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Narrative Review

Analgesic Efficacy and Adverse Effects of Meperidine in Managing Postoperative or Labor Pain: A Narrative Review of Randomized Controlled Trials

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Background: Meperidine, a synthetic opioid, has a rapid onset and short duration of action. Mounting evidence has challenged meperidine's analgesic benefits, and concerns have been raised about its safety profile. Despite recommendations to restrict the prescription of meperidine, the drug remains frequently used.

Objectives: The aim of this study was to evaluate the evidence regarding the efficacy and safety of meperidine for acute postoperative and labor pain.

Study Design: This was a narrative review of the analgesic efficacy and side effects of meperidine compared to other analgesic drugs for acute postoperative and labor pain in adults.

Setting: Randomized controlled trials that compared the analgesic efficacy and side effect profile of meperidine versus another analgesic drug in adult patients were evaluated.

Methods: A systemized search of randomized controlled trials studying meperidine for acute postoperative or labor pain in the adult patient population from PubMed, Medline, and EMBASE was performed. Included studies reported on different routes of meperidine administration including intramuscular, intravenous, and patient-controlled analgesia in various surgical procedures such as abdominal surgery, Cesarean section, gynecological surgery, orthopedic surgery, cardiothoracic surgery, as well as for labor analgesia. Meperidine's analgesic efficacy and safety profile were compared to other opioids (morphine, tramadol, fentanyl, buprenorphine, nalbuphine, and pentazocine), nonsteroidal anti-inflammatory drugs (ketorolac, diclofenac, and indomethacin), dipyrone, ketamine, and bupivacaine.

Results: A total of 62 randomized controlled trials published between 1972 and 2018 were reviewed. Meperidine had a similar or inferior analgesic efficacy compared to other analgesics for acute postoperative or labor pain. Meperidine was associated with more sedation and respiratory depression.

Limitations: The sample sizes of many clinical studies were small, and therefore probably insufficiently powered to detect differences in uncommon side effects, such as central nervous system toxicity. In addition, some of the included clinical studies were old.

Conclusion: Considering the availability of other effective analgesics with potentially fewer side effects, the use of meperidine for acute postoperative or labor pain should not be recommended.

Key words: Acute postoperative pain, adverse effects, labor analgesia, meperidine, pethidine

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Poor acute postoperative pain control is associated with reduced patient satisfaction, delayed recovery, increased morbidity, progression to chronic pain, and overall reduced quality of life (1-4). Opioids are commonly used for the management of acute postoperative pain, and are administered via the oral, sublingual, or parenteral [intramuscular (IM), subcutaneous (SC), intravenous (IV)] routes. Frequently used opioids include fentanyl, meperidine, morphine, hydromorphone, and oxycodone (5,6).

Meperidine was the first synthetic opioid used in humans (7). Oral and injectable formulations are available, and the latter is used subcutaneously, intramuscularly, intravenously, and for neuraxial anesthesia. Typical dosages range from 50 mg to 150 mg orally, 25 mg to 100 mg via SC or IM injection, and 25 mg to 50 mg IV, with repeated doses every 3 to 4 hours as necessary (8,9). Oral meperidine is subject to extensive first-pass metabolism resulting in low oral bioavailability, and this is rarely used (10).

Although early reports attested to the analgesic efficacy and safety of meperidine (11), closer scrutiny revealed these were mostly only case reports (10). Advantages of meperidine include its rapid onset and short duration of action (7). However, there is growing evidence against the alleged benefits of meperidine, and concerns have been raised regarding its safety profile (4,12,13). In addition to typical opioid-related side effects such as constipation and drowsiness, meperidine has also been associated with serious side effects including central nervous system excitation and serotonin syndrome (10). It is also associated with intoxicating effects, making it considerably addictive (10). These concerns have led to guidelines and recommendations advocating the use of other opioid drugs and the removal of meperidine from health-system formularies (7,14-16).

Despite recommendations against meperidine prescription, the drug is still frequently used in many parts of the world (17,18). A study showed that 1 in 8 older surgical patients were prescribed meperidine (17). This suggests that awareness and knowledge about the potential problems and analgesic efficacy of meperidine may still be lacking amongst the overall population of health care professionals. This may be worsened by the fact that there is currently a lack of review of clinical evidence on the efficacy, tolerability, and safety of meperidine for postoperative pain management. Previous reviews of meperidine in acute postoperative pain included only a small number of studies (10,19), or only looked at certain routes of administration (19). Therefore, we performed a narrative review of published randomized controlled trials that evaluated the analgesic efficacy and adverse effects of meperidine for acute postoperative pain and labor pain management.

Methods

1.1. Literature Search Strategy

A literature search in PubMed, Medline, and EMBASE databases was performed using the following keywords: ("meperidine" or "pethidine") and ("operation," "surgery," "postoperative," "operative," or "surgical") in combination with ("pain," "analgesic," or "analgesia") and ("safety," "safe," "toxicity," "adverse effect," or "adverse event") and ("efficacy," "effect," or "effectiveness"). Randomized controlled trials published in peer-reviewed journals were included. The language was restricted to English. Papers investigating meperidine in pediatric or adolescent populations were excluded. Given the search was not restricted by publication date, papers that could no longer be retrieved on the internet or hospital library were excluded. All original papers on human clinical studies published up to the period December 2018 were included.

1.2. Studies Selection

The initial literature search yielded 575 publications from PubMed and 845 from EMBASE/Medline (Fig. 1). After removal of duplicates, 1,138 articles were assessed; of these, 128 articles fulfilled the inclusion criteria based on title and abstract. These articles were then independently evaluated against the inclusion criteria by 2 investigators, and disagreements between the investigators were discussed and resolved. A total of 62 studies were included for the final analysis. Considering the heterogeneity in methodology and treatment indications among studies published between 1972 and 2018, a narrative review of these studies was performed.

1.3. Studies Characteristics

The selected studies were randomized controlled trials. Pain intensity was measured by visual analog scores (VAS – 10cm/100mm, 150mm), verbal rating scales, pain intensity difference, summed pain intensity difference scores, total relief scores, or as 3-, 4-, or 5-point pain scales. Some studies used both observer-rated and patient-rated assessments of pain. Treatment-associated adverse effects were also extracted

from these included studies.

Meperidine was given via IM injections, IV injections, a combination of IM and IV injections, IV patient-controlled analgesia (PCA), epidural infusions, patient-controlled epidural analgesia, intraarticular (IA) administration, intraperitoneal injection, SC injections, and SC infusions.

1.4. Inclusion and Exclusion Criteria

This review included randomized controlled trials that compared the analgesic efficacy and safety of meperidine to other analgesics for acute postoperative or labor pain in adult patients. Clinical studies that administered meperidine as medication for chronic pain, in the pediatric population, in oral formulation, and in the emergency room other than for surgery were excluded. Animal studies were excluded. Studies that compared different routes of meperidine in the absence of another comparator drug or placebo were ineligible for inclusion in this review. Studies not published in English, and those presented or published at conferences, revisions, editorials, or opinion articles were not included.

The data of included studies were extracted and tabulated to allow qualitative comparisons of interventions. The outcome measures chosen for comparison were analgesic efficacy (pain scores), adverse effects, and patient satisfaction.

Review and Results

2.1. Analgesic Efficacy by Surgical Setting

2.1.1. Abdominal Surgery

Fifteen studies compared the postoperative pain relief of meperidine with other analgesics after abdominal surgery (Table 1) and found that meperidine was associated with higher VAS pain scores (20-22). In one older study that included both patients who underwent abdominal surgery (specifically lower abdominal gynecological surgery) and those who had Cesarean section, analgesia provided by epidural meperidine was not significantly different from epidural bupivacaine (23). Epidural bupivacaine in combination with fentanyl resulted in significantly lower pain scores compared to IM meperidine after colorectal cancer surgery (24).

