**Side Effect Rates of Opioids in Equianalgesic Doses Via Intravenous Patient-Controlled Analgesia: A Systematic Review and Network Meta-analysis**

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**BACKGROUND:** Side effects of opioids used for the treatment of acute pain frequently limit their analgesic quality. Many studies have compared opioid side effects in patient-controlled analgesia (PCA), but it remains unclear whether there are specific side effect profiles that can be exploited when choosing an opioid for a patient. In this review, we wanted to determine the risk ratios (RRs) for the most common side effects when using different opioids for intravenous PCA in equianalgesic doses and rank the substances accordingly.

**METHODS:** A search of MEDLINE, EMBASE, the Cochrane Library (CENTRAL), and Web of Science identified 63 randomized controlled trials comparing opioids under equianalgesic conditions. Inclusion criteria were comparable pain stimulus between groups, equal coanalgesic treatment, and comparable resulting pain scores. Quality of studies was assessed using the Cochrane risk of bias tool with 6 items. Frequentistic network meta-analysis was conducted with morphine as the comparator. This method not only summarizes all estimated effects from direct comparisons of different interventions but also allows for indirect comparisons between interventions that can be linked via the common comparator, in which case the indirect evidence can be used to enhance the precision of the direct comparisons. Primary end points of this study were RRs for nausea and vomiting, pruritus, and events of sedation, as well as mean differences for scores of sedation. Events of respiratory depression were counted. Secondary end point was patient satisfaction (mean difference). The study protocol was registered at PROSPERO (CRD42017062355).

**RESULTS:** Sixteen opioid interventions were compared in the largest network (nausea and vomiting outcome) and 7 opioid interventions in the smallest network (sedation events outcome). Most interventions did not differ from morphine on the primary outcomes (side effects), with some exceptions. Buprenorphine had a significantly higher RR of nausea and vomiting, whereas fentanyl had a lower RR of nausea and vomiting. Nalbuphine, butorphanol, methadone, and pethidine/meperidine had a lower risk of pruritus. Respiratory depression was rare (22 of 2452 patients). Pethidine/meperidine, fentanyl, and oxymorphone caused significantly lower sedation scores. Tramadol caused significantly lower satisfaction scores, whereas oxycodone, alfentanil, remifentanil, fentanyl, and pethidine/meperidine caused significantly higher satisfaction scores.

**CONCLUSIONS:** The opiate chosen for treatment most likely has little effect on the incidence of pruritus and nausea/vomiting, although considerable differences exist in terms of better and worse opioids in the presented rankings. Larger differences between drugs were observed with regard to sedation and patient satisfaction, and choosing the appropriate opioid may help to improve PCA in this regard. (Anesth Analg XXX;XXX:00–00)

**KEY POINTS**

- **Question:** Are there substances among opioids that cause common therapy-limiting side effects (nausea, vomiting, pruritus, sedation, and respiratory depression) less frequently or may lead to increased satisfaction in patient-controlled analgesia?
- **Findings:** Significant substance-related differences were seen in the sedative potentials and satisfaction scores, while risks for nausea and vomiting and pruritus were rather homogenous, and the event of respiratory depression occurred too rarely in patient-controlled analgesia to draw a meaningful conclusion.
- **Meaning:** Patient-controlled analgesia may be improved by the choice of an opioid regarding the level of sedation and patient satisfaction, while nausea and vomiting and pruritus seem to depend mainly on the total opioid dose and individual tolerance.
Opioids are the first-line medication for moderate-to-severe postoperative pain. Their side effects often limit analgesic therapy. To compare them, several prerequisites should be met. Because opioid side effects are dose dependent, it is important to compare them in equivalent doses. Comparable pain scores between groups of patients are useful and yet no guarantee in this regard. The pain stimulus in the treatment groups of a study must be comparable, otherwise pain scores may be equal but result in less opioids being used in the group with the less painful intervention and thus result in side effects being observed less frequently. The use of nonsteroidal anti-inflammatory drugs and coanalgesics should be equal between groups because opioid-sparing effects may also skew results. The side effects can be hidden by antiemetics, laxatives, antipruritics, or other prophylactic of therapeutic measures to reduce these complaints. Again, use of such drugs should also be equally distributed among groups. Last, the population of a study contributing to a review like this should also be comparable. The overall incidence of nausea and vomiting should be higher in a study that includes only women and compares opioid A against opioid B, but the risk ratio (RR) of occurrence that results from the pharmacological difference between the 2 opioids used in the groups should stay the same.

