Summary Report

Meperidine hydrochloride

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Table of Contents

Table of Tables

Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HCl	Hydrochloride
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of meperidine hydrochloride (meperidine HCl; UNII code: N8E7F7Q170), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how meperidine HCl is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how meperidine HCl has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of meperidine HCl and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Meperidine HCl (also known as pethidine HCl) was nominated for inclusion on the 503B Bulks List by Pentec Health, the Specialty Sterile Pharmaceutical Society (SSPS), and US Compounding Pharmacy.

Meperidine HCl was nominated for anesthesia and the treatment of moderate to severe pain (such as chronic non-malignant or labor pain) via intravenous and intrathecal injections in solutions ranging from 0.2-200 mg/mL.

The nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of meperidine HCl.[6-9]

Reasons provided for nomination to the 503B Bulks List included:

- Practitioners often prescribe doses that require higher strengths or concentrations than those available in FDA-approved products or use in combinations with other medications.
- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- According to SPSS, in order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.
- Manufacturer backorder.
- When a different strength or dosage form is ordered by the practitioner or when ready-to-use packaging is required by the facility.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of meperidine HCl products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for meperidine HCl; name variations of meperidine HCl were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing meperidine HCl. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: meperidine HCl, epidural or intrathecal administration, and therapeutic use for anesthesia or analgesia (refer to Appendix 1 for full search strategies). Intravenous administration was not considered for systematic literature review due to the availability of an FDA-approved intravenous injection product. Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on March 26, 2020. In addition, the ECRI Guidelines Trust® repository was searched on March 26, 2020 for clinical practice guidelines that recommended the use of meperidine HCl and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which meperidine HCl was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not

specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if meperidine HCl was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; or as a rescue medication in a trial not designed to evaluate the effect of meperidine HCl. Studies in which meperidine HCl was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of meperidine HCl; setting; total number of patients; number of patients who received meperidine HCl; patient population; indication for use of meperidine HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of meperidine HCl in a combination product; use and formulation of meperidine HCl in a compounded product; use of meperidine HCl compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances meperidine HCl was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use meperidine HCl: anesthesiology, pain management, and surgery. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of meperidine HCl in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 3 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact

information was available, the “contact us” tab on the association website was used. An email describing the project and requesting distribution of the survey to the association’s members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 4 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Meperidine HCl is available as an FDA-approved product in the nominated intravenous form and ROA.
- Meperidine HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for meperidine HCl.
- Meperidine HCl is available in the nominated intravenous dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, and UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Meperidine HCl	10-100 mg/mL	Injectable	Injection	Prescription	Prior to 01/01/1982

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Table 2. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Meperidine HCl Pethidine HCl	50 mg/mL	Solution	Injection, intramuscular, intravenous, subcutaneous	Abu Dhabi	Active	–
				Australia	Schedule 8 – Controlled drug	05/23/1994
				Belgium	Medical prescription	02/25/2016
				Canada	Narcotic (CDSA I)	12/31/1987
				Hong Kong	Prescription only	02/04/1987
				Ireland	Prescription-only non-renewable	04/01/1978
				Namibia	–	09/03/1989
				New Zealand	Class 3B controlled drug	08/08/1985
				Saudi Arabia	Prescription	–
				UK	Prescription-only medication	05/10/1982

Abbreviations: "– ", not mentioned.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Results of literature review

Study selection

Database searches yielded 1822 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1256 titles and abstracts were screened. After screening, the full text of 303 articles was reviewed. Finally, 54 studies were included. Two hundred forty-nine studies were excluded for the following reasons: wrong study design (187 studies); wrong dosage form or ROA (35); meperidine HCl used as brand or proprietary product (10); unable to obtain full text (7); duplicate study (3); meperidine HCl only mentioned briefly (3); language other than English (2); meperidine HCl not used clinically (1); wrong substance (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 54 included studies were published between 1984 and 2019. There were 48 experimental studies, 4 observational studies, 2 descriptive studies, and 0 clinical practice guidelines. The 54 studies were conducted in the following countries: Canada, China, Denmark, Egypt, France, India, Iran, Jamaica, Malawi, Nepal, Nigeria, Romania, Singapore, South Korea, Thailand, Turkey, UK, and US.

A total of 4504 patients participated in the 54 included studies. The number of patients in each study ranged from 1 to 1022.

Outcome measures differed among the included studies and included: sensory and motor blockade, pain scores, duration of analgesia, need for rescue analgesia, and side effects.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of meperidine HCl

One thousand three hundred seventy-two patients received meperidine HCl for spinal anesthesia, administered intrathecally in doses ranging from 0.5 mg/kg to 1.8 mg/kg. Duration of treatment ranged from 1 to 2 doses. Forty-one patients received meperidine HCl for continuous spinal anesthesia, administered intrathecally in doses ranging from 8.6 mg/day to 24 mg/day. Duration of treatment ranged from 8 weeks to 9 months. Ninety-six patients received meperidine HCl for combined spinal-epidural anesthesia, administered once intrathecally in doses ranging from 10 mg to 70 mg. Ninety-nine patients received meperidine HCl for analgesia, administered as 1 to 3 injections of 75 mg. Fifty patients received meperidine HCl for saddle block, administered once intrathecally at 0.5 mg/kg.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Meperidine HCl was not used as a compounded product, nor was it used in a combination product.

In 28 studies, the authors' concluding statement recommended the use of meperidine HCl for spinal anesthesia, combined spinal-epidural anesthesia, analgesia, and saddle block.[9-36] In 8 studies, the authors concluded that the use of meperidine HCl was not recommended for spinal anesthesia or combined spinal-epidural anesthesia.[37-44] In 10 studies, the authors concluded that further studies were necessary for the use of intrathecal meperidine for spinal anesthesia, continuous spinal anesthesia, and combined spinal-epidural anesthesia.[45-54] In 5 studies, the authors recommend

reserving the use of meperidine HCl when the patient is unable to tolerate a local anesthetic or in situations where resources are limited.[55-59] In 3 studies, the authors conclusion did not address the use of meperidine HCl.[60-62]

Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 54 included studies, 8 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of meperidine HCl.