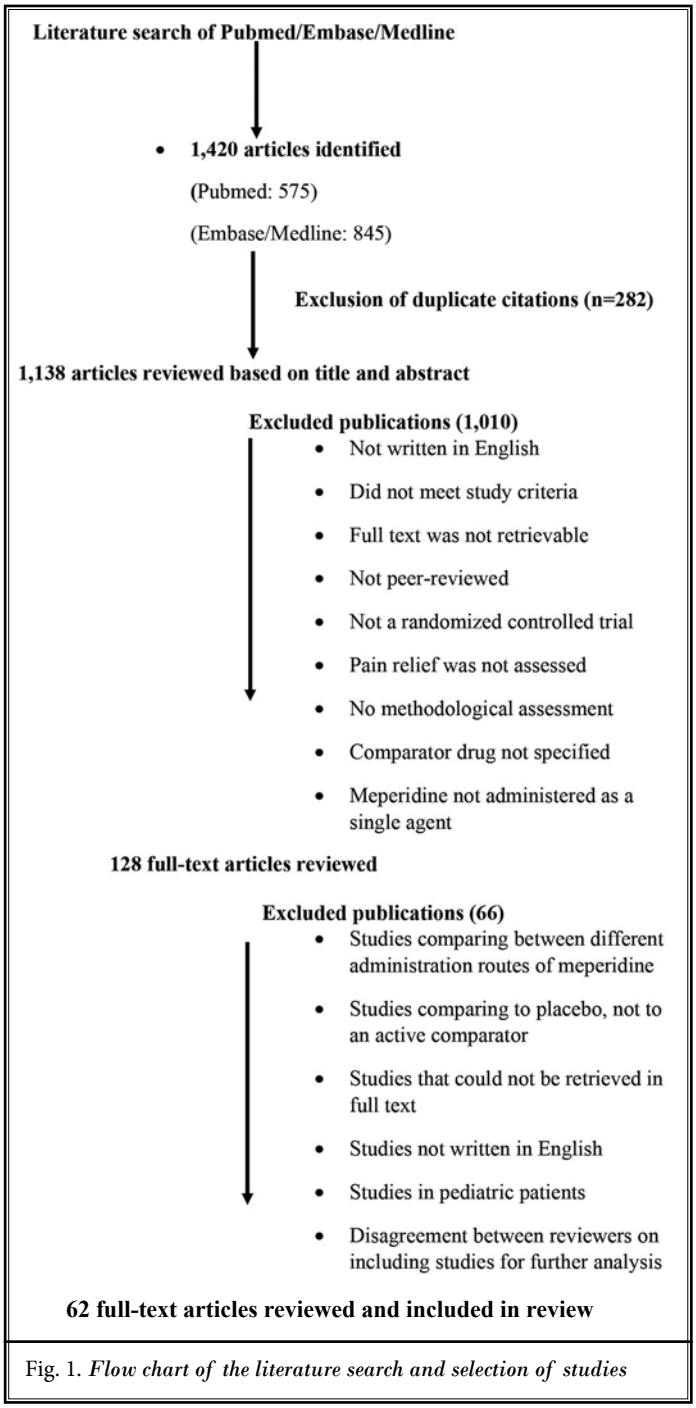

Fig. 1. *Flow chart of the literature search and selection of studies*

Two studies comparing meperidine to morphine revealed that patients on meperidine experienced significantly more pain (25,26). The first study compared IM meperidine to PCA morphine after vertical gastroplasty, while the second study compared PCA meperidine to PCA morphine for major ab-

Table 1. *Randomized controlled trials of meperidine in managing pain after abdominal surgery*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency and Administration Routes	Surgery Type	Number of Patients	Mean Age [Gender]	Analgesic Results	Adverse Event
Salman et al (2013) [20]	Bupivacaine	IV PCA meperidine (loading and infusion doses at 0.1 mL/kg) Epidural bupivacaine (loading and infusion doses at 0.1 mL/kg)	Abdominal aortic surgery (elective)	80	59.4 ± 9.7 [M/F = 38/2] 61.7 ± 8.1 [M/F = 39/1]	Epidural bupivacaine had lower sedation and VAS scores than IV meperidine (P < .05 each).	Postoperative nausea was more prevalent in the meperidine group (P < .05).
Raddi et al (2009) [21]	Bupivacaine	IV meperidine (1 mg/kg) Bupivacaine 0.5% injected intra-pleurally (20 mL)	Open cholecystectomy	100	45.72 ± 7.12 [M/F = 20/30] 45.68 ± 7.93 [M/F = 21/29]	At 30 min after drug administration, IV meperidine had a significantly higher mean VAS score (P < .01). At every subsequent time interval (30-360 min), IV meperidine consistently had significantly higher mean VAS scores (P < .001).	There were no clinical complications for bupivacaine. 18% of the IV meperidine group had postoperative nausea and vomiting.
Ebrahimifard et al (2013) [22]	Bupivacaine	IV meperidine (25 mg) IP 0.5% bupivacaine (20 cm3)	Laparoscopic cholecystectomy	48	47 ± 11 [M/F = 4/16] 49 ± 10 [M/F = 5/15]	At 1, 4, and 8 hrs after surgery, VAS pain scores were significantly lower with bupivacaine than with meperidine (P = .035, .048, and .009, respectively). There was no significant difference between the groups 24 hrs after the procedure (P = .223).	Nausea and vomiting were lower in the bupivacaine group.
Brownridge et al (1985) [23]	Bupivacaine	IM meperidine (100 mg) Epidural meperidine (50 mg) Epidural bupivacaine (25 mg)	Lower abdominal surgery (The study also included patients with Cesarean section.)	19	NS (All patients were female in this study.)	Analgesia provided by epidural meperidine 50 mg was superior to IM meperidine 100 mg (P < .05) but not statistically better than epidural bupivacaine.	There were no clinically significant differences in sedation, nausea, itching, respiratory rate, or blood pressure.
Rimaitis et al (2003) [24]	Bupivacaine with fentanyl	IM meperidine (0.5 mg/kg) every 4 hrs Epidural continuous infusion bupivacaine (1.0 mg/mL) with fentanyl (5 mg/mL) at a rate of 3-6 mL/hr	Colorectal cancer surgery	100	67 ± 11 [M/F = 24/26] 65 ± 13 [M/F = 25/25]	VAS pain scores at rest and on coughing were significantly better in the epidural analgesia group than in the systemic IM meperidine analgesia group (P < .05).	The meperidine group had more sedation, nausea and vomiting (P < .05). The bupivacaine group had more pruritus (P < .05). No statistically significant differences (P = .62) in postoperative complications were found between the 2 groups.

Table 1 (cont.). *Randomized controlled trials of meperidine in managing pain after abdominal surgery*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency and Administration Routes	Surgery Type	Number of Patients	Mean Age [Gender]	Analgesic Results	Adverse Event
Kyzer et al (1995) [25]	Morphine	IM meperidine (50-100 mg) every 3-4 hrs as needed IV PCA morphine (5 mg, lockout interval 5 min in recovery room, followed by 2 mg dose lockout interval 15 min)	Sialastic ring vertical gastroplasty	23	37 (19-42)* [M/F = 4/7] 34 (22-56)* [M/F = 5/7]	The difference in the amount of narcotics used between the groups was statistically significant ($P < .005$). Significantly higher pain scores were seen in the meperidine group ($P < .01$).	There was a significantly higher incidence of wound infection in the IV PCA morphine group (no P value).
Plummer et al (1997) [26]	Morphine	IV PCA meperidine (bolus doses of 9, 12, or 18 mg) IV PCA morphine (bolus doses of 0.75, 1.0, or 1.5 mg)	Major abdominal surgery	102	63 (23-86)* [M/F = 25/25] 62 (24-89)* [M/F = 24/28]	Pain on sitting ($P = .037$) but not pain at rest ($P = .8$) was significantly less in patients receiving morphine.	Severity of nausea, mood disturbances, and incidence of unusual dreams did not differ significantly between the drugs.
Woodhouse et al (1999) [27]	Morphine Fentanyl	IV PCA One syringe each of morphine (bolus 1 mg), meperidine (bolus 10 mg), and fentanyl (bolus 10 mg) plus an additional syringe of the drug the patient received first. PCA given for 32 hours post operation.	Abdominal surgery (The study also included patients who went through orthopaedic surgery.)	82	47 ± 16** [NS]	No significant differences in pain scores were found between the opioids.	There were significantly fewer reports of sedation in patients on fentanyl versus morphine ($P = .003$) or meperidine ($P = .03$). No significant differences in the incidence of nausea, vomiting, pruritus were found between the groups.
Kølliker et at (1972) [28]	Pentazocine	IV meperidine (50 mg per 70 kg) IV pentazocine (15 mg per 70 kg) IV saline (placebo) All patients pre-medicated before surgery with 50 mg of meperidine per 70 kg Additional pentazocine and meperidine given after surgery	Upper abdominal surgery	91	NS [M/F = 10/23] NS [M/F = 6/13] NS [M/F = 16/23]	Meperidine had better pain relief efficacy than pentazocine ($P < .05$) (investigator assessment). Pentazocine was an effective analgesic drug, but at the dosage employed, it was less potent and had a shorter duration than meperidine ($P < .05$).	More patients with meperidine experienced nausea. a (80%)
Paymaster et al (1977) [29]	Pentazocine Meptazinol	IM meperidine (100 mg) IM meptazinol (100 mg) IM pentazocine (60 mg)	Abdominal surgery or orthopaedic surgery	75	45.0 ± 2.4 [M/F = 3/22] 44.2 ± 1.6 [M/F = 3/22] 44.4 ± 2.2 [M/F = 3/22]	No differences in pain relief were found among the 3 drugs.	Twelve percent of the group receiving pentazocine, 28% of meptazinol, and 40% of meperidine group had side effects (nausea, vomiting, confusion, pallor, sweating), but these differences were not statistically significant.

