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Adjuvant Analgesic Use in the Critically Ill: A Systematic Review and Meta-Analysis

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Objectives: This systematic review and meta-analysis addresses the efficacy and safety of nonopioid adjunctive analgesics for patients in the ICU.

Data Sources: We searched PubMed, Embase, the Cochrane Library, CINAHL Plus, and Web of Science.

Study Selection: Two independent reviewers screened citations. Eligible studies included randomized controlled trials comparing efficacy and safety of an adjuvant-plus-opioid regimen to opioids alone in adult ICU patients.

Data Extraction: We conducted duplicate screening of citations and data abstraction.

Data Synthesis: Of 10,949 initial citations, we identified 34 eligible trials. These trials examined acetaminophen, carbamazepine, clonidine, dexmedetomidine, gabapentin, ketamine, magnesium sulfate, nefopam, nonsteroidal anti-inflammatory drugs (including diclofenac, indomethacin, and ketoprofen), pregabalin, and tramadol as adjunctive analgesics. Use of any adjuvant in addition to an opioid as compared to an opioid alone led to reductions in patient-reported pain scores at 24 hours (standard mean difference, -0.88 ; 95% CI, -1.29 to -0.47 ; low certainty) and decreased opioid consumption (in oral morphine equivalents over 24 hr; mean difference, 25.89 mg less; 95% CI, 19.97–31.81 mg less; low certainty). In terms of individual medications, reductions in opioid use were demonstrated with acetaminophen (mean difference, 36.17 mg less; 95% CI, 7.86–64.47 mg less; low certainty), carbamazepine (mean difference, 54.69 mg less; 95% CI, 40.39–to 68.99 mg less; moderate certainty), dexmedetomidine (mean difference, 10.21 mg less; 95% CI, 1.06–19.37 mg less; low certainty), ketamine (mean difference, 36.81 mg less; 95% CI, 27.32–46.30 mg less; low certainty), nefopam (mean difference, 70.89 mg less; 95% CI, 64.46–77.32 mg less; low certainty), nonsteroidal anti-inflammatory drugs (mean difference, 11.07 mg less; 95% CI, 2.7–19.44 mg less; low certainty), and tramadol (mean difference, 22.14 mg less; 95% CI, 6.67–37.61 mg less; moderate certainty).

Conclusions: Clinicians should consider using adjunct agents to limit opioid exposure and improve pain scores in critically ill patients.

Key Words: acute pain; analgesics, nonnarcotic; analgesics, opioid; critical illness; meta-analysis; pain management

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Opioids are commonly used in critically ill patients with the intent to treat pain and facilitate administration of critical care. Observational research has shown opioids are used in over 80% of mechanically ventilated ICU patients (1). However, opioid use has been associated with serious side effects

such as respiratory depression (2), gastrointestinal dysfunction (3), and immunosuppression (4). Older adults, a growing proportion of ICU admissions, may be even more susceptible to side effects of opioids due to altered pharmacokinetics, polypharmacy, and decreased physiologic reserve (5).

At the same time, acute pain causes distress for patients, caregivers, and families (6). Furthermore, inadequate treatment of acute pain is a well-known risk factor for the development of chronic pain, which may occur in up to 33% of ICU survivors (7, 8). Both the use of opioids and memories of severe acute pain have been linked to development of post-traumatic stress disorder after ICU discharge (6).

Use of adjuvant medications, in addition to opioids, may help provide effective analgesia while minimizing unwanted side effects. There is evidence for the use of nonopioid analgesics in other acute care settings such as emergency departments (9) and postanesthetic care units (10), but the efficacy and degree of use of nonopioid analgesics in ICU are not well documented.

The 2018 Society of Critical Care Medicine (SCCM) guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS guidelines) recommended the use of a limited number of adjuvants in addition to opioids. Initial searches and data summaries were performed in support of the PADIS guideline, which summarized published evidence up to 2015 (11). However, subsequent to the publication of these guidelines, the scope of this review was expanded, and searches updated in order to include the latest data. Here we present results of a systematic review and meta-analysis summarizing the current evidence for opioid-sparing adjuvant analgesics in adult ICU patients.

MATERIALS AND METHODS

This study was registered in the PROSPERO International Prospective Register of Systematic Reviews (identification number: CRD42017057044) on February 1, 2017.