As the first synthetic opioid, meperidine HCl (also known as pethidine) was synthesized in 1939 and was first used to treat labor pain in women in the early 1940's.[47,63] One study noted that structurally, meperidine HCl displays similarities to conventional local anesthetics, with a hydrophilic group (tertiary amine) and a hydrophobic group (aromatic) that are linked by an ester bond.[47] These local anesthetic properties differentiate meperidine HCl from other lipophilic opioids such as fentanyl or sufentanil.[58] Another aspect to take into consideration with meperidine is the presence of metabolites, which are associated with central nervous system toxicity with prolonged administration.[64,65]

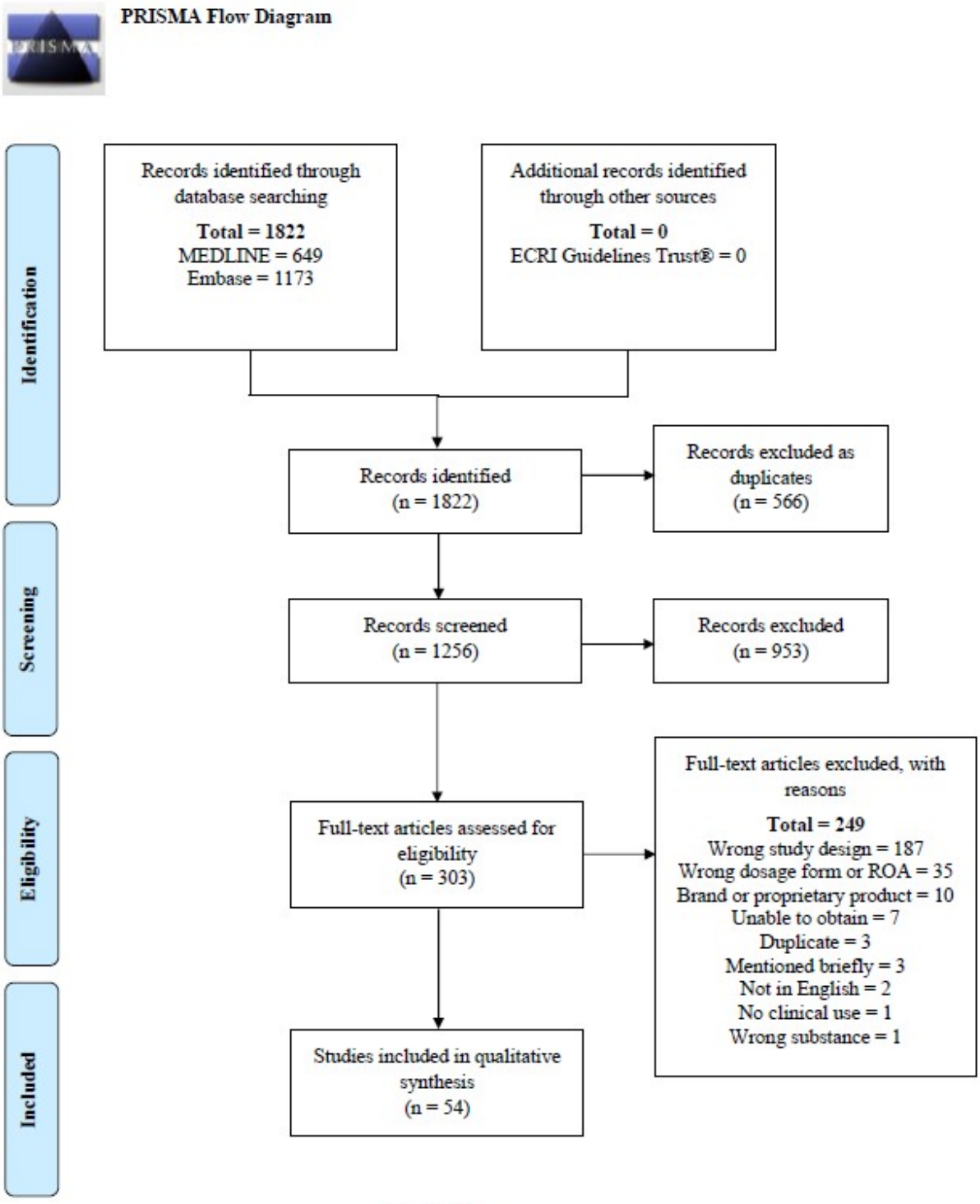
Meperidine HCl is a lipophilic drug, with peak cerebrospinal fluid (CSF) concentrations occurring and decreasing four times faster than morphine when administered via epidural route.[66] Intrathecal opioid administration offers benefits over epidural injection including faster onset and lower systemic diffusion.[67] As with epidural administration, the lipophilicity of the chosen opioid is an important consideration; more lipophilic drugs, such as fentanyl and sufentanil, are removed from the cerebrospinal fluid very quickly, which results in them having an effect on fewer spinal levels.[67] More hydrophilic drugs, such as morphine and hydromorphone, have demonstrated a greater rostral spread and a significant effect across multiple spine levels in comparison.[67] Like with epidural administration, more hydrophilic opioids are associated with a delayed, but longer duration of analgesia, as well as an increased incidence of side effects while more lipophilic agents have a faster onset of analgesia, but a shorter duration of action and decreased side effects.[68]

The FDA has recommended that intrathecal drug therapy is indicated for moderate-to-severe trunk and limb pain, and intractable pain that has been refractory to conservative treatment attempts; the Polyanalgesic Consensus Conference (PACC) noted that while there is interest in using intrathecal therapy to cover focal extremity pain, support in the literature is lacking, with only anecdotal reports.[69] More specific disease indications for intrathecal drug delivery included: axial neck or back pain in patients who were not candidates for surgery (multiple compression fractures, discogenic pain, spinal stenosis, diffuse multiple-level spondylosis); failed back surgery syndrome; abdominal or pelvic pain (visceral, somatic); extremity pain (radicular pain, joint pain); complex regional pain syndrome; trunk pain (postherpetic neuralgia, post-thoracotomy syndromes); cancer pain (direct invasion and chemotherapy-related); and situations where analgesic efficacy with systemic opioid delivery is complicated by intolerable side effects.[69]

Besides being used for anesthesia, meperidine HCl also has a history of being used for shivering, a "relatively frequent complication associated with spinal, and general anesthesia that can be distressing to patients and can occasionally result in deleterious sequelae."[22] The 3 major factors that contribute to core hypothermia during regional anesthesia are described as "heat loss to the environment, inhibition of central thermoregulatory control, and redistribution of body heat," and spinal anesthesia is thought to cause a "loss of thermoregulatory vasoconstriction and a loss of heat by heat redistribution from core to peripheral parts of the body."[22] One included study commented that shivering may occur in up to 56.7% of patients undergoing surgery with spinal anesthesia, and

complications can include undesirable cardiovascular effects, surgical difficulties, clot dislodgment, and postoperative bleeding.[46] Per a study by Davoudi et al, other intravenous agents such as clonidine, ketanserin, magnesium sulfate, and physostigmine have been suggested to treat shivering and small doses of intrathecal meperidine HCl has been investigated for the prevention of shivering.[46,70] While the mechanism that allows intravenous meperidine HCl to treat shivering is not fully understood, it appears to be more effective than other μ-opioid agonists (fentanyl, alfentanil, sufentanil, morphine).[22,25] It is thought that meperidine HCl's anti-shiver effect may be related to agonist activation of the κ-opioid receptors, anticholinergic action, biogenic monoamine reuptake inhibition, NMDA receptor antagonism, or stimulation of α-adrenoceptors.[15,25,39]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive[9,18]	2
Observational[13,45,49,61]	4
Experimental[10-12,14-17,19-44,46-48,50-60,62]	48