Table 1 (cont.). *Randomized controlled trials of meperidine in managing pain after abdominal surgery*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency and Administration Routes	Surgery Type	Number of Patients	Mean Age [Gender]	Analgesic Results	Adverse Event
Carl et al (1987) [30]	Buprenorphine	IM meperidine (75 mg per injection) Sublingual buprenorphine (0.4 mg) IM buprenorphine (0.3 mg)	Major abdominal surgery	54	58, 52, 55 of 3 groups*** [NS]	Median pain intensity differences showed equal pain relief in all 3 groups.	Five patients on meperidine had respiratory acidosis; 3 required IPPV treatment, and one case in the IM buprenorphine group required IPPV treatment. Significantly more patients on IM meperidine had nausea.
Patel et al (1980) [31]	Dipyrone	IM meperidine (100 mg) IM dipyrone (2.5 mg)	Elective exploratory laparotomy	100	58, 52, 55 of 3 groups*** [NS]	Maximum pain relief was seen 2 hours after drug administration in both groups and there was no statistically significant difference in pain scores.	No treatment-related adverse effects were recorded. In the meperidine group, one patient had rigors, and another had retention of urine.
Hew et al (1987) [32]	Nalbuphine	IM meperidine (75 mg) IV nalbuphine (20 mg) IV nalbuphine (40 mg) Medication given for 2 hours	Abdominal surgery (the study also included patients who went through orthopaedic surgery)	150	42 ± 11 [M/F = 19/31] 40 ± 11 [M/F = 9/41] 40 ± 11 [M/F = 8/42]	The analgesic efficacy of nalbuphine (both 20 mg and 40 mg) was similar to meperidine 75 mg. No significant differences were found in pain intensity, pain intensity differences, or in pain relief.	Twenty-two percent of patients on meperidine and 2%-6% patients on nalbuphine 20 mg had nausea and vomiting. This difference was statistically significant. No differences were found between nalbuphine 40 mg and meperidine.
Folsland et al (1990) [33]	Ketorolac	IM meperidine (100 mg) IM ketorolac (10 mg) IM ketorolac (30 mg) IM placebo	Major abdominal surgery	129	57.0 ± 16.3 [M/F = 16/11] 57.4 ± 13.8 [M/F = 7/25] 54.7 ± 16.8 [M/F = 17/12] 57.7 ± 16.7 [M/F = 20/12]	During the first 2 hours, meperidine had significantly better pain relief efficacy than ketorolac or placebo ($P < .05$). At 4-7 hours after drug administration, there was no significant difference in pain scores.	Seven patients on 10 mg ketorolac, 2 on 30 mg ketorolac, 8 on 100 mg meperidine, and 2 on placebo had nausea.

Table 1 (cont.). *Randomized controlled trials of meperidine in managing pain after abdominal surgery*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency and Administration Routes	Surgery Type	Number of Patients	Mean Age [Gender]	Analgesic Results	Adverse Event
Petersson et al (1986) [34]	Physostigmine	IV meperidine chloride (50 mg) IV physostigmine salicylate (2 mg) IV saline (placebo)	Abdominal surgery (the study also included patients who went through orthopedic surgery, ENT)	60	48.2 ± 15.7 [M/F = 5/15] 45.7 ± 15.7 [M/F = 3/17] 47.0 ± 16.6 [M/F = 3/17]	After 15 minutes, there was no difference between physostigmine and meperidine. From 30 minutes onwards, meperidine had significantly reduced pain scores versus placebo and physostigmine ($P <$ .05).	One patient each in the meperidine and placebo groups and 6 patients in the physostigmine group had nausea. No other side effects related to the test drugs were noted. The meperidine group had a higher level of sedation ($P <$ .05) until one hour post administration.

Abbreviations: ENT, Ear, Nose, and Throat; F, female; IM, intramuscular; IP, intraperitoneal; IPPV, intermittent positive-pressure ventilation; IV, intravenous; M, male; NS, not specified; PCA, patient controlled analgesia; VAS, Visual Analog Scale
*Data were presented as mean (range)
**Data were presented regardless of treatment groups
***Data were presented as median only and not specific to each group

dominal surgery. A study of patients who either underwent abdominal or orthopedic surgery, however, found no significant differences in pain scores between PCA meperidine and PCA morphine (27). Intravenous pentazocine was less potent than IV meperidine in patients who underwent upper abdominal surgery (28), and a study investigating the same drugs intramuscularly after abdominal surgery found no significant difference in pain relief between the 2 analgesics (29).

Other clinical studies showed that IM meperidine had similar analgesic efficacy as sublingual buprenorphine after major abdominal surgery (30), IM dipyrone after elective exploratory laporatomy (31), and IV nalbuphine (32) and IM ketorolac (33) after abdominal surgery. A study published in 1986 demonstrated that meperidine had better analgesic efficacy than IV physostigmine following major abdominal surgery (34).

2.1.2. Labor Analgesia

Thirteen studies compared the analgesic efficacy of IM or IV meperidine for labor pain control versus other analgesics (Table 2), and most of them reported inferior analgesic efficacy compared to meperidine (35-45) except 2 studies comparing meperidine with tramadol (46) and saline (47). A study by Keskin et al (46) showed a significantly greater reduction in labor pain after administration of meperidine compared to tramadol according to the Wong-Baker Faces Pain Rating Scale in the first 30 and 60 minutes, but similar pain control was observed afterwards. One study found meperidine plus promazine to have less effective analgesia when compared to epidural bupivacaine (35). Four other studies showed that IM meperidine had significantly inferior analgesic efficacy compared to epidural bupivacaine, remifentanil, and diamorphine for labor pain control (36,37,40,43-45). Additionally, IV PCA meperidine compared to epidural bupivacaine during spontaneous labor had significantly less analgesic efficacy (38). Submucous paracervical blockade with bupivacaine provided significantly better pain relief than IM meperidine during labor (39). Two studies comparing parental meperidine with SC or intranasal fentanyl (41) and IV paracetamol (42) showed similar outcomes in labor pain control.

2.1.3 Cesarean Section

Seven studies reported on the use of meperidine in patients who underwent Cesarean section (Table 3). Intramuscular meperidine was as effective in controlling post-Cesarean section pain as oral methadone (48), but less effective than IM or rectal diclofenac in 3 other studies (49-51). Comparable analgesic efficacy was reported from one study comparing SC meperidine with oral diclofenac (52). Two studies showed that PCA

Table 2. *Randomized controlled trials of meperidine in managing pain after spontaneous or induced labor.*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency and Administration Routes	Surgery Type	Number of Patients	Mean Age	Analgesic Results	Adverse Event
Harrison et al (1987) [35]	TENS Entonox Bupivacaine	IM 50 mg meperidine + 50 mg promazine TENS Entonox Lumbar epidural 0.375% bupivacaine (5 mL)	Labor	170	NS	Eighty-eight percent of patients on epidural said it was fully effective; 90% on Entonox, 96% on TENS, and 54% on meperidine plus promazine found partial relief. Eighty-two percent of patients on TENS and 80% on meperidine plus promazine required additional analgesia.	There was no significant difference between any of the groups in terms of cord pH or Apgar scores at 1 and 5 minutes.
Philipsen et al (1989) [36]	Bupivacaine	IM meperidine (75 mg). Epidural bupivacaine 0.375% (1 mL/10 kg)	Labor – spontaneous	112	26 (18-40)* 25 (19-37)*	The analgesic efficacy of the epidural blockade was significantly better than that of parenteral meperidine (P <.001).	There were no differences in neonatal cord blood partial pressure of carbon dioxide, pH, or Apgar scores.
Jain et al (2003) [37]	Bupivacaine with fentanyl Tramadol	IM meperidine (50 mg for weight ≤ 50 kg, 75 mg for 50-75 kg, and 100 mg if > 75 kg. If a repeat dose was required within 4 hours, half of the initial dose was given, with a maximum of 200 mg in 4 hours, or 400 mg in 24 hours. Each dose of meperidine was combined with promethazine (25 mg). Epidural bupivacaine 0.15% (15 mg) and fentanyl (30 mg) Tramadol 1 mg/kg	Labor	126	24.8 ± 2.6 25.7 ± 3.1 24.1 ± 2.8	Significantly more patients on epidural bupivacaine achieved complete pain relief versus tramadol or meperidine (P < .001).	In the epidural group, 40% had urinary retention and 16% had motor weakness. Sedation was the only side effect seen in the meperidine (41% intrapartum and 66% postpartum) tramadol groups (9% intra- and postpartum) (P < .01). Respiratory depression was seen in 3 neonates in the meperidine group and 2 in the tramadol group. Three neonates in the meperidine group and 2 in the tramadol group had poor respiratory efforts, which improved on use of naloxone and with assisted ventilation for a few minutes.
Sharma et al (1997) [38]	Bupivacaine with fentanyl	IV PCA meperidine (50 mg) and promethazine hydrochloride (25 mg). IV PCA of 10-mg bolus/10 minutes as needed for first hour, 15 mg/10 minutes as needed until delivery. Continuous epidural infusion of 0.125% bupivacaine with 2 μg/mL fentanyl followed by an initial infusion rate of 8-10 mL/hr	Labor	715	21.8 ± 5 22.3 ± 5	Women who received epidural bupivacaine reported lower pain scores during labour and delivery compared to patient-controlled IV meperidine analgesia.	Women who received epidural analgesia had a significantly higher incidence of hypotension compared to meperidine (P < .001). There was no significant difference in the incidence of nausea and vomiting between the 2 groups. Sedation scores were significantly higher with IV PCA compared with epidural analgesia (P < .001). Significantly more neonates required naloxone for depressed respiration with meperidine than epidural analgesia (P < .05).

