A Qualitative Systematic Review of the Role of *N*-Methyl-D-Aspartate Receptor Antagonists in Preventive Analgesia

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We evaluated in a qualitative systematic review the effect of *N*-methyl-D-aspartate (NMDA) receptor antagonists on reducing postoperative pain and analgesic consumption beyond the clinical duration of action of the target drug (preventive analgesia). Randomized trials examining the use of an NMDA antagonist in the perioperative period were sought by using a MEDLINE (1966–2003) and EMBASE (1985–2003) search. Reference sections of relevant articles were reviewed, and additional articles were obtained if they evaluated postoperative analgesia after the administration of NMDA antagonists. The primary outcome was a reduction in pain, analgesic consumption, or both in a time period beyond five half-lives of the drug under examination. Secondary outcomes included time to first analgesic request and adverse effects. Forty articles met the inclusion criteria (24 ketamine, 12 dextromethorphan, and 4 magnesium). The evidence in favor of preventive analgesia was strongest in the case of dextromethorphan and ketamine, with 67% and 58%, respectively, of studies demonstrating a reduction in pain, analgesic consumption, or both beyond the clinical duration of action of the drug concerned. None of the four studies examining magnesium demonstrated preventive analgesia.

The *N*-methyl-D-aspartate (NMDA) receptor is an excitatory amino acid receptor that has been implicated in the modulation of prolonged pain states in animal models (1). NMDA antagonists, such as ketamine and dextromethorphan, have been shown to be useful in the reduction of acute postoperative pain, analgesic consumption, or both when they are added to more conventional means of providing analgesia, such as opioids and nonsteroidal antiinflammatory drugs, in the perioperative period (1,2).

Intraoperative and postoperative noxious inputs may cause central sensitization, but analgesic interventions given before the noxious stimulus may attenuate or block sensitization and, hence, reduce acute pain (3). The concept of preemptive analgesia was initially put forward by Crile (4) and then by Wall (3), who suggested that the administration of opioids or local anesthetics before surgery might reduce the C-fiber-induced injury barrage associated with incision and, thereby, the intensity of postoperative pain. This first definition of preemptive analgesia did not include the imperative to compare a preoperative intervention with a postoperative intervention. This requirement, adopted shortly thereafter (5), imposed a constraint that limited the demonstration of preemptive analgesia to experimental designs with less potential for clinically significant effects. The evidence in support of preemptive analgesia by this strictest of definitions has been equivocal, and a recent systematic review of the literature examining the role of preemptive analgesia and the role of timing of analgesia demonstrated no overall benefit of this concept (6).

However, since the introduction of the term *preemptive analgesia* into the pain and anesthesia literature, the concept has evolved. The previously held belief that it was the surgical incision that triggered central sensitization has been expanded to include the sensitizing effects of preoperative noxious inputs and pain, as well as other noxious intraoperative and postoperative stimuli. This would suggest that the previous definition of preemptive analgesia is too restrictive (7),

Joel Katz is supported by a Canada Research Chair in Health Psychology at York University, Toronto, ON, Canada.

because an analgesic intervention given after surgical incision (e.g., during or after surgery) may also reduce central sensitization and thus decrease postoperative pain intensity. We can evaluate this possibility only by adding a control group that does not receive the analgesic intervention, a group that receives the intervention before and after surgery, or both groups. Unfortunately, many negative studies examining for a preemptive analgesic effect do not include appropriate control groups and hence may be missing an important effect.

The term *preventive analgesia* (8) was introduced to emphasize the fact that central sensitization is induced by noxious preoperative and postoperative inputs and has been used to describe a reduction in postoperative pain intensity, analgesic use, or both beyond the clinical duration of action of the target preventive drug (9,10). Thus, in the absence of a postincisional intervention, the finding that pain or analgesic consumption is reduced beyond the pharmacological duration of action relative to an untreated or placebo control condition is evidence of a preventive analgesic effect. Thus, the aim of preventive analgesia is to reduce central sensitization that arises from noxious inputs across the entire perioperative period and not just from those brought about by incision. The concept of preventive analgesia, therefore, has greater clinical relevance than does preemptive analgesia (8,10).

Although many drugs have demonstrated evidence of preventive analgesic benefit (9), treatments that are likely to prevent the development of central excitability may have the greatest benefit. Because antagonists at the NMDA receptor have potential for attenuating central sensitization, we conducted a systematic review of the literature to determine the extent to which NMDA antagonists have yielded preventive analgesic effects when given during the perioperative period.

Methods

We systematically conducted a search of the MEDLINE and EMBASE databases from 1966 to April 2003 (MEDLINE) and from 1985 to April 2003 (EMBASE) by using the following key words and limiting the search strategy to English language reports in humans: "pre-emptive analgesia" or "preemptive analgesia," "pre-operative," "preoperative," "post-operative," "postoperative," "pre-incision," "preincision," "post-incision," "postincision," and "timing." These key words were then cross-referenced with the following: NMDA, ketamine, memantine, amantadine, dextromethorphan, magnesium, and methadone. Reference sections of relevant articles were reviewed, and additional articles were obtained if they evaluated postoperative analgesia after the administration of NMDA antagonists. Authors were not contacted for original data.

The criteria for assessing the quality of reports as described by Jadad et al. (11) were used, and the quality score was recorded. Studies without randomization and blinding were excluded. Therefore, the minimum score of an included study was 2, and the maximum score was 5. In addition to a randomized protocol and double-blinded assessment of pain and analgesic use, studies also had to include a report of pain or hyperalgesia by using a reliable and valid measure (e.g., visual analog scale, numeric rating scale, verbal descriptor scale, quantitative sensory testing, or pressure algometry), a report of analgesic consumption, and, for studies that assessed the effect of timing according to the definition of preventive analgesia, consumption of analgesics reported at a point in time that exceeded the duration of action of the target drug whose effect on postoperative pain was being examined. For the purposes of this review, a point in time equivalent to five half-lives of the drug under examination was taken as exceeding the clinical duration of action of the drug. This criterion, although stringent, was chosen to ensure that observed effects were not simply direct analgesic effects of residual drug. The stated half-life of each drug was determined and found to be 3 h for ketamine (12), 2–4 h for dextromethorphan (13), 20 h for methadone (14), and 5 h for ionized magnesium (15). The final criterion was the absence of methodological problems that render results ambiguous and make interpretation difficult.