Table 4. Number of studies by country

Country	**Number of Studies**
Canada[16,27]	2
China[50]	1
Denmark[35]	1
Egypt[39,40]	2
France[28,33,53]	3
India[36,38,42]	3
Iran[10,15,19-21,25,31,32,37,46,51,52]	12
Jamaica[47]	1
Malawi[57]	1
Nepal[11,24]	2
Nigeria[12,58]	2
Romania[60]	1
Singapore[43]	1
South Korea[22,54]	2
Thailand[41]	1
Turkey[34]	1
UK[14,48,55,56]	4
US[9,13,17,18,23,26,29,30,44,45,49,59,61,62]	14
	Total US: 14 Total Non-US Countries: 40

Table 5. Summary of included studies

Refer to Appendix 2

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Spinal anesthesia[13,17,23,26,29,30,45,49,59]	10-60 mg 0.5-1 mg/kg	1-5%	Solution	Intrathecal	1-2 doses
Continuous spinal anesthesia[9,18,62]	Test 12.5 mg Infusion 8.6-10.3 mg/day	0.02-0.6%	Solution	Intrathecal	At least 9 months
	24 mg/day Bolus 1 mg/30 minutes				Until patient's death, 8 weeks after hospital discharge
	Initial 10 mg Bolus 7 mg	–	–		–
Combined spinal-epidural anesthesia[61]	–	–	Solution	Intrathecal	Once

Abbreviations: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Spinal anesthesia[10-12,14-16,19-22,24,25,27,28,31-33,37-43,46-48,50-52,55-58,60]	6-100 mg 0.5-1.8 mg/kg	0.3-5%	Solution	Intrathecal	Once
Combined spinal-epidural anesthesia[34,54]	10-70 mg	–	Solution	Intrathecal	Once
Analgesia[35]	75 mg	–	Solution	–	1-3 injections
Continuous spinal anesthesia[53]	Mean 18.2 mg ± 4.8	1%	Solution	Intrathecal	Administer 0.5 mL every 5 minutes until required block was achieved
Saddle block (or caudal anesthesia)[36]	0.5 mg/kg	5%	Solution	Intrathecal	Once

Abbreviations: "–", not mentioned.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Ten SMEs discussed meperidine HCl. Amongst these 10 SMEs, there were 7 medical doctors, 1 pharmacist, and 2 dentists. The SMEs specialized and/or were board-certified in anesthesiology, dentistry, oral and maxillofacial surgery, pain management, palliative care, pediatric anesthesia, and primary care and family medicine, working in academia, academic medical center, hospital/health system, and private practice/clinic. The SMEs had been in practice for 15 to 34 years.

Only one of the SMEs said that they had provided meperidine HCl for epidural administration in the past. Multiple SMEs who specialized in anesthesiology said that they have never given meperidine HCl for patients in labor and delivery, though one said that they knew of other practitioners who had. One SME said that the only time they would use meperidine HCl for labor is if the patient was shivering. Meperidine HCl is typically administered via the intravenous route for postoperative rigors, also referred to by practitioners as "shivering" and "anesthesia shakes." Rigors typically occur more often in adult or teenage patients, with one anesthesiologist saying that they probably give meperidine HCl for rigors once or twice per week when working with adult patients; rigors are not typically seen in younger pediatric patients. When being used for rigors, typically only one or two intravenous doses are necessary, with the dose ranging between 25 and 100 mg. One SME said that they have not seen a change in meperidine HCl being used for rigors over time, though other anesthesiologists said that 90% of rigors can be solved with using warm or hot air blankets to cover the patient. They said that shivering involves 2 parts where both core and skin temperature matters. As a result, by keeping the skin warm, the core temperature can be moderately low, and the patient will not shiver. In the rare situation where the hot blanket method fails, the practitioners will provide meperidine HCl.

Several SMEs who specialized in anesthesiology, palliative care, and primary care said that part of the reason that meperidine HCl has fallen out of favor is due to the accumulation of an active metabolite, normeperidine, and the resultant side effects such as muscle twitching, myoclonus, seizures, and death due to central nervous system (CNS) toxicity. One SME said that meperidine HCl was removed from the main formulary at the hospital they worked at because of its active metabolites; practitioners would have to justify the use every time they wanted to use meperidine HCl. Another SME added that meperidine HCl has an atropine-like effect and can increase the patient's heart rate. Several SMEs in pain management, palliative care, and primary care said that they do not use meperidine HCl for pain anymore because of its side effects; there are safer options available. One of these SMEs said that meperidine HCl is a terrible drug and should be removed from the market entirely.

One SME specializing in dentistry said that they use oral liquid Demerol® (meperidine HCl) for pediatric sedation alongside compounded Vistaril® (hydroxyzine). Another SME said that meperidine HCl is popular in the medical field, but they do not use it in their dental practice.

As far as compounded anesthetics are concerned, one SME who specialized in anesthesiology said that they used single ingredient drugs in anesthesia; they had no experience with compounding multiple powders together. Furthermore, they rarely mix products in the same syringe stating that this is frowned upon due to potential compatibility concerns. The exception would be regional or epidural anesthesia where they might add fentanyl or morphine to a local anesthetic to reduce the number of injections. Several SMEs who specialized in anesthesiology talked about using prefilled syringes that were produced by a third party and added that the Anesthesia Patient Safety Foundation (APSF) and the Joint Commission prefer that anesthesiologists use prefilled syringes; drawing up each product increases the potential for error and sterility concerns and that prefilled syringes offer less waste and fewer errors,

though it is also more expensive. One SME said that epidural infusions are typically compounded by the hospital pharmacy, though perioperative antibiotics are either prepared by the pharmacy or the anesthesiologist themselves in the operating room. Another SME said that they see compounded drugs as convenient, but the only real application would be for epidural mixes. Everything else is typically mixed by the anesthesiologists themselves before administration. One of the anesthesiologists said that they have had problems with drugs being on shortage. In some cases, they can adjust, for example if fentanyl is on backorder, then they can use morphine and alter their technique. Other drugs, such as backordered propofol, do not have alternatives. They noted that outsourcing facilities typically have a 2-3-month lead-in time between when the drug goes on shortage and when they are able to produce the product.