Data Sources and Searches

In collaboration with an experienced medical librarian (12), we developed the search strategy using keywords for the concepts of intensive care, cardiac or abdominal surgery, medications, and pain. The search was not limited by language or date. The PubMed search strategy can be found in **Supplemental Data 1** (Supplemental Digital Content 1, <http://links.lww.com/CCX/A223>). We searched PubMed, Embase, the Cochrane Collaboration, CINAHL, and Web of Science from inception to October 1, 2019. We also reviewed conference abstracts from the European Society of Intensive Care Medicine and SCCM for the last 2 years.

Study Selection

We included randomized controlled trials (RCTs) comparing the efficacy of an adjuvant-plus-opioid regimen to opioids alone in adult (over 18 yr old) ICU patients. Opioid regimens could include both scheduled and PRN (as needed) doses or PRN only. Studies comparing multiple adjuvant regimens to one another without a placebo/control group were excluded. For the purposes of this

study, tramadol was considered a nonopioid adjuvant medication. Trials evaluating interventions that started outside of the ICU (e.g., in the operating room), were solely peri-procedural (e.g., for burn dressing changes or line insertions), or were regional in nature (e.g., peripheral nerve blocks or epidural catheters) were excluded.

Screening of search results, data collection, and risk of bias assessments were conducted in duplicate by two independent reviewers. Reviewers performed screening in two stages, initially assessing titles and abstracts, and then full articles. We recorded reasons for exclusion at the full article review stage. We included the following outcomes: pain scores (at 24 hr, or the closest reported time point), opioid consumption during the intervention period, duration of mechanical ventilation, ICU length of stay, and adverse events.

Data Abstraction and Quality Assessment

We performed data extraction independently and in duplicate using predefined data abstraction forms. A third reviewer resolved disagreements. Abstracted data included characteristics of study participants (i.e., age, gender, acuity, surgical [vs medical]); the treatment regimen for both opioid alone and adjuvant analgesic arms; the type and timing of formal pain assessments; duration of follow-up; target sedation levels; number of patients included and randomized; and the outcome data. When necessary, we contacted authors of eligible studies to request supplemental data. We converted reported data on opioid consumption into 24-hour oral morphine equivalents (OME) using standardized methods (13).

We assessed risk of bias using the Cochrane Collaboration's tool for risk of bias assessment (14). We assessed the overall certainty of evidence for each intervention using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (15).

Data Analysis

We performed all analyses using RevMan software, Version 5.3 (The Cochrane Collaboration, 2014) (16) and using the random-effects model. We present results using mean difference (MD) or standard mean difference (SMD) with 95% CI. For studies that did not report SD, we converted interquartile ranges to SD using methods suggested by the Cochrane Collaboration (17). When outcomes were reported only graphically, we used an online plot digitizer to obtain numeric estimates for analysis (18).

RESULTS

The flow diagram for the systematic review is outlined in **Figure 1**. Of 10,949 citations initially identified in the search, 7,497 remained after removal of duplicates, 7,263 were excluded at title and abstract screening, and 200 at full-text review leaving 34 trials that met eligibility criteria. Of these, 11 studied dexmedetomidine (19–29), seven studied acetaminophen (30–36), six studied nonsteroidal anti-inflammatory drugs (NSAIDs) (including diclofenac, indomethacin, and ketoprofen) (30, 31, 33, 37–39), four studied ketamine (40–43), three studied nefopam (37, 44, 45), two studied tramadol (30, 46), two studied gabapentin (47, 48), two studied carbamazepine (48, 49), one studied clonidine (50), one studied

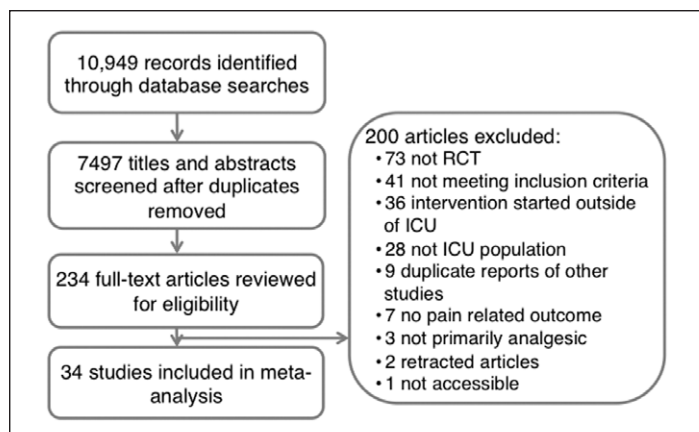


Figure 1. Study flow diagram. RCT = randomized controlled trial.

