Preventive analgesia and beyond: current status, evidence, and future directions

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KEY LEARNING POINTS

- *What is preemptive analgesia?* The classic definition of preemptive analgesia requires two groups of patients to receive identical treatment before or after incision or surgery. The only difference between the two groups is the timing of administration of the pharmacological agent relative to incision. The constraint to include a postincision or postsurgical treatment group is methodologically appealing, because in the presence of a positive result, it provides a window of time within which the observed effect occurred, and thus points to possible mechanisms underlying the effect: the classic view assumes that the intraoperative nociceptive barrage contributes to a greater extent to postoperative pain than does the postoperative nociceptive barrage. However, this view is too restrictive and narrow in part because we know that sensitization is induced by factors other than the peripheral nociceptive barrage associated with incision and subsequent noxious intraoperative events.
- *What is preventive analgesia?* A broader approach to the prevention of postoperative pain has evolved that aims to minimize the deleterious immediate and long-term effects of noxious perioperative afferent input. The focus of preventive analgesia is not on the relative timing of analgesic or anesthetic interventions, but on attenuating the impact of the peripheral nociceptive barrage associated with noxious preoperative, intraoperative, and/or postoperative events/stimuli. These stimuli induce peripheral and central sensitization which increase postoperative pain intensity and analgesic requirements. Preventing sensitization will reduce pain and analgesic requirements. Preventive analgesia is demonstrated when postoperative pain and/or analgesic use are reduced beyond the clinical duration of action of the target agent which we have defined as 5.5 half-lives of the target agent. This requirement ensures that the observed effects are not analgesic effects.
- *What does the recent preemptive analgesia literature tell us?* The results of the present literature review indicate that the proportion of significant preemptive effects (0.63) is not significantly different from the proportion of negative preemptive effects (0.37) across the different classes of drugs studied ($p = 0.36$). This is understandable when one considers that both preincisional and postincisional (or postsurgical) noxious inputs contribute to postoperative sensitization, pain, and analgesic consumption. The most likely conclusion,

therefore, is that for a certain proportion of studies of preemptive analgesia, the postincision or postsurgical administration condition is as beneficial in reducing central sensitization as is the preoperative condition, but these benefits go undetected when the comparison is made between the two groups. The lack of a control group in studies of preemptive analgesia is a serious limitation that confounds interpretation of the results and has contributed to the premature and erroneous conclusion that there is no clinical benefit to preoperative nociceptive blockade.

- *What does the recent preventive analgesia literature tell us?* In contrast to the results for preemptive analgesia, the proportion of significant preventive effects (0.72) is significantly greater than the proportion of negative effects (0.28) across the different classes of drugs studied ($p = 0.03$). Overall, administration of these agents appears to reduce pain, analgesic consumption, or both at a point in time that exceeds 5.5 half-lives of the target agent. Since these extended effects are observed after the clinical actions of the agents have worn off, they are not analgesic effects. Rather, these effects appear to be due to the reduction in perioperative peripheral and central sensitization associated with preventive analgesia. The benefits of preventive analgesia are clinically relevant and include reduced pain and/or analgesic consumption that extend beyond the duration of action of the target drug.
- *What other important factors do we need to measure perioperatively?* Measures of postoperative pain and analgesic use are important, but given the prominent role played by psychosocial factors in the experience of preoperative, acute postoperative, and chronic postsurgical pain, relevant psychological, emotional, and physical variables should be routinely assessed before and after surgery. Assessment of these additional domains of functioning may help to shed light on the predictors of severe acute postoperative pain, the processes involved in recovery from surgery, and the risk factors for developing chronic postsurgical pain.

BACKGROUND LITERATURE

Acute postoperative pain management has been dominated by an outdated concept of pain. Pain is viewed as the end product of a passive system that faithfully transmits a peripheral "pain" signal from receptor to a "pain centre" in the brain.[1] This view has resulted in a strategy for managing postoperative pain that is inadequate, in part, because it treats the patient only after the pain is well established. Patients arrive in the post-anesthetic care unit after surgery, often in extreme pain, where they then receive multiple doses of opioids in an effort to bring the pain down to a tolerable level. However, basic science and clinical data show that brief, noxious inputs or frank injury due to C-fiber activation (e.g. cutting tissue, nerve, and bone) induce long-lasting changes in central neural function that persist well after the offending stimulus has been removed or the injury has healed.[2,3] This view of pain, involving a dynamic interplay between peripheral and central mechanisms, is inconsistent with the outdated notion that pain results from transmission of impulses along a straight-through pathway from the site of injury to the brain.[1]

The practice of treating pain only after it has become well entrenched is slowly being supplanted by a preventive approach that aims to block transmission of the primary afferent injury barrage before, during, and after surgery.[4,5,6,7] The idea behind this approach is not simply that it reduces nociception and stress during surgery – although these are obviously worthwhile goals. The hypothesis is that the transmission of noxious afferent input from the periphery (e.g. arising from preoperative pain, incision, noxious intraoperative events, postoperative inflammation, and ectopia) to the spinal cord induces a prolonged state of central neural sensitization or hyperexcitability that amplifies subsequent input from the wound and leads to heightened postoperative pain and a greater requirement for postoperative analgesics. By interrupting the transmission of the peripheral nociceptive barrage to the spinal cord at various points in time throughout the perioperative period, a preventive approach aims to block the induction of central sensitization, resulting in reduced pain intensity and lower analgesic requirements. The goal of this chapter is to critically review the recent literature on preemptive and preventive analgesia. The first section provides a description of the perioperative targets of a preventive analgesic approach. This is followed by a brief review of the factors that have been shown to predict the development of acute and chronic postsurgical pain. Next, the history and recent progress in preemptive analgesia are presented with emphasis on the confusion and lack of clarity that characterizes the field. Under Controversy and confusion about preemptive analgesia, we attempt to clear up the confusion by highlighting clinical trial designs and examples from the literature that distinguish preventive analgesia from preemptive analgesia. This is followed by a quantitative review of the preemptive and preventive analgesia literatures (see below under Preventive analgesia), organized according to class of drug administered. Outcomes are described in terms of the presence or absence or a preemptive or preventive effect and a detailed tabular summary is presented of all studies that met our criteria for inclusion in the review. The chapter concludes with recommendations for future research.

TARGETS OF A PREVENTIVE APPROACH TO ACUTE PAIN MANAGEMENT

The perioperative period can be divided into three distinct phases: preoperative, intraoperative, and postoperative (**Figure 9.1**). Specific factors within these phases contribute to the development of acute postoperative pain. These factors include: (1) preoperative noxious inputs and pain; (2) C-fiber injury barrage arising from the cutting of skin, muscle, nerve and bone, wound retraction, etc.; and (3) postoperative peripheral nociceptive activity, including that arising from the inflammatory response and ectopic neural activity in the case of postsurgical nerve injury. Each of these factors can contribute to peripheral and central sensitization and each is a legitimate target for a preventive approach. The relative contribution of these three factors to acute postoperative pain is dependent on the surgical procedure, extent and nature of tissue damage, duration of surgery, timing of treatments relative to incision, pharmacokinetics of the agent(s) used preoperatively, presence or absence of additional analgesia intraoperatively, nature of postoperative analgesia, and a host of other variables. Minimizing the negative impact of as many of these factors as possible in the three phases will increase the likelihood of preventing the induction and maintenance of peripheral and central sensitization. Preventing sensitization will reduce pain and analgesic requirements.

Figure 9.1 depicts the eight possible treatment combinations of administering or not administering analgesics across the three perioperative phases (preoperative, intraoperative, and postoperative). The preoperative period encompasses interventions that begin days before surgery and up to those administered just minutes before skin incision. The intraoperative period includes interventions started immediately after incision to those initiated just prior to the end of surgery (i.e. skin closure). The postoperative period includes interventions started immediately after the end of surgery and may extend for days or weeks thereafter. Within each phase there is potential for extensive variability in the timing of administration of analgesic agents. While this potential is greatest in the pre- and postoperative phases (e.g. ranging from minutes to days or weeks) even within the intraoperative period, evidence shows that there are considerable interstudy differences in timing of the postincisional intervention (e.g. ranging from minutes to hours).

PREDICTORS OF ACUTE AND CHRONIC POSTSURGICAL PAIN

The ability to predict who will develop severe acute postoperative pain and who will go on to develop chronic postsurgical pain is at the heart of efforts to understand

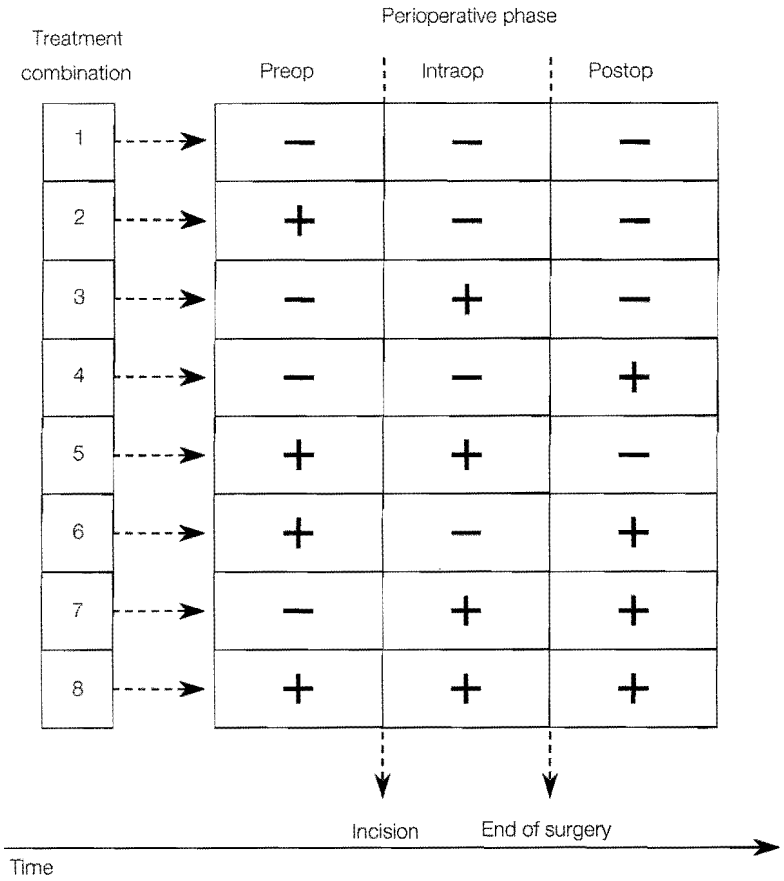

Figure 9.1 Schematic representation showing the administration (+) or non-administration (−) of analgesic agents across the three perioperative phases of surgery (preop, preoperative; intraop, intraoperative; postop, postoperative). The administration or nonadministration of analgesics during the three phases yields eight different treatment combinations and 28 possible two-group designs to evaluate the efficacy of preemptive and preventive analgesia. The classic preemptive analgesia design requires two groups of patients to receive identical treatment before or after incision or surgery (treatment combination 2 versus 3 and 2 versus 4). This represents only one of many possible hypotheses concerning the effects of blocking noxious perioperative inputs on postoperative pain and analgesic consumption.

the role played by the various factors within the three perioperative phases depicted in **Figure 9.1**. One of the most robust findings to emerge from the postoperative pain and anesthesia literatures is that current pain predicts future pain.[8, 9, 10, 11] This appears to be true across surgery types and regardless of time frame. Preoperative pain intensity or pain duration is a risk factor for development of severe early acute postoperative pain,[12] acute pain days,[13, 14, 15, 16, 17] and weeks[18] after surgery, as well as long-term postsurgical pain.[14, 15, 18, 19, 20, 21, 22] Preoperative pain ratings in response to the cold pressor task,[23] suprathreshold heat pain stimuli,[24] and a first-degree burn injury[25] also predict acute postoperative pain intensity days after surgery. Severity of acute postoperative pain not only predicts pain after discharge,[18, 26] but it is also a risk factor for development of chronic postsurgical pain.[27, 28, 29, 30, 31, 32]

No other factor is as consistently related to the development of future pain problems as is current pain. Younger age,[12, 18] female gender,[12, 18] anxiety,[12, 19] and various other psychological variables[8, 33, 34, 35, 36] predict postoperative pain in some studies, but not with the consistency or magnitude with which pain predicts pain. What must be determined is the aspect(s) of pain that is predictive. Is it something about the pain *per se* (e.g. intensity, quality, duration) or the individuals who report the pain (e.g. response bias, psychological vulnerability, genetic predisposition)? Will reducing surgery-induced sensitization alter the course of acute pain and lead to a decreased incidence of long-term pain problems? What factors are responsible for the transition of acute postoperative pain to chronic, intractable, pathological pain? We do not have answers to these important questions but one of the factors that has been linked to increased pain and analgesic consumption in the short and long term is the perioperative peripheral nociceptive injury barrage associated with surgery. The remainder of this chapter will focus on an evidence-based presentation of the literature that examines the efficacy of preemptive and preventive interventions aimed at reducing surgically induced sensitization.

HISTORY AND RECENT PROGRESS IN PREEMPTIVE ANALGESIA

The idea that acute postoperative pain might be intensified by a state of central neural hyperexcitability induced during surgery was first proposed by Crile (see Katz[37]) and later by Wall[38] who suggested that "preemptive preoperative analgesia" would block the induction of central neural sensitization brought about by incision and thus reduce acute postoperative pain intensity. Since its introduction into the pain and anesthesia literatures, this concept has been refined, based in part on confirmatory and contradictory evidence from clinical studies, new developments in basic science, and critical thought. The suggestion that surgical incision triggered central sensitization[38] has been expanded to include the sensitizing effects of preoperative noxious inputs and pain, other noxious intraoperative stimuli, as well as postoperative peripheral and central inflammatory mediators and ectopic neural activity.

It is now well documented that while general anesthesia may attenuate transmission of afferent injury barrage from the periphery to the spinal cord and brain, it does not block it.[39] Moreover, systemic opioids may not provide a sufficiently dense blockade of spinal nociceptive neurons to prevent central sensitization.[40] The clinical significance of these findings for patients who receive general anesthesia during surgery is that although they are unconscious, the processes leading to sensitization of dorsal horn neurons are largely unaffected by general anesthesia or routine doses of opioids. This sets the stage for heightened postoperative pain and an increased requirement for analgesics.

CONTROVERSY AND CONFUSION ABOUT PREEMPTIVE ANALGESIA

Debate over the appropriate definition of preemptive analgesia[5, 6, 41, 42, 43, 44, 45, 46, 47] has spawned a variety of different terms, including anoci-association,[48] preemptive preoperative analgesia,[38] preemptive analgesia,[49] preventive analgesia,[4, 6] balanced periemptive analgesia,[50] broad versus narrow preemptive analgesia,[51] and protective analgesia.[52] Substantial confusion has developed over the benefits and meaning of preemptive analgesia.

Two general approaches have dominated the literature.[53] The classic view of preemptive analgesia[49] requires two groups of patients to receive identical treatment before or after incision or surgery (treatment combination 2 versus 3 and 2 versus 4 in **Figure 9.1**). Accordingly, the only difference between the two groups is the timing of administration of the pharmacological agent relative to incision with one group receiving the target agent before surgery, and the other, after incision or surgery (see **Figures 9.2** and **9.3** depicting studies by Katz *et al.*[54] and Dierking *et al.*[55] who used these designs, respectively). The constraint to include a postincision or postsurgical treatment group is methodologically appealing because in the presence of a positive result, it provides a window of time within which the observed effect occurred and thus points to possible mechanisms underlying the effect. However, this view of preemptive analgesia is too restrictive and narrow[5, 6, 56] in part because we do not know the relative extent to which pre-, intra-, and postoperative peripheral nociceptive inputs contribute to central sensitization and postoperative pain.