The concept of intravenous patient-controlled analgesia (PCA) has proven to be a reliable way of achieving good and relatively equal analgesia. This method is widely used, primarily in the postoperative setting, giving patients access to potent opioids immediately and on demand. Overdosing with potential respiratory depression rarely occurs with PCA due to pumps being programmed with bolus doses and lockout intervals, making this method of application safe and attractive.

The objective of this systematic review is to determine how much the choice of an opioid delivered via PCA pump influences the occurrence of common side effects like nausea and vomiting, pruritus, sedation, and respiratory depression, as well as patient satisfaction.

METHODS

Study Registration and Reporting

The presented study has been registered at PROSPERO before data analysis (CRD42017062355). Reporting followed the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses.” The completed checklist can be found in the electronic version of this article.

Search Strategy

Our search strategy followed the patient(s)/population/problem, intervention, comparison/control, outcome process and was developed in cooperation with librarians of the Central Medical Library Marburg.

Patients/Population (P).

Patients of interest were using PCA in a study setting.

Intervention (I) and Control/Comparison (C).

Because, in this review, all pairwise (or multiple) comparisons were eligible, I and C were searched as 1 aspect. We searched for ≥2 different opioids connected with a logical “AND” in the title or abstract of a study, covering all possible combinations of a list of substance names. Alternatively, the search term “comparison” with a proximity operator to “opioids” prevented exclusion of studies comparing opioids without mentioning the substance names in their title or abstract.

Outcome (O).

To maximize the completeness of reported side effects, the outcome section was left unrestricted in this search.

All search terms were varied in spelling or truncated; medical subject headings were added if existing. Search fields were title, abstract, and medical subject headings. Text words and medical subject headings were combined freely. Filters used to find randomized controlled trials (RCTs) were the sensitivity- and precision-maximizing filter for MEDLINE via Ovid developed by Lefebvre et al8 and “best optimization of sensitivity and specificity” RCT filter for EMBASE via Ovid developed by Wong et al9 as recommended in the Cochrane handbook. No filters were used for searching the databases Web of Science and the Cochrane Library (CENTRAL). The full search strategy can be found in the Supplemental Digital Content, Document, http://links.lww.com/AA/C621.

We searched MEDLINE, Web of Science, and CENTRAL on February 12, 2016, and EMBASE on June 4, 2016, and did a literature update search on May 6, 2017, for all databases.

Data Sources

A collection of studies was conducted by H.-C.D. and S.O.; missing studies were then searched by the librarians of the Central Medical Library Marburg. For missing information on searched studies, corresponding authors were contacted via email, followed by a reminder email 2 weeks later. No language restrictions were made. Studies in German and French were covered by the authors’ team; articles in other languages were translated to English via neural machine translation software (Google LLC, Mountain View, CA). Unclear translation results would be translated by a professional service.

Study Selection

The process of screening titles and abstracts was separately performed by ≥2 authors for each study, as was full-text screening and risk of bias evaluation. Discrepancies were handled by agreement or voting of a third author.

Eligibility Criteria

Only fully reported RCTs comparing ≥2 different opioids via intravenous PCA, under otherwise same conditions, were eligible for data extraction. Required conditions were comparable pain stimulus or type of surgery, equal treatment with nonsteroidal anti-inflammatory drugs, coanalgesics, and amount of rescue analgesics, as well as equal treatment of opioid-related side effects. Criteria for equianalgesia were met if 1 (the same) group had a higher pain score than the other at all time points of the study but did at no point exceed the other by 1.5 (on a 0–10 scale). Alternatively, if each group had ≥1 time point during the study period at which it had the higher pain score of the 2, the score difference could be above 1.5, but not exceed 2.5 at any time point.
Risk of Bias Evaluation

The risk of bias evaluation followed the recommendations from the Cochrane Risk of Bias evaluation manual, released by Cochrane Germany, which is based on the Cochrane Handbook, but encourages a more decisive evaluation toward high- and low-risk judgment in some aspects. All studies included in this review were characterized for their patient collective, methods, setting, groups, length, interventions, and end points. The risks of bias was then evaluated with a focus on random sequence generation, allocation concealment (both selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias) while keeping an open category for risk of other bias. Two authors performed a risk of bias evaluation, and all decisions to include or exclude a study were discussed and made in consensus.