Table 2 (cont.). *Randomized controlled trials of meperidine in managing pain after spontaneous or induced labor.*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency and Administration Routes	Surgery Type	Number of Patients	Mean Age	Analgesic Results	Adverse Event
Jensen et al (1984) [39]	Bupivacaine	IM meperidine (75 mg) Submucous paracervical blockade 0.25% bupivacaine (12 mL)	Labor	117	NS	Seventy-eight percent of the women in the paracervical blockade group achieved full or acceptable pain relief vs 31% in the meperidine group ($P < .01$). Average pain relief in paracervical blockade group was higher than meperidine at 20, 40, and 60 minutes.	Two infants in the paracervical blockade group and one in the meperidine group had transient foetal bradycardia. Fetal distress (umbilical artery pH of 7.15 or less and/or a one-minute Apgar score of 7 or less) was more frequent in the meperidine group versus paracervical blockade group ($P < .05$).
Ng et al (2011) [40]	Remifentanil	IM meperidine (50-75 mg) IV PCA bolus of Remifentanil (25-30 µg per bolus)	Labor	68	29 ± 5 28 ± 5	Women who received patient-controlled remifentanil reported lower pain scores during labour and delivery compared to IM meperidine analgesia.	There were no differences in opioid-related adverse outcomes between groups. Nausea, vomiting, and pruritus were rare, but dizziness was common with both treatments.
Fleet et al (2015) [41]	Fentanyl	IM meperidine (100 mg/2 mL; initial dose 100 mg and repeated dose after 3-4 hours if required, maximum total dose of 200 mg) SC Fentanyl (200 mcg-bolus dose; after one hour additional 50 mcg every 15 minutes as requested, up to 650 mcg) IN Fentanyl (54 mcg; maximum hourly dose was 600 mcg with a maximum total dose of 1200 mcg)	Labor	156	28.6 ± 4.7 29.9 ± 5.5 29.0 ± 6.3	There was no significant difference between groups for reductions in pain scores, but all groups reported clinically significant reductions in pain scores (mean range 1.2-16; $P < .001$).	Women in fentanyl groups experienced less sedation ($P \leq .03$), shorter labors by at least 2 hours ($P < .05$), and fewer difficulties establishing breastfeeding ($P < .01$). Neonates in the meperidine group were more likely to require nursery admission ($P < .02$).
Elbohoty et al (2012) [42]	Paracetamol	IV meperidine (50 mg) IV paracetamol (1,000 mg)	Labor	52	NS	Both potency and duration of paracetamol was no less than that of meperidine.	Dizziness, blurred vision and vomiting were observed in 64% of women given meperidine, while none were reported for paracetamol. one-minute Apgar scores were significantly lower in the pethidine group.

Table 2 (cont.). *Randomized controlled trials of meperidine in managing pain after spontaneous or induced labor.*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency and Administration Routes	Surgery Type	Number of Patients	Mean Age	Analgesic Results	Adverse Event
Loughnan et al (2000) [43]	Bupivacaine	IM meperidine (300 mg) Epidural bupivacaine (initial dose 0.25% bupivacaine in 10-15 mL followed by infusion of 0.125% bupivacaine at 10-15 mL/hr until second stage).	Labor	614	26.6 (15-39)** 26.9 (14-42)**	Women in the epidural group were significantly more likely to grade their pain relief as good or excellent in the first and second stages ($P < .001$). Mode of delivery was similar between groups, but there was a slight but insignificant decrease in the normal vaginal delivery rate in the epidural group ($P = .9$).	NS
Wee et al (2014) [44]	Diamorphine	IM meperidine (150 mg) IM diamorphine (7.5 mg)	Labor	484	28.7 ± 5.6 28.7 ± 6.1	There was better pain relief with diamorphine at 60 minutes and over the whole 3-hour period with a significant reduction in VAS scores from baseline ($P < .001$).	Women in the diamorphine group were more likely to have hemoglobin saturation $SpO_2 < 97\%$ at 60 minutes ($P = .04$) without clinically significant hypoxia. Women in the diamorphine group were more likely to experience one or more nausea events during the whole 3-hour period ($P = .047$. There was more moderate or severe neonatal sedation in the meperidine group 2 hours after delivery ($P = .04$).
Douma et al (2010) [45]	Remifentanil Fentanyl	IV PCA meperidine (49.5 mg-loading and 5-mg boluses with a maximum dose limit of 200 mg) IV PCA remifentanil (40 µg-loading dose and 40 µg per bolus with maximum dose limit of 1200 µg/hr) IV PCA fentanyl (50 µg-loading and boluses of 20 µg with a maximum dose limit of 240 µg/hr)	Labor	159	33.6 ± 5.5 33.1 ± 5.0 33.5 ± 4.1	Remifentanil was associated with the greatest decrease in pain scores, but the differences were significant only at one hour (meperidine vs. remifentanil, $P < .001$; remifentanil vs. fentanyl, $P < .01$). Overall satisfaction scores were higher with remifentanil, but produced more sedation and itching.	More periods of desaturation ($SaO_2 <$ 95%) were observed for remifentanil and fentanyl. There were no significant differences in fetal outcome between the 3 groups.

Table 2 (cont.). *Randomized controlled trials of meperidine in managing pain after spontaneous or induced labor.*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency and Administration Routes	Surgery Type	Number of Patients	Mean Age	Analgesic Results	Adverse Event
Keskin et al (2003) [46]	Tramadol	IM meperidine (100 mg) IM tramadol (100 mg)	Labor	59	25.07 22.43	Pain relief was greater in the meperidine group at 30 and 60 minutes after drug administration (P <.05).	Incidence of nausea and fatigue was statistically higher in the tramadol group at 60 minutes (P < .05). Both groups reported a significant decrease in systolic and diastolic blood pressure and an increase in heart rate. No significant differences in duration of labor and Apgar scores were found between groups.
Tsui et al (2004) [47]	Saline	IM meperidine (100 mg) IM saline (placebo) (100 mg)	Labor	50	28.4 ± 4.4 28.4 ± 5.1	There was a significant reduction in VAS pain scores at 30 minutes in the meperidine group	Significantly higher sedation scores were observed in the meperidine group than in the control group at 15 minutes (P = .002) and at 30 minutes (P = .005). Similar other maternal side effects and neonatal outcomes were found in both groups.

Abbreviations: Apgar, Appearance, Pulse, Grimace, Activity, and Respiration; IM, intramuscular; IN, intranasal; IV, intravenous; NS, not specified; PCA, patient controlled analgesia; SC, subcutaneous; TENS, transcutaneous electrical nerve stimulation; VAS, Visual Analog Scale.
*Data presented as median (range).
**Data presented as mean (range).

meperidine had less analgesic efficacy when compared to PCA and epidural morphine (53,54), or PCA oxymorphone (54).

2.1.4. Gynecological Surgery

Nine studies investigated the analgesic effect of meperidine versus other analgesics after gynecological surgery (Table 4). Three studies found no significant difference in analgesia between meperidine and morphine when used intravenously or as PCA after elective total abdominal hysterectomy, elective gynecological surgery, or abdominal hysterectomy (55-57). One study found IM meperidine to be more effective than PCA morphine following laparoscopic ovarian cystectomy (58). PCA meperidine had similar analgesic efficacy as PCA tramadol after abdominal hysterectomy (57,59), and IM meperidine provided equal analgesia when compared to sublingual buprenorphine after laparotomy (60). Parenteral meperidine was less effective for pain control versus parenteral dipyrone after gynecological surgery (61), and intraperitoneal (IP) meperidine was less effective than IP bupivacaine for pain relief after laparoscopic tubal ligation (62). After postpartum episiotomy, IM meperidine provided less pain relief than IM metkephamid (63).

2.1.5. Orthopedic Surgery

Nine studies compared meperidine to other analgesics in patients who underwent orthopedic surgery (Table 5). Although in the first 30 minutes postsurgery meperidine produced a lower pain intensity compared to tramadol, overall similar effectiveness on the pain endpoint was noted between IV meperidine and IV tramadol after total hip or total knee replacement (64), and between IM meperidine and IM ketorolac after major orthopedic surgery (65). Intramuscular meperidine was less effective than IM diclofenac after hip replacement for arthrosis (66) and IM nalbuphine after elective surgery (67). Two studies comparing IA meperidine with IA morphine after arthroscopic meniscectomy or

Table 3. *Randomized controlled trials of meperidine in managing pain after Cesarean section.*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency and Administration Routes	Surgery Type	Number of Patients	Mean Age	Analgesic Results	Adverse Event
Shahraki et al (2012) [48]	Methadone	IM meperidine (0.7 mg/kg every 6 hours for 24 hours) Oral methadone (0.7 mg/kg – every 6 hours for 24 hours) All patients were given a single dose of IM meperidine (50 mg) in the recovery room	Cesarean section	102	27.3 ± 4.7 28.4 ± 4.3	There were no significant differences in pain scores between groups in each follow-up period.	There was no difference in terms of complications. No complication was reported in neonates of the 2 groups during the first 72 hours of the follow-up period.
Rahmanpoor et al (2007) [49]	Diclofenac	Meperidine 25 mg followed by 25 mg every 8 hours for the first 24 hours 100 mg rectal;diclofenac followed by 100 mg diclofenac every 8 hours for the first 24 hours	Cesarean section	122	26 ± 5.2 25.69 ± 5.8	VAS scores for pain were significantly lower for diclofenac at all time points (i.e., $P = .046$ for the first 4 hours post-operation; $P = .005$ for 20-24 hours after operation).	There were no differences in the incidences of vomiting and ileus.
Bozkurt et al (2009) [50]	Diclofenac sodium	Meperidine (6 x 50 mg) IM diclofenac sodium (2 x 75 mg) IM diclofenac sodium (2 x 75 mg) with additional breakthrough IM meperidine (50 mg) if needed	Cesarean section	130	29.6 ± 6.02 30.98 ± 5.06 29.25 ± 5.88	Diclofenac had lower mean pain scores versus meperidine at rest and during coughing ($P < .05$ for both).	There were no statistically significant differences in itching, nausea, vomiting and abdominal distension between groups. Diclofenac and diclofenac plus meperidine resulted in significantly less sedation compared to meperidine ($P < .05$).
Soroori et al (2006) [51]	Diclofenac	Rectal suppository diclofenac (100 mg) at the end of operation and 8, 16, and 24 hours after the operation IM meperidine 1 mg/kg at the end of operation and 8, 16, and 24 hours after the operation	Cesarean section	240	27.2 ± 6.5 26.4 ± 5.6	Diclofenac had significantly lower pain scores than meperidine at 10, 18, and 26 hours after surgery ($P < .05$).	Eleven cases of dizziness occurred in the meperidine group. No dizziness was reported in the diclofenac group. Sedation was significantly higher in the meperidine group. Nausea and vomiting occurred at similar rates in both groups.
Marzida et al (2009) [52]	Diclofenac	Subcutaneous meperidine (1 mg/kg every 8 hours and additional doses made available on request) Oral diclofenac (75 mg twice daily) All patients received 2-2.5 mL of 0.5% heavy bupivacaine	Cesarean section	40	30.4 ± 4.4 31.4 ± 5.6	Pain relief was adequate and comparable in both groups with similar mean Visual Analog Scores during the second and third day of the study period.	The incidence of nausea and vomiting was similar in both groups. Those in the meperidine group were significantly more sedated than those in the diclofenac group ($P = .024$). No other adverse events were recorded.