The narrow conceptualization of preemptive analgesia in conjunction with the classic pre- versus postsurgery design assumes that the intraoperative nociceptive barrage contributes to a greater extent to postoperative pain than does the postoperative nociceptive barrage. However, the

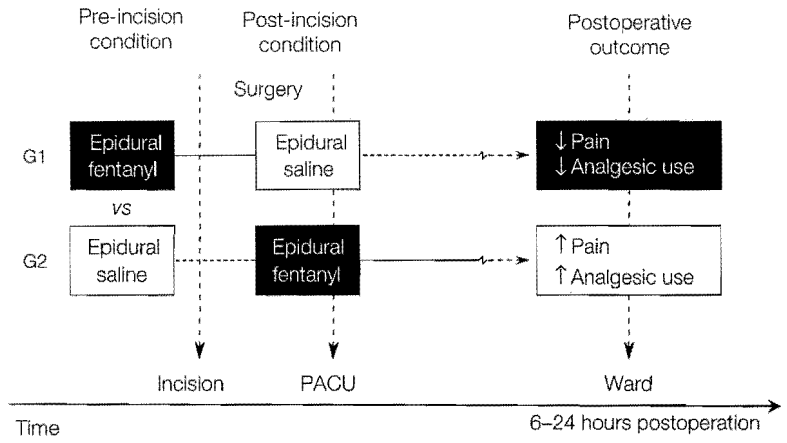

Figure 9.2 Experimental design and expected postoperative outcome for studies of preemptive analgesia in which a preincisional intervention is compared with the very same intervention initiated after incision, but before the end of surgery (treatment combination 2 versus 3 in **Figure 9.1**). This design was used in the study by Katz *et al.*[54][II] in which the two groups of patients undergoing lateral thoracotomy received epidural fentanyl or saline before, and epidural saline or fentanyl 15 minutes after, incision, respectively. Pain ratings in the group that received preincisional epidural fentanyl were significantly lower six hours after surgery and morphine consumption was significantly lower between 12 and 24 hours after surgery.

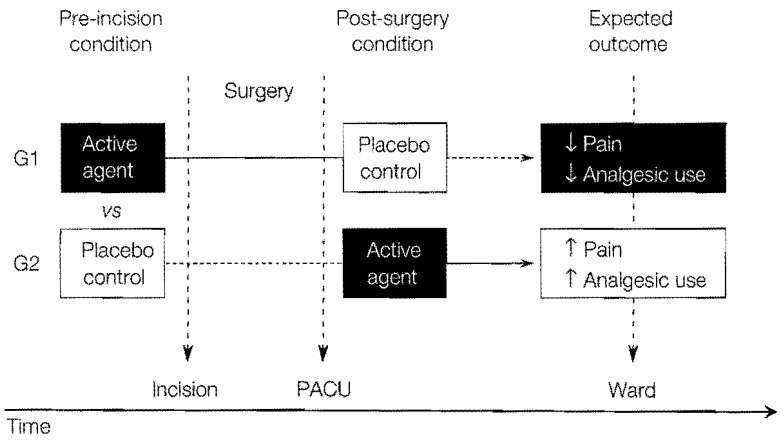

Figure 9.3 Experimental design and expected postoperative outcome for studies of preemptive analgesia in which a preincision intervention is compared with the very same intervention initiated after surgery (treatment combination 2 versus 4 in **Figure 9.1**). According to the classic view of preemptive analgesia, the expected outcome is based on the assumption that the intraoperative nociceptive barrage contributes to a greater extent to postoperative pain and analgesic use than do postoperative noxious inputs. This design was used in the study by Dierking *et al.*[55] who compared a lidocaine inguinal field block administered 15 minutes before hernia repair with the same treatment administered immediately after surgery. Significant differences in pain or analgesic use were not found between the pre- and postsurgical treatment groups raising the possibility that a preventive effect went undetected due to lack of a control group (see **Figures 9.4** and **9.5**).

design does not allow for other equally plausible alternatives. For certain surgical procedures, central sensitization may be induced to an equal extent by incision and intraoperative trauma on the one hand (i.e. in the postsurgical treatment group) and postoperative inflammatory inputs and/or ectopia on the other (i.e. in the preoperative treatment group) which would lead to nonsignificant intergroup differences in pain and analgesic consumption.[57, 58]

Two-group studies that fail to find significant differences in postoperative pain or analgesic consumption between groups treated before or after incision or surgery are inherently flawed because of the absence of an appropriate control group (e.g. treatment combination 1 or 8, or both in **Figure 9.1**). The negative results may point to the relative efficacy in reducing central sensitization of postincisional or postsurgical blockade and not the inefficacy of preoperative blockade (for examples, see **Figures 9.4** and **9.5** depicting studies Katz *et al.*[57, 58] and Gordon *et al.*[59]). Recent studies[57, 58] have highlighted the critical importance of a standard treatment control group. Inclusion of such as group has made it possible to

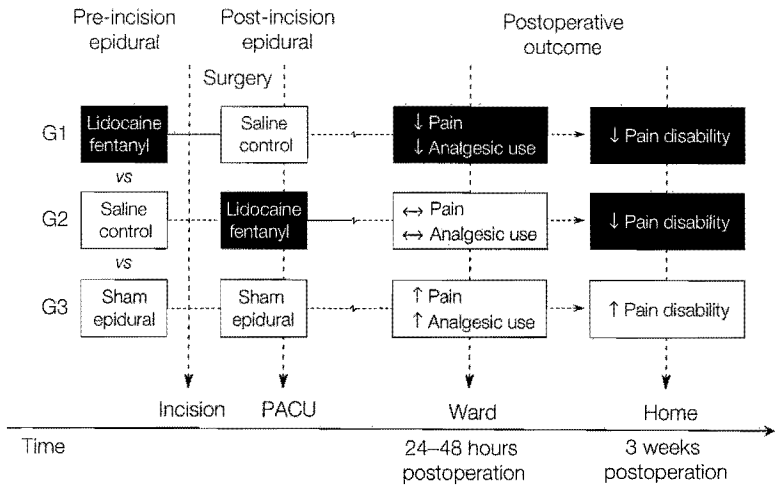

Figure 9.4 Experimental design (treatment combination 1 versus 2 versus 3 in **Figure 9.1**) used by Katz *et al.*[57,58][II] to address the design flaw inherent in two-group studies of preemptive analgesia (**Figure 9.2**). In females undergoing abdominal gynecological surgery by laparotomy, preincisional (G1) but not postincisional (G2) administration of epidural lidocaine and fentanyl was associated with a significantly lower rate of morphine use, lower cumulative morphine consumption, and reduced hyperalgesia compared with a sham epidural condition (G3).[58][II] Three-week follow up showed that pain disability ratings were significantly lower in the two groups that received the epidural when compared with the standard treatment group.[57][II] Results highlight the importance of including a standard treatment control group to avoid the problems of interpretation that arise when two-group studies of preemptive analgesia (pre- versus postincision) fail to find the anticipated effects.

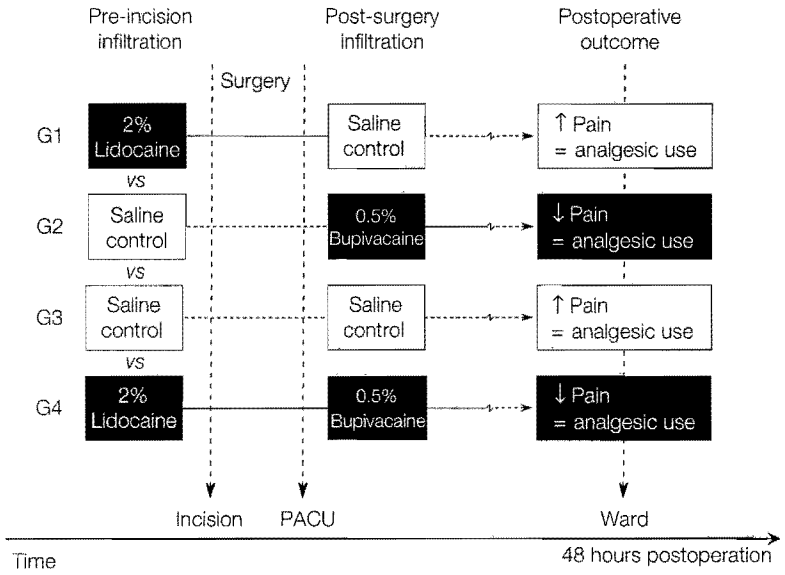

Figure 9.5 Experimental design used by Gordon *et al.*[59][II] to assess the relative effects on late postoperative pain of blocking, or not blocking, noxious intraoperative and/or postoperative inputs (treatment combination 1 versus 2 versus 4 versus 6 in **Figure 9.1**). Patients were randomly assigned in a double-blinded manner to receive a local anesthetic (lidocaine or bupivacaine) or saline before and/or at the end of third molar extraction surgery. Preventive analgesia is demonstrated by the finding that 48 hours after surgery, pain intensity was significantly less in the groups whose postoperative pain was blocked by bupivacaine (G2, G4) compared with preoperative administration of lidocaine (G1) or the saline control group (G3). The results suggest that for third molar extraction surgery, the peripheral nociceptive barrage in the hours following surgery contributes to a greater extent to central sensitization and late postoperative pain than does the intraoperative nociceptive barrage since local anesthetic blockade after surgery was more efficacious than preoperative blockade.

demonstrate reductions in acute postoperative pain and morphine consumption,[58] as well as pain disability three weeks after surgery[57] that would otherwise have gone undetected using the classic, two-group design.

The near exclusive focus in the literature on the narrow view of preemptive analgesia has had the unintended effect of diverting attention away from other clinically significant findings because they do not conform to what

has become the accepted definition of preemptive analgesia.[4] For example, certain studies[60, 61] evaluate the effects of altering the timing of administration of various analgesic agents in a manner similar to that described above for the classic two-group preemptive analgesia design, except that the intent is not to compare pre- versus postincisional or postsurgical treatments. Rather, as illustrated in **Figure 9.6**, both groups may receive the target intervention preoperatively, differing only in how long before surgery the treatment is given.[61] Such a study evaluates the effect on postoperative pain and analgesic consumption of blocking versus not blocking preoperative pain in the context of intraoperative and postoperative epidural blockade and demonstrates that relief of preoperative pain is associated with reduced analgesic use 48 hours after surgery.[61] Finally, other reports[59] have demonstrated that for certain types of surgery, blocking the peripheral nociceptive barrage in the hours after surgery decreases pain at later time periods, whereas blocking the intraoperative nociceptive barrage does not (**Figure 9.5**). Taken together, these shortcomings of the classic view of preemptive analgesia, and its associated design, indicate that an expanded conceptualization and explication of the rationale for, and effects of, blockade across the three perioperative phases is required to move us beyond the current state of confusion that pervades the field of preemptive analgesia.

PREVENTIVE ANALGESIA

A more encompassing approach, termed preventive analgesia,[4, 6] has evolved with the aim of minimizing sensitization induced by noxious perioperative stimuli including those arising preoperatively, intraoperatively, and postoperatively. A preventive analgesic effect is demonstrated when postoperative pain and/or analgesic consumption is reduced relative to another treatment, and/or a placebo treatment or no treatment as long as the effect is observed at a point in time that exceeds the clinical duration of action of the target agent (e.g. treatment combination 1 versus 2, 1 versus 5, or 1 versus 8 in **Figure 9.1**). The requirement that the reduced pain and/or analgesic consumption be observed after the duration of action of the target agent ensures that the preventive effect is not simply an analgesic effect. As we have previously pointed out,[4, 5, 56][I] such a design does not provide information about the factors underlying the effect or the time frame within which the effect occurred due the absence of a post-treatment condition (see **Figures 9.7** and **9.8** for illustrations of studies by Tverskoy *et al.*[62][II] and Reuben *et al.*,[63][II] respectively, who used these designs).

Demonstration of a preventive effect does not require that an intervention be initiated before surgery; the timing of treatment may be during the procedure (e.g. treatment combination 1 versus 3 in **Figure 9.1**) or even after surgery (e.g. treatment combination 1 versus 4 in **Figure 9.1**). For example, a preventive effect is present if postoperative administration of a target analgesic agent, but not a placebo, results in reduced postoperative pain or analgesic consumption after the effects of the target agent have worn off (for a case in point see **Figure 9.9** depicting the study by Reuben *et al.*[64][II]). In fact, any two or more treatment combinations in **Figure 9.1** can produce preventive effects. The focus of preventive analgesia is not on the relative timing of analgesic or anesthetic interventions, but on attenuating the impact of noxious perioperative stimuli that induce peripheral and central sensitization and that increase postoperative pain intensity and

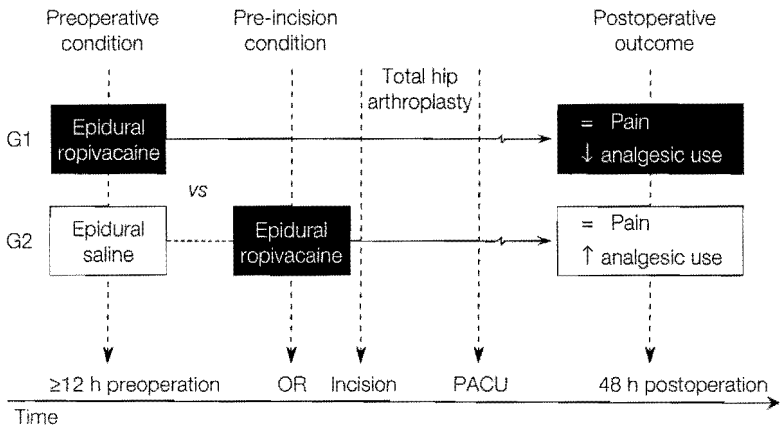

Figure 9.6 Two-group experimental design used by Klasen *et al.*[61][II] comparing the administration of an active agent at different times before surgery in order to examine the effect on postoperative pain and analgesic consumption of blocking versus not blocking preoperative pain in the context of intraoperative and postoperative epidural blockade (treatment combination 8 versus 8 in **Figure 9.1**). This study[61][II] demonstrates that relief of preoperative pain by epidural ropivacaine for at least 12 hours before surgery followed by intraoperative epidural ropivacaine (G1) is associated with reduced patient-controlled epidural analgesia (PCEA) ropivacaine consumption 48 hours after surgery compared with preoperative epidural saline and intraoperative epidural ropivacaine (G2).

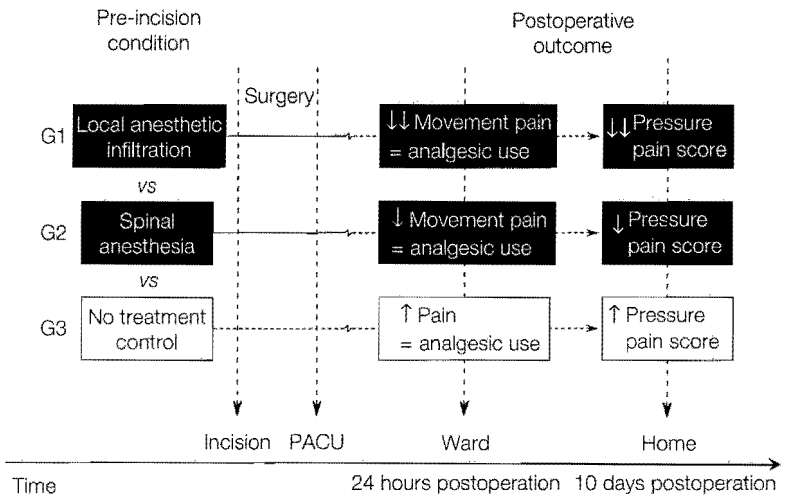

Figure 9.7 Experimental design comparing two different preoperative interventions with a no treatment control condition (treatment combination 1 versus 2 versus 2 in **Figure 9.1**). This design was used by Tverskoy *et al.*[62][II] in the very first prospective study of preventive analgesia. Patients undergoing inguinal herniorraphy were randomly assigned to receive one of three types of anesthesia: general plus preoperative local anesthetic infiltration (G1), spinal (G2), or general (G3). While anesthesia (infiltration or spinal) significantly decreased movement-associated pain intensity at 24 hours after surgery compared with the control group, the infiltration group reported the least pain overall. This pattern of pain scores was still apparent ten days after surgery in response to mechanical pressure applied to the wound.