magnesium sulfate (51), and one studied pregabalin (52). Several studies had multiple intervention arms studying more than one adjuvant analgesic in comparison to an opioid alone. Most studies (25/34, 74%) focused on surgical ICU patients, and two focused on only Guillain-Barré syndrome patients; the remainder evaluated a mixed medical-surgical population. Full characteristics of the included studies are described in **Table 1**. **Supplemental Table 1** (Supplemental Digital Content 1, <http://links.lww.com/CCX/A223>) presents the risk of bias for each study. Eighteen studies were judged to be at low risk of bias and four at high risk of bias; the overall risk of bias was unclear for the remaining 12.

Pain Scores

Use of any adjuvant, in addition to an opioid, led to reductions in patient-reported pain scores at 24 hours (SMD, 0.88 lower; 95% CI, 1.29–0.47 lower; low certainty; see **Figure 2** for forest plot and **Supplemental Table 2** [Supplemental Digital Content 1, <http://links.lww.com/CCX/A223>] for GRADE assessments). Examining individual medications, only adjunctive acetaminophen (SMD, 1.65 lower; 95% CI, 3.28–0.02 lower) demonstrated lower pain scores at 24 hours as compared with opioids alone. However, this estimate is based on very low certainty evidence and limited by imprecision.

Opioid Consumption

Decreased opioid consumption (in OME over 24 hr) was demonstrated with the use of any adjuvant analgesic (MD, 25.89 mg less; 95% CI, 19.97–31.81 mg less; low certainty; see **Figure 3** for forest plot and **Supplemental Table 2** [Supplemental Digital Content 1, <http://links.lww.com/CCX/A223>] for GRADE assessments). Among individual medications, reductions in opioid use (24 hr morphine equivalent) were demonstrated with dexmedetomidine (MD, 10.21 mg less; 95% CI, 1.06–19.37 mg less; low certainty), nefopam (MD, 70.89 mg less; 95% CI, 64.46–77.32 mg less; low certainty), NSAIDs (MD, 11.07 mg less; 95% CI, 2.7–19.44 mg less; low certainty), acetaminophen (MD, 36.17 mg less; 95% CI, 7.86–64.47 mg less; low certainty), carbamazepine (MD, 54.69 mg less; 95% CI, 40.39–68.99 mg less; moderate certainty), ketamine (MD, 36.81 mg less; 95% CI, 27.32–46.30 mg less; low certainty), and tramadol (MD, 22.14 mg less; 95% CI, 6.67–37.61 mg less; moderate certainty).

Duration of Mechanical Ventilation and ICU Stay

Reductions in duration of mechanical ventilation (1.13 hr less; 95% CI, 0.39–1.86 hr less) and ICU length of stay (0.19 d less; 95% CI, 0.11–0.27 d less) were shown with use of any adjuvant analgesic, although this was based on very low certainty evidence and the magnitude of difference was of minimal clinical importance. No individual adjuvant medication demonstrated an effect on either duration of mechanical ventilation or ICU length of stay. See **Supplemental Table 2** (Supplemental Digital Content 1, <http://links.lww.com/CCX/A223>) for both the data and GRADE assessments.

Adverse Events

Very few adverse events were reported across the included studies. Given this, and the heterogeneity in how these were reported, we were unable to summarize this outcome quantitatively. **Supplemental Table 3** (Supplemental Digital Content 1, <http://links.lww.com/CCX/A223>) provides a narrative summary of adverse events.

Subgroup Analysis

Subgroup analysis demonstrated consistent reductions in pain scores and opioid consumption in medical ICU patients, surgical ICU patients, and cardiac surgical ICU patients (**Supplemental Figs. 1–4**, Supplemental Digital Content 1, <http://links.lww.com/CCX/A223>). There were no credible subgroup effects seen.

DISCUSSION

This systematic review and meta-analysis is the most comprehensive and current summary of adjuvant analgesic medications in ICU patients. We have expanded on the 2018 PADIS guideline to provide results of a broader, more recent search, and report on a larger number of agents (11).

