to 0.5% lidocaine for intravenous regional anesthesia (IVRA) reduced postoperative pain and analgesic consumption. Surprisingly, acetaminophen was more effective than ketorolac in shortening the onset time of sensory block and delaying tourniquet pain onset time [31]. However, an IVRA technique utilizing 0.5% lidocaine (at a dose of 1.5 mg/kg) with ketorolac (0.15 mg/kg) did provide highly effective perioperative anesthesia and analgesia for hand and wrist surgery [32]. The preoperative i.v. co-administration of ketorolac (1 mg/kg) and acetaminophen (20 mg/kg) was a safe and effective method for relieving postoperative pain and demon-

strated highly significant fentanyl-sparing effects in small children undergoing outpatient inguinal hernia repair procedures [33]. The combination of acetaminophen and an NSAID may offer superior analgesia compared with either drug alone [34^{••}]. For example, premedication with acetaminophen, 2 g orally (p.o.), and celecoxib, 200 mg p.o., improved pain control after outpatient ENT procedures with local analgesia [35]. Intranasal ketorolac (31.5 mg) was also well tolerated and provided rapid and effective pain relief in oral surgery patients for a period up to 8 h [36]. Studies also suggest that in combination with local anesthetic infiltration, ketorolac (30 mg i.v. or injected with the local anesthetic) is highly effective in improving pain control after superficial surgical procedures and allowed patients to be discharged to home more than 1 h earlier without producing hematomas or wound complications in the postdischarge period [37].

Glucocorticoid steroids can also provide beneficial effects when administered in appropriate doses as part of a multimodal analgesic regimen in the perioperative setting [8,38,39]. Dexamethasone, 16 mg p.o., when used as an adjuvant to acetaminophen (2 g p.o.), rofecoxib (50 mg p.o.), and local anesthetic infiltration helped to reduce pain and to prolong analgesic effect from 24 to 72 h after breast surgery [40]. Other recent studies have confirmed that a rational combination of different nonopioid analgesics when given as part of multimodal analgesia reduces postoperative pain [41–43]. Importantly, when dexamethasone, 4 mg i.v., was administered to patients undergoing anorectal surgery, it reduced the time to discharge home and did not increase the incidence of wound complications [44].

The gabapentinoid compounds have also been used as part of multimodal analgesic in the postoperative period. Although gabapentin reduced the amount of morphine used for postoperative pain control after lower abdominal and spinal fusion surgery, opioid-related side-effects were not reduced. Perioperative use of gabapentin seems to be an effective adjunct to improve pain control in the early stages of recovery in children and adolescents undergoing spine surgery [45–49]. Preoperative gabapentin 1200 mg, dexamethasone 8 mg, and ketamine 0.15 mg/kg combined with paracetamol 1 g and ketorolac 15 mg reduced overall pain scores in patients after hip arthroplasty as compared with paracetamol and ketorolac alone. Interestingly, morphine consumption was not reduced [43]. Further trials are needed to delineate the optimal dose, timing, and duration of gabapentin use following surgery.

Pregabalin, 150 mg p.o., has been reported to attenuate postoperative pain after laparoscopic cholecystectomy [41,50] and reduced chronic neuropathic pain after total knee arthroplasty (TKA) (300 mg) when administered

before TKA and for 14 days after TKA (150–50 mg twice daily). In addition to reducing opioid analgesic consumption, these patients had a better range of motion during the first 30 days of rehabilitation. Of note, the pregabalin-treated patients experienced a higher incidence sedation and confusion in the early postoperative period [51^{*}]. Jokela *et al.* [52] also found a better analgesia during the early recovery after day-case gynecological laparoscopic surgery after premedication with pregabalin 150 mg p.o. in combination with ibuprofen 800 mg, but there was no reduction in the postoperative analgesic requirement. However, a single preoperative dose of pregabalin (75–300 mg p.o.) may produce unwanted side-effects without improving postoperative pain management [53,54]. Pregabalin 300 mg p.o. was ineffective when administered for preventing and attenuating postlaparoscopic shoulder pain after laparoscopic cholecystectomy. Analogous to the findings of White *et al.* [53], use of high-dose pregabalin was associated with a greater incidence of ‘oversedation’ 2-h postoperatively [55]. A multimodal analgesic regimen consisting of pregabalin 150 mg, acetaminophen 975 mg, and celecoxib 400 mg orally administered preoperatively was effective in reducing intraoperative and postoperative opioid use in patients undergoing robotic-assisted laparoscopic radical prostatectomy [56].