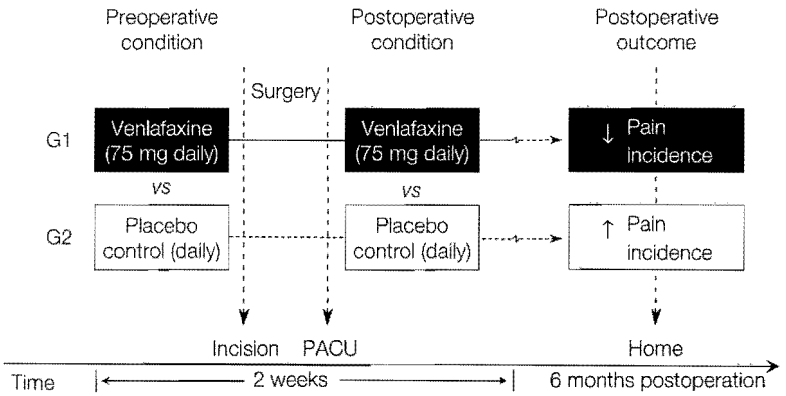

Figure 9.8 Experimental design comparing a preoperative plus postsurgical intervention with a placebo control condition (treatment combination 1 versus 8 in **Figure 9.1**). Preventive analgesia is demonstrated if the preoperative plus postsurgical intervention condition shows less pain and/or analgesic consumption than the placebo control group beyond the clinical duration of action of the target analgesic. This design was used by Reuben *et al.*[63][II] who randomly assigned females to receive venlafaxine (75 mg daily) or placebo (daily) for a two-week period beginning the night before radical mastectomy. Six-month follow up showed that the incidence of chest wall pain, arm pain, and axilla pain was significantly lower in the venlafaxine group than the placebo group.

analgesic requirements. A preventive analgesic effect involves demonstrating reduced pain and/or analgesic use beyond the clinical duration of action of the target agent.

RATIONALE FOR PRESENT REVIEW

Recent evidence-based reviews of randomized, double-blind studies reported in the literature on preemptive[4, 47, 52, 65, 66][I] and preventive[4, 47, 67][I] analgesia suggest that there are clinically significant benefits associated with both approaches to postoperative pain prevention, although the positive evidence is more abundant for the latter than the former. The more equivocal results for preemptive analgesia likely reflect the fact that intraoperative and postoperative noxious inputs contribute to central sensitization, thus diminishing the magnitude of the effect when pre- and posttreated groups are compared. The aim of the present review is to critically evaluate the recent literature on preemptive and preventive analgesia and to compare and contrast the results from both approaches.

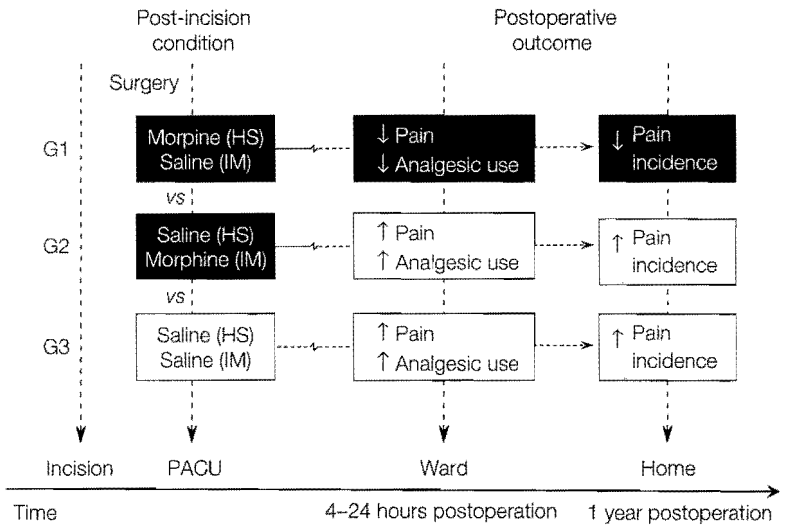

Figure 9.9 Experimental design comparing two postincision analgesic interventions with a placebo or no treatment control condition (treatment combination 1 versus 4 versus 4 in **Figure 9.1**). Preventive analgesia is demonstrated if the postincision condition shows less pain and/or analgesic consumption than the control group beyond the clinical duration of action of the target analgesic. This design was used by Reuben *et al.*[64][II] who showed that morphine, but not saline, administered into the iliac bone graft harvest site (HS) during cervical spinal fusion surgery reduced short-term pain and analgesic consumption, as well as the incidence of chronic donor site pain one year after surgery when compared with a group that received intramuscular morphine and a placebo control group that received saline. The study illustrates that preventive analgesia can be achieved even when the analgesic intervention is started after incision and bone graft harvest (i.e. in the context of an unchecked peripheral nociceptive injury barrage during surgery).

SEARCH STRATEGIES AND CRITERIA FOR INCLUDING STUDIES

A PubMed database search was conducted from January 2001 to September 2006. Search strategies were limited to English language and studies using human subjects. Each of the following key words was searched: pre-emptive analgesia, preemptive analgesia, preempts, pre-operative, preoperative, postoperative, pre-incision, preincision, post-incision, postincision. A second search was conducted using the same time period and the same limits. The terms searched were as follows: (gabapentin *or* NSAIDs *or* (NSAIDs and preoperative) *or* (NSAIDs and postoperative) *or* NMDA *or* (NMDA and preoperative) or (NMDA and postoperative) or opioids or (opioid and preemptive) or (opioid and preoperative) or (opioid and postoperative) or local anesthetics or (local anesthetics and preemptive) or (local anesthetics and preoperative) or (local anesthetics and postoperative)).

The above search strategies yielded 333 publications which were retrieved and reviewed by both authors. All clinical trials were evaluated according to the following inclusion criteria for entry into the present review: (1) randomized; (2) double-blind assessments of pain and analgesic use; (3) report of pain using a reliable and valid measure; (4) report of analgesic consumption; (5) absence of design flaws, methodological problems, or confounds that render interpretation of the results ambiguous. Trials that fit the above definition of preventive analgesia were considered not relevant and were not considered further if they did not report measures of postoperative pain and analgesic consumption at a point in time that equaled or exceeded 5.5 half-lives of the target agent. This criterion was included to ensure that the observed effects are not simply analgesic effects. We excluded clinical trials that involved third molar extraction and those evaluating neuraxial opioids due to controversy over half-life data.[68] **Table 9.1** lists the half-lives of the drugs used for the present chapter.

Of the 333 publications, 61 clinical trials were identified that met the above inclusion and exclusion criteria. **Table 9.2** contains the 34 studies that were excluded from review, showing which one or more of the five inclusion criteria were not met. The 61 studies were evaluated and scored for methodological quality by both authors using the Jadad quality index scale.[72] The scale uses a six point (0–5) rating system (in which lower quality articles receive lower scores) to assess the likelihood of bias in pain research reports based on descriptions of randomization, blinding, and withdrawals. A data extraction process was performed on the articles that met inclusion criteria. The following items were collected: publication details, sample size, surgical procedure, nature and timing of interventions, target agent, route and dose of target agent, nature and time after surgery of preemptive or preventive effect.

Table 9.3 shows the various experimental designs (depicted in **Figure 9.1**) and the frequency with which

Table 9.1 Half-lives of drugs and source of half-live information used in studies of preventive analgesia.

Drug/source of information	Half-life	Criterion value of 5.5 half-lives
Local anesthetics		
Bupivacaine[69]	i.v.: 3.5 hours	i.v.: 19.25 hours
	epidural: 2–5 hours	epidural: 27.5 hours
	PNB: 4–12 hours	PNB: 66 hours
	Infilt: 2–8 hours	Infilt: 44 hours
Lidocaine[69]	i.v.: 1.6 hours	i.v.: 8.8 hours
	epidural: 1–3 hours	epidural: 16.5 hours
	PNB: 1–3 hours	PNB: 16.5 hours
	Infilt: 1–4 hours	Infilt: 22 hours
Mexiletine[70]	10–12 hours	66 hours
Ropivacaine[69]	i.v.: 1.9 hours	i.v.: 10.45 hours
	epidural: 2–6 hours	epidural: 33 hours
	PNB: 5–8 hours	PNB: 44 hours
	Infilt: 2–6 hours	Infilt: 33 hours
Nonsteroidal anti-inflammatory drugs		
Celecoxib[71]	6–12 hours	66 hours
Flurbiprofen[71]	6 hours	33 hours
Ibuprofen[71]	2–4 hours	22 hours
Ketoprofen[71]	2 hours	11 hours
Ketorolac[71]	4–6 hours	33 hours
Piroxicam[71]	45–50 hours	11.4 days
Potassium diclofenac[69]	1.5 hours	8.25 hours
Rofecoxib	17 hours	93.5 hours
Tenoxicam[69]	60 hours	13.75 days
NMDA receptor antagonists		
Dextromethorphan[69]	1.2–3.9 hours	21.45 hours
Ketamine[70]	2.5–3 hours	16.5 hours
Magnesium[70]	8 hours	44 hours
Opioids		
Fentanyl[70]	3–4 hours	22 hours
Morphine[70]	4 hours	22 hours
Pethidine[70]	3 hours	16.5 hours
Remifentanil[70]	8–20 minutes	1.8 hours
Sufentanil[70]	3–4 hours	22 hours
Other analgesic and nonanalgesic agents		
Paracetamol (acetaminophen)[70]	4 hours	22 hours
Clonidine[70]	6–20 hours	4.6 days
Dexmedetomidine[70]	2 hours	11 hours
Gabapentin[69]	6–7 hours	38.5 hours
Nitroglycerin[70]	1–4 minutes	1.5 hours
Promethazine[70]	9–16 hours	3.6 days
Venlafaxine[70]	11 hours	60.5 hours

i.m., intramuscular; Infilt, infiltration; i.v., intravenous; NMDA, *N*-methyl-D-aspartate; p.o., per os; PNB, peripheral nerve block.

Also shown is the criterion value of 5.5 half lives used to determine inclusion of studies evaluating preventive analgesia (i.e. with a no treatment or placebo control group). Only studies that reported a measure of pain and analgesic consumption beyond the criterion value were eligible for inclusion in the present review as assessing preventive effects. This requirement was not in place for studies of preemptive analgesia (i.e. in which treatment control groups received the same intervention but at different times).

Table 9.2 Studies excluded from review in the present chapter for failing to meet one or more of the following criteria: randomized (R), double-blind assessments (DB), report of pain using a reliable and valid measure (P), report of analgesic consumption (A), and absence of methodological problem, design flaw, or confound that renders interpretation of the results ambiguous (MF).

Author	Year	Drug class	Criterion not met
Lee *et al.*[73]	2001	LA	R
Senturk *et al.*[31]	2002	LA	DB
Yegin *et al.*[74]	2003	LA	DB
Senagore *et al.*[75]	2003	LA	DB
Cerfolio *et al.*[76]	2003	LA	A
Korhonen *et al.*[77]	2004	LA	DB
Karakaya *et al.*[78]	2004	LA	DB
Lee-Elliott *et al.*[79]	2004	LA	DB
Batra *et al.*[80]	2005	LA	DB
Sundarathiti *et al.*[81]	2005	LA	DB
Abramov *et al.*[82]	2005	LA	MF
Herbland *et al.*[83]	2006	LA	A
Seet *et al.*[84]	2006	LA	DB
Yukawa *et al.*[85]	2005	Multimodal	DB
Busch *et al.*[86]	2006	Multimodal	DB
Subramaniam *et al.*[87]	2001	NMDA antagonist	P
Papaziogas *et al.*[88]	2001	NMDA antagonist	A
Weinbroum *et al.*[89]	2001	NMDA antagonist	R
Weinbroum *et al.*[90]	2002	NMDA antagonist	MF
Weinbroum[91]	2002	NMDA antagonist	R
Weinbroum *et al.*[92]	2003	NMDA antagonist	MF
O'Flaherty and Lin[93]	2003	NMDA antagonist	A, P
Hayes *et al.*[94]	2004	NMDA antagonist	A
Bolcal *et al.*[95]	2005	NMDA antagonist	DB
Carney *et al.*[96]	2001	NSAID	R
Mallory *et al.*[97]	2002	NSAID	R, DB
Wnek *et al.*[98]	2004	NSAID	DB
Nikanne *et al.*[99]	2005	NSAID	A
Canbay *et al.*[100]	2006	NSAID	A
Louizos *et al.*[101]	2006	NSAID	DB
Wordliczek *et al.*[102]	2002	Opioid	DB
Machida *et al.*[103]	2004	Opioid	DB
Bellissant *et al.*[104]	2004	Opioid	P
De Pietri *et al.*[105]	2006	Opioid	DB

LA, local anesthetic; NSAID, nonsteroidal anti-inflammatory drug; NMDA, *N*-methyl-D-aspartate.

they were used across the 61 studies for each class of analgesic and anesthetic agent. For each design, the table also shows whether the effect being evaluated is preemptive or preventive as defined above. The enormous variability in timing of treatment is evident from the fact that 23 different designs have been implemented. **Table 9.4** summarizes the outcomes of the studies reviewed below according to the target agent administered, including gabapentin, local anesthetics, opioids, nonsteroidal anti-inflammatory drugs (NSAID), *N*-methyl-D-aspartate (NMDA) receptor antagonists, multimodal therapy (three or more target agents), and other, traditionally, non-analgesic/anesthetic agents. Positive studies are defined as those that report a significant preemptive or preventive effect (i.e. reduced pain or analgesic consumption, or both). Negative studies are defined as those for which the treatment and control groups did not differ significantly in terms of pain or analgesic consumption. Also listed in the table is the frequency of studies reporting effects opposite to that predicted (e.g. in a study of preemptive analgesia, the postsurgical treatment group demonstrated significantly less pain and/or used fewer analgesics than the preincisional treatment group).

LITERATURE REVIEW

Gabapentin

Gabapentin is a structural analogue of γ-aminobutyric acid (GABA) and was introduced into clinical practice as an anticonvulsant drug. Its main binding site is believed to be the alpha-2-delta subunit of voltage-dependent calcium channels, but its full mechanism of action is not well understood.[106] Other postulated mechanisms of action have been proposed, such as selectively activating $GABA_B$ receptors, selectively enhancing the NMDA current at GABAergic interneurons, or blocking α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor-mediated transmission in the spinal cord.[106] More recently, gabapentin has been shown to increase tonic inhibitory conductance in mammalian hippocampal neurons.[107] Thus, a combination of peripheral and central effects likely mediate the clinical effects of this drug.