A preventive analgesic effect was confirmed if pain, analgesic consumption, or both were significantly reduced ($P < 0.05$) five half-lives beyond the administration of the NMDA antagonist under examination or

Table 1. Excluded Studies by Criteria

Criteria not fulfilled	No. Studies	References
Inadequate blinding	6	16–21
No control group	11	22–32
Not randomized	9	33–41
No preventive analysis possible beyond five half-lives	53	42–94
Inadequate pain measure	9	95–103
Case report	2	104, 105
Not perioperative	4	106–109
Negative preemptive study with no placebo control	2	110, 111

Table 2. Study Quality Score by Drug and Positive or Negative Outcome

Drug	Positive studies[a]	Negative studies[a]	*P* value
Ketamine	3.5 (2–5)	4 (2–4)	0.7
Dextromethorphan	3.5 (2–5)	4.5 (4–5)	0.8
Magnesium	NA	4 (3–5)	NA

NA = not applicable.
[a] Median (range).

if the first analgesic request occurred beyond five half-lives of the drug concerned, and if it was significantly longer than that in the control group ($P < 0.05$). Positive preemptive analgesic studies in which pain, analgesic consumption, or both were reduced in a preincisional group in relation to a postincisional group and placebo control were also included. However, negative preemptive studies that did not include a placebo control group were excluded, because it could not be determined whether a preventive analgesic effect had occurred (both preincisional and postincisional groups may have received analgesic benefit, and these groups could not be contrasted with a placebo control group).

Differences in study quality (11) were analyzed with the Mann-Whitney *U*-test by using SPSS for Windows Version 9.0 (SPSS Inc., Chicago, IL). $P < 0.05$ was considered significant.

Results

The MEDLINE and EMBASE searches identified 136 articles that examined the use of an NMDA antagonist for perioperative pain management. Forty studies fulfilled the inclusion criteria outlined previously. Ninety-six studies were excluded. The most frequent reason for exclusion ($n = 53$ studies) was the failure to design the study to test for a preventive analgesic effect (i.e., absence of pain and/or analgesic data beyond five half-lives of the drug). Two studies were excluded because they were negative preemptive studies with no placebo control group. Two were case reports, 4 did not examine a surgical population, and 35 were excluded because of methodological flaws. Table 1 [[16–20,21–25,26–36,37–50,51–61,62–75,76–86,87–100,101–111]]lists the studies that were excluded from the review and shows which of the inclusion criteria were not met.

Of the included studies, 24 examined the use of ketamine (112–135), 12 examined dextromethorphan (136–147), and 4 examined magnesium (148–151). A total of 2034 patients were studied, and the number of patients in the studies ranged from a minimum of 18 in a study using a crossover design (133) to a maximum of 121 patients in the largest randomized controlled trial (112). Study quality across the positive and negative studies for each drug is presented in Table 2. There were no significant differences in study quality between studies that found positive or negative outcomes for each drug.

Quantitative analysis of the degree of analgesic benefit was not performed because of the variability of consistency of reporting of numerical pain and analgesic consumption data. Thirty-six (90%) of 40 studies presented data in tables together with significance levels (*P* values) or in other formats that allowed for assessment of the degree of benefit but did not allow for quantitative analysis. Instead, data have been presented in table format for each drug, as performed for other recent qualitative systematic reviews (152).

Twenty-four studies examined ketamine (Table 3), and 14 (58%) demonstrated a positive preemptive or preventive analgesic effect. Three studies used a preemptive design (113,115,134), and 21 studies used a preventive design. Of the 10 negative studies, 6 did not demonstrate any direct analgesic effect of the intervention. Patients enrolled in these studies underwent a variety of surgical procedures, including ambulatory and major inpatient surgery, and doses ranged from 0.15 to 1 mg/kg. There was no obvious effect of surgical type on the success of the preventive intervention, and success did not depend on the dose administered.

Ketamine was administered IV in nine positive studies and seven negative studies, epidurally or intrathecally in four positive and three negative studies, and subcutaneously in one positive study. Most studies (both positive and negative) coadministered opioids with ketamine. However, in two positive studies, an analgesic benefit was demonstrated with the NMDA antagonist alone (without coadministered opioid) (116,121).

Twenty of 24 studies documented evaluation of adverse effects, including psychomimetic effects. Twelve studies documented no adverse effects. Seven studies documented adverse effects but found no difference between treatment and control groups. One study documented psychomimetic effects related to epidural ketamine 20 mg (120).

Twelve studies examined the use of dextromethorphan (Table 4), and eight (67%) demonstrated evidence of a preemptive or preventive analgesic effect. Three studies used a preemptive (136,138,145) and nine studies used a preventive design. Of the four negative studies, two (141,142) did not demonstrate any direct effect of the analgesic intervention.

Both positive and negative studies used a variety of major and minor surgical procedures, and the success of the preventive intervention did not appear to be associated with the type of surgery. Dosages varied from 0.5 mg/kg to 150 mg and did not appear to be associated with the success of the intervention. Two of the studies in the negative group (141,142) used a smaller dose by the oral route that was not associated with a direct analgesic effect. Positive studies used both oral (four studies) and IV or IM routes, whereas all four negative studies used the oral route.

All but one study coadministered an opioid for analgesia, and therefore preventive analgesia may have been related to a reduction in opioid tolerance in many studies. One study (147) that did not use a coadministered opioid demonstrated a direct analgesic effect of the dextromethorphan itself.

