Preventive Analgesia: Quo Vadimus?

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The classic definition of preemptive analgesia requires 2 groups of patients to receive identical treatment before or after incision or surgery. The only difference between the 2 groups is the timing of administration of the drug 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. 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 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 duration of action of the target drug, which we have defined as 5.5 half-lives of the target drug. This requirement ensures that the observed effects are not direct analgesic effects. In this article, we briefly review the history of preemptive analgesia and relate it to the broader concept of preventive analgesia. We highlight clinical trial designs and examples from the literature that distinguish preventive analgesia from preemptive analgesia and conclude with suggestions for future research.

The past 20 years have seen a concerted effort from basic science and clinical researchers in pain and anesthesia to minimize acute postoperative pain, reduce analgesic consumption, and decrease the risk of the transition to pain chronicity. 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,[1–4] as well as to stop the neurochemical cascade that leads to chronic pain by postsynaptic receptor blockade, e.g., via *N*-methyl-d-aspartate receptor (NMDA-R) antagonists, by neuroprotection of antinociceptive dorsal horn interneurons, arresting glial reaction, and preventing the phenotypic switch that causes some interneurons to become pronociceptive.[5–11]

The idea behind this approach is not simply that it reduces nociception and stress during surgery, although these are obviously worthwhile goals. The hypothesis, based on the basic science studies,[12–17] is that the transmission of noxious and nonnoxious afferent input from the periphery to the spinal cord induces a prolonged state of central neural sensitization or hyperexcitability that amplifies subsequent input from the wound and surrounding tissue and leads to heightened postoperative pain and a greater requirement for postoperative analgesics. The sources of central sensitization are varied and include afferent input arising from preoperative pain, injury discharge from cut primary afferents, other noxious intraoperative events (e.g., retraction), as well as postoperative inflammation that develops over hours, days, and weeks later and leads to hyperexcitability and ectopic activity in injured and nearby uninjured primary afferents, and in their somata in dorsal root ganglia. By interrupting the transmission of the peripheral nociceptive barrage to the spinal cord throughout the perioperative period, a preventive approach aims to block the induction of central sensitization, resulting in less intense postoperative pain intensity and lower analgesic requirements.[1]

In this article, we briefly review the history of preemptive analgesia and relate it to the broader concept of preventive analgesia. We highlight clinical trial designs and examples from the literature that distinguish preventive analgesia from preemptive analgesia and conclude with suggestions for future research.

A BRIEF HISTORY OF PREEMPTIVE ANALGESIA

George Washington Crile[18,19] was the first to propose that acute and long-term postoperative pain would be intensified by intraoperative tissue damage that induced a long-lasting state of central neural hyperexcitability. He also reasoned that a combined multimodal regimen, including, among other drugs, chloroform, ether, and local anesthesia, would prevent the development of painful scars through

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what he termed "anoci-association."[18,20] Later, Hutchins and Reynolds[21] showed that referred tooth pain, 2 months after dental treatment performed under nitrous oxide or without anesthesia, could be elicited by stimulation of the ipsilateral maxillary sinus ostium, providing evidence for a "prolonged central excitatory state." Reynolds and Hutchins[22] demonstrated that a procaine block during dental procedures prevented the appearance of referred tooth pain for up to 2 weeks, whereas referred pain developed in teeth without the block.

Interest in the mechanisms underlying these effects was rekindled by basic science studies conducted by Wall et al.[23] who showed that injury to a peripheral nerve triggers an afferent barrage consisting of a high-frequency burst of neural activity that differs from the response to natural stimuli in peak frequency, duration, and the number of firing units. They termed this neural signal the "injury discharge." Subsequent experiments demonstrated that attenuation of the injury discharge in rodents, by administration of opioids,[13,14] local anesthetics,[12,15,16,24,25] NMDA-R blockers,[17] ralfinamide,[26] and other substances, before nerve injury, prevented the development of postinjury spinal hyperexcitability and chronic pain-related behaviors. In contrast, augmentation of the naturally occurring injury discharge by electrical tetanization of the injured nerve,[15,16,27] or by blocking the constitutive-tonic spinal glycinergic inhibition by glycine-1 receptor blockade, increased these behaviors.[17] These treatments were significantly less effective when administered only minutes after the injury once the cascade of pathophysiological changes involved in prolonged peripheral and central excitability had been triggered.

In 1988, Patrick Wall[32] coined the term "preemptive preoperative analgesia" and in so doing set in motion the present-day movement to prevent acute and chronic postsurgical pain. Wall proposed that preoperative local anesthesia and morphine would block the induction of central neural sensitization brought about by surgical incision and thus reduce acute postoperative pain intensity. Since that time, the concept has been refined, based on evidence from clinical trials, advances in the basic science of pain, and critical thought. The idea that surgical incision is the trigger of central sensitization[32] has been broadened 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.[33]

It is believed that injury discharge initiates a cascade of processes leading to the transition from acute to chronic pain that include excitotoxic destruction of normally antinociceptive inhibitory neurons in the dorsal horn, glial reaction, afferent-maintained central sensitization, and a switch of GABAergic interneurons in the dorsal horn from being normally antinociceptive to pronociceptive interneurons.[11,28–31]

It is now well documented that although general anesthesia may attenuate synaptic transmission of afferent injury discharge from the periphery to the spinal cord and brain, it does not completely block it.[34] Moreover, systemic opioids may not provide a sufficiently effective blockade of the neurotransmission of spinal nociceptive neurons to prevent central sensitization.[35] 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 spinal and medullary dorsal horn neurons are largely unaffected by general anesthesia[36] or routine doses of opioids.[35] This sets the stage for heightened postoperative pain and an increased requirement for analgesics.