Gabapentin has been demonstrated to be effective in the treatment of neuropathic pain, diabetic neuropathy, postherpetic neuralgia, and reflex sympathetic dystrophy.[108] Gabapentin has been described as an anti-hyperalgesic drug that selectively affects the nociceptive process involving central sensitization.[108] In volunteers, oral gabapentin profoundly suppressed established cutaneous hyperalgesia after heat-capsaicin sensitization and was able to prevent the development of cutaneous sensitization.[109]

Over the past six years, there have been 20 clinical trials examining the effects of gabapentin on postoperative pain.[110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129] All but two of these studies[114, 123] have found that gabapentin significantly reduces pain, as well as the amount of postoperative opioid required (16–67 percent).

Table 9.5 shows the six studies that were found to have examined designs assessing preemptive and preventive analgesic effects of perioperative gabapentin. The Jadad *et al.*[72] quality index scores of the six articles ranged from four to five with a mean $\pm$S.D. of 4.3 ± 0.52. Of the six

Table 9.3 Variety and frequency of experimental designs used to evaluate the preemptive and/or preventive effects of different classes of analgesic agents.

Design number	Treatment combinations in Figure 9.1	Preemptive and/or preventive	Gabapentin	Local anesthetics	Opioids	NSAIDs	NMDA antagonists	Multimodal	Other	Total No. of studies
1	1, 2	PV	1	–	1	1	5	1	3	12
2	1, 2, 3	PE and PV	1	2	–	–	1	–	–	4
3	1, 2, 3, 5	PE and PV	–	1	–	–	–	–	–	1
4	1, 2, 4	PE and PV	–	–	–	3	1	–	1	5
5	1, 2, 5	PE and PV	–	–	–	–	1	–	–	1
6	1, 3, 3, 3	PE and PV	–	–	1	–	–	–	–	1
7	1, 3, 5	PE and PV	–	–	–	–	1	–	–	1
8	1, 4	PV	–	1	–	1	–	–	–	2
9	1, 4, 4	PV	–	1	–	–	–	–	–	1
10	1, 4, 6	PE and PV	–	–	–	1	–	–	–	1
11	1, 5	PV	–	1	–	–	3	–	–	4
12	1, 8	PV	2	2	–	2	1	1	–	8
13	1, 8, 8	PV	1	–	–	–	–	–	–	1
14	1, 8, 8, 8	PV	1	–	–	–	–	–	–	1
15	2, 2	PE	–	–	–	1	–	–	–	1
16	2, 3	PE	–	–	–	2	–	–	–	2
17	2, 4	PE	–	2	2	2	–	2	–	8
18	2, 4, 5	PE and PV	–	–	–	–	1	–	–	1
19	2, 4, 6	PE and PV	–	–	–	1	–	–	–	1
20	3, 4	PE	–	–	1	–	–	–	–	1
21	4, 4, 4	PV	–	–	–	–	–	1	–	1
22	4, 8	PE	–	2	–	–	–	–	–	2
23	8, 8	PE	–	1	–	–	–	–	–	1
Total			6	13	5	14	14	5	4	61

NSAIDs, nonsteroidal anti-inflammatory drugs; NMDA, *N*-methyl-D-aspartate; PE, preemptive; PV, preventive.
Each design (column 1) is defined in terms of specific treatment combinations (column 2) depicted in **Figure 9.1**. Each design is also described as evaluating preemptive and/or preventive effects (column 3).

Table 9.4 Summary of studies according to target agent administered showing total number of studies, number (%) with positive and negative preemptive and preventive effects.

Agent(s)	No. studies	Preemptive effects		Preventive effects		Opposite effects (%)	Total No. effects (%)
		Positive (%)	Negative (%)	Positive (%)	Negative (%)		
Gabapentin	6	0 (0)	1 (16.7)	4 (66.6)	1 (16.7)	0 (0)	6 (100)
Local anesthetics	13	3 (20)	3 (20)	6 (40)	1 (6.7)	2 (13.3)	15 (100)
Opioids	5	3 (60)	1 (20)	0 (0)	1 (20)	0 (0)	5 (100)
NSAIDs	14	7 (43.8)	3 (18.8)	4 (25)	2 (12.4)	0 (0)	16 (100)
NMDA antagonists	14	2 (11.8)	1 (5.9)	9 (53)	4 (23.4)	1 (5.9)	17 (100)
Multimodal	5	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	0 (0)	6 (100)
Other	4	1 (25)	0 (0)	3 (75)	0 (42.9)	0 (0)	4 (100)
Total[a]	61	17[b] (24.6)	10 (14.5)	28[c] (40.6)	11 (15.9)	3 (4.4)	69 (100)

Also shown is the number (%) of studies reporting effects opposite to that predicted and the total number of effects. The total number of effects exceeds the number of studies because some studies were designed to evaluate both preemptive and preventive effects. See text for definition of preemptive and preventive effects.
[a] $p = 0.02$ for z-test comparison of proportion of total positive preemptive plus preventive effects (0.64) versus proportion of total negative preemptive plus preventive effects (0.31).
[b] $p = 0.36$ for z-test comparison of proportion of total positive preemptive effects ($17/27 = 0.63$) versus proportion of total negative preemptive effects ($10/27 = 0.37$).
[c] $p = 0.03$ for z-test comparison of proportion of total positive preventive effects ($28/39 = 0.72$) versus proportion of total negative preventive effects ($11/39 = 0.28$).
NSAIDs, nonsteroidal anti-inflammatory drugs; NMDA, *N*-methyl-D-aspartate.

Table 9.5 Studies examining the preemptive and preventive effects of perioperative gabapentin.

Author	Surgical procedure (No. patients)	Treatment combinations (Figure 9.1)	Group: first intervention drug/ second intervention drug	Route and dose	Timing of first intervention	Timing of second intervention	Quality score	Nature and time after surgery of preventive and/or preemptive analgesic effects
Menigaux *et al.*[117]	Arthroscopic anterior cruciate ligament repair (40)	1, 2	GA plus: G1: GABA/na G2: PLA/na	p.o. 1200 mg	1–2 h preop	NA	4	[a]Preventive effect – yes VAS pain: no inter-group differences beyond t1/2 = 5.5 lives Cumulative i.v. PCA morphine consumption: G1 < G2 at 48 h [a]First/maximal and passive/active flexion on post-op day 2: G1 < G2
Fassoulaki *et al.*[114]	Abdominal hysterectomy (60)	1, 8	GA plus: G1: GABA/GABA G2: PLA/PLA	400 mg p.o.	18 h preoperation and every 6 h (3 doses) until surgery	Continues on same schedule until 5 days postoperatively	4	[a]Preventive effect – yes One month follow up: [a]Pain incidence: G1 < G2 Analgesic use: G1 = G2
Turan *et al.*[129]	Abdominal hysterectomy (100)	1, 8, 8, 8	GA plus: G1: PLA/PLA G2: ROF+PLA/ ROF+ PLA G3: GABA+PLA/ GABA+PLA G4: ROF+GABA/ ROF+GABA	ROF p.o. 50 mg GABA p.o. 1.2 g	1 h preoperatively	9 a.m. on the first and second postoperative days	5	Preventive effect – no 3-month follow up No intergroup differences in pain incidence

(*Continued over*)

Turan *et al.*[127]	Elective lower limb surgery (40)	1, 8	GA plus: G1: PLA/PLA G2: GABA/GABA	1.2 g p.o.	1 h preoperatively	9 a.m. on the first and second postoperative days	5	[a]Preventive effect – yes VRS-R pain: no inter-group differences beyond $t_5 = 5.5$ lives [a]PCEA requirements: G2 < G1 at 48–72 h PARACET usage: G2 < G1
Pandey *et al.*[122]	Open donor nephrectomy (60)	1, 2, 3	GA plus: G1: GABA/PLA G2: PLA/GABA G3: PLA/PLA	GABA p.o. 600 mg GABA 600 mg NG	2 h preoperatively	Immediately after surgical incision	4	Preventive effect – na Preemptive effect – no VAS-R: G1 = G2 < G3 at 0, 6, 12, 18, and 24 h Fentanyl use: G1 < G3 = G2
Fassoulaki *et al.*[113]	Breast cancer surgery (75)	1, 8, 8	GA plus: G1: MEXIL+PLA/MEXIL+PLA G2: GABA+PLA/GABA+PLA G3: PLA+PLA/PLA+PLA	MEXIL p.o. 200 mg TID postoperatively GABA p.o. 400 mg TID postoperatively	One dosage the evening before the operation	TID for 10 days postoperatively	4	[a]Preventive effect – yes [a]3 month follow up chronic pain characteristics: Neuropathic/burning pain: G1 = G2 < G3 Analgesic use: no intergroup differences

[a]Nature and time after surgery of preventive analgesic effects.

G, group; GA, general anesthesia; GABA, gabapentin; i.v., intravenous; MEXIL, mexiletine; na, not applicable; NG, nasogastric; PARACET, paracetamol; PCEA, patient-controlled epidural analgesia; PLA, placebo; p.o., per os; ROF, rofecoxib; TID, three times daily; VAS-R/M, visual analog scale pain score at rest/on movement.

studies identified, only one fits the classification of a preemptive design.[122] The other five studies[113, 114, 117, 127, 129] provided data to assess the preventive effects of gabapentin beyond the 5.5 half-lives (40 hours) after the final administration of the drug. Four of the five studies (80 percent) demonstrated impressive preventive effects in favor of the gabapentin treated versus placebo control group. Perioperative gabapentin administration was associated with a significant decrease in postoperative opioid consumption,[117, 127][II] a reduction in the incidence of pain at the surgical incision site one month after surgery,[114][II] and a reduction in neuropathic pain three months after surgery.[113][II]

Only one study[122][II] evaluated the preemptive effects of gabapentin. Pandey and colleagues[122][II] compared preincisional versus immediate postincisional administration of gabapentin (600 mg) with a placebo control group (treatment combination 1 versus 2 versus 3 in **Figure 9.1**) in open donor nephrectomy patients. The results showed that patients in the pre- and postincision groups had significantly lower pain and used less fentanyl than those in the control group. The absence of a preemptive effect likely is due to the fact that the gabapentin was given too early after incision in the postincisional group.

The optimal dose of gabapentin for perioperative use has not been established, but a recent meta-analysis[130] and systematic review[131] suggest that doses between 600 and 1200 mg have robust opioid-sparing and pain-relieving effects in the acute postoperative period. The preventive effects of gabapentin are quite promising. For example, the study by Menigaux *et al.*[117] demonstrated the effectiveness of gabapentin in decreasing anxiety scores and improving early functional recovery after anterior cruciate ligament knee surgery. Patients treated with one preoperative dose of 1200 mg of gabapentin had significantly improved range of motion on active and passive knee flexion on postoperative day two in comparison to placebo-treated patients.

Although only six studies have examined the preemptive or preventive effects of gabapentin in the perioperative period, the perioperative pain-reducing and opioid-sparing effects of gabapentin beyond the acute perioperative period are quite promising; including the possibility that pain incidence may be reduced up to three months after surgery. Future studies are needed to clarify the optimal dosing and timing of gabapentin in the perioperative period.

Local anesthetics

Table 9.6 describes the 13 studies that were found to have examined designs assessing preemptive and preventive analgesic effects using local anesthetic agents. Surgical procedures included major gynecologic surgery by laparotomy,[57, 58, 132] major abdominal surgery,[133] thoracic surgery,[134] median sternotomy,[135] laparoscopic surgery,[136] laparoscopic cholecystecomy,[137] appendectomy,[138] total hip replacement,[61] total knee arthroplasty,[139] knee arthroscopy,[140, 141] and craniotomy.[142] Routes of administration included epidural[58, 61, 132, 134] intravenous (i.v.),[133, 135] subcutaneous (s.c.),[136, 137, 138, 142] intra-articular (i.a.),[140, 141] and a combination of intramuscular (i.m.), s.c., and i.a.[139]

Although only two[58, 134] of the 13 studies were designed to assess the effects of co-administration of a local anesthetic and an opioid, all but two studies[61, 139] administered opioids at induction of general anesthesia and/or during surgery, so that it is not possible to attribute effects solely to the target local anesthetic agent.

As shown in **Table 9.4**, of the 15 effects that were tested (in the 13 trials), 37.5 percent (3/8) showed significant preemptive effects, approximately 87 percent (6/7) showed significant preventive effects, and 25 percent (2/8) showed preemptive effects that were opposite in direction to the hypothesized effect, in that the postincisional group showed reduced pain compared with the preincisional group. Of note is the study by Katz *et al.*,[58][II] who found that short-term beneficial effects of preventive epidural analgesia (whether administered before or after incision) translated into less pain disability at three weeks but not six months after surgery.[57]

Opioid analgesics

The effect of preinjury treatment with opioids on preventing spinal postinjury hyperexcitability is well documented.[143] Early studies by Woolf and Wall[144] showed that the amount of morphine required to prevent the development of this spinal hyperexcitability was ten-fold less than the amount required to reverse it after it was well established. More recent animal studies have also shown that the application of mu-opiate receptor agonists preempt development of hyperalgesia and allodynia following inflammation, surgery, or nerve injury.[145, 146]

However, the efficacy of opioid pretreatment in decreasing central sensitization and thus reducing pain is somewhat more equivocal in human trials. Several studies have demonstrated that preoperative opioid administration reduces postoperative pain and consumption of analgesics when compared with postoperative administration[147] or a placebo control,[148] the latter effect occurring beyond the clinical duration of action of the target opioid. However, others have failed to demonstrate preemptive effects.[149] A growing body of evidence over the past ten years has also suggested that under certain conditions opioids may induce some forms of central sensitization and facilitate development of hyperalgesia.[150] Despite the mixed picture of opioids with respect to their hyperalgesic and analgesic actions, they continue to have a major role in perioperative pain management.

Table 9.7 shows the five studies that were found to have examined designs assessing preemptive and

Table 9.6 Studies examining the preemptive and preventive effects of local anesthetics (± opioid) as the target treatment.

Author	Procedure (No. patients)	Treatment combinations (Figure 9.1)	Group: First intervention drug/ second intervention drug	Route and dose	Timing of first intervention	Timing of second intervention	Quality score	Nature and time after surgery of preventive and/or preemptive analgesic effects
Katz *et al.*[58] and Katz and Cohen[57]	Major gynecologic surgery by laparotomy (141)	1, 2, 3	GA plus: G1: LID+FENT/ SAL G2: SAL/ LID+FENT G3: SAL/SAL	Epidural 12 mL LID 2 Epidural FENT 4 μg/kg	After placement of epidural catheter before incision	40 min post-incision	5	[a]Preventive effect – yes [b]Preemptive effect – yes VAS-R: No inter group differences, [a]VAS-M: G1 < G3 at 24 h Hourly PCA Morphine: [b]G1 < G2 = G3 for day 1; [a,b]G1 < G2 < G3 for day 2 Von Frey pain threshold at 24 h: [a]G1 > G3 at 24 h 3-week follow-up: Pain Disability Index: [a]G1 = G2 < G3 No differences analgesic use 6 month follow-up: No differences in pain incidence, intensity, disability or analgesic use
Neustein *et al.*[134]	Thoracic surgery (32)	4, 8	GA plus: G1: BUP+FENT/ BUP+FENT/ BUP+FENT G2: SAL/SAL/ BUP+FENT	Epidural 20 mg BUP and 100 μg FENT followed by an intra-operative infusion of BUP 0.1 and FENT 10 μg/mL at 6 mL per h reduced to 2 mL per h in PACU	After induction but pre-incision followed by intra op infusions	Postoperative infusion started in PACU (G1, G2)	3	[b]Preemptive effect – no VAS pain: G1 < G2 at 0–6 h (exact time of effect not known) PCEA: no differences in median epidural infusion rate

(*Continued over*)

Table 9.6 Studies examining the preemptive and preventive effects of local anesthetics (± opioid) as the target treatment (continued).