Several anesthesiologist SMEs said that they could not think of a situation where they would want to use a higher concentration opioid than what is already commercially available. One SME who specialized in palliative care said that they try to minimize the use of compounded drugs due to limited data. Furthermore, they said that "A lot of hospice nurses suffer under a misperception about compounds. Hospice nurses tend to think you can take any tablet or capsule and put it into the rectum and everything is great, which is not true. They think anything you put into a base, you can slab it onto intact skin and it's going to be absorbed and do well. It is not true. I am not a fan."

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website.

A separate survey was distributed by the Ambulatory Surgery Center Association (ASCA); 230 people responded to this survey (refer to Appendix 3 for survey instrument).

One hundred ten survey respondents (54% of 203 people who responded to this question) utilized a 503B outsourcing facility to acquire compounded drugs; 93 survey respondents (46%) did not utilize a 503B outsourcing facility. Three respondents (1.03% of 290 responses, where respondents were allowed to select multiple drug products) obtained meperidine HCl from a 503B outsourcing facility (refer to Table 15).

The most common types of procedures performed at the facilities where the ASCA survey respondents worked were ophthalmology (115, 17% of responses, where respondents were allowed to select multiple procedure types); orthopedics (89, 13%); pain (80, 12%); podiatry (74, 11%); and plastics (72, 10%) (refer to Table 16).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which meperidine HCl prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded meperidine HCl

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded meperidine HCl

No respondents to survey distributed via professional medical associations

Table 15. Ambulatory Surgery Center Association respondents' familiarity with compounding terms

Compounded drugs (medications prepared to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	153
Somewhat familiar	70
Not familiar	7
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	118
Somewhat familiar	91
Not familiar	21
503B Outsourcing facility (a facility that compounds larger quantities without a patient-specific prescription)	**Responses, n (N=230)**
Very familiar	97
Somewhat familiar	86
Not familiar	47

Table 16. Products obtained from a 503B outsourcing facility

Product	**Responses, n (N=290)[a]**
Amitriptyline / Ketoprofen / Oxymetazoline	1
Budesonide	2
Calcium gluconate	2
Droperidol	2
Epinephrine	11

Epinephrine for ophthalmic administration	16
Epinephrine / Lidocaine for ophthalmic administration	31
Epinephrine / Bupivacaine / Fentanyl	3
Fentanyl	10
Flurbiprofen	3
Flurbiprofen for ophthalmic administration	6
Hydromorphone	5
Ipamorelin	1
Ketoprofen / Nifedipine	3
Lidocaine / Epinephrine / Tetracaine	13
Meperidine	3
Morphine	5
Naloxone	5
Neomycin	5
Phentolamine	1
Promethazine	5
Remifentanil	4
Sufentanil	2
Tramadol	2
None of the above	75
Do not obtain any compounded drugs from 503B outsourcing facility	74

[a]Survey respondents allowed to select multiple products.

Table 17. Type of specialty procedures performed at ambulatory surgery facility

Procedure Type	Responses, n (N=686)[a]
Dental	23
Dermatology	9
Endoscopy	65
Neurosurgery	22
Obstetrics/gynecology	39
Ophthalmology	115
Otolaryngology	58
Orthopedics	89
Pain	80
Plastics	72
Podiatry	74
Other[b]	40

[a]Survey respondents were allowed to select multiple procedure types.
[b]No respondents provided description for 'Other' procedure type.

CONCLUSION

Meperidine HCl was nominated for inclusion on the 503B Bulks List as intravenous and intrathecal injections for anesthesia and the treatment of moderate to severe pain (such as chronic non-malignant or labor pain). Meperidine HCl is available in the nominated dosage form and intravenous ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, UK and US.

From the literature review and interviews, meperidine HCl was the first synthetic opioid, first synthesized in 1939 and used to treat labor pain in the early 1940's. In addition to being a lipophilic opioid, meperidine HCl is structurally similar to conventional local anesthetics, giving it similar therapeutic properties. Furthermore, meperidine HCl has also been historically used for rigors or "shivering," a relatively frequent side effect associated with spinal anesthesia with complications including undesirable cardiovascular effects, surgical difficulties, clot dislodgment, and postoperative bleeding. While none of the SMEs reported using meperidine HCl for its original indication in labor and delivery, the SMEs were familiar with its use in patients with rigors, with patients receiving one or two doses of intravenous meperidine for this indication. However, some anesthesiologists said that they prefer to use warm or hot air blankets to treat shivering. Multiple practitioners from anesthesiology, palliative care, and primary care commented on the side effects associated with meperidine HCl's active metabolite, normeperidine, as a large reason for it falling out of use. While the one or two doses needed for rigors are unlikely to result in accumulation, regular use can result in CNS toxicity and cause seizures, muscle twitching, myoclonus, and death. As a result, many SMEs said that they either do not use meperidine HCl at all, or only use it for rigors. The only SME who said that they use meperidine HCl for a different indication was a dentist, who used oral liquid meperidine HCl and hydroxyzine for pediatric sedation. Many anesthesiologists said that drawing up each dose into a syringe increases the potential for error and issues with sterility; prefilled syringes are more expensive but offer less waste and fewer errors and are preferred by ASPF and the Joint Commission. They also noted that there is a 2-3-month delay between a product going on backorder and when it is available from outsourcing facilities; this is an issue if it is a drug that they do not have an alternative. A specialist in palliative care said that they try to minimize use of compounded drugs due to limited data and misconceptions on the part of hospice nurses about what can be used and where.

Zero people responded to the survey distributed via professional medical associations and available on the project website. Amongst respondents to the ASCA survey, 3 (1.03% of 290 responses, where respondents were allowed to select multiple drug products) obtained meperidine HCl from a 503B outsourcing facility.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 25, 2020
- Date last searched: March 26, 2020
- Limits: Humans (search hedge); English language
- Number of results: 649

1	meperidine/	5653
2	meperid#n$.tw.	2683
3	mephedin$.tw.	2
4	mepirid#n$.tw.	3
5	petantin$.tw.	0
6	peth#din$.tw.	2421
7	pet#din$.tw.	11
8	or/1-7	7691
9	infusions, spinal/	152
10	exp injections, spinal/	15963
11	epidural space/	4476
12	spinal$.tw.	263487
13	intraspinal$.tw.	4982
14	epidural$.tw.	41548
15	extradural$.tw.	6694
16	extra dural$.tw.	139
17	peridural$.tw.	2057
18	peri dural$.tw.	6
19	caudal$.tw.	45080
20	intracaudal$.tw.	11