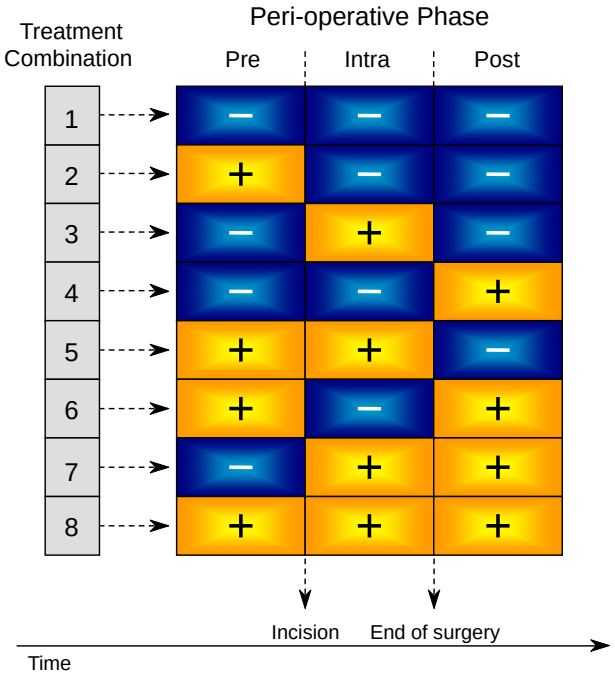

Figure 1. Schematic representation showing the administration (+) or nonadministration (—) of drugs across the preoperative, intraoperative, and postoperative phases of surgery, yielding 8 different treatment combinations and 28 possible 2-group designs to evaluate the efficacy of preemptive and preventive analgesia. The classic preemptive analgesia design requires 2 groups of patients to receive identical treatment before or after incision or surgery (treatment combinations 2 vs 3 and 2 vs 4). This represents only one of many possible hypotheses concerning the effects of blocking noxious perioperative inputs on postoperative pain and analgesic consumption. (Adapted with permission from Katz.[98])

TARGETS OF A PREVENTIVE APPROACH TO ACUTE AND CHRONIC PAIN MANAGEMENT

The perioperative period comprises 3 fairly distinct temporal phases: preoperative, intraoperative, and postoperative (Fig. 1). Factors within these 3 phases contribute to the development of acute postoperative pain. These factors include (1) genetic predisposition, psychological vulnerability,[33] nongenetic environmental variables (e.g., expectations, cultural, dietary, and more), preoperative noxious inputs, and pain; (2) intraoperative nociceptive unmyelinated (C fibers and type IV) and myelinated (A-δ, type III, and contributing A-β and type II) afferents carrying injury discharges brought about by cutting skin, fascia and muscle, tendons, nerves, viscera, and bone; wound retraction; manipulation of organs; chemical irritation by sterilizing substances and by natural substances released from injured tissues, e.g., nerve growth factor; inflamed tissues; etc.; and (3) postoperative afferent inputs from regenerating wounded

tissues including the inflammatory response and neuropathic ectopic neural activity from regenerating afferents nerves.

Each of the above factors contributes to peripheral and central sensitization and each is a potential target for a preventive approach to reducing postoperative pain intensity and the transition to pain chronicity. We do not know all of the variables, nor the relative extent to which the known factors within these 3 phases trigger postoperative pain and maintain it in chronicity. Nevertheless, based on basic science and clinical research, we suggest that the intensity and incidence of postoperative pain will depend on past experience with pain, psychological, emotional, and social factors involved in pain perception, the surgical procedure, including the extent and nature of tissue damage, duration of surgery; timing and nature of drugs given relative to tissue damage; pharmacokinetics of the drug(s) used; presence or absence of supplementary adjuvant analgesia administered intraoperatively; the nature of the postoperative analgesia; and many other variables, including the genetic makeup that confers a greater or lesser likelihood to be affected by any of the variables listed above. Minimizing the negative impact and maximizing the beneficial effects of as many of these variables across the 3 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 1 shows the 8 possible treatment combinations of giving or not giving analgesics across the 3 perioperative phases. The preoperative phase encompasses interventions that begin days before surgery, up to those administered just minutes before skin incision. The intraoperative phase includes interventions started immediately after incision to those initiated just before the end of surgery (e.g., skin closure). The postoperative phase includes interventions started immediately after the end of surgery and may extend days or weeks after hospital discharge. There is potential for considerable variation in the timing and duration of administration of analgesics, especially within the preoperative and postoperative phases, which have been only partially investigated in rodent models and in the clinical setting. However, even within the intraoperative phase, evidence shows that there are extensive differences among studies on when (and for how long) analgesics are given.[37]

CONTROVERSY AND CONFUSION ABOUT PREEMPTIVE ANALGESIA

The issue of how best to define, evaluate, and administer preemptive analgesia has led to much controversy and confusion, and even to scientific fraud.[38] Debate over the appropriate definition of preemptive analgesia[2,3,36,39–44] has produced a variety of different terms including preemptive analgesia,[45] preventive analgesia,[1,3] balanced perieemptive analgesia,[46] broad versus narrow preemptive analgesia,[4] protective analgesia,[47] and preemptive antihyperalgesia.[48] Others seem to have ignored the debate and, instead, simply define preemptive analgesia as the administration of analgesics before surgery.[49–51]

Two empirical approaches have dominated the clinical literature.[52] The classic view of preemptive analgesia[45] involves 2 groups of patients who receive identical treatment before or after skin incision or the end of surgery (treatment combination 2 vs 3 and 2 vs 4 in Fig. 1). The only difference between the 2 groups is the timing of administration of the target drug relative to incision, that is, one group receives the target drug before surgery, and the other group, after the incision (e.g., Katz et al.[53,54]) or at the end of surgery (e.g., Dierking et al.[55] and Fagan et al.[56]) (Fig. 2). The inclusion of a postincisional or postsurgical treatment control group is methodologically appealing, because in the event of a significant between-group difference in pain and/or analgesic consumption in favor of the presurgery group, it provides a window of time within which the observed outcome(s) was triggered and thus points to possible mechanisms underlying the effect. Despite this advantage, the classic view of preemptive analgesia is too restrictive and narrow,[2,3,20] 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 classic pre- versus postsurgery design (Fig. 2) assumes that the intraoperative nociceptive barrage contributes to a greater extent to postoperative pain than does the postoperative nociceptive barrage. However, this assumption and the corresponding design do not allow for other plausible alternatives. For some surgical procedures, it is conceivable that central sensitization is 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 ectopic neural activity, on the other (i.e., in the preoperative treatment group), which would lead to nonsignificant intergroup differences in pain and analgesic consumption.[57–59]