Table 3 (cont.). *Randomized controlled trials of meperidine in managing pain after Cesarean section.*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency and Administration Routes	Surgery Type	Number of Patients	Mean Age	Analgesic Results	Adverse Event
Cade et al (1993) [53]	Morphine	IV PCA meperidine (2 different bolus doses: 10 mg and 20 mg) Epidural morphine (3.5 mg in 5 mL saline)	Cesarean section	132	NS	Epidural morphine had the greatest pain relief efficacy (average pain score of 1.8 vs 1.9-3.4 for meperidine).	In the morphine group, nausea, vomiting, dizziness, and pruritus were significantly more frequent (P = .003, .006, .05, and P < .001, respectively), while drowsiness was significantly less frequent (P = .05) than in other groups. Numbness was uncommon and was not significantly different between groups (P = .22).
Sinatra et al (1989) [54]	Morphine Oxymorphone	IV PCA meperidine (18 mg) every 8 minutes as needed within 24 hours IV PCA morphine (1.8 mg) every 8 minutes as needed within 24 hours IV PCA oxymorphone (0.3 mg) every 8 minutes as needed within 24 hours	Cesarean section	75	NS	All patients achieved an excellent level of analgesia at rest. The percentage of patients reporting severe pain during movement was highest with meperidine (P < .05). VAS scores over 24 hours were similar between groups.	Oxymorphone was associated with the highest incidence of nausea and vomiting (P < .05). Morphine had significantly increased rates of sedation compared to meperidine and oxymorphone (P < .05).

Abbreviations: IM, intramuscular; IV, intravenous; NS, not specified; PCA, patient-controlled analgesia; VAS, Visual Analog Scale.

arthroscopic anterior cruciate ligament reconstruction found IA meperidine to be less effective for pain relief compared to IA morphine (68,69). Another study showed that although IA meperidine provided early analgesic efficacy, it was less durable than IA morphine after arthroscopic meniscectomy (70). One study found IA morphine, meperidine, and fentanyl to have comparable analgesia after arthroscopic knee joint surgery (71). Intraarticular meperidine had similar analgesic efficacy to IA methadone after arthroscopic meniscectomy (68), and to IA fentanyl after arthroscopic knee joint surgery or knee arthroscopic meniscectomy (71,72).

2.1.6. Cardiothoracic Surgery

Three studies investigated the analgesic effects of meperidine in cardiothoracic surgery (Table 6). Intramuscular meperidine had a similar analgesic efficacy to IM ketamine after thoracic surgery (73), and IV meperidine also had a similar analgesic efficacy to IV morphine and IV ketobemidone post open-heart surgery (74). The analgesic effect of PCA meperidine following open-heart surgery was similar to PCA fentanyl and PCA remifentanil, and better than PCA tramadol (75).

2.1.7. Other Types of Surgery

Seven studies investigated the analgesic efficacy of meperidine in other surgical settings (Table 7). In patients who underwent tonsillectomy, IM meperidine showed similar efficacy to IM tilidine and rectally administered indomethacin (76). One study showed that patient-controlled epidural meperidine was less effective for pain relief compared to patient-controlled

Table 4. *Randomized controlled trials of meperidine in managing pain after gynecological surgery.*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency, and Administration Routes	Surgery Type	Number of Patients	Mean Age	Analgesic Results	Adverse Event
Stanley et al (1996) [55]	Morphine	IV PCA meperidine (bolus dose 20 mg) IV PCA morphine (bolus dose 2 mg) Increments were given every 2-4 minutes by the anaesthetist until pain control was judged to be comfortable and satisfactory by the patient.	Elective total abdominal hysterectomy	40	39 (25-49)* 43 (20-65)	There were no significant differences in the VAS scores for pain, nausea, sedation, or satisfaction between the groups.	There were no significant differences in postoperative sedation, nausea, and requirements for anti-emetics. Four patients on meperidine withdrew due to postoperative confusion; one patient on morphine withdrew due to intractable nausea and vomiting.
Ezri et al (2002) [56]	Morphine	IV meperidine (20 mg) IV morphine (2 mg)	Gynaecologic surgery	200	54 (29-79)** 55 (28-79)**	The pain scores were similar in both groups. Patients receiving meperidine had a significantly better ($P < .05$) self-reported well-being score at 15 minutes and 1 hour post PACU admission, compared to patients receiving morphine.	No major complications were noted in either group – no decreased respiratory rate, no episodes of decreased oxygen saturation below 90%. Sedation scores were similar. Significantly more patients on meperidine required anti-emetics than patients on morphine ($P < .05$).
Unlugenc et al (2008) [57]	Morphine Tramadol	Initial dose of IV meperidine (1 mg/kg) and IV PCA bolus of meperidine (0.2 mg/kg) as needed. Initial dose of IV morphine (0.1 mg/kg) and IV PCA bolus of morphine (0.02 mg/kg) as needed Initial dose of IV tramadol (1 mg/kg) and IV PCA bolus of tramadol (0.2 mg/kg) as needed	Abdominal hysterectomies	90	NS	There were no significant differences among groups in mean pain scores at any time point.	There was no significant difference in the incidence of side effects among the groups.
Bayar et al (2008) [58]	Morphine	IM meperidine (1 mg/kg) (3 injections on the first postoperative day). Initial dose of IV PCA morphine (0.1 mg/kg); 1 mg/hr basal rate, 1 mg bolus dose	Laparoscopic ovarian cystectomy	31	37.8 ± 5.4 35.4 ± 8.3	PCA morphine was associated with significantly higher pain scores compared to equivalent doses of IM meperidine ($P = .001$).	The IM meperidine group had significantly higher postoperative mean scores on Beck's Depression Inventory and Beck's Anxiety Inventory ($P = .03$ and $P = .045$, respectively).

Abbreviations: IM, intramuscular; IP, intraperitoneal; IV, intravenous; NS, not specified; PACU, post-anesthesia care unit; PCA, patient controlled analgesia; VAS, Visual Analog Scale. *Data were presented as mean (range). **Data were presented as median (range)

Table 4 (cont.). *Randomized controlled trials of meperidine in managing pain after gynecological surgery.*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency, and Administration Routes	Surgery Type	Number of Patients	Mean Age	Analgesic Results	Adverse Event
Shamim et al (2006) [59]	Tramadol	IV PCA meperidine (10 mg/hr continuous infusion, 5-mg bolus dose) . IV PCA tramadol (10 mg/ hr basal infusion and 5-mg bolus dose). All patients underwent induction of anaesthesia with 1 mg/ kg of meperidine	Abdominal hysterectomies	60	46.5 ± 4.42 45.86 ± 3.94	There were no significant differences in pain scores between groups. Mean drug consumption was significantly less with tramadol than with meperidine (P < .05).	The incidences of nausea and vomiting were similar in both groups. Tramadol caused significantly less sedation than meperidine (P < .05)
Moa et al (1990) [60]	Buprenorphine	IM meperidine (75 mg) Sublingual buprenorphine (0.4 mg)	Lower laparotomy	96	44 ± 10 44 ± 9	There were no significant differences in pain scores between groups.	There were no significant differences between the groups regarding respiratory depression, nausea, and vomiting. Nausea was frequent in both groups.
Bloch et al (1985) [61]	Dipyrone	IM meperidine (100 mg) IM dipyrone (2500 mg)	Abdominal hysterectomies	119	40.3 42.7	The meperidine group had higher total pain severity and total pain VAS scores; dipyrone was superior in total pain relief scores.	No serious events were recorded. Meperidine had significantly higher sedation as measured by a total sedation analog scale (P = .002).
Colbert et al (2000) [62]	Bupivacaine with epinephrine	IM meperidine (50 mg) plus IP bupivacaine. IP meperidine (50 mg) plus IP bupivacaine. Dosage of bupivacaine as 80 mL of 0.125% bupivacaine with 1:200,000 epinephrine IP	Laparoscopic tubal ligation	100	36.9 ± 4.1 36.6 ± 4.1	Pain scores were significantly lower in the IP meperidine group both at rest (P < .01) and with movement (P < .05).	There were no significant differences between the nausea scores and the number of patients who vomited postoperatively in the 2 groups.
Bloomfield et al (1983) [63]	Metkephamid	IM meperidine (100 mg) IM metkephamid (70 mg and 140 mg)	Postpartum episiotomy	59	NS	Patients who received 140 mg metkephamid had better summed pain relief, summed pain intensity differences, and global pain relief scores than those who received 100 mg meperidine (P < .001, P < .001, and P < .002 respectively). Patients who received 100 mg meperidine had better summed pain relief (P < .002) and intensity difference (P < .02) than those who received 70 mg metkephamid.	Although there were patients in the meperidine groups who experienced side effects, the numbers were not statistically different from the placebo or metkephamid groups.