21	arachnoid$.tw.	8044
22	subarachnoid$.tw.	35062
23	intrathecal$.tw.	23454
24	intra thecal$.tw.	74
25	or/9-24	384665
26	anesthesia/	62422
27	anesthesia, obstetrical/	12953
28	anesthesia, spinal/	12102
29	analgesia/	19738
30	analgesia, epidural/	8126
31	analgesia, obstetrical/	3936
32	exp pain/	389954
33	pain management/	32988
34	shivering/	1816
35	dt.fs.	2189838
36	ad.fs.	1396544
37	tu.fs.	2195842
38	pc.fs.	1267073
39	an?esth$.tw.	370762
40	analges$.tw.	120937
41	pain$.tw.	676467
42	shiver$.tw.	4010
43	therap$.tw.	2714825
44	treat$.tw.	5374507
45	prevent$.tw.	1384416
46	prophyla$.tw.	161581

47	or/26-46	10014663
48	and/8,25,47	842
49	exp animals/ not humans/	4682817
50	48 not 49	787
51	limit 50 to english language	649

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 26, 2020
- Limits: Humans (search hedge); English language
- Number of results: 1173

1	pethidine'/mj	10099
2	meperiden*':ti,ab,tn	3
3	meperidin*':ti,ab,tn	3979
4	mephedin*':ti,ab,tn	14
5	mepiriden*':ti,ab,tn	0
6	mepiridin*':ti,ab,tn	9
7	petadin*':ti,ab,tn	1
8	petantin*':ti,ab,tn	5
9	pethedin*':ti,ab,tn	53
10	pethidin*':ti,ab,tn	4245
11	petidin*':ti,ab,tn	75
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	14449
13	intraspinal drug administration'/de	3443
14	epidural drug administration'/de	8848
15	intrathecal drug administration'/de	20957
16	intracaudal drug administration'/de	16
17	epidural space'/de	6318
18	spinal*':ti,ab	361933
19	intraspinal*':ti,ab	6715
20	epidural*':ti,ab	58657
21	extradural*':ti,ab	8871
22	extra dural*':ti,ab	238

23	peridural*':ti,ab	2986
24	peri dural*':ti,ab	12
25	caudal*':ti,ab	58148
26	intracaudal*':ti,ab	17
27	arachnoid*':ti,ab	12157
28	subarachnoid*':ti,ab	49567
29	intrathecal*':ti,ab	34643
30	intra thecal*':ti,ab	230
31	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	532801
32	anesthesia'/de	136938
33	epidural anesthesia'/exp	33996
34	obstetric anesthesia'/exp	15290
35	spinal anesthesia'/de	25575
36	analgesia'/de	126264
37	epidural analgesia'/de	2261
38	postoperative analgesia'/de	16855
39	pain'/exp	1363803
40	shivering'/de	6557
41	drug dose':lnk	622258
42	drug administration':lnk	1722607
43	drug therapy':lnk	3852451
44	prevention':lnk	1161499
45	an$esth*':ti,ab	537957
46	analges*':ti,ab	178190
47	pain*':ti,ab	1037337
48	therap*':ti,ab	4088832

49	treat*':ti,ab	7793039
50	prevent*':ti,ab	1882553
51	prophyla*':ti,ab	258018
52	shiver*':ti,ab	5889
53	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52	13821025
54	#12 AND #31 AND #53	1638
55	[animals]/lim NOT [humans]/lim	6009256
56	#54 NOT #55	1562
57	#54 NOT #55 AND [english]/lim	1173

Appendix 2. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication: Pain					
Acalovschi and Bodolea, 1997, Romania[60]	–	45 Patients scheduled for orthopedic surgery Meperidine (60%, mean 43 y ± 14) Meperidine and epinephrine (47%, mean 54 y ± 17) Meperidine and clonidine (60%, mean 42 y ± 16)	• Meperidine (15) • Meperidine and epinephrine (15) • Meperidine and clonidine (15)	Onset of sensory blockade; onset, time, and duration of motor block; number of patients who had a motor block in both legs	The addition of epinephrine and clonidine to intrathecal meperidine prolongs the duration and motor blockades; however, only clonidine prolongs postoperative analgesia, though use is limited by side effects (hypotension, bradycardia, and sedation)
Aminisaman and Hasani, 2019, Iran[19]	–	66 In-patients undergoing lower limb orthopedic surgery (48.5%, >60 y)	• Subarachnoid bupivacaine • Subarachnoid meperidine	Duration of anesthesia and analgesia; hemodynamic changes and complications	Compared to bupivacaine, meperidine is a more efficient spinal anesthetic due to longer analgesic time, similar hemodynamic changes, and fewer headaches and shivering
Amiri *et al.*, 2012, Iran[20]	Single-blind randomized clinical trial	32 In-patients undergoing intertrochanteric surgery Lumbar plexus (50%, mean 64.4 y ± 14.7) Femoral nerve block plus spinal anesthesia (43.7%, mean 65.6 y ± 12.6)	• Lumbar plexus (16) • Femoral nerve block plus spinal anesthesia with bupivacaine and meperidine (16)	Time of performing and achieving block; time to first demand for analgesia; operation time	Femoral nerve block plus spinal anesthesia is safe and comparable to lumbar plexus block; can provide more effective anesthesia and longer-lasting analgesia

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Anaraki and Mirzaei, 2012, Iran[21]	Randomized double-blind clinical trial	77 Patients scheduled for elective suprapubic open prostatectomy Meperidine (100%, mean 68.11 y ± 8.11) Control (100%, mean 67.23 y ± 8.36)	• Meperidine (38) • Control (39)	Level of sensory block; time to reach maximum sensory sensation; duration of sensory/motor block; duration of analgesia; hemodynamic changes; need for analgesic drug; transient neurological symptoms	Low-dose meperidine in addition to lidocaine has a minimal effect on intraoperative blood pressure changes, but prevents postoperative blood pressure increases and reduces bleeding
Bayar *et al.*, 2017, Turkey[34]	–	60 Patients undergoing open prostatectomy (100%, age not specified)	Intrathecal meperidine at dose of: • 40 mg (15) • 50 mg (15) • 60 mg (15) • 70 mg (15)	Duration of the block procedure; duration of surgery; highest sensory block level; anesthetic complications	Intrathecal meperidine at 60 mg is a sufficient analgesic with minimal side effects in open prostate surgery
Booth *et al.*, 2000, US[44]	–	34 In-patients requiring labor analgesia (0%, age not specified)	Combined spinal-epidural anesthesia with: • Bupivacaine and fentanyl (11) • Meperidine 15 mg (10) • Meperidine 25 mg (11)	Duration of analgesia	"Although intrathecal meperidine could potentially prolong subarachnoid analgesia during labor, its use was associated with a significant incidence of nausea or vomiting. These data do not support the use of subarachnoid meperidine in doses of 15 or 25 mg for labor analgesia."
Boreen *et al.*, 1992, US[45]	–	10 In-patients undergoing labor (0%, age not specified)	• Meperidine	Pain intensity; request further labor analgesics; mean duration of analgesia; side-effects	While intrathecal meperidine is promising for analgesia in labor, the effect on maternal blood pressure, fetal heart rate pattern, and the progress of labor need to be determined