Two-group studies that fail to find significant differences in postoperative pain (or analgesic consumption) between groups treated before versus after incision, or surgery, are confounded because of the absence of an appropriate control group (e.g., treatment combination 1, 8, or both; Fig. 1). The absence of significant differences in postoperative pain or analgesic consumption between groups may point to the relative efficacy in reducing central sensitization of postincisional or postsurgical blockade, and not to the inefficacy of preoperative blockade (e.g., see Figs. 3 and 4 depicting studies of Katz et al.[57,58] and Gordon et al.,[60] respectively). The results of several studies[57–59] have highlighted the critical importance of including a standard treatment control group. In doing so, they have made it possible to demonstrate reductions in acute postoperative pain,[58,59] morphine consumption,[58] and pain disability 3 weeks after surgery[57] (Fig. 3) that otherwise would have gone undetected using the classic 2-group design (Fig. 3). Inclusion of relevant control conditions also permits the conclusion that although preincisional local anesthetic infiltration is better than postincisional infiltration, the latter condition, nevertheless, results in significantly lower pain intensity scores and analgesic consumption up to 24 hours after surgery than does postincisional saline infiltration.[61] These results raise the important question of how to interpret the many negative studies of preemptive analgesia. Although it is true that negative trials point to the

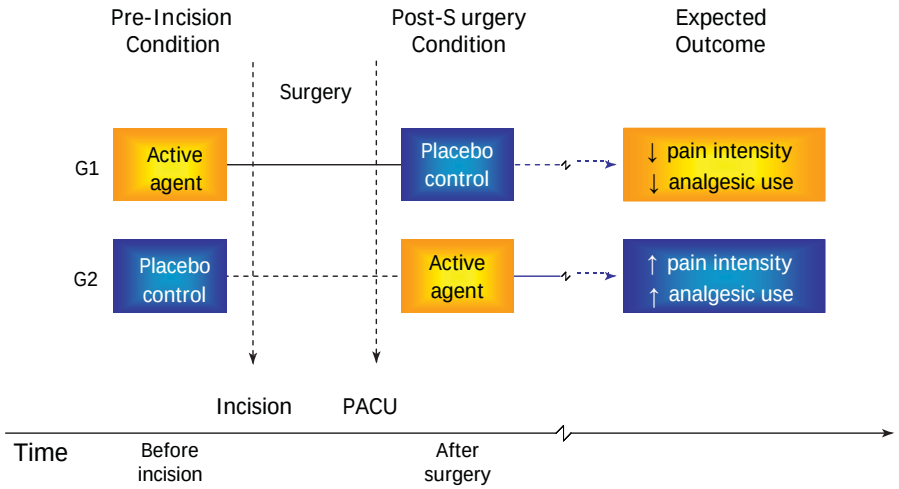

Figure 2. Experimental design showing expected postoperative outcome under the classic view of preemptive analgesia in which a preincisional intervention is compared with the very same intervention initiated after incision (treatment combination 2 vs 3; Fig. 1) or surgery (treatment combination 2 vs 4; Fig. 1). This design was used in the study by Katz et al.,[54] in which 2 groups (G1, G2) of patients undergoing lower abdominal surgery received epidural bupivacaine or saline approximately 40 minutes before and 30 minutes after the incision, respectively. McGill Pain Questionnaire pain ratings in the group that received the preincisional epidural bupivacaine were significantly lower at 24 and 72 hours after surgery and morphine consumption by IV patient-controlled analgesia was significantly lower between 12 and 24 hours after surgery. According to the classic view of preemptive analgesia, the expected outcome shown in the figure is based on the hypothesis that the intraoperative nociceptive barrage contributes to a greater extent to postoperative pain and analgesic use than do postoperative noxious inputs. Fagan et al.[56] compared intraarticular bupivacaine and epinephrine or saline administered 15 minutes before knee arthroscopy with the same treatments administered immediately after surgery. Significant differences in pain or analgesic use were not observed between the 2 groups. The absence of a control group (e.g., treatment combination 1, treatment combination 8, or both in Fig. 1) and lack of pain assessment at later time points raise the possibility that a preventive effect went undetected. PACU = postanesthesia care unit. (Adapted from Katz and Clarke.[37])

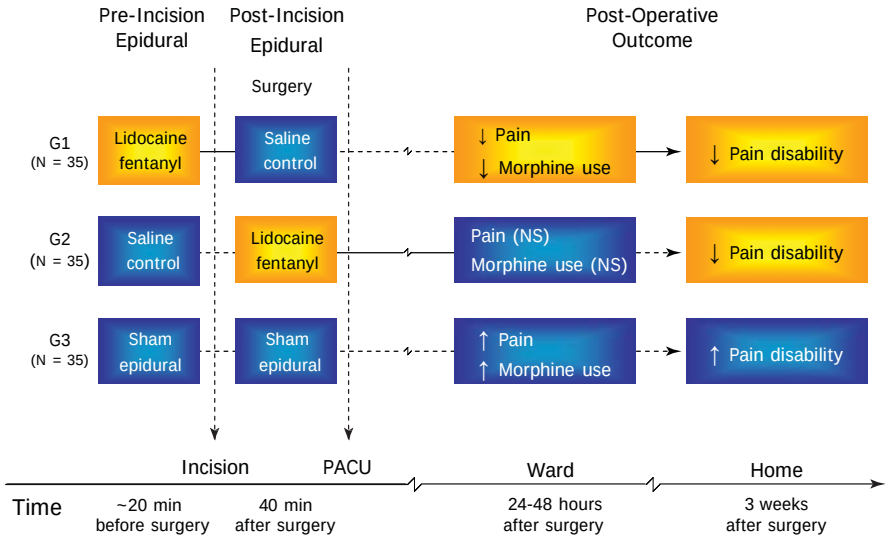

Figure 3. Experimental design (treatment combinations 1 vs 2 vs 3; Fig. 1) used by Katz et al.[57,58] to address the methodological flaw inherent in the classic 2-group studies of preemptive analgesia (e.g., Fig. 2) that have failed to find significant differences in pain/analgesic use. Preincisional (G1) but not postincisional (G2) administration of epidural lidocaine and fentanyl was associated with significantly lower cumulative patient-controlled analgesia morphine consumption at 48 hours after surgery, less-intense movement-evoked pain scores, and reduced hyperalgesia 24 hours after surgery compared with a sham epidural condition (G3).[58] Follow-up at 3 weeks after surgery, but not at 6 months, showed that pain disability ratings were significantly lower in the 2 groups that received epidural lidocaine and fentanyl (G1 and G2) compared with the standard treatment group (G3).[57] These results point to the importance of adding a standard treatment control group to avoid problems of interpretation when 2-group studies do not support the hypothesized outcome. NS = not significant; PACU = postanesthesia care unit (Adapted from Katz and Clarke.[37]).