Perioperative multimodal analgesia with oral oxycodone, gabapentin, and acetaminophen provided advantages over standard i.v. PCA after major orthopedic surgery [57]. The local infiltration with ropivacaine (400 mg), ketorolac (30 mg), and epinephrine (0.5 mg) provided excellent pain relief and lower morphine consumption following TKA, resulting in shorter time to home readiness and higher patient satisfaction [58]. When ketorolac, 30 mg i.v., was administered in combination with esmolol 1 mg/kg i.v. and dexamethasone 4 mg i.v., as well as local anesthetic infiltration with bupivacaine 0.5% and rectal acetaminophen 1.5 mg, for major ambulatory laparoscopic surgery procedures, the ability to achieve a fast-track recovery was significantly improved 15.6 vs. 1.4% for the multimodal and control group of patients’, respectively [59]. Mean patient satisfaction was also higher in the multimodal analgesia group of patients (96 ± 6 vs. 79 ± 11) on a 0–100 scale ($P < 0.05$). Of interest (and potential clinical importance), ketorolac as an analgesic adjuvant is alleged to decrease the risk of breast cancer relapse compared with other analgesic medications [60^{*}].

The administration of local anesthetics via a wide variety of routes of administration is crucial for improving the perioperative outcomes after day-case surgery. In addition to local wound infiltration and infiltration, other topical and parenteral routes of administration have been studied. For example, the administration of intranasal lidocaine in combination with naphazoline decreased both intraoperative and postoperative pain and reduced

rescue analgesic requirements in the postoperative period [61]. Although intra-abdominal administration of levobupivacaine was alleged to produce satisfactory analgesia in patients undergoing abdominal hysterectomy procedures, the study was flawed due to the failure to include a placebo control group [62].

The administration of i.v. lidocaine has been shown to reduce surgery-induced immune alterations, postoperative pain scores, postoperative analgesic requirements, and intraoperative anesthetic requirements, as well as contribute to a faster return of bowel function and decreased length of hospital stay. Use of i.v. lidocaine was reported to improve the ability of patients to ambulate after day-case surgery procedures [63–68], thereby facilitating the recovery process. However, Bryson *et al.* [69] have failed to demonstrate that intraoperative administration of i.v. lidocaine reduces hospital stay or improves objective measures of analgesia and recovery following abdominal hysterectomy. Clearly, further studies are needed to assess whether lidocaine has a beneficial effect in patients undergoing short day-case surgery procedures with more severe postoperative pain and to determine the optimum dose, timing, and duration of infusion of lidocaine in this setting [70].

The use of continuous local anesthetic techniques (e.g., for perineural blocks or wound infiltration) has become increasingly popular due to their ability to control moderate-to-severe pain after major ambulatory orthopedic surgery procedures [71–75]. The availability of disposable local anesthetic infusion systems and the encouraging results from these early perineural infusion studies have led to the increasing popularity of these techniques for pain control in the postdischarge period. However, the clear benefits of these approaches for managing pain after ambulatory surgery must be balanced against the cost of the equipment and the resources needed to safely manage these systems outside the hospital environment.