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Chaudhari *et al.*, 1996, India[36]	Comparative study	100 Patients undergoing perianal surgery (gender and age not specified)	• Pethidine (50) • Lignocaine (50)	Onset of sensory and motor blockade; end of sensory blockade; duration of postoperative analgesia; pain scores; incidence of complications	Intrathecal pethidine provides excellent analgesia, though the time taken to onset of action is significantly longer; the authors said that the lack of any serious side effects makes it a safe technique
Chun *et al.*, 2010, South Korea[22]	Prospective, randomized, double-blind study	50 Patients undergoing transurethral prostatectomy Meperidine (100%, mean 67.3 y ± 7.4) Control (100%, mean 65.8 y ± 7.8)	• Meperidine (25) • Control (25)	Sensory block level; blood pressure; heart rate; sublingual temperature; incidence and intensity of shivering, pruritus, nausea, and vomiting	Meperidine added to intrathecal bupivacaine reduces incidence and severity of shivering
Chung *et al.*, 1997, US[23]	Double-blinded, randomized	49 In-patients undergoing cesarean delivery (0%, range 22-40 y)	• Meperidine (17) • Morphine (16) • Meperidine and morphine in combination (16)	Incidence and severity of side-effects; respiratory depression; amount of patient-controlled analgesia (PCA) needed; pain and satisfaction scores	The combination of subarachnoid meperidine and morphine provided more uniform analgesia, higher satisfaction, and a lower requirement for PCA than either opioid alone
Davoudi *et al.*, 2007, Iran[46]	Randomized controlled trial	80 Patients undergoing transurethral prostate resection Meperidine (100%, mean 72.7 y ± 9.3) Control (100%, mean 70.0 y ± 9.9)	• Meperidine (40) • Control (40)	Maximum level of sensory block; shivering; blood pressure; body temperature; arterial oxygen saturation	The addition of low-dose meperidine to the intrathecal mixture reduces the incidence of shivering without increasing side effects; further studies are needed to replicate results

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Ehikhametalor and Nelson, 2001, Jamaica[47]	–	90 In-patients receiving surgery on the lower limbs, perineum, and inguinal areas Bupivacaine (60.9%, mean 51.2 y ± 20.31) Meperidine (70.5%, mean 50.63 y ± 16.73)	• Hyperbaric bupivacaine (46) • Intrathecal meperidine (44)	Onset of sensory and motor block	Meperidine can be used as the sole anesthetic agent for lower limb operations; pethidine may also be considered an alternative local anesthetic when patients are allergic to the conventional option, or if the conventional local anesthetic is unavailable; further research is needed to determine the role of meperidine as a local anesthetic
Farzi *et al.*, 2014, Iran[10]	Double-blinded, randomized, placebo-controlled study	195 Patients undergoing cesarean section Placebo (0%, mean 32.16 y ± 7.31) Meperidine (0%, mean 28.64 y ± 6.14) Fentanyl (0%, mean 27.73 y ± 6.01)	• Placebo (65) • Meperidine (65) • Fentanyl (65)	Mean duration of sensory and motor block and sensory level; Apgar scores; prevalence of complications	While addition of meperidine or fentanyl to lidocaine and epinephrine increases duration of postoperative analgesia, meperidine is a recommended adjuvant because of longer analgesia duration and decreased complications
Gautam, 2012, Nepal[24]	–	200 In-patients undergoing elective laparoscopic cholecystectomy (gender and age not specified)	• Standard endotracheal general anesthesia (100) • Spinal anesthesia with bupivacaine admixed with fentanyl and meperidine (100)	Complications; intraoperative need for vasoactive medications; duration of hospital stay; pain scores; consumption of parenteral opioids; cost of anesthesia; patient satisfaction	When compared to general anesthesia, spinal anesthesia provides better postoperative pain control and decreased postoperative opioid consumption

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Grace *et al.*, 1994, UK[55]	–	90 Patients undergoing total hip replacement (47%, range 43-80 y)	• Bupivacaine and morphine (30) • Sodium chloride (30) • Meperidine and clonidine (30)	Time to maximum levels of sensory block; time to 2-segment regression of block; PCA request	Meperidine and clonidine produced acceptable anesthesia; however, when compared to the morphine group, the pethidine group showed more hypotension without additional analgesia; the authors said that the technique is not indicated for routine use, but may be helpful if patient is allergic to other local anesthetic agents
Grace and Fee, 1995, UK[56]	–	60 Patients undergoing urological surgery Bupivacaine (100%, mean 67 y ± 7) Meperidine 0.5 mg (100%, mean 68 y ± 6) Meperidine 0.75 mg (100%, mean 69 y ± 8)	• Bupivacaine (19) • Meperidine 0.5 mg (21) • Meperidine 0.75 mg (20)	Time to obtain sensory block; maximum extent of block; median time to complete regression of block; patient score; mean arterial blood pressure; adverse events	Intrathecal meperidine is similar to bupivacaine in being able to provide analgesia into the postoperative period; since intrathecal meperidine may result in respiratory depression, the authors said that it is likely to be reserved for patients with local anesthetic allergy, or in situations where resources are limited
Hansen and Hansen, 1999, Malawi[57]	Prospective, single-blinded, randomized study	45 In-patients undergoing transvesical prostatectomy, hernia repair, or hemorrhoidectomy Meperidine 1.2 mg/kg (100%, mean 45 y ± 18) Meperidine 1.5 mg/kg (100%, mean 47 y ± 15) Meperidine 1.8 mg/kg (100%, mean 46 y ± 16)	• Meperidine 1.2 mg/kg (15) • Meperidine 1.5 mg/kg (15) • Meperidine 1.8 mg/kg (15)	Duration and level of sensory block; time to maximal cephalic spread of the sensory block; respiratory depression; complaints of pain	The authors said that for countries where local anesthetics are not always available, intrathecal meperidine may be an alternative for use in spinal anesthesia
Harvey *et al.*, 1997, US[9]	Case report	1 In-patient with chronic, non-malignant low-back pain and bilateral leg pain refractory to other treatments (0%, 69 y)	• Meperidine (1)	Pain relief; safety	Continuous infusion of intrathecal meperidine may be an effective alternative for chronic pain