Primary End Points

The primary end points of this review were nausea and vomiting, pruritus, sedation, respiratory depression on a dichotomous basis, and sedation reported as continuous rating scores. Nausea and vomiting in the postoperative setting are often referred to as postoperative nausea and vomiting (PONV), but because this study was not limited to postoperative PCA, we report this side effect as nausea and vomiting.

Secondary End Points

The secondary end point was patient satisfaction on a numerical rating scale. Furthermore, PCA pump programming data were extracted (Supplemental Digital Content, Document, http://links.lww.com/AA/C621).

Data Management

Events of side effects were extracted as dichotomous data. Side effect rates reported as percent of patients were calculated back into dichotomous data (events). Scores for sedation and satisfaction were converted to a 0–10 scale for comparison and extracted as continuous data. This was the case for sedation and satisfaction scores, where 0 was defined as no sedation or satisfaction and 10 was the highest possible level of sedation or satisfaction. Also extracted were the characteristics of every included study, consisting of patients, pain stimulus, interventions, PCA device setup, study period, and methodological aspects (randomization method, blinding, and reporting).

Statistics

The first assumption a network meta-analysis makes is the transitivity assumption. It states that the treatment effects are, to some extent, stable among all included studies, therefore allowing indirect comparisons, which is what the network meta-analysis adds to the already existing direct evidence. To fulfill this assumption, we put high emphasis on the equianalgesia criteria as well as equal distribution of coanalgesics, antiemetics, etc, as described in the introduction. The second assumption is that the evidence base for the network meta-analysis is adequate and not biased; therefore, we performed a comprehensive literature search followed by a risk of bias assessment as described above. Network meta-analysis was then done using frequentist methods, with morphine as the comparator. All interventions (opioids) were tested against morphine combining the direct and indirect evidences and testing for a higher, respectively lower RR or mean difference (MD) depending on the type of data. Heterogeneity describes the situation in which multiple studies for a single comparison have different values for the estimated treatment effect. Because some heterogeneity is likely to occur with 63 studies included in the review, a random-effects model was used for all calculations. Statistical significance was considered for $P < .05$. Data used were cases and events per intervention and study for dichotomous end points. For continuous end points, we used cases, mean, and standard deviation per intervention and study. Consistency and inconsistency in network meta-analysis refer to the situation in which both direct and indirect evidences are available for the same comparison of interventions; the higher the discrepancy, the higher the inconsistency. Inconsistency was reported as $I^2$ values, calculated from a full design-by-treatment interaction Q statistics model. Ranking followed probability score ($P$ score) calculation from the surface under the cumulative ranking curve (SUCRA) method. We used the package netmeta in R (R Development Core Team, Vienna, Austria). This tool calculates weighted averages of direct and indirect estimates for every comparison in the network but takes the direct evidence proportions into account when determining these weights. Risk of bias tables were created in RevMan (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Search Results

The database search of MEDLINE, Web of Science, EMBASE, and CENTRAL on December 2, 2016 yielded 5587 citations. After the removal of 3092 duplicates, 2492 studies remained for title and abstract scan (Figure 1).

We assessed 166 full texts for eligibility, of which 63 met the inclusion criteria. In the case of insufficiently reported data or unclear methods, the corresponding authors were contacted via email for additional information on their

Figure 1. Flow diagram of the literature review.
study data, but none of these requests was answered. A list of included and excluded studies with reasons for exclusion can be found in the Supplemental Digital Content, Document, http://links.lww.com/AA/C621. Within the process, 13 studies were translated via neural machine translation software, of which 9 could be included in the review. Four of the translated studies had to be excluded due to methodological flaws: 2 did not equally distribute coanalgesics and antiemetics among groups, 1 was not randomized, and 1 did not provide equianalgesia as defined in the inclusion criteria. Software translation did not result in unclear information on study methods, and no further translation services were required.

The total number of patients differs among the comparisons of side effect rates due to not every study reporting all end points. Most investigations included data regarding nausea and vomiting (n = 4614), followed by pruritus (n = 3480), sedation events (n = 1528), subjective (n = 213) or objective (n = 956) scores, and patient satisfaction scores (n = 1476). Respiratory depression was reported in most studies but rarely observed.

**Description of Studies**

The smallest study included in this review included 17 patients, and the largest study included 500 patients. Most studies included were conducted in the postoperative setting in which nausea and vomiting could be referred to as PONV, yet there were others with PCA for painful conditions like labor, oral mucositis after bone marrow transplantation, or endoscopy. Nausea and vomiting can therefore not be referred to as PONV in this review. A detailed description of included studies and their methodological aspects (patients, painful interventions/conditions, study period, PCA settings, etc) can be found in the Supplemental Digital Content, Document, http://links.lww.com/AA/C621.