Our search results support PADIS conditional recommendations for the use of acetaminophen, ketamine, nefopam, and carbamazepine in reducing daily opioid consumption. Although our analysis also found similar efficacy with NSAIDs, the PADIS guidelines suggested against routine use of NSAIDs (despite their potential opioid-sparing effects) due to unpublished anticipated concerns regarding side effects such as bleeding and renal dysfunction (11).

In order to pool data from studies that included different opioids in their analgesic regimens, we have converted the opioid consumption reported in individual articles to OME. This was done using standardized conversion methods, with input from content experts including critical care pharmacists. However, the differences in opioid types and regimens used in individual studies limit the ability to directly compare absolute opioid consumption between studies.

Our results are consistent with a recent meta-analysis that also aimed to summarize the use of nonopioid analgesics for ICU patients (53). In comparison to this review, our search was broader and included more citations, more eligible studies, and more potential adjunctive medications leading to more precise and clinically useful results.

The data analysis demonstrated a signal for potential analgesic benefit through lower pain scores from the use of IV

TABLE 1. Characteristics of Included Studies

References	Opioid	Adjuvant(s)	Duration of Intervention	Patient Subgroup	Mean Age (yr)	% Female Patients
Abu-Halaweh et al (19)	Morphine	Dexmedetomidine	24 hr	Surgical-bariatric	34	77
Anvaripour et al (20)	Methadone	Dexmedetomidine	24 hr	Surgical-cardiac	58	37
Arslan et al (30)	Fentanyl	Paracetamol, diclofenac, tramadol	24 hr	Surgical-cardiac	56	16
Azeem et al (21)	Fentanyl + morphine	Dexmedetomidine	24 hr	Surgical-cardiac	66	53
Bameshki et al (31)	Morphine	Diclofenac, acetaminophen	24 hr	Surgical-general	54	33
But et al (46)	Morphine	Tramadol	24 hr	Surgical-cardiac	65	30
Cheng et al (22)	Tramadol	Dexmedetomidine	3–7 d	Surgical-general	58	40
Eremenko and Kuslieva (32)	Trimeperidine	Acetaminophen	18 hr	Surgical-cardiac	60	24
Eremenko et al (44)	Trimeperidine	Ketoprofen, nefopam	24 hr	Surgical-cardiac	51	38
Eremenko et al (37)	Trimeperidine	Nefopam	24 hr	Surgical-cardiac	58	41
Farasatinasab et al (50)	Fentanyl + morphine	Clonidine	3–7 d	Mixed ICU	57	35
Fayaz et al (33)	Morphine	Diclofenac, acetaminophen	24 hr	Surgical-cardiac	63	40
Guillou et al (40)	Morphine	Ketamine	48 hr	Surgical-general	60	27
Hynninen et al (38)	Various	Diclofenac, ketoprofen, indomethacin	12 hr	Surgical-cardiac	58	18
Joachimsson et al (41)	Ketobemidone	Ketamine	8 hr	Surgical-general	61	28
Kim et al (45)	Fentanyl	Nefopam	48 hr	Surgical-cardiac	60	31
Korkmaz Dişli et al (23)	Morphine	Dexmedetomidine	48 hr	Surgical-cardiac	59	71
Martin et al (24)	Morphine	Dexmedetomidine	12–24 hr	Surgical-mixed	61	31
Memiş et al (51)	Sufentanil	Magnesium sulfate	6 hr	Mixed ICU	50	NR
Memis et al (34)	Meperidine	Acetaminophen	24 hr	Surgical-mixed	59	40
Meurant and Bodart (52)	Piritramide	Pregabalin	35 d	Surgical-trauma	38	34
Moskowitz et al (47)	Various	Gabapentin	7 d	Trauma	44	20
Pandey et al (48)	Fentanyl	Gabapentin, carbamazepine	7 d	Medical GBS	32	39
Perbet et al (42)	Remifentanil	Ketamine	7 d	Mixed ICU	62	33
Priye et al (25)	Fentanyl	Dexmedetomidine	12 hr	Surgical-cardiac	43	48
Rapanos et al (39)	Morphine	Indomethacin	12 hr	Surgical-cardiac	61	21
Shaikh et al (35)	Morphine	Acetaminophen	24 hr	Mixed ICU	42	28
Skrobik et al (26)	Fentanyl	Dexmedetomidine	21 d	Mixed ICU	62	36
Su et al (27)	Morphine	Dexmedetomidine	24 hr	Surgical-mixed	NR	NR
Subramaniam et al (36)	Morphine equivalents	Acetaminophen	48 hr	Surgical-cardiac	68	16
Takieddine et al (43)	Various	Ketamine	4 d	Trauma	32	20
Tripathi and Kaushik (49)	Meperidine	Carbamazepine	72 hr	Medical GBS	33	42
Venn et al (28)	Morphine	Dexmedetomidine	24 hr	Surgical-mixed	64	26
Zhao et al (29)	Fentanyl	Dexmedetomidine	24 hr	Surgical-neurosurgical	43	55