Table 3. Studies Examining Ketamine That Met Inclusion Criteria

Study	Quality score (0–5)	No. Patients/procedure	Co-admin opioid	Groups (treatment combination)
Aida (112)	4	121/distal or total gastrectomy	Yes	Pre-med hydroxyzine 1 mg/kg + atropine 0.01 mg/kg GA plus: G1: MORep G2: KET IV G3: COMB G4: control
Choe (113)	3	60/subtotal gastrectomy	Yes	GA plus epidural; G1: Morph + KET pre-ind G2: Morph + KET intra-op
Menigaux (123)	4	45/arthroscopic ACL repair	Yes	Pre-med oral hydroxyzine 100 mg 1–2 h pre-op GA plus: G1: pre-inc; KET + saline G2: Post-inc; Saline + KET Control group: saline + saline
Tverskoy (133)	3	18/unilateral & bilateral herniorrhaphy	Yes	GA plus: bilateral repair—Bupiv + KET & Bupiv Unilateral repair—Bupiv + KET or Bupiv
Fu (115)	3	40/abdominal surgery	Yes	Midazolam 0.05 mg/kg at induction GA plus KET; Pre-inc bolus + infusion Post-inc bolus only
Wong (134)	2	45/total knee replacement	Yes	Pre-med diazepam 5 mg IV Group G: GA + post-inc intervention Group EB: epidural + pre-inc intervention Group EA: epidural + post-inc intervention
Himmelseher (116)	5	37/unilateral total knee arthroplasty	No	Midazolam 3.75–7.5 mg oral pre-med 1 h pre-op G1: epidural Ropiv + S(+)-KET & sedation G2: epidural Ropiv + saline & sedation
Menigaux (124)	5	50/arthroscopic meniscal surgery	Yes	Hydroxyzine 100 mg oral pre-med, 1–2 h pre-op GA TCI propofol plus; G1: KET G2: control
Mortero (125)	3	39/day surgery	Yes	Midazolam 1–3 mg IV pre-med + fentanyl 50 μg IV Infusion of study drug during surgery: G1: propofol alone G2: propofol + KET 0.98 mg/mL
Stubhaug (129)	5	20/nephrectomy	Yes	GA + bolus study drug followed by 48-h infusion G1: KET: 0.5 mg/kg bolus + 2 mg · kg^{-1} · min^{-1} for 24 h then 1 mg · kg^{-1} · min^{-1} up to 48 h G2: placebo: saline bolus + infusion only

Table 3. *(Continued)*

Route/dose/timing	Systemic analgesic	Direct analgesic effect	Preventive/preemptive analysis[a]
IV KET bolus 1 mg/kg 10 min pre-inc + infusion at 0.5 mg · kg^{-1} · h^{-1} until skin closure Epidural morphine bolus 0.06 mg/kg 40 min pre-inc + infusion at 0.02 mg · kg^{-1} · h^{-1} until skin closure. MORep: MORep only KET IV: KET IV only COMB: both MORep & KET IV Control: saline epidural and IV bolus + infusion	Naloxone 0.008 mg/kg IV at end of surgery Post-op PCA morphine	Yes	Preventive effect; lowest VAS & Analg. Req. over 48 h with combination of MORep & IV KET COMB < KET IV < MORep < control Significant difference in VAS & Analg. Req. over 48 h
Epidural injection G1: KET 60 mg + morphine 2 mg pre-ind of GA & 8 mL of saline intra-op after removal of specimen G2: 8 mL of saline pre-ind of GA & KET 60 mg + morphine 2 mg intra-op after removal of specimen	Post-op epidural Bupiv 0.25% 8 mL + 2 mg morphine	Yes	Preemptive effect; more supplemental analgesia required in G2 versus G1; duration of analgesia G1 > G2
IV bolus injections; 10 min after induction, before inflation of tourniquet, and at end of surgery Pre-inc: KET 0.15 mg/kg at induction & saline at end of surgery Post-inc: saline at induction & KET 0.15 mg/kg at end of surgery Control: saline both at induction and end of surgery	Sufentanil 0.2 g/kg + 0.25 mg · kg^{-1} · min^{-1} post-op PCA morphine	Yes	Preventive effect; significant difference in Analg. Req. over 24 & 48 h Control > Pre-inc = Post-inc; no significant difference in VAS
10 mL wound infiltration at end of surgery Bilateral—one side Bupiv 0.5% + KET 0.3% & other side Bupiv alone Unilateral—cases randomized to receive either Bupiv 0.5% + KET 0.3% or Bupiv 0.5% alone	Post-op dipyrone 0.5 g PO meperidine 25 mg IM	Yes	Peripheral preventive effect; in patients with bilateral repair pain threshold level increased with addition of KET to Bupiv compared with contralateral side
IV KET bolus 0.5 mg/kg + infusion 10 mg · kg^{-1} · min^{-1} Pre-inc: bolus at induction + infusion started & discontinued at wound closure Post-inc: bolus at wound closure only	No intra-op opioids; post-op PCA morphine	Yes	Preemptive effect; significant difference in Analg. Req. over 48 h; Post-inc > Pre-inc; no significant difference in VAS
Group G: GA plus pre-inc epidural saline 15 mL, intra-op epidural saline 10 mL + morphine 1.5 mg + KET 20 mg 30 min after skin incision Group EB: epidural lidocaine 2% 15 mL & morphine 1.5 mg + KET 20 mg 30 min pre-inc Group EA: pre-inc epidural lidocaine 2% 15 mL & morphine 1.5 mg + KET 20 mg 30 min post-inc	Post-op PCA morphine & 10 mL epidural bolus of lidocaine 0.32% + morphine 1 mg + KET 10 mg every 12 h for 72 h	Yes	Preemptive effect Group EB: epidural + pre-inc intervention—least Analg. Req. and lowest VAS at 12 & 72 h Group EB < Group EA < Group G
Intra-op sedation with IV propofol or midazolam in all cases Bolus Ropiv 45 min pre-op Intervention 10 min pre-inc Epidural block dermatome >T12 G1: Ropiv 1% 10–20 mL epidural bolus + S(+)-KET 0.25 mg/kg G2: Ropiv 1% 10–20 mL epidural bolus + saline	Post-op PCEA Ropiv rescue analgesia; diclofenac 50–100 mg or acetaminophen 0.5–1 g PR followed by metamizol 1–2 g IV persistent pain; Ropiv epidural bolus or infusion Piritramide 1.5–7.5 mg SC/IV or IV PCA	Yes	Preventive effect; Analg. Req. (PCEA Ropiv) & VAS at 24 & 48 h G2 > G1 Time to first analgesia, sensory block similar Analg. Req. NSAIDs & opioids G1 = G2
GA TCI propofol intervention; IV bolus just after induction G1: KET 0.15 mg/kg KET diluted in 10 mL of saline G2: control; 10 mL saline	Alfentanil 20 μg/kg IA Bupiv 0.5% + morphine 5 mg at end of arthroscopy Post-op morphine 3 mg every 5 min PRN All patients received naproxen 550 mg on discharge; naproxen 550 mg + acetaminophen 800 mg/ dextropropoxyphene 60 mg every 6 h PRN	Yes	Preventive effect; Analg. Req. & VAS throughout study KET < control
Infusion of study drug pre-op 0.3–0.5 mL · kg^{-1} · min^{-1} Fentanyl 50 μg increments for pain	In PACU: morphine 2 mg IV for VAS > 30 mm Hydrocodone PO for pain after discharge	Yes	Preventive effect; pain and analgesic consumption significantly reduced on Day 3 post-op
Post-ind of GA and pre-inc intervention KET 0.5 mg/kg IV bolus, then 2 mg · kg^{-1} · min^{-1} infusion for 24 h, then 1 mg · kg^{-1} · min^{-1} infusion for 48 h Placebo IV bolus and infusion of identical volumes of saline	PCA morphine for post-op pain	Yes	Preventive effect; significantly reduced area of punctate hyperalgesia in the KET group up to seventh postoperative day and reduced wind-up pain on Day 3