Table 5. *Randomized controlled trials of meperidine in managing pain after orthopedic surgery.*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency, and Administration Routes	Surgery Type	Number of Patients	Mean Age [Gender]	Analgesic Results	Adverse Event
Tarradell et al (1996) [64]	Tramadol	IV meperidine (100 mg) IV tramadol (100 mg) IV saline	Orthopaedic surgery	48	63.8 ± 1.8 68.9 ± 1.5 65.1 ± 1.4 [M/F = 6/10] in all groups	For the first 30 minutes, meperidine produced lower pain intensity scores than tramadol ($P < .05$). Meperidine and tramadol had a similar number of patients who had to be rescued. Both opioids produced a similar degree of analgesia in patients who were not rescued.	There were no significant differences in vomiting between the meperidine and tramadol groups. One case of urinary retention and one case of hypotension were observed in the meperidine group. Meperidine was associated with a significantly higher ($P < .01$) level of respiratory depression ($PaCO_2$) from 5 minutes to 1 hour post administration. Meperidine showed a significantly higher level of sedation in the first 30 minutes of treatment when compared to tramadol ($P < .05$).
DeAndrade et al (1996) [65]	Ketorolac	IM meperidine (100 mg) IM ketorolac (60 mg followed by 30 mg) IM placebo Doses were repeated every 2-6 hours as necessary for 5 days, up to a maximum of 4 doses per 24 hours.	Orthopaedic surgery	244	45.3 (18-87)* [M/F = 121/79]	The 6-hour summed pain intensity difference and total pain relief scores were significantly higher with ketorolac than with meperidine or placebo. The mean daily categorical pain intensity scores were comparable with ketorolac and meperidine, and both were significantly superior to placebo.	Ketorolac was significantly better tolerated than meperidine, and the number of patients reporting adverse events was lower with ketorolac than meperidine. Meperidine resulted in significantly more sedation compared to ketorolac or placebo: $P < .001$ at 1 hour; $P \leq .01$at 2 hours. Self-reports of somnolence were statistically significantly greater with meperidine (90%) than either ketorolac (74%) or placebo (44%). More patients who received meperidine (98%) reported at least one adverse event compared with either ketorolac (86%) or placebo (70%) (overall $P < .001$; $P = .028$ for each pairwise comparison).
Lindgren et al (1985) [66]	Diclofenac	IM meperidine (50 mg) IM diclofenac (75 mg) IM placebo A second injection was usually administered after 3.5 hours.	Hip surgery	68	66 ± 10 [M/F =11/12] 67 ± 8 [M/F =11/11] 65 ± 9 [M/F = 10/13]	Diclofenac group ($P < .001$) had better pain relief than the meperidine ($P < .01$) and placebo groups.	More patients in the meperidine group experienced drowsiness and vomiting compared to the other 2 groups.

Table 5. (cont.) *Randomized controlled trials of meperidine in managing pain after orthopedic surgery.*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency, and Administration Routes	Surgery Type	Number of Patients	Mean Age [Gender]	Analgesic Results	Adverse Event
Brock-Utne et al (1985) [67]	Nalbuphine	IM meperidine (100 mg) IM nalbuphine (20 mg)	Orthopaedic surgery	60	39.2 ± 4.03 [NS] 39.4 ± 4.01 [NS]	VAS scores were statistically lower in the nalbuphine group at 3 (P < .02) and 6 hours (P < .05) for nalbuphine vs meperidine.	The respiration rates in the meperidine group were significantly more depressed 30 minutes after the injection than in the nalbuphine group (P < .05), but this difference was not clinically relevant. Nalbuphine caused less depression of both systolic and diastolic blood pressure at both 30 and 60 minutes (P < .001).There was no statistically significant difference in pulse rates between the 2 groups.
Arti et al (2013) [68]	Methadone Morphine	IA meperidine (50 mg) IA methadone (5 mg) IA morphine (5 mg) All patients received bupivacaine 0.5% + 1 in 200,000 epinephrine	Arthroscopic knee surgery – meniscectomy	140	NS	Morphine in comparison to meperidine or methadone is more beneficial in reducing pain or analgesic need when it was added to bupivacaine injection following surgery. On the first day post operation, there was significantly less pain in the morphine group vs in the methadone, meperidine, and control groups (P < .05).	Not available
Arti et al (2011) [69]	Methadone Morphine Tramadol	IA meperidine (37.5 mg) IA methadone (5 mg) IA morphine (5 mg) IA tramadol (100 mg) All patients received 0.5% bupivacaine	Arthroscopic knee surgery – anterior cruciate ligament reconstruction	150	26.8 ± 7.8 (M/F = 23/7) 28.9 ± 7.63 (M/F = 22/8) 31.5 ± 5.9 (M/F = 23/7) 27.5 ± 7.4 (M/F = 22/8)	Morphine had better pain relief efficacy (VAS score 1.7 (P = .024) than meperidine (VAS score 1.7) in the first 4 hours after surgery.	Not available

Table 5. (cont.) *Randomized controlled trials of meperidine in managing pain after orthopedic surgery.*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency, and Administration Routes	Surgery Type	Number of Patients	Mean Age [Gender]	Analgesic Results	Adverse Event
Lyons et al (1995) [70]	Morphine	IA meperidine (50 mg) IA morphine (5 mg) IA saline (placebo) All patients received standard postoperative analgesia (bolus doses of IV meperidine 25 mg in the recovery room or mefenamic acid 500 mg orally on request in the ward). Patients were discharged with mefenamic acid to take 6 hourly as required.	Arthroscopic knee surgery	60	32.1 (18-57)** (M/F = 15/5) 29.5 (18-48)** (M/F = 17/3) 32.1 (18-57)** (M/F = 15/5)	Both treatment groups had significantly lower pain scores compared with placebo. Patients in the meperidine group had significantly lower pain scores than the morphine group at 0.5, 1, and 2 hours post operation ($P < .05$), but significantly higher scores at 12 and 24 hours ($P < .05$).	Not available
Söderlund et al (1997) [71]	Morphine Fentanyl	IA/IM meperidine (10 mg) IA/IM morphine (1 mg) IA/IM fentanyl (10 μg)	Arthroscopic knee surgery	70	26.8 ± 7.8 (M/F = 23/7)	There were no significant differences in postoperative pain intensity or need for analgesics.	All patients could be discharged from the hospitals as normal, and no specific side effects were recorded during the first 24 hours.
Saryazdi et al (2006) [72]	Fentanyl Dexamethasone	IA meperidine (20 mg) IA fentanyl (50 μg) IA dexamethasone (8 mg)	Arthroscopic knee surgery	48	26 ± 8 24.7 ± 6.01 26 ± 4.9 [All patients are male in this study]	Better postoperative analgesia, lower pain scores, and shorter time-to-walk were found with fentanyl and meperidine compared to dexamethasone, but the results were not significantly different between the fentanyl and meperidine groups.	Not available

Abbreviations: IA, intraarticular; IM, intramuscular; IV, intravenous; NS, not specified; $PaCO_2$, partial pressure of carbon dioxide; PCA, patient controlled analgesia; VAS, Visual Analog Scale; M, male; F, female

*Data were presented as mean (range) for patients evaluable for efficacy analysis regardless of treatment groups

**Data were presented as mean (range)

Table 6. *Randomized controlled trials of meperidine in managing pain after cardiothoracic surgery*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency, and Administration routes	Surgery Type	Number of Patients	Mean Age [Gender]	Analgesic Results	Adverse Event
Dich-Nielsen et al (1992) [73]	Ketamine	One IM injection of meperidine (1 mg/kg) One IM injection of ketamine (1mg/kg) Injections were repeated if the effect declined	Pulmonary surgery	30	64 (31-73)* [NS] 61 (28-73)* [NS]	There was no significant difference between the analgesic effects of ketamine and meperidine.	The incidence of adverse reactions was low and not significantly different between the groups. Meperidine was associated with a significantly higher ($P < .05$) level of respiratory depression ($PaCO_2$) from 30 minutes to 3 hours post administration.
Ohqvist et al (1991) [74]	Morphine Ketobemidone	IV morphine (0.5 mg/mL) IV meperidine (5 mg/mL) IV ketobemidone (0.375 mg/mL) Continuous infusions were applied	Open-heart surgery	81	63 ± 1.6 [M/F = 20/7] 61 ± 2.3 [M/F = 22/4] 61 ± 1.8 [M/F = 20/8]	There were no significant differences in pain relief between the 3 analgesics.	There were no significant differences in side effects like shivering, nausea, or vomiting between the 3 analgesics.
Oztekin et al (2006) [75]	Morphine Fentanyl Remifentanil Tramadol	Meperidine: 0.7 mg/kg/hr-IV infusion dose; 10 mg/kg/hr-bolus dose Morphine: 0.1 mg/kg/hr-IV infusion dose; 1 mg/kg/hr-bolus dose Fentanyl: 0.3 mcg/kg/hr-IV infusion dose; 25 mcg/kg/hr-bolus dose Remifentanil: 0.6 mcg/kg/hr-IV infusion dose; 10 mcg/kg/hr-bolus dose Tramadol: 0.07 mg/kg/hr-IV infusion dose; 10 mg/kg/hr-bolus dose IV PCA with continuous background infusion	Open heart surgery with sternotomy	50	49 ± 15.18 [M/F = 8/2] 58.8 ± 7.96 [M/F = 8/2] 55.1 ± 6.98 [M/F = 6/4] 57.12 ± 11.99 [M/F = 7/3] 55.33 ± 12.75 [M/F = 7/3]	Tramadol had significantly higher VAS score (4; $P = .001$) vs meperidine (3) at 24 hours post-operation. Patients in the meperidine group required the lowest number of additional bolus doses ($P = .001$).	Mean levels of minute ventilation, heart rate, $PaCO_2$, oxygen saturation, and SBP after 24 hours were not significantly different between groups. Remifentanil and meperidine had fewer side effects than the other 3 drugs.