GBS = Guillain-Barré syndrome, NR = not reported.

acetaminophen or dexmedetomidine. However, we were unable to summarize side effects such as hypotension, which has been associated with these agents (54–57). Tramadol also showed a signal for a potential opioid-sparing effect in analysis, although

widespread use in ICU patients is limited by its formulation only as tablet that cannot be crushed and administered enterally, and by side effects, which are of concern particularly in patients with renal dysfunction (58).

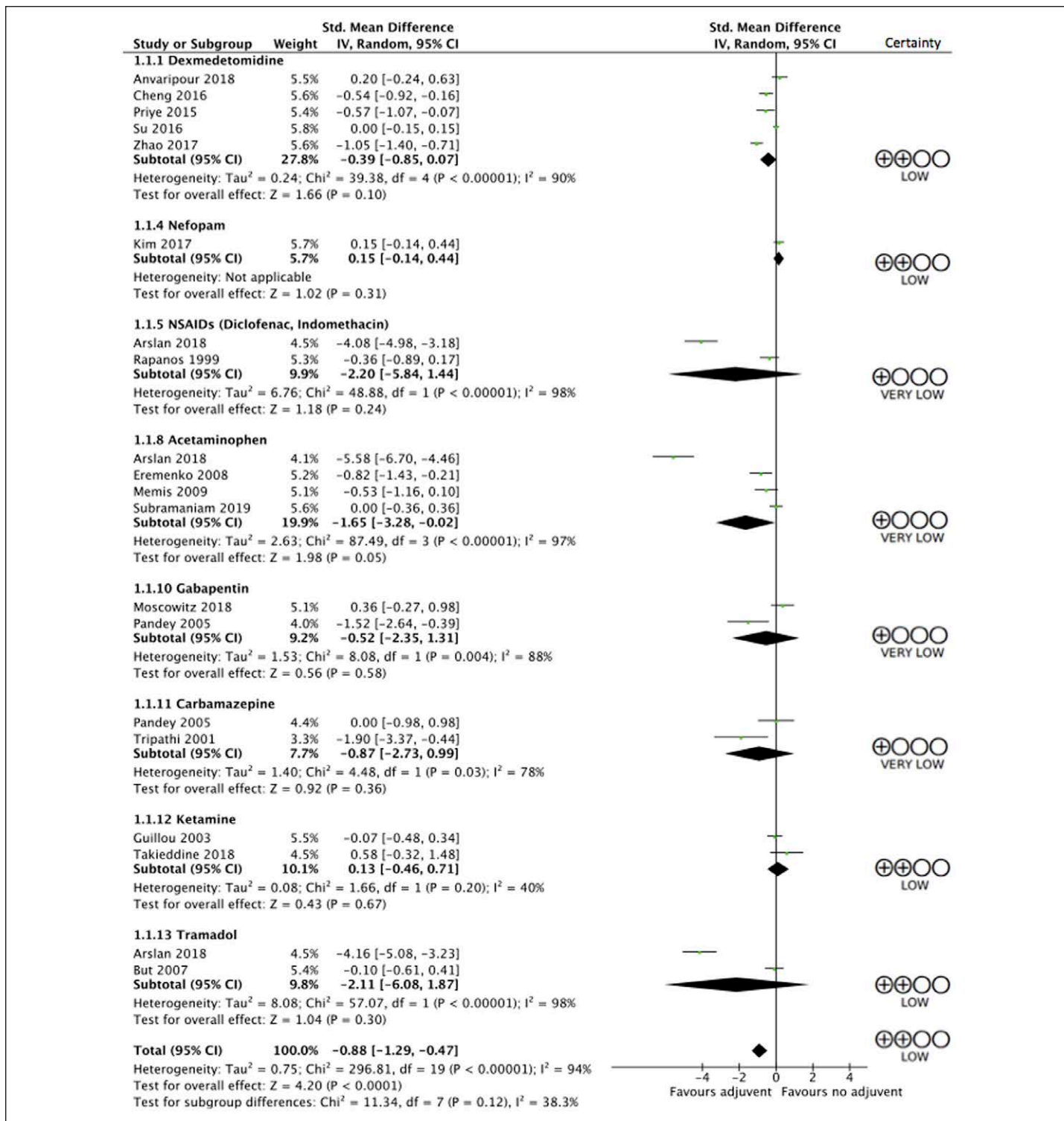


Figure 2. Forest plot of pain scores at 24 hr after intervention. *df* = degrees of freedom, NSAIDs = nonsteroidal anti-inflammatory drugs.

This analysis also showed a reduction in opioid consumption and improved pain scores with use of dexmedetomidine. There is increasing interest in the use of dexmedetomidine as a sedative in intensive care (56). Although recent evidence shows no benefit over standard sedation in the general ICU population (59), there may be utility in patients with pathologies such as alcohol or drug withdrawal (55). Some studies suggest a direct analgesic effect of

dexmedetomidine (60), although there is also a suggestion that its opioid-sparing properties may be due to altered perception of pain and anxiolysis, rather than direct analgesia (61). Regardless of its mechanism, dexmedetomidine may be a useful adjunct and sedative medication for patients in whom opioid-sparing is a priority.

Studies of regional anesthesia techniques or of interventions started outside of the ICU (e.g., those started in the operating