The use of transcutaneous electrical nerve (TENS) stimulation at paravertebral dermatomes corresponding to the surgical incision and/or acupoints (TAES) has also been reported to improve postoperative pain management [76]. Because these techniques cause few if any adverse effects, their use as an adjunct to conventional pharmaceutical approaches should be considered as part of multimodal analgesic regimens in the future, particularly for patients in whom conventional analgesic techniques fail and/or are accompanied by severe medication-related adverse events [76–79].

Despite the considerable advances which have been made in the management of perioperative pain, a significant proportion of surgical patients still suffer from inadequate pain control. A multimodal analgesic regimen

should be adjusted to meet the needs of the individual patient by taking into consideration their pre-existing medical conditions, types of surgery, and previous experiences related to both acute and chronic pain management. The individual differences in pain sensitivity is related to a combination of still inadequately understood genetic and environmental factors, which influence central and peripheral modulation of pain signaling [80]. However, recent human genetic studies suggest that single nucleotide polymorphisms of specific genes, such as the μ -opioid receptor gene and the catechol-*O*-methyltransferase gene, are associated with differences in basal pain sensitivity, with altered pain-induced μ -opioid receptor binding in the central nervous system, response to opioid analgesics, and the development of chronic pain following an acute injury [81–85].

Conclusion

The use of multimodal analgesia technique offers multiple benefits for the patient and the healthcare system in line with the goals of modern ambulatory (day-case) surgery [86]. The current armamentarium of analgesic medications and techniques include a wide spectrum of pharmaceutical products and nonpharmacologic products with the aim to reduce postoperative pain, opioid use, and related adverse effects (such as nausea and vomiting, constipation, urinary retention), duration of the hospital stay, and perioperative care costs, while still providing for a high-quality recovery for the patient undergoing day-case surgery. Although 10 years may not have been long enough to decipher the enigmas associated with postoperative pain management, we are clearly making progress and hopefully ‘pain-free’ recovery after all ambulatory surgery procedures will be possible with effective multimodal analgesic regimens before the end of the current decade.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 778).