**Risk of Bias Evaluation**

The results from the risk of bias evaluation can be found in Figures 2 and 3. A low risk of bias was given in 233 times of the total 378 items, an unclear risk in 115 cases, and a high risk 30 times. Twenty-three studies remained without any high risk of bias in all categories. Eight studies had a low risk of bias in all categories. The detailed evaluation sheets for all included studies can be found in the Supplemental Digital Content, Document, http://links.lww.com/AA/C621.

**Side Effect Risks**

**Nausea and Vomiting.** Thirty-nine studies reported nausea and vomiting as dichotomous data. Three studies reported nausea as scores only and were not included into the presented calculation of RRs. Data were handled as “overall” nausea and vomiting events over the duration of the study because they were not reported separately in most studies. If incidences of nausea and vomiting were reported separately, then the greater value (usually nausea) was taken into analysis. Because occurrence of 1 does not exclude the other, nausea and vomiting events were not added up. Figure 4A shows the network of studies that contributed to the calculations of RRs for nausea and vomiting, which are presented in Figure 5A. Most comparisons are linked to morphine, which was the comparator for the calculations. Risk of nausea and vomiting was higher with buprenorphine (RR, 1.37 [1.05–1.80]) compared to morphine. Fentanyl (RR, 0.82 [0.67–1.00]) did reach significance toward a lower risk for nausea and vomiting. The inconsistency in this network was P = 0%. A percentage of indirect evidence >50% is reported for alfentanil (90%), sufentanil (58%), and remifentanil (57%).

**Pruritus.** With 39 studies reporting dichotomous data on pruritus, the network for this side effect is smaller than the 1 for nausea and vomiting. It is presented in Figure 4B. The estimated RRs for the incidence of pruritus are shown in Figure 5B. Morphine as the comparator intervention had the second highest RR of causing pruritus. Compared to morphine, nalbuphine (RR, 0.07 [0.01–0.60]), butorphanol (RR, 0.10 [0.01–0.83]), methadone (RR, 0.17 [0.03–0.90]), and pethidine/meperidine (RR, 0.47 [0.25–0.87]) had a significantly lower risk of causing pruritus. The inconsistency in this network was P = 16.7%. A percentage of indirect evidence >50% is reported for remifentanil (62%) and sufentanil (55%).

**Sedation.** Thirty-one studies reported sedation. Reported events of unwanted (over)sedation were extracted as dichotomous data. Objective scores (eg, Richmond Agitation Sedation Scale, Ramsay Sedation Scale, or custom scales) in the individual study were extracted as continuous data. Furthermore, subjective sedation scores were extracted (also as continuous data). When sedation was reported as a score, no study reported both objective and subjective scores; therefore, a maximum of 1 sedation score end point per study was available. To increase statistical power, objective and subjective sedation scores were pooled. The networks and forest plots are shown below for sedation events (Figures 4C and 5C) and sedation scores (Figures 4D and 5D). Both networks for sedation are star networks,
and most comparisons are only direct ones. Pethidine/meperidine (MD, −1.70 [−2.77 to −0.62]), fentanyl (MD, −1.57 [−2.91 to −0.23]), and oxymorphone (MD, −1.40 [−2.41 to −0.39]) had a significantly lower weighted mean sedation score than morphine. Inconsistency in the network for sedation scores was $I^2 = 73.5\%$. In the network for sedation events, inconsistency was $I^2 = 1.2\%$. No significant results were seen in the network for sedation events. A percentage of indirect evidence >50% is reported for fentanyl (54%) in the network of sedation scores. In the network for sedation events, oxycodone had the highest proportion of indirect evidence with 70%. After inconsistency analysis of the comparisons with morphine, the direct and indirect estimates for fentanyl, oxymorphone, and sufentanil (all compared with morphine) showed the most inconsistency. Thus, the estimates combining only direct evidence in the comparison with morphine are given for these 3: fentanyl (MD, −1.00 [−2.97 to 0.97]), oxymorphone (MD, −1.64 [−2.68 to −0.60]), and sufentanil (MD, 0.82 [−0.77 to 2.41]).