Table 3. *(Continued)*

Study	Quality score (0–5)	No. Patients/procedure	Co-admin opioid	Groups (treatment combination)
Lauretti (121)	3	60/anterior and posterior vaginoplasty	No	IV midazolam pre-med 0.05 mg/kg + study drug
Tverskoy (132)	3	27/TAH	Yes	Midazolam 2 mg IV pre-med GA with; G1: fentanyl G2: KET G3: control
Tanaka (131)	4	66/minor pediatric surgery	Yes	PR pre-med study drug pre-GA; G1: midazolam G2: KET: 5 mg/kg G3: KET: 7 mg/kg G4: KET: 10 mg/kg
Subramaniam (130)	5	40/major upper abdominal surgery	Yes	Pre-med diazepam 10 mg 2 h pre-ind 10 mL epidural study drug G1: MORep G2: KET + MORep
Mathisen (122)	4	60/laparoscopic cholecystectomy	Yes	Pre-ind midazolam 2 mg IV GA plus; PRE: (R)-KET POST: (R)-KET placebo; saline
Papaziogas (126)	4	53/laparoscopic cholecystectomy	Yes	Oral diazepam 0.15 mg/kg 1 h pre-op GA plus; G1: pre-inc placebo G2: pre-inc placebo + Ropiv 0.1% infusion G3: pre-inc KET + Ropiv 0.1% infusion
Jaksch (118)	4	30/arthroscopic ACL repair	Yes	Oral midazolam 7.5 mg pre-med 1 h pre-inc GA plus; KET or saline
Dahl (114)	4	89/TAH	Yes	Midazolam 0.07 mg/kg IM 1 h pre-op GA plus; G1: placebo G2: pre-inc KET G3: KET at skin closure
Kathirvel (119)	3	30/intracavity brachytherapy for carcinoma of cervix	No	Diazepam 0.2 mg/kg PO 2 h pre-op Spinal anesthesia with; Bupiv alone Bupiv + KET
Huang (117)	4	60/knee arthroscopy	Yes	Spinal anesthesia + G1: IA saline G2: IM KET 0.5 mg/kg G3: IA KET 0.5 mg/kg
Roytblat (128)	3	22/open cholecystectomy	Yes	GA + G1: KET 0.15 mg/kg IV G2: saline
Kirdemir (120)	3	30/abdominal surgery	Yes	GA + thoracic epidural with 12.5 mg Bupiv + G1: 50 mg KET G2: 0.5 mg neostigmine G3: saline control