Abbreviations: F, female; IM, intramuscular; IV, intravenous; M, male; MMCHS, morphine-soaked microfibrillar collagen hemostatic sponge on the surface of the dural sac; NS, not specified; $PaCO_2$, arterial partial pressure of carbon dioxide; PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; PRN, as needed; VAS, Visual Analog Scale

*Data were presented regardless of treatment groups

**Data were presented as sex ratio

***Data were presented as mean (range)

epidural fentanyl after hypospadias surgery (77). A study in urological surgery observed better pain relief using IV meperidine when compared to IV tramadol (78). In a study involving patients who underwent oral surgery, IM meperidine was less efficacious than IM ketorolac (79). One other study found IM meperidine to be superior to diclofenac suppository for laminectomy (80). Finally, IM meperidine had a comparable analgesic effect to transnasal butorphanol for anal fistulotomy (81).

2.2. Side Effects and Safety Outcomes

All included studies revealed at least one opioid-related adverse effect of meperidine including nausea, vomiting, sedation, pruritus, alterations in cardiopulmonary function, dry mouth, shivering, sweating,

Table 7. *Randomized controlled trials of meperidine in managing pain after cardiothoracic surgery*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency, and Administration Routes	Surgery Type	Number of Patients	Mean Age [Gender]	Analgesic Results	Adverse Event
Saarnivaara et al (1980) [76]	Tilidine Indomethacin	IM meperidine 1 mg/kg IM tilidine 2.5 mg/kg Indomethacin 100 mg suppository	Tonsillectomy	87	25.5 ± 8.8 [M/F = 11/18] 24.7 ± 9.9 [M/F = 8/21] 26.5 ± 11.0 [M/F = 8/21]	No significant differences in the analgesic efficacies of meperidine, tilidine, and indomethacin.	Bleeding from the operative site occurred significantly more in the tilidine (24%) and indomethacin (28%) vs meperidine (4%) groups.
Sengezer et al (2002) [77]		Loading dose: 5 mL bupivacaine (0.125%) plus 50 μg fentanyl in 10 mL saline . Continuous infusion: 2 μg fentanyl mixed 0.125% bupivacaine in 1 mL saline solution at 3 mL/hr . PCEA: 5 mL 2μg fentanyl mixed 0.125% bupivacaine in 1 mL saline. 1 mg/kg IM meperidine followed by 1 mg/kg meperidine every 4 hours PRN	Hypospadias surgery	20	18.3 ± 1.2 All are male patients.	Bupivacaine plus fentanyl had significantly lower VAS pain scores compared to IM meperidine on days 1 through 6 ($P < .05$).	No significant differences in side effects were reported.
Mojtahedzadeh et al (2004) [78]	Tramadol	Bolus: 100 mg-IV tramadol PCA: IV 50 mg tramadol Bolus: 50 mg IV meperidine PCA: IV 25 mg meperidine	Urological surgery	60	44.63 ± 19.97 [M:F = 1:0.3]** 45.46 ± 18.10 [M:F = 1:0.4]**	No significant differences between tramadol and meperidine in the first 7 hours post surgery. Meperidine provided superior analgesia at 8, 12, and 16 hours post surgery ($P < .05$).	The $PaCO_2$ at 1 and 4 hours post surgery showed greater $PaCO_2$ retention ($P < .001$) with meperidine. Meperidine associated with greater drowsiness ($P < .001$). Tramadol associated with increased sweating ($P < .01$) and IV metoclopramide used to treat nausea ($P < .05$).

Table 7 (cont.). *Randomized controlled trials of meperidine in managing pain after cardiothoracic surgery*

Author (yr) [citation]	Comparative Drug	Dose, Dosing Frequency, and Administration Routes	Surgery Type	Number of Patients	Mean Age [Gender]	Analgesic Results	Adverse Event
Fricke et al (1992) [79]	Ketorolac	IM ketorolac 10 mg IM ketorolac 30 mg IM ketorolac 90 mg IM meperidine 50 mg IM meperidine 100 mg	Oral surgery	145	23.0 (15-35)*** [M/F = 21/19] 24.3 (16-46)*** [M/F = 22/18] 23.9 (17-37)*** [M/F = 18/22] 23.9 (16-35)*** [M/F = 17/22] 23.0 (17-36)*** [M/F = 20/20]	Thirty mg and 90 mg IM ketorolac had a similar efficacy profile. Thirty mg IM ketorolac was significantly better than 10 mg IM ketorolac, 50 mg or 100 mg IM meperidine ($P < .05$).	Patients treated with 100 mg IM meperidine significantly more drowsy compared to those treated with any doses of ketorolac at 30 minutes and one hour post dosing ($P < .05$) and more drowsy at 2-hour mark compared to 10 mg and 90 mg IM ketorolac ($P < .05$). Significantly more in the meperidine groups reported adverse events compared to ketorolac groups ($P < .05$). Nervous system-related side effects (vertigo, dizziness) twice as common in meperidine groups. More pallor in meperidine groups (33% each) vs ketorolac groups (3%-10%). Twenty percent of meperidine-receiving patients had digestive system adverse events vs 3% when providing ketorolac. Vomiting occurred in 6% vs 1% in the meperidine vs ketorolac groups.
Emamhadi et al (2008) [80]	Diclofenac	IM meperidine 0.5 mg/kg every 8 hours 100 mg diclofenac suppository every 8 hours	Laminectomy	100	NS [M/F = 23/27] NS [M/F = 27/23]	Meperidine resulted in a significantly lower VAS pain score ($P < .05$).	There were no significant differences in side effects.
Mai et al (2009) [81]	Butorphanol	Transnasal butorphanol 1 mg every 4 hours IM meperidine 0.8 mg/kg every 4 hours	Fistulectomy	60	37.7 ± 10.76 [M/F = 20/10] 38.9 ± 10.89 [M/F = 22/8]	Pain VAS scores were similar in both groups.	There were no significant differences in side effects.

Abbreviations: F, female; IM, intramuscular; IV, intravenous; M, male; MMCHS, morphine-soaked microfibrillar collagen hemostatic sponge on the surface of the dural sac; NS, not specified; PaCO2, arterial partial pressure of carbon dioxide; PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; PRN, as needed; VAS, Visual Analog Scale

*Data were presented regardless of treatment groups

**Data were presented as sex ratio

***Data were presented as mean (range)

dizziness, light-headedness, headache, postoperative confusion, mood changes, hallucinations, and myoclonic jerks. None of the included studies reported on addiction or abuse potential of meperidine, euphoria, serotonin syndrome, or central nervous system toxicity. Adverse events reported in most of the studies did not include a statistical analysis of the safety parameters. Moreover, the reporting methods varied. Depending on the data availability, the safety profile of meperidine in this study is reported as causing more, equal, or less of a specific adverse effect than the comparator.

2.2.1. Meperidine versus Morphine

Morphine was the most common comparator of meperidine. Intravenous or PCA meperidine was associated with a higher incidence of vomiting (55-57) and similar level of sedation (27,55,56,75) compared to IV, PCA, or epidural morphine. One study reported PCA morphine to cause more sedation when compared to PCA meperidine after Cesarean section (54). In another study comparing IM meperidine with PCA morphine after laparoscopic ovarian cystectomy, patients receiving IM meperidine experienced more anxiety and depressive mood changes (58). Two studies compared PCA morphine with PCA or IM meperidine. The first involved postvertical gastroplasty and the second consisted of patients who either underwent orthopedic or abdominal surgery. Both studies found no difference in the occurrence of nausea, vomiting, and pruritus, despite the lower morphine equi-analgesic doses of meperidine (25,27). Other studies reported no significant differences in nausea, sedation, pruritus, and shivering between equi-analgesic PCA doses of morphine and meperidine after gynecological surgeries (55,57). One study found that PCA meperidine was associated with less nausea, vomiting, and headache than PCA morphine in patients who underwent open heart surgery (75).

2.2.2. Meperidine versus Tramadol

Three studies compared PCA or IV meperidine with PCA or IV tramadol in patients after total abdominal hysterectomies, orthopedic surgery, or urological surgery. In these studies, PCA or IV meperidine was associated with more sedation (59,64,78), increased respiratory depression, and higher carbon dioxide retention than PCA and IV tramadol (64,78). Intravenous tramadol resulted in higher rates of nausea compared to IV meperidine for urological surgery (78). One study reported no significant difference in the rates of vomiting between IV tramadol and IV meperidine for orthopedic surgery (64). Another study found no difference in the incidences of shivering, pruritus, and nausea when comparing PCA meperidine with PCA tramadol after abdominal hysterectomy (57).