equivalence of pre- and postsurgical treatments, they cannot address the issue of whether these 2 equivalent treatments differ from not administering treatment or its administration both pre- and postsurgically.

The clinical literature has almost exclusively focused on the narrow view of preemptive analgesia using the 2-group design depicted in Figure 2. This has had the unintended effect of diverting attention away from other clinically

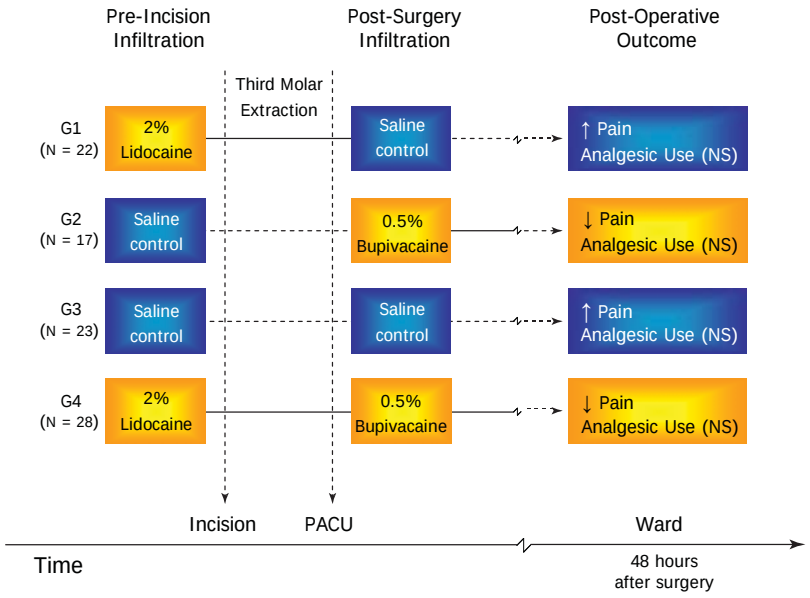

Figure 4. The experimental design used by Gordon et al.[60] to assess the relative effects on late postoperative pain of blocking, or not blocking, noxious intraoperative and/or postoperative inputs (treatment combinations 1 vs 2 vs 4 vs 6; Fig. 1). Patients were randomly assigned in a double-blind manner to receive a local anesthetic (lidocaine or bupivacaine) or saline before and/or at the end of a third molar extraction surgery. Preventive analgesia is demonstrated by the finding that 48 hours after surgery, pain intensity was significantly less in the groups of patients 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 after surgery contributes to a greater extent to central sensitization and late postoperative pain than does the intraoperative nociceptive barrage because the local anesthetic blockade after surgery was more effective than the preoperative blockade. NS = not significant; PACU = postanesthesia care unit. (Adapted from Katz and Clarke.[37])

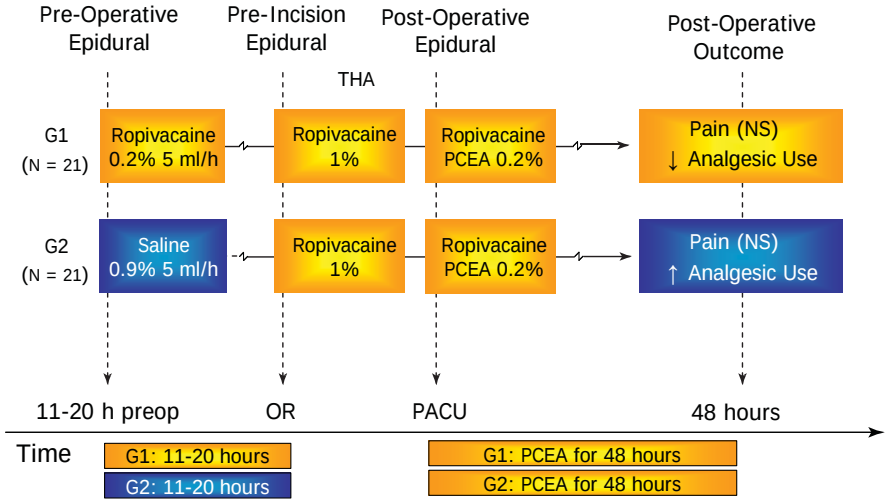

Figure 5. Two-group experimental design used by Klasen et al.,[63] comparing administration of epidural ropivacaine at different times before total hip arthroplasty (THA) surgery. This study examined the effect on postoperative pain and analgesic consumption of blocking versus not blocking preoperative pain for up to 20 hours in the context of effective intraoperative and postoperative epidural blockade in group 1 (G1) and group 2 (G2) (treatment combination 7 vs 8 in Fig. 1). The results show that in G1, relief of preoperative pain using epidural ropivacaine was associated with lower patient-controlled epidural analgesia (PCEA) consumption and fewer PCEA demands 48 hours after surgery compared with preoperative epidural saline in G2. NS = not significantly different between G1 and G2; OR = operating room; PACU = postanesthesia care unit. (Adapted from Katz and Clarke.[37])