Table 3. *(Continued)*

Route/dose/timing	Systemic analgesic	Direct analgesic effect	Preventive/preemptive analysis[a]
Groups: 1. IV saline + IT Bupiv 20 mg 2. IV saline + IT Bupiv 20 mg + IT neostigmine 50 μg 3. IV KET 0.2 mg/kg + IT Bupiv + saline 4. IV KET 0.2 mg/kg + IT Bupiv 20 mg + IT neostigmine 50 μg 5. IV fentanyl 1 μg/kg + IT Bupiv + saline 6. IV fentanyl 1 μg/kg + IT Bupiv 20 mg + IT neostigmine 50 μg	Diclofenac 75 mg IM if necessary for post-op pain	Yes	Preventive effect; significantly decreased VAS at 24 h in KET/neostigmine group compared with control
GA: Thiopental 3 mg/kg induction of anesthesia & isoflurane maintenance Intervention: IV injection as part of GA and intra-op maintenance infusion Fentanyl: GA + fentanyl 5 μg/kg + 0.02 mg · kg^{-1} · min^{-1} KET: GA + KET 2 mg/kg + 20 mg · kg^{-1} · min^{-1} Control: GA only	Post-op 0–9 h PCA meperidine 9–24 h meperidine 50 mg every 4 h	Yes	Preventive effect; significant decrease in hyperalgesia at 48 h KET = fentanyl < control
Observed after pre-med before GA GA induced + maintained Sevo + 67% N_2O Intubated after atropine 0.01 mg/kg + vecuronium 0.1 mg/kg Midazolam: 1 mg/kg 15 min before GA KET: 5 mg/kg 45 min before GA KET: 7 mg/kg 45 min before GA KET: 10 mg/kg 45 min before GA	Acetaminophen 50–100 mg PR pentazocine 0.5 mg/kg IV	Yes	Preventive effect; significant increased time to first analgesia in KET: 7 mg/kg & KET: 10 mg/kg groups compared with midazolam & KET: 5 mg/kg groups
Epidural catheter inserted pre-inc injection G1: MORep 50 μg/kg G2: epidural morphine 50 μg/kg + KET 1 mg/kg	N_2O intra-op IV morphine 0.05–0.2 mg/kg intra-op MORep 0.05 mg/kg post-op	Yes	Preventive effect; significant increased time to first analgesia; G2 > G1 Analg. Req.; G2 < G1
IV injection at 3–10 min pre-inc & at skin closure PRE: (R)-KET 1.0 mg/kg pre-inc & saline at skin closure POST: saline pre-inc & (R)-KET 1.0 mg/kg at skin closure Placebo: saline pre-inc & saline at skin closure	Pre-ind IV ketorolac 30 mg Induction fentanyl 1.5–2.0 μg/kg bolus Bupiv skin infiltration pre-inc Intra-op alfentanil 0.5–1.0 mg bolus if required Post-op PCA meperidine + acetaminophen 1G PR Acetaminophen 500 mg + codeine 30 mg at home	Yes	No preventive effect; no significant difference in VAS or Analg. Req. PCA meperidine or other analgesic consumption at 4 h, 24 h & 7 days PRE = POST = placebo, direct analgesic effect occurred in post group
Pre-inc IV bolus intervention Pre-inc local infiltration of port sites with 20 mL Ropiv 1% G1: IV saline + saline infiltration G2: IV saline + Ropiv 1% infiltration G3: IV KET 1 mg/kg + Ropiv 1% infiltration	Fentanyl 3–5 μg/kg post-op Diclofenac 50–100 mg PR dextropropoxyphene 75 mg PO meperidine 50 mg IM	Yes	No preventive effect; no significant difference in VAS at 24 & 48 h G1 = G2 = G3 Analg. Req. G1 > G2 = G3; direct analgesic effect occurred in G3 at 6 and 12 h
After induction & at least 5 min pre-inc IV bolus followed by 50 mL infusion until 2 h after emergence from anesthesia KET: 0.5 mg/kg bolus + 2 mg · kg^{-1} · h^{-1} infusion Saline: 0.1 mL/kg bolus + 0.06 mg · kg^{-1} · h^{-1} infusion	Remifentanil 0.125–1.0 mg · kg^{-1} · min^{-1} 15 min before wound closure lornoxicam 8 mg & morphine 5 mg Post-op morphine PCA	No	No preventive effect; no significant difference in VAS or Analg. Req.
IV bolus 5 min before skin incision and on completion of skin closure G1: saline pre-inc & saline at closure G2: KET 0.4 mg/kg pre-inc & saline at closure G3: saline pre-inc & KET 0.4 mg/kg at closure	Alfentanil 15 μg/kg ketobemidone 4 mg IV Post-op ketobemidone 1 mg IV Acetaminophen 1G every 8 h PR	Yes	No preventive effect; no significant difference in VAS or Analg. Req. G1 = G2 = G3; direct effect of KET in post group at 1 h
Spinal anesthesia with hyperbaric Bupiv (0.5%) 10 mg or hyperbaric Bupiv (0.5%) 7.5 mg + KET 25 mg	No intra-op opioids/N_2O post-op diclofenac 75 mg IM	No	No preventive effect; no significant difference in VAS or Analg. Req. Bupiv + KET more side effects
Spinal anesthesia with 12.5–15 mg Bupiv IA or IM injection given on completion of surgery	Rescue pain relief with meperidine 1 mg/kg every 4 h if required	No	No preventive effect
GA including 3 μg/kg fentanyl KET or saline given 5 min before surgical incision	PCA morphine + continuous infusion	Yes	No preventive effect; direct analgesic effect with reduced VAS up to 4 h and reduced cumulative morphine consumption over 24 h
GA with no supplemental analgesics	Epidural morphine 2 mg on VAS >3	No	No preventive effect

Table 3. *(Continued)*

Study	Quality score (0–5)	No. Patients/procedure	Co-admin opioid	Groups (treatment combination)
Peat (127)	2	20/TAH	Yes	Epidural after induction of GA G1: KET G2: diamorphine
Wilder-Smith (135)	4	45/TAH	Yes	Before & after induction; G1: fentanyl G2: magnesium G3: KET

Co-admin = coadministered; Pre-med = premedication; GA = general anesthesia; MORep = epidural morphine; KET = ketamine; Bupiv = bupivacaine; Ropiv = ropivacaine; Sevo = sevoflurane; SC = subcutaneous; PO = per oral; PR = per rectum; COMB = combination; PCA = patient-controlled analgesia; VAS = visual analog scale; Analg. Req. = analgesic requirement; PACU = postanesthesia care unit; Pre-ind = pre-induction; Pre-op = preoperative; Pre-inc = preincision; Post-inc = postincision; Intra-op = during surgery; Post-op = after surgery; PCEA = patient-controlled epidural analgesia; TCI = target-controlled infusion; IT = intrathecal; IA = intraarticular; ACL = anterior cruciate ligament; TAH = total abdominal hysterectomy; G = group; Pre-GA = before general anesthesia; PRE = before; POST = after; TCI = target-controlled infusion; PRN = as needed; NSAID = nonsteroidal antiinflammatory drug.