**Satisfaction.** Satisfaction was reported as either score data or dichotomous events of an “excellent” rating for the PCA or events of “patients who would want the same treatment next time.” Five studies reported satisfaction as events and could not be connected in a network. For the 17 studies that reported score data, network and forest plots are shown in Figures 4E and 5E. In the network for satisfaction scores, 12 of 19 comparisons are direct with morphine and 7 are between other opioids. It had the highest proportion of indirect evidence in this review. The inconsistency in this network was $I^2 = 0\%$. Tramadol (MD, −1.12 [−2.15 to −0.09]) caused significantly lower satisfaction scores than morphine, whereas oxycodone (MD, 2.00 [1.18–2.82]), alfentanil (MD, 1.95 [1.06–2.85]), remifentanil (MD, 1.80 [1.12–2.48]), fentanyl (MD, 0.96 [0.39–1.52]), and pethidine/meperidine (MD, 0.59 [0.18–1.00]) caused significantly higher satisfaction scores than morphine. No intervention with a proportion of indirect evidence >50% is reported in this network.

**Respiratory Depression.** Respiratory depression was an end point of many studies but rarely occurred. Network meta-analysis was not conducted on these data because most studies reported 0 events of respiratory depression, and continuity correction would have been an impactful number of events added to the total. A high incidence of respiratory depression was reported by the study of Mazanikov et al, in which propofol was routinely administered in addition to the PCA, resulting in respiratory depression in >30% of their cases (for all groups). In addition, 38 studies reported respiratory depression, with 22 events in 2452 patients being highest in sufentanil (9 of 253 cases, 3.6%), alfentanil (1 of 49 cases, 2%), remifentanil (2 of 106 cases, 1.9%), and morphine (7 of 835 cases, 0.8%).

**DISCUSSION**

In this study, we give an overview of the risks for incidence of certain side effects of opioids when compared in strictly equianalgesic doses via PCA. We reviewed the current literature on the 4 largest available databases with a search strategy that made no restrictions on side effects and covered virtually all opioids. The search strategy development and literature-collating process were in collaboration with librarians and can be considered comprehensive.
The definition of equianalgesia in terms of pain scores is in concordance with the reviews of Farrar et al.79 and Cepeda et al.80 Farrar et al.79 reported clinical pain relief at a pain score reduction of 2 (on a 0–10 scale), and Cepeda et al.80 saw a minimal clinical difference between patients starting at a reported pain score difference of 1.3 and consider 2.4 “much” clinical difference. The cutoff of 2.5 for this study might seem high, but as described, it was only allowed to be that high if each group had the higher pain score at least once over the study period and was otherwise 1.5.

Therefore, no systematic alteration toward 1 group regarding the overall opioid doses and expected side effects should have happened. Wrong PCA device programming should not be possible if all equianalgesia criteria are met because it would lead to an imbalance in pain scores and therefore exclusion.

Despite the plethora of available studies comparing different opioids directly via PCA, our network meta-analysis is unique. We found 2 studies to be methodologically somewhat similar. A network meta-analysis of opioid
Side Effects of Opioids in PCA

Side effects in chronic pain was conducted by Meng et al, with 1 distinction being that equianalgesia was not investigated, but side effects of long-term opioid therapy (e.g., constipation) were of interest and side effects were pooled for more statistical power. The study also analyzed and ranked satisfaction regarding the opioid used, reaching similar results to ours. Oxycodeone and fentanyl showed the highest, morphine and hydromorphone intermediate, and tramadol the least satisfaction. The other study was performed by Murphy et al and compared tramadol versus “all opioids” in a conventional meta-analysis, concluding that tramadol causes significantly less pruritus and significantly more nausea and vomiting. Murphy et al pooled data from 12 studies, of which 8 compared tramadol to morphine, whereas we did not pool data but did include 9 of the 12 studies in our own analysis; the remaining were discussed but discarded. The mentioned differences in pruritus and nausea regarding tramadol versus morphine were not observed in our study.

A limitation of this study is that only basic side effects of opioids are characterized and, furthermore, only intravenous, short-term—use side effects. Despite conclusions from the rankings regarding certain adverse effects, known and sometimes unique advantages and disadvantages of substances influence the choice of an opioid. Examples are full and partial agonism at the opioid receptor, agonisms at other receptors with beneficial effects, pharmacodynamics, toxic metabolites, and potential severe side effects (e.g., seizures) being discussed. Yet opioids are used worldwide, with regimes for PCA varying among practitioners, hospitals, and countries regarding not only preference and experience but also drug approval laws, availability, and cost. However, this review focuses on side effects that all opioids share; therefore, we think comparing them directly and altogether is logical and helpful. A limitation of a network meta-analysis lies within the strong assumptions it makes, such as the transitivity assumption. Inconsistency calculations can help confirm or deny this assumption, although they are not guaranteed to be correct.