significant findings because they do not conform to what has become the accepted definition of preemptive analgesia.[1] For example, some studies[62,63] have examined differences in timing of administration of analgesics as described above for the classic 2-group design, except that the aim is not to compare pre- versus postincisional or postsurgical treatments. Instead, both groups may receive the target intervention before surgery, differing only in how long before surgery the treatment is administered.[63] As shown in Figure 5, Klasen et al.[63] evaluated the effect on postoperative pain and analgesic consumption of blocking (for approximately 12 hours before surgery) versus not blocking preoperative pain in the context of intraoperative and postoperative epidural blockade and demonstrated that relief of preoperative pain is associated with reduced analgesic use 48 hours after surgery. Others[60] have shown that blocking the peripheral nociceptive barrage in the hours after surgery decreases pain at later time periods, whereas blocking the intraoperative nociceptive barrage does not (Fig. 4), suggesting that in these cases, postoperative factors contribute to a greater extent to the outcomes than intraoperative factors. Such studies highlight the shortcoming of the classic view of preemptive analgesia. They have provided the rationale and impetus for a broader conceptualization of blocking afferent injury–related inputs across the 3 perioperative phases, to move the field of preemptive analgesia beyond the state of confusion that has arisen. It is interesting to note that when Wall first introduced the term "preemptive preoperative analgesia," he did so with specific reference to 3 clinical studies,[64–66] none of which used the classic 2-group design that has since dominated the field.

PREVENTIVE ANALGESIA

A more encompassing approach, termed "preventive analgesia,"[1,3] 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 are reduced relative to another treatment, a placebo treatment, or to no treatment, as long as the effect is observed at a point in time that exceeds the clinical duration of action of the target drug (e.g., treatment combinations 1 vs 2, or 1 vs 5, or 1 vs 8; Fig. 1). The requirement that the reduced pain

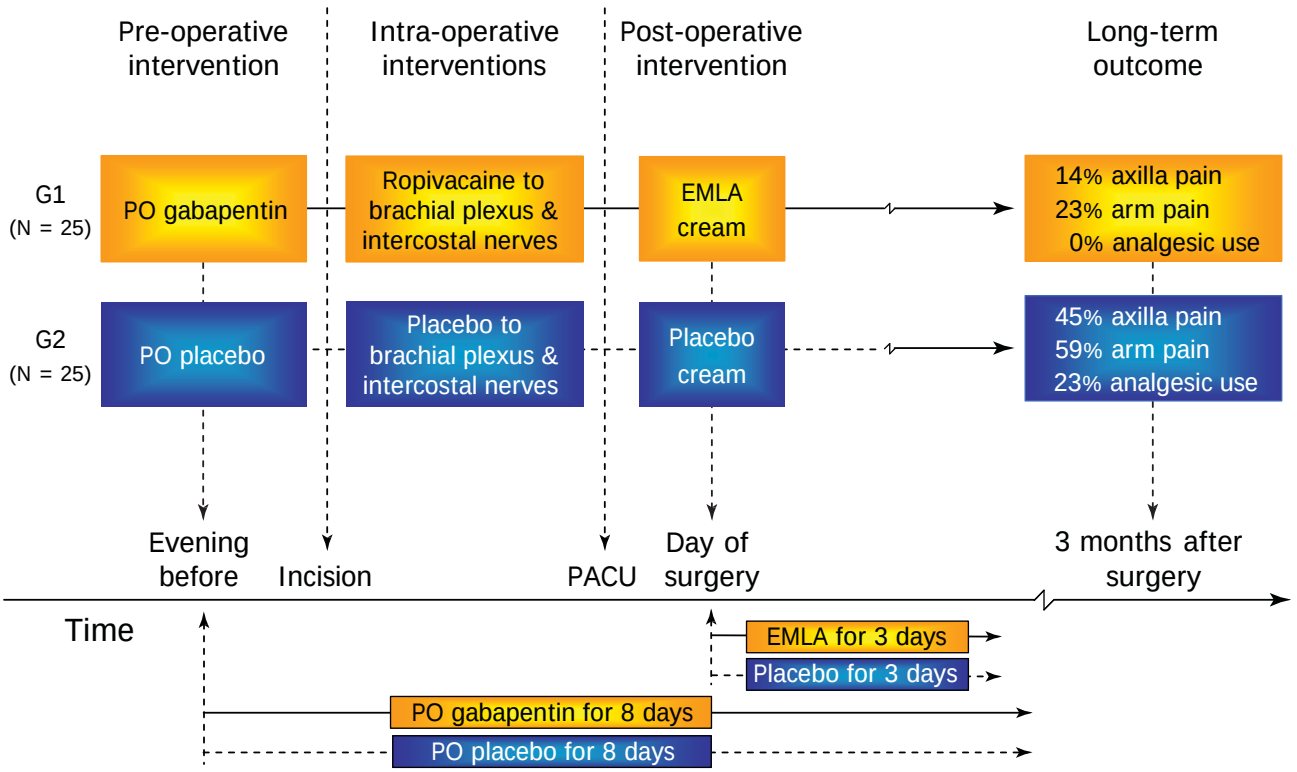

Figure 6. Experimental design used by Fassoulaki et al.,[67] comparing multiple treatments versus placebo control conditions across the 3 perioperative phases (treatment combination 1 vs 8 in Fig. 1). Preventive analgesia is demonstrated if the active treatment group shows lower pain scores and/or less analgesic consumption than the placebo control group beyond the duration of action of the target analgesics administered. Fassoulaki et al.[67] examined the preventive effect of oral (PO) gabapentin, local anesthetic infiltration, and a local anesthetic cream (EMLA) versus placebo in women undergoing breast cancer surgery. The treatment group showed a significantly lower incidence of pain as well as lower analgesic consumption 3 months but not 6 months after surgery. PACU = postanesthesia care unit. (Adapted with permission from Katz and Seltzer.[33])

and/or analgesic consumption be observed after the duration of action of the target drug ensures that the preventive effect is not simply an analgesic effect. As we have previously indicated,[1,2,20] such a design does not provide information about the factors underlying the effect or the timeframe within which the effect occurred because of the absence of a posttreatment condition (Fig. 6 illustrates the study by Fassoulaki et al.,[67] who used treatment combination 1 vs 8). Moreover, a major drawback to not having a postincisional or postsurgical control group is the requirement to know that the observed effect (i.e., less pain and/or less analgesic use) has occurred after the duration of action of the target drug. Otherwise, the observed effect may be an analgesic effect (i.e., attributable to the drug's action) and not a preventive effect (e.g., resulting in a prolonged reduction in central sensitization or its complete prevention). We have adopted the accepted criterion of >5.5 half lives of the target drug as a cutoff for determining when the drug is no longer pharmacologically active.[37,68] However, this is not a concern for studies that evaluate the effects of preventive analgesia on persistent postsurgical pain measured weeks and months after the target drug was last administered.