[a] Preventive analysis column concerns pain and/or analgesic consumption only beyond five half-lives of *N*-methyl-D-aspartate antagonist administration.

Adverse effects related to opioids were described in 11 of 12 studies, but no statistical difference was determined between groups. One study did not document adverse effects (147).

Four studies examined magnesium, and none demonstrated a preventive analgesic benefit (Table 5). Two of the four studies did not demonstrate a direct analgesic effect. Surgical type was limited to major abdominal or pelvic surgery, and all studies coadministered an opioid. Magnesium was administered by the IV route in all four studies. All studies documented opioid-related adverse effects but no statistical difference was found between groups.

Discussion

Adherence to the narrow definition of preemptive analgesia that currently dominates the literature may have led to a large proportion of negative results. This is especially true for studies that did not include a placebo control group to control for the possibility that the presurgical and postsurgical interventions provided an equal overall benefit in reducing central sensitization (7,154). This methodological shortcoming has limited the potential clinical utility of the narrow definition because central sensitization may be induced by noxious stimuli throughout the perioperative period and not only by skin incision (7,154). The limited clinical utility of the narrow definition of preemptive analgesia was demonstrated by a recent systematic review (6).

Preventive analgesia provides a broader, more clinically relevant concept in which the administration of a drug at any point in the perioperative period and the presumed associated reduction in central sensitization may reduce pain, analgesic consumption, or both beyond the clinical activity of the target drug. The NMDA antagonists would appear to be potentially useful drugs in this regard because of their effect in reducing central hypersensitivity and wind-up-like states in humans.

The results of this systematic review showed that ketamine and dextromethorphan produced a significant preventive analgesic benefit in 58% and 67% of studies, respectively. This is in addition to the benefit that in all positive preventive studies, a direct analgesic benefit of the drug occurred in the early postoperative period. It is interesting that in a large proportion (56%) of the studies that did not find a preventive analgesic effect, a direct effect of the target drug also was absent. This strongly suggests that central sensitization was unaffected by these interventions, both immediately and in the longer term.

NMDA antagonists may reduce pain, opioid consumption, or both by two non-mutually exclusive mechanisms. The first is the more widely recognized reduction in central hypersensitivity, but NMDA antagonists have also been seen to reduce opioid tolerance in many animal and human studies. In this review, 22 ketamine and 11 dextromethorphan studies coadministered opioid analgesics with the NMDA antagonists. The analgesic benefit or reduction in opioid consumption in these studies therefore may have been due, at least in part, to a reduction of acute opioid tolerance. The other three positive studies (two ketamine and one dextromethorphan) did not coadminister opioid with the NMDA antagonist, suggesting that the reduction in pain intensity or analgesic use was due to an NMDA-mediated reduction in central sensitization brought about by the preventive analgesic intervention (although other possibilities include effects due to drug action at other receptor sites).

Many surgical procedures were included in both positive and negative studies, and there did not appear to be one specific procedure that yielded more benefit than any other. In the dextromethorphan studies, all four negative studies used the oral route, and in two of these trials at smaller doses of drug, there was no direct analgesic effect of the intervention.

Table 3. *(Continued)*

Route/dose/timing	Systemic analgesic	Direct analgesic effect	Preventive/preemptive analysis[a]
Epidural injection during closure of wound G1: KET; 30 mg in 3 mL saline G2: diamorphine; 5 mg in 3 mL saline	Intra-op fentanyl 3 μg/kg	No	No preventive effect
3 min pre-ind IV bolus intervention 5 min pre-inc IV bolus intervention G1: fentanyl 1.5 μg/kg + 0.75 μg/kg G2: magnesium 20 mg/kg + 10 mg/kg G3: KET 0.5 mg/kg + 0.25 mg/kg	Morphine PCA	No	No preventive effect, no significant difference in VAS or Analg. Req. between groups

It may be that dextromethorphan should be administered parenterally in a dose of at least 1 mg/kg for maximal preventive effect. A variety of doses of ketamine, from 0.15 to 1 mg/kg, were used, although the spread of doses was similar in both positive and negative studies.

Magnesium demonstrated no preventive analgesic effect in the four studies examined. It is difficult to understand why magnesium should have less effect than other drugs. It is possible either that the magnesium is removed from extracellular fluid rapidly or that the ion is specific to the NMDA receptor channel and does not influence the receptor sites to which other NMDA antagonists bind and thus reduce pain, analgesic consumption, or both. It is important to note that in two of four studies, the administration of magnesium did not demonstrate any direct benefit (pain or analgesic reduction) and that, therefore, it is unlikely to have shown effects later in time.

This is the first systematic review to attempt to evaluate the efficacy of preventive analgesia by examining the analgesic benefit five half-lives beyond analgesic administration. It was critical to select this time point because unlike with most studies of preemptive analgesia, preventive analgesia does not involve a postincisional analgesic intervention. We chose five half-lives to exclude as much as possible any direct effect of the NMDA antagonist. However, to avoid excluding most studies, we chose a point at which <5% of the plasma drug concentration would remain. We could be criticized for being overly stringent and might have chosen, for example, three half-lives. In fact, changing the criterion to three half-lives would lead to inclusion of an additional six studies: two of these were negative (one dextromethorphan and one magnesium), and four, all using ketamine, were positive. Therefore, changing the cutoff to three half-lives would actually strengthen our review for the ketamine result, slightly weaken the dextromethorphan result, and leave the magnesium result unchanged.

This systematic review was limited to English-language reports and therefore may be missing data from important studies published in other languages. However, it has been reported that language-limited reports do not lead to biased estimates of intervention effectiveness (155). If the same holds true for the field of preventive analgesia, then our exclusion of the non-English literature would be not be expected to alter our findings and conclusions.