Author	Procedure (No. patients)	Treatment combinations (Figure 9.1)	Group: First intervention drug/ second intervention drug	Route and dose	Timing of first intervention	Timing of second intervention	Quality score	Nature and time after surgery of preventive and/or preemptive analgesic effects
Vendittoli *et al.*[139]	Total knee arthroplasty (42)	1, 8	Spinal BUP plus: G1: Nad/Nad/Nad G2: ROP/ROP/ROP	i.m. (deep tissues) 275 mg s.c. 125 mg i.a. 150 mg	i.m. before prosthesis implantation	s.c. before wound closure and i.a. on first day postoperation	4	[a]Preventive effect – yes [a]VAS pain at 2 days: G2 < G1 Analgesic use: G2 < G1 up to 48 h Active assisted knee flexion day 1–5: No inter group differences
Koppert *et al.*[133]	Major abdominal surgery (40)	1, 8	GA plus: G1: SAL/na G2: LID/na	i.v. LID bolus 1.5 mg/kg followed by i.v. LID infusion 1.5 mg/kg/h	Bolus after intubation; infusion started 30 min before surgical incision and maintained until 60 min post op	na	5	[a]Preventive effect – yes VRS-R: No differences post-op at any time VRS-MAUC: [a]G2 < G1 24–48 h and 48–72 h PCA morphine: [a]G2 < G1 at 36–48, 48–60 and 60–72 h Cumulative PCA morphine: G2 < G1
Lohsiriwat *et al.*[138]	Appendectomy (123)	1, 5	GA plus: G1: SAL/na G2: BUP/na	s.c. 10 mL 0.5	5 min before incision and just after incision of skin and s.c. tissue	na	3	[a]Preventive effect – yes [a]VAS-M: G2 < G1 at 48 h Total morphine consumption: G2 < G1 at 48 h
Lam *et al.*[136]	Laparoscopy (144)	1, 2, 3	GA plus: G1: LID/SAL G2: SAL/LID G3: SAL/SAL	s.c. 10 mL 1 LID	Before incision	Before closure	5	[b]Preemptive effect – opposite [a]Preventive effect – yes Pain levels: [a]G2 < G3 at 24 h [b]G2 < G1 at 24 h No differences in analgesic consumption prior to discharge

(*Continued over*)

Burmeister *et al.*[132]	Major gynecological surgery (30)	4, 8	GA plus: G1: PLA/ROP G2: ROP/ROP	Epidural bolus 10 mL 0.375 followed by epidural infusion 6 mL/h	Bolus before induction; infusion until end of skin closure	At end of skin closure; continuously until 24 hours postoperatively	4	Preemptive effect – no
Nguyen *et al.*[142]	Craniotomy (30)	1, 4	GA plus: G1: na/ROP G2: na/PLA	s.c. 20 mL 0.75	na	At skin closure	4	Preventive effects – no
Louizos *et al.*[137]	Laparoscopic cholecystectomy (108)	1, 2, 3, 5	GA plus: G1: SAL/SAL G2: L-BUP/SAL G3: SAL/L-BUP G4: L-BUP/L-BUP	s.c. 20 mL 0.25 L-BUP i.p. 20 mL 0.25 L-BUP	Before incision	Before skin closure	4	Preventive effect – na [b]Preemptive effect – opposite [b]Incidence of right shoulder pain: G3 < G2
Fagan *et al.*[141]	Knee arthroscopy (40)	2, 4	GA plus: G1: BUP+EPI/PLA G2: PLA/BUP+EPI	i.a. 15 mL 0.5	15 min preoperation	After surgery	5	Preemptive effect – no
Tuncer *et al.*[140]	Arthroscopic knee surgery (40)	2, 4	i.v. sedation plus: G1: BUP/SAL G2: SAL/BUP	i.a. BUP 20 mL 0.25	30 min before incision	Immediately after skin closure	3	[b]Preemptive effect – yes [b]VAS-R/M: G1 < G2 at 1, 2, 4 and 6 h
Klasen *et al.*[61]	Total hip replacement (42)	8[c], 8	i.v. sedation plus: G1: ROP/ROP G2: SAL/ROP	Epidural: ROP 0.2 at 5 mL/h	Continuously starting 12 h preoperation up until arrival in OR	Pre-incision 1 ROP to achieve sensory blockade to T8 and throughout surgery	4	[b]Preemptive effect – yes VAS pain: No intergroup differences post-operation [b]Total PCEA ROP consumption at 48 h: G1 < G2
White *et al.*[135]	Median sternotomy (36)	1, 4, 4	GA plus: G1: na/PLA G2: na/BUP 0.25 G3: na/BUP 0.5	i.v. infusion 4 mL/h	na	Continuously from end of surgery until 48 h post-operation	3	[a]Preventive effect – yes [a]VAS Pain: G3 < G1 at 72 h Mean i.v. PCA morphine usage: G3 < G1 at 72 h [a]Hospital stay: G3 < G1

AUC, area under the curve; FENT, fentanyl; G, group; GA, general anesthesia; i.a., intaarticular; i.p., intraperitoneal; i.v., intravenous; L-BUP, levo-bupivacaine; LID, lidocaine; na, not applicable; Nad, nothing administered; OR, operating room; PACU, postanesthetic care unit; PCEA, patient controlled epidural analgesia; PLA, placebo; ROP, ropivacaine; SAL, saline; s.c., subcutaneous.

[a]Nature and time after surgery of preventive analgesic effects.

[b]Nature and time after surgery of preemptive analgesic effects.

[c]The classification of this study as evaluating preemptive analgesia is not entirely accurate. While it does evaluate the effect of altering the timing of administration, it does not do so before versus after incision.

Table 9.7 Studies examining the preemptive and preventive effects opioids as the target treatment.

Author	Procedure (No. of patients)	Treatment combinations (Figure 9.1)	Group: First intervention drug/ second intervention drug	Route and dose	Timing of first intervention	Timing of second intervention	Quality Score	Nature and time after surgery of preventive and/or preemptive analgesic effects
Reuben *et al.*[155]	Arthroscopic knee surgery (40)	2, 4	IV sedation plus IA BUP plus: G1: MORPH/Nad G2: Nad/MORPH	MORPH i.a. 3 mg	30 min preoperation	At end of surgery	3	Preemptive – yes VAS-R/M: G1 = G2 at 1, 2 and 24 h 24 h analgesic consumption: G1 < G2
McCarty *et al.*[153]	Anterior cruciate ligament reconstruction (62)	1, 2	GA plus post-operation femoral nerve block: G1: PLA/na G2: MORPH/na	5 mg i.a.	After induction but pre-incision	na	3	Preventive effect – no
Mavioglu *et al.*[152]	Total abdominal hysterectomy (64)	3, 4[a]	GA plus: G1: PETH/Nad G2: Nad/PETH	0.5 mg/kg i.v.+bolus doses of 10 mg	During closure of fascia	In PACU	4	Preemptive – yes VAS-R: G1 < G2 at 0, 15, 30, 60 and 120 min PETH use: G1 < G2 at 0–15, 15–30, 30–60 and 60–120 min

(*Continued over*)

Munoz *et al.*[154]	Laparoscopic cholecystectomy (120)	1, 3, 3, 3[a]	GA plus: G1: SAL/SAL/SAL G2: SAL/SAL/MORPH G3: SAL/MORPH/SAL G4: MORPH/SAL/SAL	MORPH i.v.150 μg/kg	First intervention: >40 min from end of surgery Second intervention: 20–40 min from end of surgery	Third intervention <20 min from end of surgery	4	Preventive effect – na Preemptive effect – no
Akural *et al.*[151]	Abdominal hysterectomy (41)	2, 4	GA plus: G1: SUFENT/SAL G2: SAL/SUFENT	Epidural 50 μg	20 min pre-anesthesia	20 min after closure of peritoneum	3	Preemptive effect – yes NRS pain-R/M: no inter group differences postop to 1 month PCEA SUFENT consumption: G1<G2 at 8–16 h Touch detection threshold AUC for 4 days: G1<G2 Pain threshold AUC for 4 days: G1<G2

AUC, area under the curve; BUP, bupivacaine; G, group; GA, general anesthesia; i.a., inta-articular; i.v., intravenous; min, minutes; MORPH, morphine; na, not applicable; NRS pain – R/M, numeric rating scale for pain at rest/on movement; Nad, nothing administered; PACU, postanesthetic care unit; PCEA, patient controlled epidural analgesia; PETH, pethidine; PLA, placebo; SAL, saline; SUFENT, sufentanil; VAS-R/M, visual analog scale pain score at rest/movement.

[a]The classification of this study as evaluating preemptive analgesia is not entirely accurate. While it does evaluate the effect of altering the timing of administration, it does not do so before versus after incision.

preventive analgesic effects of opioids in the perioperative period.[151, 152, 153, 154, 155] The Jadad *et al.*[72] quality index scores of the five articles ranged from three to four with a mean ± S.D. of 3.4 ± 0.55. Routes of administration included were i.a. (morphine), i.v. (pethidine [meperidine], morphine) and epidural (sufentanil, treatment combination 2 versus 4 in **Figure 9.1**). The relatively few studies examining the preventive effects of opioids (i.e. five) was due to our exclusion of all trials involving neuraxial opioids since there is a lack of a consensus on half-life values of opioids delivered by the epidural and spinal routes.[68] The five trials included in **Table 9.7** studied the effects of opioids in the following four surgical populations: total abdominal hysterectomy,[151, 152] laparoscopic cholecystectomy,[154] anterior cruciate ligament repair,[153] and arthroscopic meniscectomy.[155]

Of the five studies, four used preemptive designs (three positive[151, 152, 155][II] and one negative[154]), while only one[153] met the criteria for a preventive trial. Reuben *et al.*[155][II] (treatment combination 2 versus 4 in **Figure 9.1**) demonstrated that preoperative i.a. injection of morphine was superior to postoperative injection in decreasing pain scores and morphine consumption following arthroscopic knee surgery. Akural *et al.*[151][II] (treatment combination 2 versus 4 in **Figure 9.1**) demonstrated that preoperative epidural sufentanil was superior to epidural sufentanil administration near the end of surgery. Postoperative pain was significantly lower in the pre- versus postincisional group for up to four days after surgery.[151][II] The only negative preemptive study[154] used a clinically nonrelevant design (treatment combination 1 versus 3 versus 3 versus 3 in **Figure 9.1**) and evaluated the effects on postoperative pain and analgesic consumption of i.v. morphine administered at three time points during laparoscopic cholecystectomy versus a saline control. The sole preventive study[153] we identified compared the effects of preincisional i.a. morphine compared to placebo in patients undergoing anterior cruciate ligament reconstruction. The authors did not find evidence of an effect of i.a. morphine on pain or analgesic consumption, but this not surprising since all patients received postoperative femoral nerve blocks with at least 20 mL of 0.5 percent bupivacaine. Thus, the only plausible conclusion is that i.a. morphine provides no additional benefit when combined with effective postoperative femoral nerve blocks.

Opioids continue to have a significant role in perioperative pain management despite significant adverse effects such as nausea, vomiting, sedation, pruritus, constipation, urinary retention, and respiratory depression.[156] The problem of accurately identifying the half-life of neuraxially administered opioids[68] essentially limited our review of these agents to studies using preemptive designs. Longer follow-up times after surgery (e.g. weeks or months) would obviate the problem of determining an accurate half-life of epidural and spinal opioids. More research is needed to clarify the role of opioids in preemptive/preventive analgesia.

NSAIDs

The analgesic effects of NSAIDs have been attributed to their anti-inflammatory actions in inhibiting the synthesis of prostaglandins.[157] Prostaglandin (PG) synthesis is essential for the generation of inflammatory pain and this depends not only on prostaglandin production at the site of inflammation, but also on the actions of prostaglandins synthesized within the central nervous system (CNS). Prostaglandins derive from arachidonic acid liberated from phospholipids in the cell membrane by the action of phospholipase A_2 (PLA_2) enzymes.[158] Cyclooxygenase (COX) catalyzes the first two reactions of the PG pathway. The identification of two COX isoforms, COX-1 and COX-2, led to intense efforts to characterize the relative contribution of each isoform to prostaglandin production in specific situations.[158]

Marked increases in PLA_2 and COX-2 expression occur at the site of peripheral inflammation. Prostaglandins themselves do not produce pain, but sensitize receptors at the site of injury to a variety of neurochemicals (e.g. bradykinin, serotonin, substance P, calcitonin gene-related peptide).[157] Recent evidence has also demonstrated that peripheral inflammation induces a widespread increase in COX-2 and prostaglandin synthase expression in neurons and nonneuronal cells in the spinal cord.[159] An elevation of COX-2 also occurs at many levels in the brain, mainly in the endothelial cells of the brain vasculature.

Samad *et al.*[158] proposed two signaling systems through which peripheral injury and its inflammatory sequelae are relayed to the CNS. The first is the traditional, electrically mediated transmission system, in which neural activity in sensitized nerve fibers innervating inflamed tissue signals the location of injury, as well as the onset, duration, and nature of any stimuli applied to this tissue. The second is a nonneuronally mediated system in which a humoral signaling molecule (or molecules), originating in inflamed tissue, acts via the bloodstream to produce a widespread induction of COX-2 in the CNS. Following peripheral injury, there is an immediate (within minutes) and delayed (within hours) spinal release of PGE_2, the former produced by COX-1 and/or COX-2, and the latter by COX-2.[157, 160] This suggests that acute postoperative pain may not be as sensitive to COX-2 inhibitors as the pain experienced some time later.[158] The net effect of both the peripheral and central actions of NSAIDs would be to prevent or attenuate development of a hyperexcitable state in spinal cord dorsal horn neurons. In terms of the patient's experience of pain after surgery, this would translate into less intense pain and a reduced requirement for postoperative analgesics. Based on data from basic science and clinical research, NSAIDs may preempt different components of postoperative pain (e.g. central and peripheral sensitization) by more than one mechanism, and prolonged blockade of inflammation by NSAIDs throughout the perioperative period and beyond has demonstrated a decrease in the development of chronic pain.

Table 9.8 shows the 14 studies that were found to have examined the preemptive and preventive effects of NSAID administration in the perioperative period. The Jadad *et al.*[72] quality index scores of the 14 articles ranged from two to five with a mean ± S.D. of 3.8 ± 0.89. Routes of administration include oral, rectal, and i.v. A variety of NSAIDs were used which differ in the extent of their anti-inflammatory activity, analgesic effects, antipyretic actions, and pharmacokinetics.

Of the 14 studies identified, ten fit the classification of a preemptive design.[60, 161, 162, 163, 164, 166, 168, 169, 170, 172] Two of the 14 studies also examined effects beyond 5.5 half-lives of the target drug, one demonstrating a positive,[170][II] and the other, a negative[169] preventive effect. The other four studies used designs that assessed the preventive effects of NSAID interventions.[165, 167, 171, 173]

Of the six studies that reported preventive effects, four (66.7 percent) reported positive findings, and of these, both Buvanendran *et al.*[167][II] and Rueben *et al.*[161][II] demonstrated significant long-term benefits at one month and one year after surgery, respectively. Buvanendran *et al.*[167] found that a two-week perioperative regimen of rofecoxib in total knee arthroplasty patients improved range of motion in comparison to controls at a one month follow up. Reuben *et al.*[161][II] administered celecoxib or placebo, to patients scheduled for spinal fusion, for five days beginning one hour before surgery. The incidence of chronic donor-site pain was significantly lower in the celecoxib group (four of 40 patients, or 10 percent) compared with the placebo group (12 of 40 patients, or 30 percent) at one year after surgery. Celecoxib-treated patients had a 74 percent lower risk for developing chronic pain than the placebo-treated patients at one year.