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Honarmand *et al.*, 2015, Iran[25]	Randomized, placebo-controlled, double-blind clinical trial	120 Patients undergoing lower extremity orthopedic surgeries Meperidine 0.1 mg/kg (80%, mean 5.42 y ± 1.17) Meperidine 0.2 mg/kg (86.7%, mean 6.37 y ± 3.16) Meperidine 0.3 mg/kg (80%, mean 2.34 y ± 1.14) Normal saline (76.7%, mean 5.4 y ± 6.16)	• Meperidine 0.1 mg/kg (30) • Meperidine 0.2 mg/kg (30) • Meperidine 0.3 mg/kg (30) • Normal saline (30)	Incidence and severity of shivering; maximum sensory block level	The higher dose of meperidine was more effective for reducing incidence and severity of shivering, with no significant hemodynamic changes
Honet *et al.*, 1992, US[26]	Prospective, double-blind study	60 In-patients undergoing labor Fentanyl (0%, mean 27 y ± 7) Meperidine (0%, mean 26 y ± 6) Sufentanil (0%, mean 28 y ± 7)	• Fentanyl (20) • Meperidine (20) • Sufentanil (20)	Average first dose to make a patient comfortable; the duration of the first dose of opioid analgesia; duration of effective opioid analgesia; visual analogue score (VAS); nausea	Intermittent spinal injection with fentanyl, meperidine, or sufentanil provides adequate labor analgesia for the first stage; however, meperidine may have advantages over the others due to more reliable analgesia
Hong and Lee, 2005, South Korea[54]	Prospective, randomized, double-blind study	119 Patients undergoing cesarean delivery Bupivacaine (0%, mean 31.3 y ± 4.5) Bupivacaine plus 0.1 mg morphine (0%, mean 30.5 y ± 3.2) Bupivacaine plus 0.2 mg morphine (0%, mean 29.7 y ± 1.8) Bupivacaine plus meperidine (0%, mean 30.8 y ± 4.3)	• Bupivacaine (30) • Bupivacaine plus 0.1 mg morphine (29) • Bupivacaine plus 0.2 mg morphine (30) • Bupivacaine plus meperidine (30)	Incidence and intensity of shivering; sensory block level; Apgar scores; dose of ephedrine or metoclopramide administered	Intrathecal meperidine decreases incidence and intensity of shivering more than morphine; the specific effect may result from a different thermal effect that alters body heat distribution, but the authors say that further evidence is needed

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Imarengiaye *et al.*, 2011, Nigeria[58]	Randomized, double blind, placebo-controlled clinical trial	50 Patients undergoing cesarean section Meperidine (0%, mean 32.2 y ± 5) Saline (0%, mean 30.7 y ± 3.9)	• Meperidine (25) • Saline (25)	Level of sensory block; duration of analgesia; Apgar scores; adverse events	The addition of meperidine to bupivacaine for spinal anesthesia appears to provide good perioperative analgesia, particularly in settings where morphine and diamorphine may not be available
Kafle, 1993, Nepal[11]	–	50 Patients undergoing cesarean section Meperidine (0%, mean 23.7 y ± 8.7) Lidocaine (0%, mean 23.2 y ± 8.0)	• Meperidine (25) • Lidocaine (25)	Sensory and motor blockade; adverse events; postoperative analgesia	Due to prolonged postoperative analgesia, intrathecal meperidine was deemed superior to heavy lidocaine
Kalu *et al.*, 2016, Nigeria[12]	–	52 In-patients undergoing short surgical procedures of the lower body (gender not specified, range 18-60 y)	• Meperidine (26) • Bupivacaine (26)	Time to recovery of pinprick sensation; plantar flexion; proprioception of the big toe; full motor recovery; side effects	Regional anesthesia with spinal meperidine should be considered for short duration and ambulatory surgery
Kavuri *et al.*, 1990, US[13]	–	6 Patients undergoing lower limb orthopedic surgery (gender not specified; mean 74.6 y)	• Meperidine (6)	Level of sensory block; motor blockade; mean onset of analgesia; adverse events	Meperidine appears to be an effective alternative for elderly patients undergoing lower limb surgery

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Khan *et al.*, 2011, Iran[37]	Prospective randomized double-blinded study	72 Patients undergoing cesarean section Bupivacaine (0%, mean 27.1 y ± 8.3) Bupivacaine plus meperidine 12.5 mg (0%, mean 28.2 y ± 7.4) Bupivacaine plus meperidine 25 mg (0%, mean 27.7 y ± 6.4)	• Bupivacaine (24) • Bupivacaine plus meperidine 12.5 mg (24) • Bupivacaine plus meperidine 25 mg (24)	Blood pressure; heart rate; skin and core temperatures	The authors do not recommend intrathecal meperidine for spinal anesthesia to prevent shivering due to increased incidence of nausea and vomiting
Kumar *et al.*, 2007, India[38]	–	60 In-patients undergoing cesarean section Morphine (0%, mean 24.6 y ± 3.1) Meperidine (0%, mean 25.0 ± 3.0)	Bupivacaine plus: • Morphine (30) • Meperidine (30)	Speed of onset; duration of motor and sensory block; adverse events; mean time to first request for analgesic	The authors recommended using morphine as an adjunct to hyperbaric bupivacaine since it provided a long duration of analgesia with fewer side effects compared to meperidine
Lewis *et al.*, 1992, UK[14]	–	Patients undergoing transurethral resection of the prostate (gender and age not specified) Number of patients was not provided	• Intrathecal bupivacaine • Intrathecal meperidine	Onset, extent, and duration of sensory and motor blockade	Meperidine is a satisfactory spinal agent for transurethral resection of the prostate
Mahmoud *et al.*, 2016, Egypt[39]	Prospective randomized double-blind study	60 Patients undergoing elective cesarean section Amino acid group (0%, mean 30.4 y ± 4.1) Meperidine group (0%, mean 30.8 y ± 3.2)	• Amino acid (30) • Meperidine (30)	Core temperature; skin temperature; shivering score	Intravenous amino acids decreased the shivering rate more than intrathecal meperidine; the amino acids also seem to be a safer and more effective alternative