A number of areas remain for future investigation with the NMDA antagonists. NMDA receptors have been isolated in the peripheral nervous system, and NMDA antagonists have been demonstrated to produce analgesic benefit in animals and volunteers (156–158). Further research is required to determine benefit in the clinical setting.

Many studies coadminister NMDA antagonists with opioid analgesics and may produce benefits through a reduction in opioid tolerance (159). Further research is required to determine whether NMDA antagonist-mediated analgesia is effected through reduction in opioid tolerance or whether these drugs have analgesic benefit in isolation. Future studies should also focus on design issues, such as appropriate control groups, standardization of pain assessment, and analgesic consumption data collection (10), to allow for quantitative systematic review and meta-analysis.

In most studies included in this systematic review, the perioperative administration of ketamine and dextromethorphan reduced pain, analgesic consumption, or both immediately and beyond the clinical duration of action of the drugs used preventively. The most likely mechanism is a reduction in NMDA receptor-mediated central sensitization.

Table 4. Studies Examining Dextromethorphan That Met Inclusion Criteria

Study	Quality score (0–5)	No. Patients/procedure	Co-admin opioid	Groups (treatment combination)
Helmy (138)	4	60/upper abdominal surgery	Yes	GA plus; PRE: Dex/saline POST: saline/Dex Control: saline/saline
Chia (136)	4	60/lower abdominal surgery	Yes	GA plus; PRE: Dex/saline POST: saline/Dex
Wu (146)	3	60/upper abdominal surgery	Yes	GA plus; Control Dex 10 mg Dex 20 mg Dex 40 mg
Kawamata (147)	3	36/tonsillectomy	No	GA plus; Control Dex 30 mg Dex 45 mg
Weinbroum (143)	3	50/day surgery, inguinal herniorrhaphy, lower limb arthroscopy	Yes	Single-shot epidural lidocaine plus; Control Dex 60 mg Dex 90 mg
Weinbroum (144)	4	75/day surgery, inguinal herniorrhaphy, lower limb arthroscopy	Yes	LA; single-shot epidural lidocaine 1.6% 16 mL LA + control GA + control LA + Dex 90 mg GA + Dex 90 mg
Henderson (139)	5	47/TAH	Yes	GA plus: G1: Dex G2: placebo control
Wu (145)	2	90/laparoscopic cholecystectomy	Yes	GA plus; Control—CPM 20 mg pre-op Group A—Dex 40 mg intra-op Group B—Dex 40 mg pre-incision
McConaghy (141)	5	53/TAH	Yes	GA plus; G1: Dex G2: placebo
Ilkjaer (153)	4	50/TAH	Yes	GA plus; G1: Dex G2: placebo
Grace (137)	4	37/laparotomy	Yes	GA plus; Pre-med G1: Dex G2: placebo
Rose (142)	5	57/adenotonsillectomy (pediatric)	Yes	GA plus: G1: Dex 0.5 mg/kg G2: Dex 1.0 mg/kg G3: placebo

Co-admin = coadministered; Dex = dextromethorphan; PO = per oral; PCA = patient-controlled analgesia; Post-op = postoperative; Pre-op = preoperative; Pre-med = premedication; Analg. Req. = analgesic requirement; VAS = visual analog scale; PRN = on demand; LA = local anesthetic; CPM = chlorpheniramine; CHEOPS = Children's Hospital of Eastern Ontario Pain Scale; TAH = total abdominal hysterectomy; GA = general anesthesia; G = group; intra-op = during surgery; pre = before; post = after; PACU = postanesthesia care unit; PR = per rectum.

[a] Preventive analysis column concerns pain and/or analgesic consumption only beyond five half-lives of *N*-methyl-D-aspartate antagonist administration.