- 1 Carr DB. The development of national guidelines for pain control: synopsis and commentary. *Eur J Pain* 2001; 5:91–98.
- 2 White PF, Kehlet H. Improving postoperative pain management: what are the unresolved issues? *Anesthesiology* 2010; 112:220–225.
- 3 Pavlin DJ, Chen C, Penazola DA, *et al.* Pain as a factor complicating recovery and discharge after ambulatory surgery. *Anesth Analg* 2002; 95:627–634.
- 4 White PF. Pain management after ambulatory surgery: where is the disconnect? *Can J Anaesth* 2008; 55:201–207.
- 5 Elvir-Lazo OL, White PF. Postoperative pain management after ambulatory surgery: role of multimodal analgesia. *Anesthesiol Clin* 2010; 28:217–224.
- 6 Baldini G, Carli F. Anesthetic and adjunctive drugs for fast-track surgery. *Curr Drug Targets* 2009; 10:667–686.
- 7 White PF, Kehlet H, Neal JM, *et al.* Role of the anesthesiologist in fast-track surgery: from multimodal analgesia to perioperative medical care. *Anesth Analg* 2007; 104:1380–1396.
- 8 White PF. Multimodal pain management: the future is now! *Curr Opin Investig Drugs* 2007; 8:517–518.
- 9 Chung F, Ritchie E, Su J. Postoperative pain in ambulatory surgery. *Anesth Analg* 1997; 85:808–816.
- 10 Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesth Analg* 2007; 105:205–221.
- 11 White PF, Kehlet H. Postoperative pain management and patient outcome: time to return to work! [editorial]. *Anesth Analg* 2007; 104:487–490.
- 12 Sun T, Sacan O, White PF, *et al.* Perioperative vs postoperative celecoxib on patient outcome after major plastic surgery procedures. *Anesth Analg* 2008; 106:950–958.
- 13 Bisgaard T. Analgesic treatment after laparoscopic cholecystectomy: a critical assessment of the evidence. *Anesthesiology* 2006; 104:835–846.
- 14 White PF, Sacan O, Tufanogullari B, *et al.* Effect of short-term postoperative celecoxib administration on patient outcome after outpatient laparoscopic surgery. *Can J Anaesth* 2007; 54:342–348.
- 15 Gan TJ, Joshi GP, Viscusi E, *et al.* Preoperative parenteral parecoxib and follow-up oral valdecoxib reduce length of stay and improve quality of patient recovery after laparoscopic cholecystectomy surgery. *Anesth Analg* 2004; 98:1665–1673.
- 16 Viscomi CM, Friend A, Parker C, *et al.* Ketamine as an adjuvant in lidocaine intravenous regional anesthesia: a randomized, double-blind, systemic control trial. *Reg Anesth Pain Med* 2009; 34:130–133.
- 17 Suzuki M. Role of *N*-methyl-D-aspartate receptor antagonists in postoperative pain management. *Curr Opin Anesthesiol* 2009; 22:618–622.
- 18 Lin TF, Yeh YC, Lin FS, *et al.* Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. *Br J Anaesth* 2009; 102:117–122.
- 19 Salman N, Uzun S, Coskun F, *et al.* Dexmedetomidine as a substitute for remifentanyl in ambulatory gynecologic laparoscopic surgery. *Saudi Med J* 2009; 30:77–81.
- A study describing the use of dexmedetomidine as alternative to opioid during laparoscopic surgery.
- 20 Collard V, Mistraretti 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; 105:1255–1262.
- 21 Coloma M, Chiu J, White P, *et al.* The use of esmolol as an alternative to remifentanyl during desflurane anesthesia for fast-track outpatient gynecologic laparoscopic surgery. *Anesth Analg* 2001; 92:352–357.
- 22 White PF, Wang BG, Tang J, *et al.* The effect of intraoperative use of esmolol and nicardipine on recovery after ambulatory surgery. *Anesth Analg* 2003; 97:1633–1638.
- 23 Chia YY, Chan MH, Ko NH, *et al.* Role of β -blockade in anaesthesia and postoperative pain management after hysterectomy. *Br J Anaesth* 2004; 93:799–805.
- 24 Ozturk T, Kaya H, Aran G, *et al.* Postoperative beneficial effects of esmolol in treated hypertensive patients undergoing laparoscopic cholecystectomy. *Br J Anaesth* 2008; 100:211–214.
- 25 Mitchell A, van Zanten SV, Inglis K, *et al.* A randomized controlled trial comparing acetaminophen plus ibuprofen versus acetaminophen plus codeine plus caffeine after outpatient general surgery. *J Am Coll Surg* 2008; 206:472–479.
- 26 Gorocs TS, Lambert M, Rinne T, *et al.* Efficacy and tolerability of ready-to-use intravenous paracetamol solution as monotherapy or as an adjunct analgesic therapy for postoperative pain in patients undergoing elective ambulatory surgery: open, prospective study. *Int J Clin Pract* 2009; 63:112–120.
- 27 Api O, Unal O, Ugurel V, *et al.* Analgesic efficacy of intravenous paracetamol for outpatient fractional curettage: a randomised, controlled trial. *Int J Clin Pract* 2009; 63:105–111.
- 28 Ohnesorge H, Bein B, Hanss H, *et al.* Paracetamol versus metamizol in the treatment of postoperative pain after breast surgery: a randomized, controlled trial. *Eur J Anaesthesiol* 2009; 26:648–653.
- 29 Jokela R, Ahonen J, Seitsonen E, *et al.* The influence of ondansetron on the analgesic effect of acetaminophen after laparoscopic hysterectomy. *Clin Pharmacol Ther* 2010; 87:672–678.
- Study addressing the suggested interaction between paracetamol and 5-hydroxytryptamine (3) antagonists.
- 30 Salihoglu Z, Yildirim M, Demireluk S, *et al.* Evaluation of intravenous paracetamol administration on postoperative pain and recovery characteristics in patients undergoing laparoscopic cholecystectomy. *Surg Laparosc Endosc Percutan Tech* 2009; 19:321–323.