2.2.3. Meperidine versus Other Opioids

PCA meperidine was associated with more sedation compared to PCA fentanyl after orthopedic or abdominal surgery but did not differ for nausea, vomiting, or pruritus (27). A study comparing PCA fentanyl with PCA meperidine after open heart surgery found higher levels of sedation with meperidine (75). The same study found that nausea and vomiting were more common with PCA fentanyl. Patients given IM meperidine were as sedated as those given sublingual buprenorphine after abdominal surgery (30). Intramuscular meperidine also resulted in higher rates of nausea, vomiting, respiratory depression, and hypotension compared to IV or IM nalbuphine after abdominal or orthopedic surgery (32,67).

One study found that IV pentazocine resulted in increased nausea versus IV meperidine after abdominal surgery (28). When comparing IM meperidine to IM meptazinol after abdominal and orthopedic surgery, similar incidences of sedation, nausea, vomiting, confusion, pallor, and sweating were observed (29). Likewise, similar incidences of nausea and vomiting were also noted when compared to sublingual buprenorphine after laparotomy (60).

Intramuscular meperidine was shown to have similar rates of nausea, vomiting, dizziness, and headache as IM tilidine after tonsillectomy (76). There were no significant differences in sedation, nausea, and dizziness between transnasal butorphanol and IM meperidine after anal surgery (81). The use of PCA oxymorphone following Cesarean delivery caused more nausea and vomiting compared to PCA meperidine, with equal levels of sedation (54). Intramuscular metkephamid resulted in similar rates of nausea, vomiting, and headache compared to IM meperidine when used for pain relief after episiotomy (63).

2.2.4. Meperidine versus Nonsteroidal Anti-inflammatory drugs

When comparing IM meperidine with IM ketorolac, meperidine was associated with significantly higher rates of sedation after orthopedic and dental surgery (65), and nausea after abdominal surgery (33). Studies comparing meperidine to diclofenac after Cesarean section and laminectomy reported a similar incidence

of side effects including nausea (50-52,80), headache (80), epigastric pain (80), vomiting (49-52), pruritus (50), and postoperative ileus (49). Meperidine was associated with significantly higher levels of sedation when compared to diclofenac (50-52). One study compared IM meperidine to rectally-administered indomethacin after tonsillectomy and found no significant difference in the incidence of nausea, vomiting, dizziness, and headache (76).

2.2.5. Meperidine versus Other Classes of Analgesics

According to 2 studies, there was no difference in the incidence of adverse events when comparing parenteral administration of dipyrone with parenteral meperidine after laparotomy and gynecological surgery (31,61), except for a significantly lower level of sedation in the IM dipyrone group (61). A study comparing IM meperidine vs IM ketamine following thoracic surgery reported significantly increased respiratory depression and heart rates in the meperidine group, but the mean arterial pressures remained unchanged (73). Other adverse reactions were evenly distributed over both groups (73).

Intravenous physostigmine salicylate resulted in higher levels of nausea when compared to IV meperidine, but physostigmine was associated with significantly lower levels of sedation than meperidine (34). When comparing IM meperidine with epidural bupivacaine plus fentanyl, meperidine resulted in significantly increased levels of sedation (37). Two studies that compared IM meperidine with epidural bupivacaine or epidural bupivacaine plus fentanyl showed no differences in the neonatal Apgar scores at 1 and 5 minutes (36,38). Higher rates of one-time Apgar scores of less than 7 with meperidine were found in one study that compared it to submucous paracervical blockade with bupivacaine (39). Neonatal respiratory depression occurred more commonly with IM meperidine compared to epidural bupivacaine with fentanyl (37).

2.3. Patient Satisfaction

Patient satisfaction rates with epidural bupivacaine alone (35), epidural bupivacaine plus fentanyl (24,37,38), IM ketorolac (65,79), transnasal butorphanol (81), and oral diclofenac (52) were higher compared to meperidine. Patient satisfaction scores in those who received meperidine did not differ from those who received suppository diclofenac (51), PCA fentanyl (27), PCA oxymorphone (54), IM tramadol (37), IV nalbuphine (32), oral methadone (48), IM meptazinol (29), or IM pentazocine (29). Moreover, patients who received IM meperidine were reportedly as satisfied as those who received IM/sublingual buprenorphine (30). Finally, 5 studies reported no difference in patient satisfaction when comparing morphine with meperidine (27,53,54).

Discussion

3.1. Summary of Evidence

Meperidine is a type of phenylpiperidine used for the treatment of moderate to severe pain (82). This narrative review aimed to consolidate evidence derived from clinical studies published until the end of 2018 to review the analgesic efficacy and safety of using meperidine in managing postoperative and labor pain.

Based on the studies in this review, meperidine generally had similar or inferior analgesic efficacy compared to other analgesics in treating acute postoperative or labor pain. Only 5 of the 62 studies included in the review showed meperidine to be more efficacious than other analgesics. According to the study by Køllliker et al in 1972 (28), IV meperidine was found to be more efficacious than IV pentazocine for upper abdominal surgery, but the authors attributed this to the use of a lower dose of pentazocine (15 mg), rather than the 25-mg dose which is equipotent to the 50-mg meperidine dose used in the study. Furthermore, it was unclear from the article how the investigators assessed pain in that study (28). Another study in 1986 showed that IV meperidine was associated with better analgesic efficacy than IV physostigmine following major abdominal surgery (34). Intravenous physostigmine's analgesic effect lasted only 15 to 30 minutes after injection, which is attributable to the drug's rapid distribution and elimination. They suggested the use of epidural or intrathecal physostigmine (34). The third study showed that the use of IM meperidine following laparoscopic ovarian cystectomy significantly lowered pain scores compared to PCA morphine, but the PCA morphine group had significantly higher patient satisfaction scores (58). In the fourth study, PCA meperidine had better analgesic efficacy than PCA tramadol following open-heart surgery (75). In the fifth study, IM meperidine was associated with greater pain relief than IM tramadol at 30 and 60 minutes after drug administration, but there were no differences after that (46). Careful interpretation of the efficacy data should be made considering the small sample sizes, different dosages, and various routes of administration across studies.

Meperidine was generally associated with higher levels of sedation and respiratory depression compared to other analgesic drugs. It was associated with a similar or higher incidence of nausea and vomiting compared to other analgesics. Only 3 studies showed that meperidine had a better safety or side-effect profile compared to other analgesics. PCA meperidine caused fewer incidences of nausea and vomiting than PCA morphine or fentanyl after open-heart surgery (75), and PCA oxymorphone after Cesarean section (54).

The clinical use of meperidine has been restricted since the 1990s (7). In 2014, the US Joint Commission's Pain Management Standards recommended restricting the use of meperidine to short-term treatment of acute pain (83). According to a 2004 safety bulletin by the Institute for Safe Medication Practices Canada, oral meperidine was not recommended, and if prescribed, the duration of parenteral meperidine should be limited to 48 hours (84). Furthermore, it was recommended that meperidine be avoided in elderly patients (84). The Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine discouraged the use of meperidine in favor of other opioids for acute postoperative pain (14). The US Food and Drug Administration has also warned that meperidine may result in opioid addiction, abuse, respiratory depression, neonatal opioid withdrawal syndrome, and interact with cytochrome P450 3A4 and monoamine oxidase (MAO) inhibitors (85).

Although the first reports on meperidine-dependency date back as far as 1940 (7,86), the reviewed studies did not report any cases of meperidine dependency or abuse. In addition, other concerns regarding meperidine included the issue of euphoria, serotonin syndrome due to drug interactions, and central nervous system toxicity (7). However, the clinical studies included in this review did not report the occurrence of these serious adverse events. These serious adverse events are generally rare. Many of the included studies had relatively small sample sizes and were probably not powered to detect these rare adverse events. Furthermore, patients with comorbid conditions that would have made them vulnerable to developing these side effects may not have met the inclusion/exclusion criteria for the randomized controlled trials. Therefore, the results of this systematic review do not really answer questions about the association between meperidine and serious adverse events for acute postoperative pain management in clinical practice.

3.2. Limitations

There were some limitations to this review. The majority of the clinical studies included younger patients, who were likely to have a lower risk of meperidine toxicity compared to older patients. Many of the included clinical studies were old, with some published in the 1970-80s. The older studies often reported a limited observation period (e.g., 24 hours). The sample sizes of the randomized studies were often less than 100 patients, and therefore probably underpowered to detect differences in the incidence of less common adverse effects. One notable limitation was that clinical trials comparing different routes of drug administration were included. For example, studies comparing IV meperidine against epidural bupivacaine were included. These studies were not excluded in order to provide a comprehensive review; however, such comparisons may lead to misleading conclusions about the analgesic efficacy of meperidine versus other analgesic drugs. In addition to the above, this narrative review was restricted to full text papers that could be retrieved.

Conclusions

In conclusion, this review article summarized the risk-benefit of meperidine for acute postoperative and labor pain control. The results suggest that other analgesic drugs with superior or equivalent analgesic efficacy and possibly fewer side effects are available. In light of these improved therapeutic options and with the data derived from this narrative review, meperidine should no longer be used as a primary analgesic intervention.

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