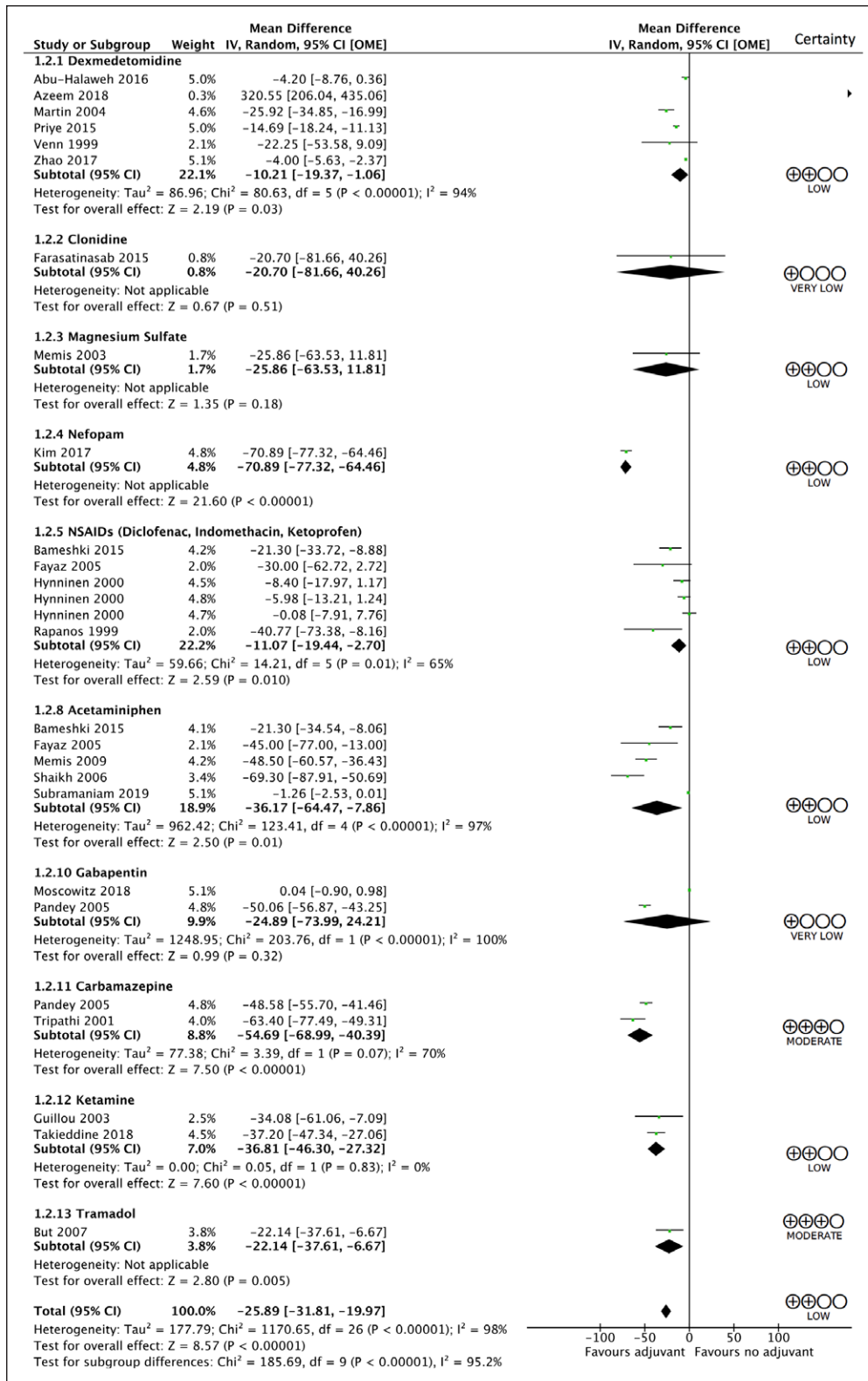


Figure 3. Forest plot of opioid consumption in first 24 hr of intervention. *df* = degrees of freedom, OME = oral morphine equivalents.

room or emergency department) were intentionally excluded from this review. We made this decision a priori in order to limit clinical heterogeneity and focus on interventions that are independent of specific regional anesthesia skill sets and equipment

and to provide guidance specific to ICU clinicians.

Most of the trials included only subgroups of surgical patients (e.g., cardiac surgery or trauma) or those with Guillain-Barré syndrome. This may limit generalizability of our results to medical patients and highlights the need for more research in this area. However, subgroup analysis demonstrated that these findings of improved pain scores and reduced opioid consumption were consistent across medical patients, surgical patients, and cardiac surgical patients.

ICU patients have a wide range of pain pathologies, and therefore pain quality and optimal treatment may vary dramatically from one patient to the next. For example, a patient with localized nociceptive pain from trauma or surgery may respond differently than one with neuropathic pain or another with diffuse musculoskeletal pain from immobility. As with many other aspects of ICU care, it is unlikely that any one intervention would be appropriate for all patients; rather, clinicians should judge the advantages and side effect profiles of each medication on a patient-by-patient basis. Although there was insufficient data to examine subgroups such as those with Guillain-Barré syndrome or trauma admissions, Table 1 summarizes the characteristics of included studies specifically highlighting the patient population which was studied. This may assist clinicians in determining the applicability of these findings to their patients. Overall, this review suggests that using some adjunctive agents, perhaps targeted to the patient type and quality of pain, is better than using opioids alone.