- 31 Ko MJ, Lee JH, Cheong SH, *et al.* Comparison of the effects of acetaminophen to ketorolac when added to lidocaine for intravenous regional anesthesia. *Korean J Anesthesiol* 2010; 58:357–361.
- 32 Singh R, Bhagwat A, Bhadoria P, Kohli A. Forearm IVRA, using 0.5% lidocaine in a dose of 1.5 mg/kg with ketorolac 0.15 mg/kg for hand and wrist surgeries. *Minerva Anesthesiol* 2010; 76:109–114.
- 33 Hong JY, Won Han S, Kim WO, Kil HK. Fentanyl sparing effects of combined ketorolac and acetaminophen for outpatient inguinal hernia repair in children. *J Urol* 2010; 183:1551–1555.
- 34 Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg* 2010; 110:1170–1179.
- A meta-analysis on the effects of combination paracetamol and NSAIDs showing beneficial effects from the combined use.
- 35 Issioui T, Klein KW, White PF, *et al.* The efficacy of premedication with celecoxib and acetaminophen in preventing pain after otolaryngologic surgery. *Anesth Analg* 2002; 94:1188–1193.
- 36 Grant GM, Mehlich DR. Intranasal ketorolac for pain secondary to third molar impaction surgery: a randomized, double-blind, placebo-controlled trial. *J Oral Maxillofac Surg* 2010; 68:1025–1031.
- 37 Coloma M, White PF, Huber PJ Jr, *et al.* The effect of ketorolac on recovery after anorectal surgery: intravenous versus local administration. *Anesth Analg* 2000; 90:1107–1110.
- 38 White PF. The changing role of nonopioid analgesic techniques in the management of postoperative pain. *Anesth Analg* 2005; 101:S5–S22.
- 39 Salerno A, Hermann R. Efficacy and safety of steroid use for postoperative pain relief. Update and review of the medical literature. *J Bone Joint Surg Am* 2006; 88:1361–1372.
- 40 Kjetil H, Sem TK, Ellen S, Johan R. The prolonged postoperative analgesic effect when dexamethasone is added to a nonsteroidal antiinflammatory drug (rofecoxib) before breast surgery. *Anesth Analg* 2007; 105:481–486.
- 41 Mathiesen O, Jacobsen LS, Holm HE, *et al.* Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. *Br J Anaesth* 2008; 101:535–541.
- 42 Mathiesen O, Rasmussen ML, Dierking G, *et al.* Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. *Acta Anaesthesiol Scand* 2009; 53:227–235.
- 43 Rasmussen ML, Mathiesen O, Dierking O, *et al.* Multimodal analgesia with gabapentin, ketamine and dexamethasone in combination with paracetamol and ketorolac after hip arthroplasty: a preliminary study. *Eur J Anaesthesiol* 2010; 27:324–330.
- 44 Coloma M, Duffy LL, White PF, *et al.* Dexamethasone facilitates discharge after outpatient anorectal surgery. *Anesth Analg* 2001; 92:85–88.
- 45 Gilron I, Orr E, Tu D, *et al.* A randomized, double-blind, controlled trial of perioperative administration of gabapentin, meloxicam and their combination for spontaneous and movement-evoked pain after ambulatory laparoscopic cholecystectomy. *Anesth Analg* 2009; 108:623–630.
- 46 Srivastava U, Kumar A, Saxena S, *et al.* Effect of preoperative gabapentin on postoperative pain and tramadol consumption after minilap open cholecystectomy: a randomized double-blind, placebo-controlled trial. *Eur J Anaesthesiol* 2010; 27:331–335.
- 47 Sen H, Sizlan A, Yanarates O, *et al.* A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. *Anesth Analg* 2009; 109:1645–1650.
- 48 Rusy L, Hainsworth K, Nelson T, *et al.* Gabapentin use in pediatric spinal fusion patients: a randomized, double-blind, controlled trial. *Anesth Analg* 2010; 110:1393–1398.
- 49 Clarke H, Pereira S, Kennedy D, *et al.* Gabapentin decreases morphine consumption and improves functional recovery following total knee arthroplasty. *Pain Res Manag* 2009; 14:217–222.
- 50 Agarwal A, Gautam S, Gupta D, *et al.* Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. *Br J Anaesth* 2008; 101:700–704.
- 51 Buvanendran A, Kroin JS, Della Valle CJ, *et al.* Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg* 2010; 110:199–207.
- A study showing positive effects from a perioperative oral pregabalin reducing acute pain and potentially to have an impact on the development of chronic pain.
- 52 Jokela R, Ahonen J, Tallgren M, *et al.* Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. *Br J Anaesth* 2008; 100:834–840.