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Table 4. *(Continued)*

Route/dose/timing	Systemic analgesic	Direct analgesic benefit	Preventive/preemptive analysis[a]
IM injection intervention; 30 min pre-incision and then 30 min before end of surgery PRE: Dex 120 mg IM then saline IM POST: saline IM then Dex 120 mg IM Placebo: saline IM then saline IM	Fentanyl 2 μg/kg Post-op meperidine PCA	Yes	Preemptive effect; median pain scores similar except at 6 h 24 h PCA consumption significantly reduced in PRE group
IV infusion Dex: 5 mg/kg in 300 mL saline/30 min Saline: 300 mL saline/30 min PRE: 30 min pre-induction POST: during skin closure	Fentanyl 3 μg/kg Post-op PCA Morphine	Yes	Preemptive effect; morphine requirements higher in POST group than PRE group on Day 1 and 2
IM injection 30 min pre-incision Control: com 20 mg DEX-10: Dex 10 mg DEX-20: Dex 20 mg DEX-40: Dex 40 mg	Fentanyl 2 μg/kg Post-op PCA Morphine	Yes	Preventive effect; all data showed dose-dependent better pain relief in Dex-premedicated patients
Oral pre-med 60 min pre-induction Control: starch tablet DEX-30: Dex 30 mg DEX-45: Dex 45 mg	No intra-op opioids Post-op loxoprofen 60 mg every 8 h PO + diclofenac 50 mg PRN suppository	Yes	Preventive effect; significantly lower VAS and Analg. Req. in Dex compared with control DEX-30 = DEX-45
Oral capsule 90 min pre-induction Control: placebo DEX-60: Dex 60 mg DEX-90: Dex 90 mg	Post-op analgesia Morphine PCA first 2 h in PACU Diclofenac 75 mg IM PRN next 4 h in PACU Diclofenac 50 mg PO PRN after discharge	Yes	Preventive effect; significantly lower Analg. Req. and VAS in DEX-60 and -90 compared with control
Oral tablet 90 min before surgery LA + placebo GA + placebo LA + Dex 90 mg GA + Dex 90 mg	Intra-op fentanyl 2.5 μg/kg Post-op analgesia Morphine PCA Diclofenac 75 mg IM PRN Diclofenac 50 mg PO PRN after discharge	Yes	Preventive effect; 50% lower Analg. Req. and VAS in DEX-90 versus control ± GA or LA
GA + G1: Dex 40 mg pre-med + 4 h post-surgery and then every 8 h for next 48 h G2: placebo control tablets as G1	Intra-op fentanyl 1.5 μg/kg PCA morphine for postoperative pain	Yes	Preventive effect; decreased VAS on movement and analgesic consumption at 72 h
Control—CPM 20 mg IM 30 min pre-op Group A: Dex 40 mg IM after removal of gallbladder Group B—Dex 40 mg IM 30 min pre-op	Fentanyl 2 μg/kg intra-op Meperidine 1 mg/kg IM post-op	Yes	Preemptive effect; time to first analgesia significant Group B > Group A > control
Oral capsule Night before surgery and 1–2 h pre-op and 8, 16, 24 h post-op G1: Dex 27 mg G2: placebo	Morphine 0.1–0.15 mg/kg Post-op PCA morphine	No	No preventive effect; no significant difference in hyperalgesia/Analg. Req./VAS at 48 h or 1 mo
Oral tablet 1 h pre-op G1: Dex 150 mg G2: placebo tablet	Fentanyl 300 μg + 50 μg/30 min boluses Post-op PCA morphine	Yes	No preventive effect; no significant difference in hyperalgesia/Analg. Req./side effects at 24 h or 3 mo Reduction in morphine consumption in Dex group in first 4 h = direct analgesic effect
Oral capsule Night before surgery and 1 h pre-op G1: Dex 60 mg G2: placebo	PCA morphine	Yes	No preventive effect; reduction in early morphine consumption in Dex group = direct analgesic effect No significant difference post-op Analg. Req. at 24 h
Oral preparation 60 min pre-op G1: Dex 0.5 mg/kg G2: Dex 1.0 mg/kg G3: placebo	IV morphine 0.075 mg/kg PR acetaminophen 25–35 mg/kg	No	No preventive effect; no significant difference in Analg. Req./CHEOPS/VAS/side effects at 24 h

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Table 5. Studies That Examined Magnesium and Met Inclusion Criteria

Study	Quality score (0–5)	No. Patients/procedure	Co-admin opioid	Groups (treatment combination)
Zarauza (150)	4	92/elective colorectal surgery	Yes	GA plus; Group C: control Group NF: nifedipine Group NM: nimodipine Group MG: $MgSO_4$
Tramer (149)	5	42/elective TAH	Yes	GA plus; G1: control G2: $MgSO_4$
Ko (148)	3	58/elective TAH with lower midline incision	Yes	GA plus; G1: control G2: $MgSO_4$
Wilder-Smith (151)	4	24/elective TAH	Yes	Fentanyl 1 μg/kg IM 1 h pre-op G1: placebo G2: $MgSO_4$

Co-admin = coadministered; GA = general anesthesia; VAS = visual analog scale; Analg. Req. = analgesic requirement; PCEA = patient-controlled epidural analgesia; Post-op = postoperative; IVI = IV infusion; TAH = total abdominal hysterectomy; $MgSO_4$ = magnesium sulphate; pre-op = before surgery; pre = before; post = after; pre-med = premedication; intra-op = intraoperative.

[a] Preventive analysis column concerns pain and/or analgesic consumption only beyond five half-lives of *N*-methyl-D-aspartate antagonist administration.

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Table 5. *(Continued)*

Route/dose/timing	Systemic analgesic	Direct analgesic benefit	Preventive analysis[a]
Oral tablet placebo or study drug 3 h before surgery <20 min post-induction IV bolus + start 20 h IV infusion of placebo or study drug Group C: placebo tablet + IV bolus + IVI Group NF: nifedipine 60 mg + placebo bolus + IVI Group NM: placebo tablet + bolus + nimodipine 30 mg · kg^{-1} · h^{-1} IVI over 20 h Group MG: placebo tablet + $MgSO_4$ 30 mg/kg bolus + 10 mg · kg^{-1} · h^{-1} IVI over 20 h	Fentanyl 4 μg/kg bolus + infusion 1 mg · kg^{-1} · h^{-1} Post-op PCA morphine If VAS >5; 2 g propacetamol IV 2 g metamizole IV	No	No preventive effect; no significant difference VAS/Analg. Req./side effects
Post-induction bolus + IV infusion 20 h G1: saline 15 mL bolus + 2.5 mL/h IVI G2: $MgSO_4$ 20% 15 mL bolus + 2.5 mL/h IVI (13 g total dose)	Fentanyl 3 μg/kg at induction 1.5 μg/kg at 5 min before incision + 1 μg/kg boluses post-op PCA morphine	Yes	No preventive effect; Analg. Req. significantly reduced in $MgSO_4$ group during first 6 h post-op but not thereafter
IV bolus + infusion for 6 h G1: saline 0.2 mL/kg bolus + IVI G2: $MgSO_4$ 25% 50 mg/kg bolus + IVI at 15 mg · kg^{-1} · h^{-1} for 6 h	Post-op PCEA (bupivacaine 0.05% + fentanyl 5 μg/mL)	No	No preventive effect; no significant difference in VAS/Analg. Req.
Slow IV bolus 5 min pre-induction + continuous IV infusion for 5 h post-op G1: placebo IV bolus + IV infusion G2: magnesium 200 mg IV bolus + 200 mg/h IVI for 5 h	Fentanyl 1 μg/kg IM pre-med Alfentanil 15 μg/kg IV bolus at induction + intra-op IV infusion at 0.03–0.05 mg · kg^{-1} · min^{-1} Morphine PCA basal infusion 0.5 mg/h + bolus 2.5 mg with 10 min lockout	Yes	No preventive effect; no significant difference in VAS/Analg. Req. except at 1 h post-op

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