Demonstration of a preventive effect does not require that an intervention be initiated before surgery; the onset of treatment may be during the procedure (e.g., treatment combination 1 vs 3; Fig. 1) or even after surgery (e.g., treatment combination 1 vs 4; Fig. 1). For example, a preventive effect is present if, when compared with the effect of a placebo treatment, a target analgesic drug administered postoperatively reduces postoperative pain or analgesic consumption for a period of time that outlasts the direct pharmacological effects of the target drug (Fig. 7 illustrates the study by Blumenthal et al.[69]). The Blumenthal et al.[69] study and others[70,71] similar to it indicate that preventive analgesia can be achieved even when the analgesic intervention is started after incision and bone graft harvest (i.e., even when the intraoperative peripheral nociceptive injury barrage is not blocked).

In fact, any 2 or more treatment combinations in Figure 1 can produce preventive effects, and the classic 2-group design used to evaluate preemptive analgesia is one of many possible ways to minimize postoperative pain. The focus of preventive analgesia is not necessarily 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 analgesic requirements. A preventive analgesic effect involves demonstrating reduced pain and/or analgesic use beyond the clinical duration of action of the target drug relative to an acceptable control condition.

Whereas earlier studies of preemptive analgesia were for the most part focused on evaluating the short-term

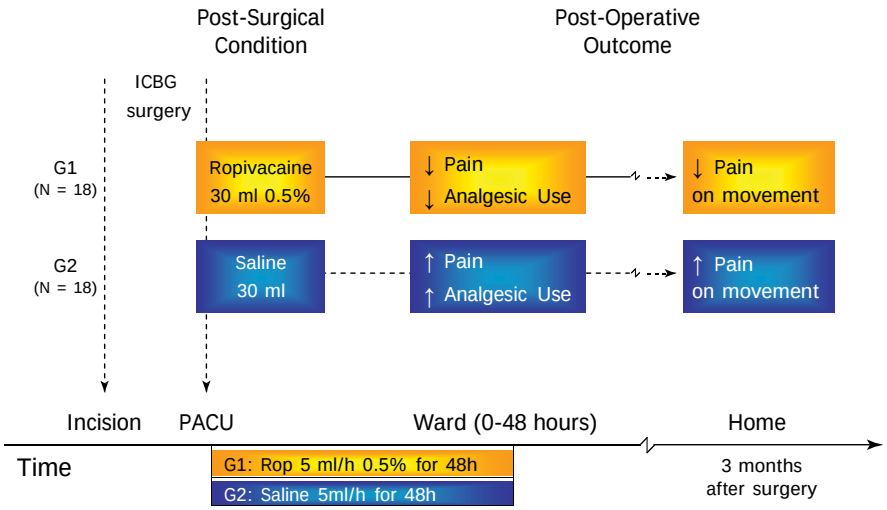

Figure 7. Experimental design comparing a postincisional analgesic intervention group (G1) with a placebo control group (G2) (treatment combination 1 vs 4 in Fig. 1). Preventive analgesia is demonstrated if the postincisional group shows less pain and/or analgesic consumption than the control group beyond the pharmacological duration of action of the target analgesic. This design was used by Blumenthal et al.,[69] who showed that a bolus of ropivacaine versus saline followed by a 48-hour infusion of ropivacaine versus saline administered into the iliac crest bone graft (ICBG) harvest site reduced acute pain and morphine consumption for the duration of the blockade. A preventive analgesic effect was demonstrated 3 months after surgery when the ropivacaine-treated group reported significantly lower pain scores on movement (but not at rest). This study illustrates that preventive analgesia can be achieved even when the analgesic intervention is started after the incision and bone graft harvest (i.e., when the afferent injury barrage during surgery was not blocked). PACU = postanesthesia care unit.

effects of pre- versus postsurgical treatment in the traditional acute pain period, the aim of more recent studies of preventive analgesia is on demonstrating longer-term effects. Two recent studies[72,73] show that perioperative administration of pregabalin reduces pain in the months after surgery. Pregabalin modulates neurotransmitter release in nociceptive pathways by changing the intrinsic activation/inactivation properties of voltage-dependent CaV2.1 calcium channels via binding to their a_2o subunit.[74] Burke and Shorten[72] found that perioperative pregabalin administration was associated with less pain intensity and improved functional outcomes 3 months after lumbar discectomy. Similarly, Buvanendran et al.[73] demonstrated that patients given a regimen of pregabalin started preoperatively, maintained throughout the perioperative hospital stay, and continued for 2 weeks after total knee arthroplasty had a reduced incidence of chronic neuropathic pain at the 3- and 6-month postsurgical follow-ups. Both studies are examples of trials that reported outcomes well beyond the 5.5 half lives of the target medications ensuring that the demonstrated long-term effects were not direct analgesic effects.