- 53 White PF, Tufanogullari B, Taylor J, *et al.* The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. *Anesth Analg* 2009; 108:1140–1145.
- 54 Paech MJ, Goy R, Chua S, *et al.* A randomized, placebo-controlled trial of preoperative oral pregabalin for postoperative pain relief after minor gynecological surgery. *Anesth Analg* 2007; 105:1449–1453.
- 55 Chang SH, Lee HW, Kim HK, *et al.* An evaluation of perioperative pregabalin for prevention and attenuation of postoperative shoulder pain after laparoscopic cholecystectomy. *Anesth Analg* 2009; 109:1284–1286.
- 56 Trabulsi EJ, Patel J, Viscusi ER, *et al.* Preemptive multimodal pain regimen reduces opioid analgesia for patients undergoing robotic-assisted laparoscopic radical prostatectomy. *Urology* 2010. [Epub ahead of print]
- 57 Rajpal S, Gordon DB, Pellino TA, *et al.* Comparison of perioperative oral multimodal analgesia versus IV PCA for spine surgery. *J Spinal Disord Tech* 2010; 23:139–145.
- 58 Essving P, Axelsson K, Kjellberg J, *et al.* Reduced morphine consumption and pain intensity with local infiltration analgesia (LIA) following total knee arthroplasty. *Acta Orthop* 2010; 81:354–360.
- 59 Coloma M, Ogunnake B, White PF. Efficacy of a multimodal analgesic regimen for outpatients undergoing laparoscopic surgery in facilitating a fast-track recovery. In: ASA meeting; Chicago, IL, August 21; 2000.
- 60 Forget P, Vandenhende J, Berliere M, *et al.* Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. *Anesth Analg* 2010; 110:1630–1635.
- A study suggesting potential long-term effects from the use of ketorolac as part of the postoperative analgesic regime.
- 61 Granier M, Dadure C, Bringuier S, *et al.* Intranasal lidocaine plus naphazoline nitrate improves surgical conditions and perioperative analgesia in septorhinoplasty surgery. *Can J Anaesth* 2009; 56:102–108.
- 62 Perniola A, Gupta A, Crafoord K, *et al.* Intraabdominal local anaesthetics for postoperative pain relief following abdominal hysterectomy: a randomized, double-blind, dose-finding study. *Eur J Anaesthesiol* 2009; 26:421–429.
- 63 Kaba A, Laurent SR, Detroz BJ, *et al.* Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. *Anesthesiology* 2007; 106:11–18.
- 64 Lauwick S, Kim DJ, Michelagnoli G, *et al.* Intraoperative infusion of lidocaine reduces postoperative fentanyl requirements in patients undergoing laparoscopic cholecystectomy. *Can J Anaesth* 2008; 55:754–760.
- 65 Lauwick S, Kim DJ, Mistraletti G, Carli F. Functional walking capacity as an outcome measure of laparoscopic prostatectomy: the effect of lidocaine infusion. *Br J Anaesth* 2009; 103:213–219.
- 66 Herroeder S, Pecher S, Schonherr ME, *et al.* Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. *Ann Surg* 2007; 246:192–200.
- 67 Groudine SB, Fisher HA, Kaufman RP Jr, *et al.* Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. *Anesth Analg* 1998; 86:235–239.
- 68 Yardeni IZ, Beilin B, Mayburd E, *et al.* The effect of perioperative intravenous lidocaine on postoperative pain and immune function. *Anesth Analg* 2009; 109:1464–1469.
- 69 Bryson G, Charapov I, Krolczyk G. Intravenous lidocaine does not reduce length of hospital stay following abdominal hysterectomy. *Can J Anaesth* 2010; 57:759–766.
- 70 McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. *Drugs* 2010; 70:1149–1163.
- 71 White PF, Issioui T, Skrivanek GD, *et al.* Use of a continuous popliteal sciatic nerve block for the management of pain after major podiatric surgery: does it improve quality of recovery? *Anesth Analg* 2003; 97:1303–1309.
- 72 Ilfeld BM, Enneking FK. Continuous peripheral nerve blocks at home: a review. *Anesth Analg* 2005; 100:1822–1833.
- 73 Ilfeld BM, Le LT, Ramjohn J, *et al.* The effects of local anesthetic concentration and dose on continuous infraclavicular nerve blocks: a multicenter, randomized, observer-masked, controlled study. *Anesth Analg* 2009; 108:345–350.
- 74 Capdevilla X, Dadure C, Bringuier S, *et al.* Effect of patient-controlled peripheral analgesia on rehabilitation and pain after ambulatory orthopaedic surgery: a multicenter randomised trial. *Anesthesiology* 2006; 105:566–573.
- 75 Liu SS, Richman JM, Thirlby R, *et al.* Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. *J Am Coll Surg* 2006; 203:914–932.