COX-2 selective inhibitors were originally marketed as safer alternatives to nonselective nonsteroidal anti-inflammatory drugs. Recent studies demonstrating a link to long-term use and cardiac and renal morbidity[174, 175] have culminated in the withdrawal of rofecoxib and valdecoxib from the marketplace. Although the evidence suggests a fairly consistent cardiovascular risk rate with rofecoxib, the evidence for cardiovascular risk with celecoxib is equivocal.[176] It is important to note that the long-term cardiovascular risk associated with COX-2 inhibitors, which resulted in the withdrawal of rofecoxib, was demonstrated in patients taking the medication for more than two years. The analgesic and opioid-sparing effects associated with COX-2 inhibition were demonstrated with short-term use (eight days at most).[161, 165, 167]

In summary, the results of the present review suggest that perioperative NSAID use is associated with clinically significant preemptive and preventive effects with a success rate approaching 70 percent. Long-term benefits at one month and one year after surgery were associated with COX-2-selective NSAID (rofecoxib/celecoxib) administration. Given their long half-life (**Table 9.1**), the anti-inflammatory properties of these agents continued to be active for some time after surgery, even when administered as a single preoperative dose.[161] This may contribute to a longstanding block of the inflammatory response and a reduction in peripheral sensitization. Prolonged central effects of NSAIDs may also contribute to the prevention of central sensitization significantly attenuating the development of hyperexcitability in spinal cord dorsal horn neurons. Further research is required to confirm and extend the initial promising short- and long-term benefits of preventive COX-2 inhibition.

NMDA receptor antagonists

A variety of agents that have an antagonistic action at the NMDA receptor are clinically available, including amantadine, dextromethorphan, ketamine, ketobemidone, memantine, and methadone. At the present time, preventive or preemptive analgesic effects have been investigated using ketamine or dextromethorphan, but not the other NMDA antagonists. Although ketamine hydrochloride[177] and dextromethorphan[178] act on a variety of receptor systems, their NMDA channel-blocking properties quickly became the focus of intense research once this receptor–ion channel complex was discovered to play a critical role in the induction and maintenance of central sensitization and pathological pain.[179, 180] The mechanism proposed to underlie the reduced opioid consumption and pain in studies of preemptive analgesia is the prevention (or reversal) of NMDA-mediated sensitization of spinal cord dorsal horn neurons.[4, 51] The NMDA channel blockers dextromethorphan and ketamine are of particular interest, therefore, in testing the hypothesis that perioperative administration will lead to reduced pain and analgesic consumption using preventive and preemptive designs.

Table 9.9 shows the 14 studies that were found to have examined designs assessing preemptive and preventive analgesic effects of ketamine ($n = 10$) or dextromethorphan ($n = 4$). The Jadad *et al.*[72] quality index scores of the 14 articles ranged from three to four with a mean ± S.D. of 4.4 ± 0.64. The most frequent designs have compared preoperative administration of dextromethorphan or ketamine with a placebo or an active agent (i.e. evaluation of preventive effects). The next most commonly used designs compare preoperative administration of dextromethorphan or ketamine with the same agent administered either intraoperatively, postoperatively, or both preoperatively and postoperatively (**Table 9.3**).

KETAMINE

The preemptive and preventive use of ketamine has been studied on a variety of surgical procedures including lower abdominal surgery,[193] total knee arthroplasty,[182, 187] gynecological laparotomy[183] and laparoscopy,[184] gastrectomy,[185] major ear, nose, and throat surgery,[186] tonsillectomy,[194]

Table 9.8 Studies examining the preemptive and preventive effects of NSAIDs.

Author	Procedure (No. of patients)	Treatment combinations (Figure 9.1)	Group: first intervention drug/ second intervention drug	Route and dose	Timing of first intervention	Timing of second intervention	Quality Score	Nature and time after surgery of preventive and/or preemptive analgesic effects
Reuben *et al.*[161]	Arthroscopic knee surgery (60)	1, 2, 4	Sedation i.v. plus IA BUP plus: G1: ROF/PLA G2: PLA/ROF G3: PLA/PLA	50 mg p.o.	1 h preoperation	15 min after surgery	4	Preventive effect – na Preemptive effect – yes Verbal Analogue Pain at rest: G1 = G2 < G3 at 2+24 h Verbal Analogue Pain at movement: G1 < G2 < G3 at 1, 2+24 h 24 h consumption of PARACET/OXYCOD: G1 < G2 = G3
Kokki and Salonen[162]	Pediatric tonsillectomy (109)	1, 4, 6	GA plus: G1: KETOP /SAL/ KETOP G2: SAL/KETOP/ KETOP G3: SAL/SAL/SAL	Bolus i.v. 0.5 mg/kg Infusion i.v. 3 mg/kg/h	Bolus 5 min after induction but before surgery	PACU bolus followed by 24 h infusion	4	Preventive effect – na Preemptive effect – no
Gramke *et al.*[163]	Laparoscopic bilateral inguinal hernia repair (52)	2, 4	GA plus: G1: PIROXI/PLA G2: PLA/PIROXI	Sublingual 40 mg	2 h preoperation	10 min postoperation	3	Preemptive effect – yes VAS-R: G1 < G2 at 6 and 20 h Cumulative i.v. PCA tramadol:
Norman *et al.*[164]	Ankle fracture surgery (48)	2, 3	GA plus: G1: KETOR/PLA G2: PLA/KETOR	30 mg i.v.	After induction, while the leg was being prepared	Immediately after tourniquet inflation (< 15 min after intervention 1)	5	Preemptive effect – yes VAS-R: G1 < G2 at 2 and 4 h PCA morphine: No inter group differences

(*Continued over*)

Reuben *et al.*[165]	Spinal fusion (80)	1, 8	GA plus infiltration of proposed incision sites with BUP plus: G1: CELECOX/ CELECOX G2: PLA/PLA	400 mg preoperation p.o., 200 BID postoperation	1 h preoperation	Every 12 h postoperation until 5th day	3	Preventive effect – yes One year follow up: Chronic donor site pain: G1 < G2 G1 patients had a 74 lower risk for chronic pain than G2
Boccara *et al.*[166]	Laparoscopic cholecystectomy (104)	2, 4	GA plus: G1: KETOP/PLA G2: PLA/KETOP G3: PARACET/PLA G4: PLA/PARACET	KETOP 100 mg i.v. PARACET 2 g i.v.	Before induction	After surgery	4	Preventive effect – na Preemptive effect – yes VAS Pain: G1 < G2 = G3 = G4 at 0, 1, 2, 3, 10 and 12 h No of pain-free patients during 24 h: G1 < G2 = G3 = G4 No. of patients with severe pain (VAS ≥ 50): G1 < G2 = G3 Cumulative nalbuphine consumption at 24 h: G1 = G2
Buvanendran *et al.*[167]	Total knee arthroplasty (70)	1, 8	Sedation (i.v.) plus spinal BUP preop plus epidural post-op plus: G1: ROF/ROF G2: PLA/PLA	50 mg per day p.o.	24 h and 1–2 h preoperation	Once daily for 5 days then 25 mg/day for 8 more days	5	Preventive effect – yes One-month follow-up: Range of motion of affected knee: G1 > G2

(*Continued over*)

Table 9.8 Studies examining the preemptive and preventive effects of NSAIDs (continued).

Author	Procedure (No. of patients)	Treatment combinations (Figure 9.1)	Group: first intervention drug/ second intervention drug	Route and dose	Timing of first intervention	Timing of second intervention	Quality Score	Nature and time after surgery of preventive and/or preemptive analgesic effects
Priya *et al.*[168]	Breast surgery (50)	2, 3	GA plus: G1: KETOP/SAL G2: SAL/KETOP	100 mg i.v.	30 min before incision	Immediately after incision	4	Preemptive effect – yes VAS pain: G1 < G2 at all time points until 10 h No. of patients requiring rescue analgesia: G1 < G2 at 2, 4, 6, 8 and 10 h
Norris *et al.*[169]	Ambulatory knee arthroscopy (127)	2, 6, 4	GA plus: G1: DICLOF/PLA G2: DICLOF/ DICLOF G3: PLA/DICLOF	50 mg p.o.	1 h preoperation	30 min postoperation	4	Preventive effect – no Preemptive effect – no Functional Score: No differences at 0, 1, 2 and 3 days VAS pain: No differences at 1, 2 and 3 days
Nakayama *et al.*[170]	Abdominal hysterectomy (45)	1, 2, 4	GA plus epidural BUP post-op plus: G1: SAL/SAL G2: FLURBIP/SAL G3: SAL/FLURBIP	1 mg/kg i.v.	30 min preoperation	At end of surgery	3	Preventive effect – yes Preemptive effect – yes VAS-R: G2 < G1 = G3 at 15 and 24 h VAS-C: G2 < G1 = G3 at 24, 48 and 72 h N of diclofenac in 24 h: G2 = G3 < G1
Bugter *et al.*[171]	Total hip surgery (50)	1, 2	Sedation (i.v.) plus spinal anesthesia plus: G1: IBU/na G2: PLA/na	600 mg p.o.	TID for 2 weeks until surgery	na	2	Preventive effect – no

(*Continued over*)

Salonen *et al.*[172]	Tonsillectomy (106)	1, 2, 4	GA plus postoperative KETOP infusion 3 mg/kg for 24 h plus: G1: KETOP/SAL G2: SAL/KETOP G3: SAL/SAL	0.5 mg/kg i.v. bolus	After induction but preincision	In the PACU	5	Preventive effect – na Preemptive effect – no
Lim *et al.*[173]	Cesarean section (48)	1, 4	Spinal anesthesia plus: G1: na/DICLOF G2: na/na	100 mg p.r.	na	After Cesarean section	3	Preventive effect – yes VAS-M: no inter group differences post-operation PCEA consumption: G1 < G2 at 12–18 h Total PCEA consumption: G1 < G2 at 24 h
O'Hanlon *et al.*[60]	Ambulatory breast biopsy (73)	2, 2[a]	GA plus wound infiltration with BUP at end of procedure plus: G1: TENOX/Nad G2: NadTENOX	20 mg i.v.	30 min preoperation	At induction of anesthesia	4	Preemptive effect – yes VAS pain: G1 < G2 at 30, 60, 120 and 240 min No. of patients requiring additional analgesia: G1 < G2 Demerol and DICLOF usage for first 4 h: G1 < G2

BID, twice daily; BUP, bupivacaine; CELECOX, celecoxib; DICLOF, diclofenac; G, group; GA, general anesthesia; IA, intaarticular; IBU, ibuprofen; IV, intravenous; KETOP, ketoprofen; KETOR, ketorolac; min, minutes; na, not applicable; Nad, nothing administered; OXYCOD, oxycodone; PACU, postanesthetic care unit; PARACET, paracetamol (acetaminophen); PCA, patient controlled analgesia; PCEA, patient controlled epidural analgesia; PIROXI, piroxicam; PLA, placebo; p.o., per os; p.r., per rectum; ROF, rofecoxib; SAL, saline; TENOX, tenoxicam; TID, three times daily; VAS-C, visual analog scale pain score when coughing; VAS-R/M, visual analog scale pain score at rest/movement.

[a]The classification of this study as evaluating preemptive analgesia is not entirely accurate. While it does evaluate the effect of altering the timing of administration, it does not do so before versus after incision.

Table 9.9 Studies examining the preemptive and preventive effects of the NMDA receptor antagonists ketamine and dextromethorphan.

Author	Procedure (No. of patients)	Treatment Combinations (Figure 9.1)	Group: First intervention drug/ second intervention drug	Route and dose	Timing of first intervention	Timing of second intervention	Quality score	Nature and time after surgery of preventive and/or preemptive analgesic effects
Helmy and Bali[181]	Upper-abdominal surgery (60)	1, 2, 3	GA plus: G1: DEXTRO/SAL G2: SAL/DEXTRO G3: SAL/SAL	120 mg i.m.	30 min before incision	30 min before end of surgery	4	Preventive effect – na Preemptive – yes VAS-R/M: G1 < G2 = G3 at 6 h Total i.v. PCA pethidine (meperidine) consumption: G1 < G2 = G3
Himmelseher *et al.*[182]	Total knee arthroplasty (37)	1, 2	Lumbar epidural ROP plus: G1: SAL/na G2: KETAM/na	Epidural 0.25 mg/kg	10 min before incision	na	5	Preventive effect – yes VAS-R/M: G2 < G1 at 24 and 48 h Cumulative PCEA ROP:
Bilgin *et al.*[183]	Gynecologic laparotomy surgery (45)	2, 4, 5	GA plus: G1: KETAM/SAL/ SAL G2: KETAM/KETAM /SAL G3: SAL/SAL/ KETAM	Bolus i.v. 0.5 mg/kg Infusion i.v. 600 µg/kg/ h (G2)	Before induction of anesthesia followed by infusion	Third intervention after wound closure (G3)	4	Preventive effect – yes Preemptive effect – opposite VAS-R: G2 = G3 < G1 at 0–24 h VAS-C: G2 = G3 < G1 at 24 h i.v. PCA morphine: G1 = G2 = G3 at 0–24 h
Kwok *et al.*[184]	Gynecologic laparoscopic surgery (135)	1, 2, 4	GA plus: G1: KETAM/SAL G2: SAL/KETAM G3: SAL/SAL	0.15 mg/kg i.v.	Immediately before induction of anesthesia	After wound closure	5	Preventive effect – no Preemptive effect – yes VAS pain: G1 < G2 = G3 at 0 to 6 h Cumulative i.m. morphine: G1 < G2 = G3

(*Continued over*)

Xie *et al.*[185]	Gastrectomy (45)	1, 2	GA plus PCEA post op plus: G1: KETAM/na G2: KETAM/na G3: SAL/na	G1: 0.5 mg/kg i.v. G2: Epidural 0.5 mg/kg	15 min before incision	na	4	Preventive effect – yes VAS-R: G1 < G3 at 24 h G2 < G3 at 24, 36 and 48 h G2 < G1 at 24, 36 and 48 h Cumulative PCEA morphine at 48 h: G2 < G1 < G3
Ganne *et al.*[186]	Major ear, nose, and throat surgery (62)	1, 5	GA plus: G1: KETAM/na G2: SAL/na	Bolus i.v. 0.15 mg/kg followed by i.v. infusion 2 μg/kg	Bolus just before induction followed by continuous infusion during anesthesia	na	5	Preventive effect – no
Adam *et al.*[187]	Total knee arthroplasty (40)	1, 8	GA plus: G1: KETAM/KETAM / KETAM G2: SAL/SAL/SAL	Bolus i.v. 0.05 mL/kg followed by intraoperation Infusion i.v. 3 μg/kg/min then reduced to 1.5 μg/kg/min for 48 h	Just after induction of anesthesia	Maintained at second level from initial bolus until emergence from anesthesia, then reduced until 48 h postoperation	5	Preventive effect – yes Maximal active knee flexion at days 6 and 7: G1 > G2 Maximal active knee flexion at 6 weeks and 3 months: G1 = G2
Katz *et al.*[188]	Radical prostatectomy (143)	1, 3, 5	GA plus: G1: KETAM/SAL G2: SAL/KETAM G3: SAL/SAL	Bolus i.v. 0.2 mg/kg followed by i.v. infusion 0.0025 mg/kg/min	Bolus 10 min before incision followed by infusion for 70 min intraoperation	Bolus 70 min after incision followed by infusion until the end of surgery	5	Preventive effect – no Preemptive effect – no VAS-R/M: no inter group differences at any time Von Frey thresholds: no inter group differences at any time Cumulative i.v. PCA morphine consumption at 72 h: G1 = G2 = G3 (but G1 vs G2 and G1 vs G3; $p = 0.08$)

(*Continued over*)

Table 9.9 Studies examining the preemptive and preventive effects of the NMDA receptor antagonists ketamine and dextromethorphan (continued).