The network geography can be described as a star network for all end points, with most comparisons linked to morphine. Because morphine is the comparator in this study, conducting a network meta-analysis gives additional information, although most of the evidence is still direct. Sixty-three eligible studies available for analysis are a decent amount, yet these are distributed over 16 opioids with 136 possible combinations of pairwise comparisons. Conducting a pairwise meta-analysis under these circumstances is problematic. In most of the possible pairings, no data would be available, and even with 1 or 2 studies on a pair of opioids, meta-analysis is still not informative. The result would be a handful of informative pairwise comparisons, while most of the 63 studies, despite the high quality of data and fulfilling all eligibility criteria, would not contribute any evidence. Network meta-analysis, however, can include all eligible studies if they can be connected to any other study in the network. Combinations of pairwise comparisons that are unique among the included studies can still enhance the precision of other estimates via indirect network connections, and vice versa.

The rankings presented range from 0 to 1 and are derived from the SUCRA, taking into account the point estimates as well as the precision of the confidence interval. A high estimate with a broad confidence interval is likely to be better than others, but the chance that it could actually be worse than others is also resembled by this method. SUCRA rankings cannot be interpreted clinically like the “number needed to treat” to prevent an event, yet they help comparing point estimates together with their confidence intervals in terms of chances of something to be better or worse than the alternatives. A total range of 0.75 or 0.76 in nausea and vomiting or pruritus from best to worst is rather large and suggests a moderate difference between the best and worst substances. This range is even higher in the satisfaction scores with 0.91 and a bit lower in the sedation networks. We do not have a sufficient pharmacological explanation for the rankings or significant results when compared to morphine, although there are some points to consider. The known characteristics of the different opioids did not influence nausea and vomiting, pruritus, or sedation in any obvious way. Buprenorphine as a partial μ-agonist had a significantly higher risk of causing nausea and vomiting. For pruritus, butorphanol (see above), nalbuphine (mixed agonist–antagonist), and methadone (pure μ-agonist) had significantly lower RRs. Although there were more significant results in the sedation scores, the least sedating substances are also different from each other. Pethidine/meperidine, which has an anticholinergic effect, ranges together with nalbuphine (see above) and fentanyl (pure μ-agonist). Further research investigating the exact mode of action on the central nervous system and other tissues is needed to explain these findings. The substantial amount of inconsistency with 73.5% in the sedation score network is surprising because the same studies and even more were included in larger networks of this study without or close to no inconsistency at all. We performed further inconsistency testing following Krahn et al. The inconsistency is a result of the 3-arm trials (dark gray and blue-colored triangles; Figure 4D), contributing relatively solid evidence to the network, especially on the morphine to pethidine/meperidine and pethidine/meperidine to fentanyl ratios. In these trials, pethidine/meperidine caused much less sedation than morphine, and fentanyl caused even less sedation than pethidine/meperidine. Although the direct comparison of morphine to fentanyl (direct data from another study) did see a reduction in sedation with fentanyl compared to morphine, it was not to the extent that the indirect calculation via pethidine/meperidine would suggest. This discrepancy causes about 50% of the inconsistency in that network. The rest of the inconsistency comes from smaller discrepancies in the butorphanol–morphine studies and the data on oxymorphone, which is part of a 3-arm trial but also has other direct and indirect links in the network. For the resulting comparisons impacted by inconsistency between direct and indirect evidence, the direct estimates are given. Regarding the combination of the 2 types of sedation scores, we performed further analysis, splitting them into 2 separate networks. The results (Supplemental Digital Content, Document, http://links.lww.com/AA/C621) were consistent in terms of their overlapping confidence intervals, although the significance for pethidine/meperidine was
META-ANALYSIS

better tolerability. gave a ranking for each side effect that can potentially be pain treatment effect). The satisfaction with fentanyl and pethidine/meperidine, while tramadol was rated the worst opioid for PCA overall (under strictly equianalgesic conditions, not due to a lower pain treatment effect).

In this review, we tried to answer the question of how much the choice of opiate influences the incidence of side effects in equianalgesic and generalizable settings. We provided a characterization of the most common opioids and gave a ranking for each side effect that can potentially be exploited when choosing a substance for a specific patient in clinical practice or considering a substance change for better tolerability. ❖

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DISCLOSURES

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