- 76** Chen L, Tang J, White PF, *et al.* The effect of location of transcutaneous electrical nerve stimulation on postoperative opioid analgesic requirement: acupoint versus nonacupoint stimulation. *Anesth Analg* 1998; 87:1129–1134.
- 77** Wang B, Tang J, White PF, *et al.* Effect of the intensity of transcutaneous acupoint electrical stimulation on the postoperative analgesic requirement. *Anesth Analg* 1997; 85:406–413.
- 78** Usichenko TI, Kuchling S, Witstruck T, *et al.* Auricular acupuncture for pain relief after ambulatory knee surgery: a randomized trial. *CMAJ* 2007; 176:179–183.
- 79** Larson J, Gutowski K, Marcus B, *et al.* The effect of electroacustimulation on postoperative nausea, vomiting, and pain in outpatient plastic surgery patients: a prospective, randomized, blinded, clinical trial. *Plast Reconstr Surg* 2010; 125:989–994.
- 80** Kim H, Clark D, Dionne RA. Genetic contributions to clinical pain and analgesia: avoiding pitfalls in genetic research. *J Pain* 2009; 10:663–693.
- 81** Fillingim RB, Kaplan L, Staud R, *et al.* The A118G single nucleotide polymorphism of the [mu]-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. *J Pain* 2005; 6:159–167.
- 82** Zubieta JK, Heitzeg MM, Smith YR, *et al.* COMT val158met genotype affects μ -opioid neurotransmitter responses to a pain stressor. *Science* 2003; 299:1240–1243.
- 83** Diatchenko L, Slade GD, Nackley AG, *et al.* Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* 2005; 14:135–143.
- 84** Andersen S, Skorpen F. Variation in the COMT gene: implications for pain perception and pain treatment. *Pharmacogenomics* 2009; 10:669–684.
- 85** Jensen KB, Lonsdorf TB, Schalling M, *et al.* Increased sensitivity to thermal pain following a single opiate dose is influenced by the COMT val158met polymorphism. *PLoS One* 2009; 4:e6016.
- 86** Joshi GP. Multimodal analgesia techniques for ambulatory surgery. *Int Anesthesiol Clin* 2005; 43:197–204.