Author	Procedure (No. of patients)	Treatment Combinations (Figure 9.1)	Group: First intervention drug/ second intervention drug	Route and dose	Timing of first intervention	Timing of second intervention	Quality score	Nature and time after surgery of preventive and/or preemptive analgesic effects
								Hourly PCA consumption: G1 < G2 = G3 from 48 h to 72 h 2 week follow-up: VAS-R: G1 = G2 = G3
Ozyalcin *et al.*[189]	Thoracotomy (60)	1, 2	GA plus: G1: KETAM+SAL/ na G2: SAL+KETAM/ na G3: SAL+SAL/na	(G1) 1 mg/kg i.m. Epidural (G2) 1 mg/kg	15 min preoperation	na	5	Preventive effect – yes At 48 h: pinprick hyperalgesia: G2 < G1 = G3 Pressure hyperalgesia: G1 = G2 < G3 Brush allodynia: G2 < G1 < G3 Cumulative PCEA morphine at 48 h: G2 < G1 < G3 Cumulative PCEA morphine BUP: G2 < G1 = G3 15 day follow up Brush allodynia: G2 < G1 < G3 Pinprick hyperalgesia: G2 < G1 = G3 Pressure hyperalgesia: G2 < G3 30 day follow-up Brush allodynia: G2 < G1 < G3

(*Continued over*)

								Pin-prick hyperalgesia: G2 < G1 < G3 Pressure hyperalgesia No intergroup differences
Yeh *et al.*[190]	Colonic surgery (90)	1, 5	GA plus thoracic epidural plus: G1: PLA/SAL G2: PLA/LID G3: DEXTRO/LID	DEXTRO i.m. 20 mg Epidural 2 LID (8-10 mL/h)	30 min preincision	Intraoperatively until end of surgery	3	Preventive effect – yes VAS-C: G1 = G2 > G3 at 24 h Cum PCEA volume at 48 h and 72 h: G1 > G2 > G3
Wu *et al.*[191]	Laparoscopic cholecystectomy (100)	1, 2, 5	GA plus: G1: PLA+PLA/na G2: DEXTRO+PLA/ na G3: PLA+LID/na	DEXTRO i.m. 40 mg LID i.v. 3 mg/kg/h until end of surgery	30 min preincision	na	4	Preventive effect – yes VAS-C: G4 < G2 < G1 = G3 at24 h Cumulative i.m. pethidine at 48 h: G4 < G3 = G2 < G1
Weinbroum *et al.*[192]	Lower body surgery (60)	1, 2	Epidural LID plus: G1: PLA/na G2: DEXTRO/na G3: DEXTRO/na	DEXTRO p.o. 60 mg (G2) DEXTRO p.o. 90 mg (G3)	90 min preoperation	na	4	Preventive effect – yes 3-day follow-up VAS Pain: G2 = G3 < G1 Analgesic use: G2 = G3 < G1
Kafali *et al.*[193]	Lower abdominal surgery (60)	1, 2	GA plus: G1: SAL/na G2: KETAM/na	150 μg/kg i.v.	Before incision	na	4	Preventive effect – yes VAS pain: G2 < G1 at 48 h Cumulative i.v. PCA Morphine to 48 h: G2 < G1 i.v. PCA morphine: G2 < G1 at 24–48 h
Van Elstraete *et al.*[194]	Tonsillectomy (40)	1, 5	GA plus: G1: KETAM/KETAM G2: SAL/SAL	0.5 mg/kg i.v. bolus followed by i.v. infusion 2 μg/kg/min	At induction of anesthesia before incision	Infusion continued until end of surgery	5	Preventive effect – no

BUP, bupivacaine; DEXTRO, dextromethorphan; G, group; GA, general anesthesia; i.m., intramuscular; i.v., intravenous; KETAM, ketamine; LID, lidocaine; Na, not applicable; PCA, patient controlled analgesia; PCEA, patient controlled epidural analgesia; PLA, placebo; ROP, ropivacaine; SAL, saline; VAS-C, visual analog scale pain score when coughing; VAS-R/M, visual analog scale pain score at rest/movement.

radical prostatectomy,[188] and thoracotomy.[189] There is usually no rationale given for the patient population studied, in spite of the fact that important differences clearly exist among the various surgical procedures that may have a bearing on the outcome of the results (e.g. duration of procedure relative to that of the target agent, extent (deep versus superficial) and nature (nerve, muscle, viscera) of tissue damage and inflammation).

Ketamine has been administered by via the i.m.,[189] i.v.,[183, 184, 185, 186, 187, 188, 193, 194] and epidural[182, 185, 189] routes. Two studies compared the route of administration, including 1.0 mg/kg ketamine i.m. or epidurally[189] and 0.5 mg/kg ketamine i.v. or epidurally.[185] In both studies,[185, 189][II] preventive effects were observed for epidural ketamine compared with the other route.

Intravenous ketamine has been administered as a single bolus dose,[184, 185, 193] or as a bolus dose followed by a continuous infusion[183, 186, 187, 188, 194] for the duration of the surgical procedure. Intravenous bolus doses of ketamine have ranged from 0.15 to 0.5 mg/kg with infusions ranging from 2–10 μg/kg/minute.

The three studies of epidural ketamine[182, 185, 189][II] administered a single, preoperative bolus dose (0.25–1.0 mg/kg) without infusion. All three showed significant preventive effects; 48 hours after surgery, pain intensity and postoperative analgesic consumption were significantly lower in the ketamine-treated patients compared with the placebo control condition.[182, 185, 189][II] In one study,[189][II] patients were followed up 15 and 30 days after surgery. At both follow-up assessments, brush-evoked allodynia and pin-prick hyperalgesia were still significantly less pronounced in the epidural ketamine group compared with the i.m. ketamine and saline control groups. The pattern of intergroup differences for pressure hyperalgesia at the wound was the same for the 15-day follow up, but the differences were no longer significant 30 days after surgery.

The surgical procedures were performed under general anesthesia in all but one of the studies, the exception being a positive preventive study of patients undergoing total knee arthroplasty with epidural ropivacaine.[182][II]

Of the ten studies evaluating ketamine, significant preventive effects were observed in seven studies.[182, 183, 184, 185, 187, 189, 193][II] One study[183] showed a preemptive effect that was opposite to what had been predicted in that the group receiving i.v. ketamine after wound closure reported significantly lower pain scores at rest and after coughing up to 24 hours after surgery compared with the preincisional group. As noted above, these results may point to the relative greater efficacy in reducing central sensitization of postsurgical i.v. ketamine versus preoperative blockade.

DEXTROMETHORPHAN

Surgical procedures for the four studies using dextromethorphan include upper abdominal surgery,[181] colonic surgery,[190] laparoscopic cholecystectomy,[191] and lower body surgery.[192] For all studies, dextromethorphan was administered by the i.m. route as a single bolus dose ranging between 20 and 120 mg, either before surgery,[89, 190, 191] or before versus during surgery.[181] Intramuscular dextromethorphan resulted in a preventive effect in three[89, 190, 191][II] of the four studies; pain intensity was significantly lower between 24 hours[190, 191][II] and three days[89][II] after a single bolus dose of i.m. dextromethorphan. The one study[181] that did not find a preventive effect did, however, show a short-term preemptive effect in that total patient-controlled analgesia (PCA) opioid consumption, as well as pain at rest and after movement six hours after surgery, were significantly lower in the group that received dextromethorphan 30 minutes before surgery versus 30 minutes before the end of surgery.

Taken together, the results of the studies that have examined administration of ketamine or dextromethorphan have proved quite successful in that approximately 65 percent (11/17) of the effects reported supported the efficacy of preemptive or preventive analgesia. As shown in **Table 9.3**, almost 69 percent (9/13) of the effects evaluating only preventive analgesia show that preoperative ketamine or dextromethorphan administration results in significantly lower pain intensity and/or reduced analgesic requirements after the duration of action of the NMDA antagonists have worn off (i.e. after more than 5.5 half-lives). These results are very similar to those reported by McCartney *et al.*[67][I] in a recent qualitative review of the preventive analgesia literature from 1966 to 2003. They found that among the clinically available NMDA receptor antagonists, dextromethorphan (67 percent (8/12) of studies) and ketamine (58 percent (14/24) of studies) showed the greatest number of significant preemptive or preventive effects. Their data show that 16 of the 30 studies (53 percent) evaluating preventive analgesia only (i.e. excluding preemptive analgesia) showed evidence of a reduction in pain, analgesic consumption, or both beyond the clinical duration of action of the drug concerned. The similarity in outcome between the present review and that of McCartney *et al.*[67][I] is unlikely to be due to the two-year (2001–2003) overlap in the literature reported since, of the 36[67][I] and 24 (present review) studies covered, only three[181, 182, 192] were common to both reviews.

The preponderance of positive studies of ketamine and dextromethorphan may be due not only to the ability of these agents to block the neural processes underlying central sensitization,[177] but in a related vein, to their ability to attenuate the development of acute opioid tolerance[7, 195] and reverse opioid-induced facilitation of nociceptive processing.[196, 197] Since opioids were administered (as premedication or during surgery) in all but three[89, 182, 183] of the studies, preoperative administration of ketamine or dextromethorphan may also have prevented acute opioid tolerance, opioid-facilitated activation

of NMDA processes, and opioid-induced hyperalgesia relative to the control group leading to a reduction in postoperative opioid requirements and postoperative pain intensity in the preoperatively treated groups.

Multimodal analgesic therapy

The rationale for a preoperative multimodal approach to postoperative pain management is to capitalize on the combined actions of a variety of classes of analgesic and anesthetic agents at different receptor sites in reducing peripheral and central sensitization.[198, 199] For the purpose of the present review, we have defined a multimodal regimen as involving administration of three or more agents in combination. Expectations of the therapeutic benefits associated with multimodal regimens include improved efficacy, lower doses, and fewer adverse effects.[200]

Table 9.10 describes the five studies[115, 201, 202, 203, 204] that evaluated the effects of multimodal, combination therapy on pain and analgesic consumption using preemptive or preventive designs. The Jadad *et al.*[72] quality index scores of the five articles ranged from two to five with a mean ± S.D. of 4.2 ± 1.3. Surgical procedures include breast cancer surgery,[115] arthroscopic knee surgery,[201, 203] nephrectomy,[202] and tonsillectomy.[204] Of the five studies, two[201, 202] evaluated preemptive effects using the classic design (treatment combination 2 versus 4 in **Figure 9.1**) and one[201][II] showed significant effects in favor of the preoperative treatment. Two[115, 204][II] of the remaining three studies[115, 203, 204] that evaluated preventive effects found significant benefits that long outlasted the clinical duration of action of the target agents. In a triple-dummy, placebo-controlled study by Fassoulaki *et al.*,[115] [II] patients undergoing breast cancer surgery received placebo or preoperative gabapentin and transdermal eutectic mixture of local anesthetics (EMLA) followed by intraoperative ropivacaine irrigation of the brachial plexus and several intercostal spaces. After surgery, patients continued to receive placebo or gabapentin every six hours for eight days in addition to transdermal EMLA daily for three days. Three months (but not six months) after surgery, patients in the multimodal treatment group had a lower incident of axilla pain, arm pain, chronic pain, and analgesic use compared with the placebo control patients. Naja *et al.*[204][II] compared the effects of no treatment with a preincisional tonsillar infiltration of a placebo solution or a solution containing lidocaine with epinephrine, bupivacaine, fentanyl, and clonidine in 90 pediatric patients undergoing tonsillectomy. Pain at rest, on jaw opening, and when eating soft foods were all significantly lower in the combination pharmacotherapy group for up to at least one week after tonsillectomy. These studies provide some of the strongest and most promising evidence of the therapeutic benefits of a (prolonged[115][II]) multimodal analgesic regimen.[204][II]

The study by Rosaeg *et al.*,[201] which compared a combination of local anesthesia, morphine, epinephrine, and ketorolac (treatment combination 2 versus 4 in **Figure 9.1**), was designed to look at long-term outcomes as well (i.e. preventive effects). The authors found that administration of their three-component analgesic drug combination resulted in lower pain scores in patients that received the intervention before versus after surgery. Pain scores and i.v. PCA morphine consumption were significantly lower during the initial stay in the postanesthesia care unit (PACU) (i.e. a positive preemptive effect). However, pain scores did not differ significantly between the groups on postoperative days one, three, and seven; thus there was no measurable long-term advantage associated with preemptive multimodal drug administration in arthroscopic knee surgery (i.e. a negative preventive effect).[201]

At first glance, the results describing the multimodal studies shown in **Table 9.10** seem equivocal. However, it is important to note the two studies[201, 203] that reported negative preventive effects and the one negative preemptive study[202] both lacked a placebo control group. Thus, the conclusion that these multimodal interventions do not exert a clinically relevant benefit may be incorrect. Until similar studies are conducted with the appropriate control condition(s), these conclusions are premature.

Other nonanalgesic agents

Table 9.11 describes the four studies that examined the preemptive and/or preventive analgesic effects of other, traditionally, nonanalgesic agents, including venlafaxine[63] [II] (a serotonin and norepinephrine reuptake inhibitor (SNRI)), promethazine[205][II] (a histamine$_1$ (H_1) receptor antagonist), nitroglycerine,[206][II] and dexmedetomidine[207] [II] (an alpha-2 agonist). All evaluated preventive effects with the exception of the study by Chia *et al.*,[205][II] in which both preemptive and preventive effects were examined (treatment combination 1 versus 2 versus 4 in **Figure 9.1**). Thus, of the five effects examined, there were three positive preventive effects,[63, 206, 207][II] one negative preventive effect[205] and one positive preemptive effect.[205][II]

The most interesting and promising of these studies, conducted by Reuben *et al.*[63][II] and depicted in **Figure 9.8**, involved administration of venlafaxine 75 mg or placebo capsules to women ($n = 50$ per group) the night before surgery and daily for two weeks after radical mastectomy. Six month follow-up assessment revealed that pain on movement, as well as the incidence of chest wall pain, arm pain, axilla pain, chronic pain, and analgesic use were all significantly lower in the venlafaxine group. Consistent with the results of a rat study,[208] the authors suggest that the lower incidence of chronic neuropathic pain six months after surgery may have been result of an SNRI-induced reduction of activity in adrenergic nociceptive pathways that contribute to central sensitization.[63]

Table 9.10 Studies examining the preemptive and preventive effects of multimodal analgesic regimens.