Although other studies[75–82] also suggest that preventive analgesia may be effective in reducing the incidence and intensity of chronic postsurgical pain, for the most part, this literature is equivocal. A careful examination of these studies raises several related issues that we must address:

1. The results show significant reduction in the incidence and/or mean intensity of long-term pain problems in some cases. However, a preventive analgesic approach does not work for everyone and, at present, we do not know for whom such an approach is effective. One might assume that the mechanisms underlying such interindividual differences in efficacy of preventive analgesia are controlled genetically, and epigenetically through individual experiences that may begin in utero and accumulate over time (e.g., early postnatal painful experiences, diet, lifestyle, and culture).[83,84] When these determinants are identified, it might be possible to extend the efficacy of preventive analgesia for certain individuals.
2. We do not understand the mechanism(s) by which chronic postsurgical pain is reduced when preventive analgesia is effective. The typical explanation for the prolonged effect is that the drug(s) prevented (obtunded) peripheral and/or central sensitization and thereby reduced long-term pain. However, there really is very little good clinical evidence that this is in fact the case because we do not have accurate measures of sensitization in humans, and even if we did, this still would not indicate that reduction in sensitization is responsible for the long-term reductions in pain incidence and/or intensity. The longer the time from the administration of the analgesic drug(s), the greater is the probability that other factors contribute to the long-term effects. For example, in discussing the effectiveness of perioperative epidural analgesia versus a sham epidural in reducing pain disability scores, but not pain intensity scores, 3 weeks after surgery,[58] Katz and Cohen[57] suggested that the reduced hyperalgesia and rate of morphine consumption within the first 2 days after surgery afforded the epidural groups a "head start" in terms of comfort level and recovery compared with the sham epidural group, possibly increasing their self-efficacy in dealing with pain or in mobilization. A similar finding has been reported with respect to activity levels 3.5 weeks after radical retropubic prostatectomy.[85] In that study, activity

levels but not pain intensity were significantly higher in patients who had received preemptive epidural bupivacaine or fentanyl. Thus, the mechanisms underlying preventive analgesia are probably more varied than currently acknowledged.

3. We do not know why preventive analgesia fails to work in some patients. One explanation that has not been investigated is that for some patients, the drug dose or the concentration of local anesthetic used simply may not be high enough, or changes in kinetics or dynamics of the drug under investigation may have an impact on the results. This is further complicated by the fact that there is considerable variability across surgical procedures in the nature of intraoperative tissue damage and nerve injury. Thus, various surgical procedures differentially affect variables within the 3 perioperative phases with respect to duration, intensity, and quality of the noxious input. As a result, the same analgesic regimen administered for 2 different procedures could lead to different outcomes and conclusions regarding the viability of preventive analgesia.
4. Another possibility is that preoperative pain interferes with the effectiveness of preventive analgesia, perhaps because central sensitization has already been established.[63,64,86,87] In general, the data indicate that for patients with presurgical pain, preoperative administration of analgesics is not followed by the expected reduction in postoperative pain intensity or analgesic consumption. We know that presurgical pain is a risk factor for the development of acute and chronic postoperative pain[33] but we do not know what aspect of presurgical pain is predictive or whether it is a causal risk factor.
5. Chronic pain is a complex experience that manifests in several major domains, which include sensory-discriminative, affective-aversive, and cognitive-evaluative. Each domain comprises several subdomains; for example, the sensory-discriminative domain consists of pain intensity (ranging from the lowest to the maximal; typical intensity), pain location (felt in the surgical field and/or can spread "extraterritorially" to areas not innervated by injured nerves, or can be felt as "mirror image" pain in the contralateral intact side/limb as well), pain type ("burning," "crushing," "electrical shock-like," etc.), and temporal (episodic or constant; if episodic, the frequency and duration of episodes is essential to document). Similar breakdown into subdomains can be demonstrated for the affective-emotive and cognitive-evaluative dimensions. Moreover, each aspect largely engages unique biochemistry, likely unique genes expressed postinjury/surgery, presenting targets for drugs presumably including those relevant for preventive treatments. However, the main outcome measures in the vast majority of randomized controlled trials are simply pain intensity and/or presence/absence of pain and analgesic use. Although there is some correlation between pain intensity and the aversive-affective aspects of the pain, this correlation is not very strong; pain intensity cannot be taken as the sole variable for the complex experience of postsurgical pain, especially when it has become chronic. It is rare to find a study of preventive analgesia that is more comprehensive in the outcome measures assessed. Of particular relevance to chronic postsurgical pain is the tendency for the anesthesia literature to focus on outcome measures of pain and analgesic use, and the psychological literature to focus on measures of pain disability or pain interference making cross-study comparisons difficult. Recommendations for assessment of core measures and domains in clinical trials[88] include relevant psychological, emotional, and physical variables in addition to those routinely assessed (i.e., pain and analgesic use). Assessment of additional domains of function 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]

FUTURE DIRECTIONS

Effective prevention of postoperative pain and its transition to chronicity involves identifying the precise mechanisms that underlie the relationship between pain at time one (e.g., preoperative pain or acute postoperative pain) and pain at time two (e.g., pain 1 year after surgery). As discussed above, and as depicted in Figure 8, the idea that pain is in some way imprinted into the central nervous system or is maintained by a state of central sensitization has provided the impetus for efforts to halt the transition to chronicity by blocking noxious perioperative impulses from reaching the central nervous system using a preemptive or preventive pharmacological approach. This approach assumes that preexisting pain, the intraoperative nociceptive barrage, and acute postoperative pain are causal risk factors in the transition to chronicity. However, if the relationship between perioperative pain and the development of chronic postsurgical pain is merely associative (i.e., noncausal), and both perioperative pain and chronic pain are caused by other factors, then no type, amount, or duration of pharmacological blockade will prevent the development of chronic postsurgical pain. One of the aims of future research is to identify the causal, modifiable, and nonmodifiable risk factors that contribute to the development of chronic postsurgical pain.

Under certain circumstances, perioperative administration of opioid analgesics may contribute to the establishment of acute opioid tolerance[89] and opioid-induced hyperalgesia.[90,91] The mechanisms underlying the reduced pain and opioid consumption arising from perioperative administration of opioids, and the increased pain and opioid consumption underlying acute opioid tolerance and opioid-induced hyperalgesia, involve competing processes associated with the NMDA-R ion channel complex. These findings have important implications for evaluating preventive analgesia when opioid analgesics are administered because the main outcome measures (pain and opioid consumption) will be directly affected by the mechanisms underlying these competing neural processes. The net effect of