Unfortunately, we were unable to pool results for adverse events as the included studies variably and heterogeneously reported these outcomes.

As outlined in Supplemental Table 3 (Supplemental Digital Content 1, <http://links.lww.com/CCX/A223>), the majority of reported adverse outcomes were short-term such as bleeding or changes in blood pressure. Although these are important, other long-term adverse effects such as delirium and

ileus, which are more challenging to measure and capture, were rarely reported in the included studies. This reflects a systemic under-reporting of harm outcomes for both opioids and adjuvant analgesic medications. Given the risks of adverse effects on many organ systems with both opioids and analgesic medications, there is a need for more careful data collection in this area.

The conclusions from this study are limited by low certainty of evidence, heterogeneity of studies (with respect to both populations and intervention regimes), and a lack of comprehensive reporting of adverse events. Strengths include a comprehensive search with explicit eligibility criteria, a priori registration of the study protocol, analysis and data collection by independent paired reviewers, input from content experts and formal evaluation of evidence certainty using GRADE methodology.

CONCLUSIONS

Clinicians should consider using adjunct agents to limit opioid exposure and improve pain scores in critically ill patients. Future RCTs are needed to better understand comparative effectiveness of different adjuncts, identify which subgroups of patients are most likely to benefit, and more adequately capture the harm that may be associated with use of these medications.

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Supplemental digital content is available for this article. Direct URL citations appear in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccejournal>).

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