Author	Procedure (No. of patients)	Design	Group: First intervention drug/second intervention drug	Route and dose	Timing of first intervention	Timing of second intervention	Quality score	Nature and time after surgery of preventive and/or preemptive analgesic effects
Fassoulaki *et al.*[115]	Breast cancer surgery (50)	1, 8	GA plus: G1: PLA+PLACRM/ SAL/ PLA+PLACRM G2: GABA+EMLA/ROP/ GABA+EMLA	GABA p.o. 400 mg Irrigation ROP 10 mL Transdermal EMLA 20 g	GABA starting 6 pm preoperation and every 6 h thereafter EMLA – 5 min before surgery Intraop – ROP irrigation of brachial plexus, third, fourth, and fifth intercostal spaces	GABA – every 6 h until 8th day postoperation EMLA – sternal area, close to the wound, around the incision in the axilla daily for 3 days postoperation	5	Preventive effect – yes 3 month follow-up Incidence of: axilla pain: G2 < G1 arm pain: G2 < G1 chronic pain: G2 < G1 analgesic use: G2 < G1 6-month follow up no group differences in pain or analgesic use
Rosaeg *et al.*,[201]	Arthroscopic knee ligament repair (40)	2, 4	GA plus: G1: ROP+MORPH+EPI +KETOR/Nad G2: Nad/ROP+MORPH +EPI+KETOR	Femoral nerve block ROP 20 mL 0.25 ROP i.a. 20 mL 0.25 MORPH i.a. 2 mg (plus EPI) KETOR i.v. 30 mg	15 min before skin incision	Immediately after completion of surgery	4	Preventive effect – no Preemptive effect – yes VRS Pain: G1 < G2 at 0.5, 1, 1.5 and 2 h Cumulative i.v. PCA morphine usage: G1 < G2 at 1, 2, 3, 4 and 5 h
Holthusen *et al.*[202]	Nephrectomy (30)	2, 4	GA plus: G1: MORPH+KETAM +CLON/Nad G2: Nad/MORPH +KETAM+CLON	150 μg/kg i.v. MORPH 150 μg/kg KETAM	15 min preoperation	Immediately after completion of surgery	2	Preemptive effect – no
Ng *et al.*[203]	Arthroscopic knee surgery (63)	4, 4, 4	LID infiltration plus: G1: na/BUP G2: na/ROP G3: na/ROP+MORPH +KETOR	BUP i.a. 150 mg ROP i.a. 150 mg ROP i.a. 150 mg MORPH 4 mg KETOR 30 mg	na	At end of surgery	5	Preventive effect – no

(*Continued over*)

Naja *et al.*[204]	Pediatric tonsillectomy (90)	1, 2	GA plus: G1: LID+EPI+BUP+FENT +CLON/na G2: SAL/na G3: Nad/na	Preincisional infiltration (each tonsil 1.5 mL) mixture of LID+EPI, BUP, FENT and CLON	Before incision	na	5	Preventive effect – yes VAS-R: G1 < G2 = G3 at 1, 2, 3, 4, 7 and 8 days VAS-R: G1 < G3 at 5, 6, 9 and 10 days VAS pain on jaw opening: G1 < G2 = G3 at 1, 2, 3, 4, 7, 8 and 10 days G1 < G3 at 5 and 6 days G1 < G2 at 9 days VAS pain when eating soft foods: G1 < G2 = G3 at 1, 2, 3, 4, 8 days No. of patients taking paracetemol (acetaminophen): G1 < G2 < G3 at 1, 2, 3, 4, 5 and 6 days No. of patients taking tramadol: G1 < G2 < G3 at 1, 2 and 3 days G1 < G2 = G3 at 4 and 5 days VAS-R: G1 < G2 = G3 at 1, 2, 3, 4, 7 and 8 days

BUP, bupivacaine; CLON, clonidine; EMLA, eutectic mixture of local anesthetics; FENT, fentanyl; G, group; GA, general anesthesia; GABA, gabapentin; i.a., inta-articular; i.v., intravenous; KETAM, ketamine; KETOR, ketorolac; LID, lidocaine; MORPH, morphine; Nad, nothing administered; PCA, patient controlled analgesia; PLA, placebo; PLACRM, placebo cream; PO, per os; ROP, ropivacaine; VAS-R, visual analog scale pain score at rest; VRS, verbal rating scale.

Table 9.11 Studies examining the preemptive and preventive effects of other nonanalgesic agents.

Author	Procedure (No. of patients)	Treatment combinations (Figure 9.1)	Group: First intervention drug/ second intervention drug	Route and Dose	Timing of first intervention	Timing of second intervention	Quality score	Nature and time after surgery of preventive and/or preemptive analgesic effects
Reuben *et al.*[63]	Radical mastectomy with axillary lymph node dissection (100)	1, 2	GA plus: G1: VENLAF/na G2: PLA/na	75 mg p.o.	Night before surgery and daily for 2 weeks post-operatively	na	5	Preventive effect – yes At 6 month follow up: Pain on movement: G1 < G2 6 month incidence of: chest wall pain: G1 < G2 arm pain: G1 < G2 axilla pain: G1 < G2 chronic pain: G1 < G2 analgesic use: G1 < G2
Chia *et al.*[205]	Total abdominal hysterectomy (90)	1, 2, 4	GA plus: G1: PROMETH/SAL G2: SAL/PROMETH G3: SAL/SAL	0.1 mg/kg i.v.	30 min preoperation	At end of surgery	4	Preventive effect – na Preemptive effect – yes VAS-R/M: No inter group differences to 24 h Cumulative PCA MORPH: G1 < G2 = G3 at 3, 6, 12 and 24 h
Unlegenc *et al.*[207]	Abdominal surgery (60)	1, 2	GA plus: G1: PLA/na G2: DEXMED/na	1 μg/kg i.v. for 10 min	10 min before anesthesia	na	4	Preventive effect – yes VAS pain: no inter group differences up to 24 h Cumulative PCA MORPH: G2 < G1 at 24 h PCA morphine 12–24 h: G2 < G1
Sen *et al.*[206]	Hand surgery (30)	1,2	Sedation i.v. plus: G1: LID/na G2: NITRO + LID/na	LID i.v. 2 3 mg/kg NITRO i.v. 200 μg	Immediately preoperation	na	4	Preventive effect – yes VAS for tourniquet pain: G2 < G1 at 30 min intraoperation VAS pain: G2 < G1 for 1st 4 h postoperation DICLOF consumption: G2 < G1 PARACET consumption: G2 < G1

DEXMED, dexmedetomidine; DICLOF, diclofenac; G, group; GA, general anesthesia; i.v., intravenous; LID, lidocaine; min, minute; MORPH, morphine; NITRO, nitroglycerin; PARACET, paracetamol (acetaminophen); PCA, patient-controlled analgesia; PLA, placebo; PROMETH, promethazine; SAL, saline; VAS-R/M, visual analog scale pain score at rest/on movement; VENLAF, venlafaxine.

RECOMMENDATIONS FOR FUTURE RESEARCH

Relationship between preexisting pain and timing of analgesic administration

We know very little about the effects of preexisting, preoperative pain on the subsequent development of acute and chronic postoperative pain. As it turns out, this important issue prompted the very first controlled study[209][III] of "preoperative preemptive analgesia"[38] which suggested that epidural anesthesia started before and continuing for the duration of surgery conferred protection from long-term phantom limb pain six months after surgery. These promising results were not supported by a subsequent randomized trial evaluating the long-term effects on phantom limb and stump pain of continuous epidural morphine and bupivacaine administered 18 hours before, during and for about one week after lower limb amputation.[15] The control group received epidural saline before and throughout surgical procedure followed by epidural morphine and bupivacaine postoperatively. There were no significant differences between the groups in pain incidence, intensity, or opioid consumption at any time up to 12 months after surgery.[15]

Other more recent studies in nonamputee populations have examined the same issue as it pertains to the development of acute, as opposed to chronic, postsurgical pain. The data suggest that in the presence of presurgical pain, preoperative administration of analgesics does not lead to the anticipated lessening of postoperative pain or analgesic consumption, perhaps because central sensitization has already been established. Postoperative pain and analgesic consumption were significantly reduced by pre- and intraoperative epidural morphine, but not saline, for patients who did not report presurgical pain.[210][II] However, among patients with presurgical pain, pre- and intraoperative epidural morphine was no more effective than saline.[210] This raises the important issue of what effect blocking preoperative pain would have on the intensity of acute postoperative pain. A recent study of patients undergoing total knee arthroplasty showed that relief of preoperative pain by epidural ropivacaine for at least 12 hours before surgery, followed by intraoperative epidural ropivacaine, reduced patient-controlled epidural analgesia (PCEA) ropivacaine consumption 48 hours after surgery compared with preoperative epidural saline and intraoperative epidural ropivacaine.[61][II] Based on these interesting and controversial findings, future studies should report presence (and duration) or absence of presurgical pain.

Offsetting the competing effects of opioid analgesia and opioid-induced tolerance and hyperalgesia

As noted above, recent basic science evidence points to the possibility that under certain circumstances, preoperative administration of opioid analgesics may contribute to the establishment of acute opioid tolerance[195] and opioid-induced hyperalgesia.[197, 211] The mechanisms underlying the reduced pain and opioid consumption brought about by preemptive opioid analgesia, and the increased pain and opioid consumption underlying acute opioid tolerance and opioid-induced hyperalgesia, involve competing processes involving the NMDA receptor–ion channel complex. These findings have important implications for the conduct of clinical studies evaluating the timing of administration of opioid analgesics since the main outcome measures (pain and opioid consumption) will be directly affected by the mechanisms underlying these competing neural processes. The net effect of this competition is to attenuate (or even reverse) the desired preemptive and preventive effects. Coadministration of opioids and low-dose NMDA antagonists or low-dose opioid antagonists has been found to interfere with the development of acute opioid tolerance[7, 212] and opioid-induced hyperalgesia.[213] A mechanism-based approach to postoperative pain management involving coadministration of these agents would be expected to facilitate the preventive and preemptive analgesic effects of opioids in patients undergoing major surgery.

Recommendations to improve the quality of studies

MEASURES OF PAIN

The most appropriate pain measurement instruments are patient-rated pain scales that have demonstrated reliability and validity (e.g. visual analog scale (VAS), numeric rating scale, McGill pain questionnaire).[214] Measurement of pain with the patient in a resting position is reported by almost all studies. However, the measurement of hyperalgesia is important. The simplest and most clinically significant test of mechanical hyperalgesia is to have the patient perform a standardized movement after surgery (e.g. sitting up from a lying position, inspirational spirometry) and rate the intensity of the pain that ensues. More sophisticated measures of primary and secondary mechanical and thermal hyperalgesia include pressure algometry applied either on or near the wound dressing[215] or on the side of the body contralateral to the incision,[216] measurement of thresholds to electrical stimulation,[217] temperature,[89] and use of pinprick, brush,[189] and Von Frey filaments[58, 188] at a distance from the wound to determine the extent of secondary mechanical allodynia and hyperalgesia. Baseline (preoperative) measures are important as is testing at a control site (e.g. a noninjured body part) to rule out a generalized effect due to factors such as anxiety, anticipatory pain, or a response bias.

MEASURES OF ANALGESIC CONSUMPTION

The degree of pain a patient experiences in the postoperative setting is in part a function of postoperative analgesic consumption. Use of patient-controlled analgesia (either i.v. or epidural) as a modality for postoperative pain management has dominated the preemptive analgesia literature. This is largely because PCA/PCEA is now the gold standard for postoperative pain management at most institutions worldwide. Analgesic consumption is usually the primary outcome measure since patients self-administer the agent to achieve a relatively constant pain level. However, from the point of view of demonstrating preemptive analgesia, analgesic consumption is not the most ideal measure because the main hypothesis deals with pain and hyperalgesia. Allowing pain to fluctuate by holding constant the level of postoperative analgesics administered would be a more direct test of the hypothesis, but this is not always feasible or ethical given the evolving standards of pain management practice.

Cumulative analgesic consumption at the end of the study is a common measure, but report of a single value may not provide specific enough information to pinpoint exactly when the effect is observed. This point is not as important if a postincision control group is employed. However, it is especially relevant in studies that evaluate the preventive effect of a preoperative intervention (i.e. when comparing it to a placebo) since it is likely that the largest difference in PCA consumption between treated and untreated groups will occur around the time of peak effect of the target agent used preventively. Cumulative analgesic consumption at the end of the study may be misleading depending on the pattern of consumption over time. For example, if a difference in analgesic consumption occurs within the first few hours after surgery, when the effects of the analgesics used preventively are still active, then this is an analgesic effect. Unless cumulative analgesic consumption is reported at multiple times across the study period, an analgesic effect may be misinterpreted as a preventive effect or a preventive effect may be missed. Likewise, report of a single value for cumulative analgesic consumption at the end of the study may result in failure to detect the presence of group differences at earlier time points. Another approach that circumvents this problem is to calculate analgesic consumption within intervals bounded by the times when pain is assessed.[54, 148, 218] This method has the advantage of specifying an interval within which an opioid-sparing effect has occurred.

SUMMARY AND CONCLUSIONS

Preoperative pain intensity is a risk factor for development of severe acute postoperative pain, as well as long-term postsurgical pain. Severity of acute postoperative pain predicts pain after discharge and also is a risk factor for chronic postsurgical pain. These findings have, in part, fueled recent preventive and preemptive efforts to reduce acute pain intensity and long-term pain problems by blocking noxious perioperative inputs.

Overall, across the classes of agents reviewed, the proportion of significant preventive and preemptive effects is significantly greater than the proportion of negative effects ($p = 0.02$, **Table 9.4**). The same is true for the proportion of positive versus negative preventive effects ($p = 0.03$, **Table 9.4**). Administration of these agents appears to reduce pain, analgesic consumption or both at a point in time that exceeds 5.5 half-lives of the target agent. Since these extended effects are observed after the clinical actions of the agents have worn off, they are not analgesic effects. Rather, these effects appear to be due to the reduction in perioperative peripheral and central sensitization in the treated patients. The greatest proportion of positive preventive effects were found for the NMDA antagonists ketamine and dextromethorphan for which significantly lower pain intensity and/or reduced analgesic requirements were found in approximately 69 percent of the effects tested. In spite of the heterogeneity in designs (**Figure 9.3**) across the 61 clinical trials (69 effects) evaluated, it appears that, in general, there is a benefit in terms of reduced pain and/or analgesic consumption that extends beyond the duration of action of the target drug.

The absence of a difference in the proportion of positive preemptive versus negative preemptive effects is understandable when one considers that both preincisional and postincisional (or postsurgical) noxious inputs contribute to postoperative sensitization.[4][I] The most likely conclusion is that for a certain proportion of studies of preemptive analgesia, the postincision or postsurgical administration condition is as beneficial in reducing central sensitization as is the preoperative condition but that these benefits go undetected when the comparison is made between the two groups. The lack of a control group in studies of preemptive analgesia is a serious limitation that confounds interpretation of the results and has contributed to the premature and erroneous conclusion that there is no clinical benefit to preoperative nociceptive blockade.

The continued use of incomplete designs that consist of preincisional and postincisional or postsurgical conditions without a standard treatment group or a complete blockade condition will hinder progress in our understanding of the benefits of preemptive analgesia. Adhering to the narrow definition of preemptive analgesia currently accepted by many in the field will perpetuate problems of interpretation and will not lead to the evolution and progress that is needed to move us beyond the current state of confusion. Inclusion of appropriate control conditions is essential if we are to advance our knowledge about the factors that contribute to acute postoperative pain and enhance our ability to detect clinical benefits

associated with blockade of noxious perioperative inputs. Future work should focus on maximizing the prevention of surgically induced sensitization by ensuring as complete a blockade as possible of nociceptive transmission throughout the three phases of the perioperative period. Long-term follow-up studies are needed to assess the efficacy of the perioperative interventions and to ascertain the true incidence of chronic post-surgical pain.

Given the prominent role of psychosocial factors in chronic pain[219] and the recent recommendations for assessment of core measures and domains in clinical trials,[220] relevant psychological, emotional, and physical variables should be added to those routinely assessed before and after surgery. Assessment of additional domains of functioning may help to shed light on the predictors of severe acute postoperative pain, the processes involved in recovery from surgery, and the risk factors for developing chronic postsurgical pain.[57]

ACKNOWLEDGMENTS

Joel Katz is supported by a Canada Research Chair in Health Psychology at York University, Toronto, Canada. We would like to thank Maria Dzyuba and Eileen Halket for retrieving the articles reviewed in this chapter and Matthew Dubins for his help with data extraction and creation of the tables.

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