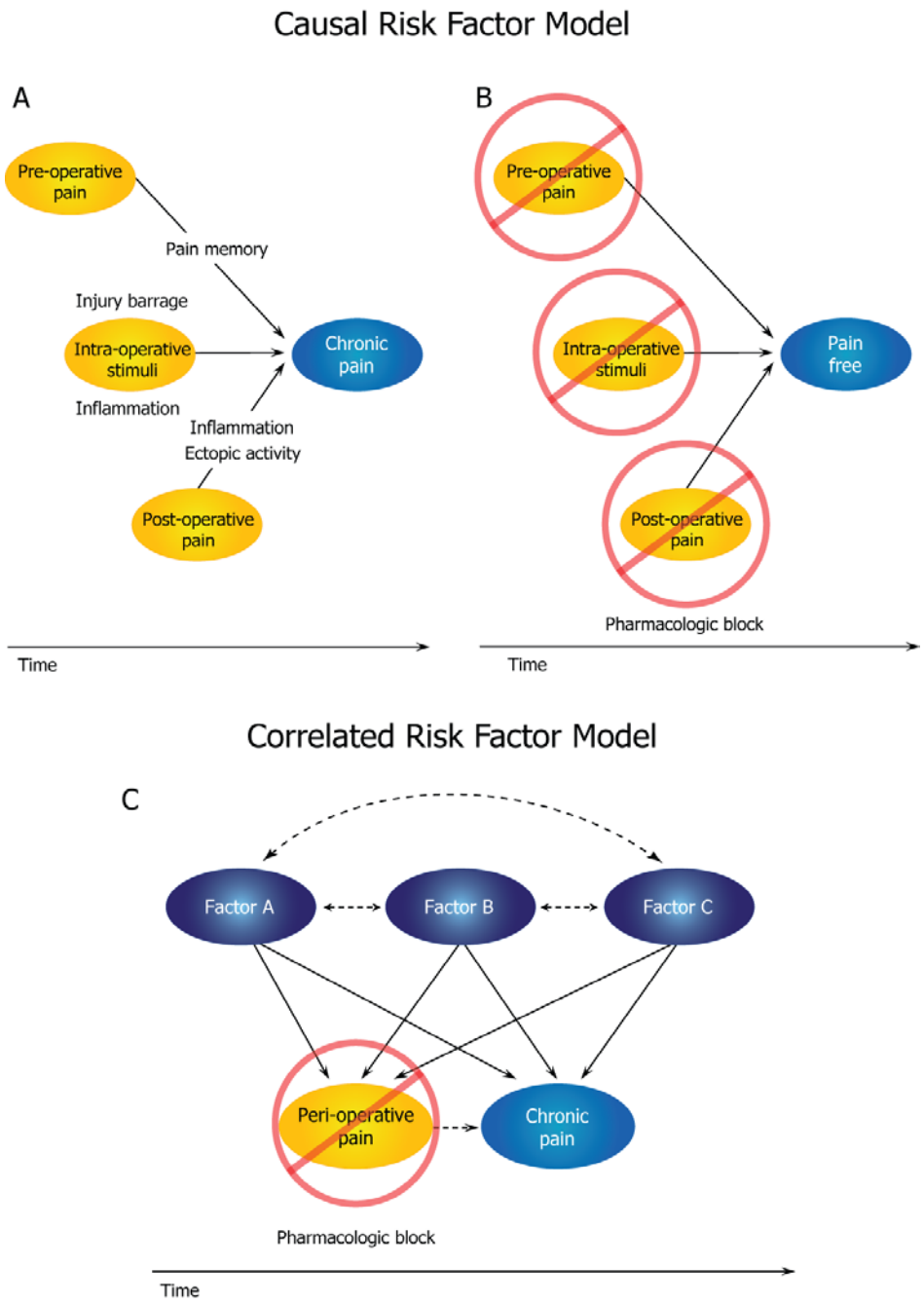

Figure 8. Schematic illustrating causal (top) and correlated (bottom) risk factor models predicting the prevention and non-prevention of chronic postsurgical pain by pharmacological blockade at various times across the perioperative period. Top, Transition to chronicity (A) may be prevented by pharmacological blockade of preoperative pain, intraoperative nociceptive barrage, and/or acute postoperative pain (B) assuming the former causes the latter. Bottom (C), Transition to chronicity will not be prevented if the relationship between these perioperative factors and the development of chronic pain is associative (i.e., noncausal) and, instead, the development of chronic pain is caused by one or more other factors that are not affected by perioperative pharmacological blockade. Solid lines between variables indicate a causal relationship. Dashed lines between variables indicate correlation, but not causality. Not shown is a dual risk factor model in which some variables linking perioperative pain/noxious stimuli and chronic postsurgical pain are causal risk factors and others are correlated risk factors. (Adapted with permission from Katz and Seltzer.[33])

this competition is to attenuate (or even reverse) the preventive analgesic effects. Coadministration of opioids and low-dose NMDA antagonists or low-dose opioid antagonists in rodents has been found to interfere with the development of acute opioid tolerance[92,93] and opioid-induced hyperalgesia.[94] Combined administration of these drugs would be expected to improve pain relief and reduce opioid consumption in patients undergoing major surgery.[95,96]

Given the importance of psychosocial factors in chronic pain[97] and recommendations for assessment of core outcome measures in clinical trials,[88] appropriate psychological, emotional, and physical variables should be measured before and after surgery when conducting studies of preventive analgesia. Inclusion of relevant domains of functioning may help in the search for causal risk and protective factors of severe acute postoperative pain, the processes involved in recovery from surgery, and for the development of chronic postsurgical pain.[33,98]

Finally, pain genetics is a promising new research field that has lagged behind the study of other human diseases. We now have powerful genetic assays to identify genes controlling the interindividual variability in developing acute and chronic postsurgical pain as well as the variance in the efficacy of preventive analgesia. However, identification of relevant genes cannot advance without the availability of cohorts for study, comprising DNA samples of individuals with a comprehensive characterization of their acute and chronic postsurgical pain phenotypes, response to preventive analgesia, previous life experiences with pain, and a detailed medical case history. There are currently no such cohorts available for study, although the genetic methodologies are at hand. As we move forward, it

will be essential to create multicenter research teams to collect such cohorts, have them genotyped in a genome-wide screen that uses a dense panel of genetic markers, and validate the findings in an independent replication cohort that uses identical phenotypes. Successfully identified targets could then be offered to the pharmacogenetic industry as a basis for research and development of the next generation of chronic pain-preventing drugs.

DISCLOSURES

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