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Maurette *et al.*, 1993, France[53]	–	35 In-patients presenting for elective surgery for neck of the femur fracture (gender not specified, mean 80.7 y ± 7.3)	• Lidocaine (16) • Lidocaine plus meperidine (19)	Dose required for induction; delay and extent of sensory block; interval between 2 injections; number of patients requiring ephedrine	The addition of meperidine decreases the initial dose of lidocaine required for induction and provides a more prolonged effect, perioperative drowsiness, and long-lasting pain relief; there is increased risk of impairment of hemodynamic stability, and further studies are needed to see if lower doses of meperidine are effective with less hemodynamic effects
Moeen and Moeen, 2017, Egypt[40]	Prospective and randomized double-blind study	90 In-patients undergoing transurethral prostatectomy Dexamethasone (100%, mean 67.8 y ± 3.45) Meperidine (100%, mean 68.5 y ± 3.36) Saline (100%, mean 68.9 y ± 2.92)	• Dexamethasone (30) • Meperidine (30) • Saline (30)	Tympanic temperature; shivering frequency and intensity; patient satisfaction with shivering prophylaxis; adverse events	Intrathecal dexamethasone was as effective as intrathecal meperidine in shivering attenuation and with fewer side effects
Murto *et al.*, 1999, Canada[27]	Randomized double-blind prospective dose-finding study	40 In-patients undergoing transurethral prostatectomy Lidocaine (100%, mean 69.2 y ± 6.5) Lidocaine plus 0.15 mg/kg meperidine (100%, mean 68.7 y ± 9.4) Lidocaine plus 0.3 mg/kg meperidine (100%, mean 64.2 y ± 8.8)	• Lidocaine (13) • Lidocaine plus 0.15 mg/kg meperidine (14) • Lidocaine plus 0.3 mg/kg meperidine (13)	Sensory block; motor block; postoperative analgesia	Adding 0.3 mg/kg meperidine to lidocaine extends analgesia without prolonging sensory or motor blockade

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Nag and Gode, 1984, India[42]	–	60 In-patients undergoing surgical operations below the level of umbilicus (75%, range 20-40 y)	• Morphine sulfate and bupivacaine (20) • Pethidine and bupivacaine (20) • Normal saline and bupivacaine (20)	Vital parameters; quality of pain relief; complications	Pethidine provided less analgesia, both in duration and quality, when compared to morphine
Nasseri *et al.*, 2017, Iran[15]	Double-blind randomized controlled trial	90 Patients undergoing cesarean section Control (0%, mean 29.8 y ± 5.3) Meperidine (0%, mean 29.4 y ± 6.02) Morphine (0%, mean 30 y ± 6.1)	• Bupivacaine (30) • Meperidine plus bupivacaine (30) • Morphine plus bupivacaine (30)	Shivering incidence; shivering time; shivering score	While the addition of either intrathecal meperidine or morphine to bupivacaine decreased the incidence and severity of shivering, intrathecal meperidine was superior
Nguyen Thi *et al.*, 1992, France[28]	Randomized, double-blind study	21 Patients undergoing orthopedic surgery (33.3%, mean 56.6 y ± 10.8)	• Bupivacaine (3) Meperidine at doses of: • 0.05 mg/kg (3) • 0.1 mg/kg (3) • 0.2 mg/kg (3) • 0.3 mg/kg (3) • 0.4 mg/kg (3) • 0.5 mg/kg (3)	Sensory blockade; postoperative analgesia	Spinal meperidine may be used to obtain analgesia immediately postoperative, though for prolonged sedation of pain, morphine may be more appropriate

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Norris *et al.*, 1994, US[61]	–	1022 In-patients admitted for vaginal delivery Epidural (0%, mean 27.3 y ± 0.3) Combined spinal epidural (0%, mean 28.4 y ± 0.3) General or spinal anesthesia only (0%, mean 26.5 y ± 0.7)	• Epidural (400) • Combined spinal-epidural with either meperidine or sufentanil (506) • General or spinal anesthesia only (98) 358 Patients who received combined spinal-epidural were reported to receive intrathecal sufentanil	Major anesthetic complications	Combined spinal-epidural anesthesia is a safe and effective alternative to epidural blockades
Norris *et al.*, 1996, US[29]	Randomized double-blind study	20 In-patients undergoing postpartum tubal ligation Lidocaine (0%, mean 31.8 y ± 4.9) Meperidine (0%, mean 29.9 y ± 4.9)	• Lidocaine (10) • Meperidine (10)	Heart rate; blood pressure; sensory block; motor block; time to first postoperative analgesic	While the anesthetic behavior was similar between the 2 interventions, and had similar side effects, meperidine caused more itching, but also provided prolonged postoperative analgesia
Osler, 1987, Denmark[35]	Randomized and double-blind	199 In-patients receiving analgesics during the first stage of labor Meptazinol (0%, mean 25.6 ± 4.2) Meperidine (0%, mean 26.5 ± 5.1)	• Meptazinol (100) • Meperidine (99)	Pulse rate; blood pressure; respiration rate; fetal heart rate; occurrence of side effects; pain relief	Meptazinol and meperidine have equal clinical value as analgesic injections
Patel *et al.*, 1990, US[30]	–	42 Patients undergoing endoscopic urologic procedures (gender not specified, range 60-87 y)	• Meperidine (22) • Lidocaine (20)	Sensory blockade; motor blockade; hemodynamic stability; intraoperative complications; postoperative analgesia	Intrathecal meperidine was effective as a spinal anesthetic and showed similarities to intrathecal lidocaine

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Roy *et al.*, 2004, Canada[16]	Prospective, double-blinded and randomized study	40 In-patients undergoing nonemergent cesarean delivery Meperidine (0%, mean 31 y ± 5) Control (0%, mean 32 y ± 6)	• Meperidine (20) • Control (20)	Sensory block level; blood pressure; core temperature; shivering intensity	The use of intrathecal meperidine was effective in reducing the incidence and intensity of shivering
Ruíz *et al.*, 2010, US[59]	Controlled randomized single-blind clinical trial	70 Patients with gynecological emergency surgery (gender and age not specified)	• Lidocaine • Meperidine	Onset of action; degree of sensitive and motor block; hemodynamic parameters; adverse events	Meperidine is a safe and effective alternative to lidocaine
Safavi *et al.*, 2014, Iran[31]	Double-blind randomized clinical trial	120 Patients undergoing orthopedic surgery of the lower limb Control (72.5%, mean 36 y ± 14) Ondansetron (67.5%, mean 38 y ± 15) Meperidine (65%, mean 38 y ± 15)	• Control (40) • Ondansetron (40) • Meperidine (40)	Shivering incidence; shivering intensity	Both intrathecal meperidine and intravenous ondansetron decrease the intensity and incidence of shivering
Safavi *et al.*, 2014, Iran[32]	Randomized double-blind placebo-controlled trial	90 Patients undergoing orthopedic lower limb surgeries Meperidine (73.3%, mean 37.2 y ± 12.2) Fentanyl (70%, mean 44.6 y ± 16) Bupivacaine (86.7%, mean 40.1 y ± 14.7)	Bupivacaine plus: • Meperidine (30) • Fentanyl (30) • Normal saline (30)	Incidence and intensity of shivering	While the addition of fentanyl or meperidine both resulted in significant decreases in shivering incidence, there was no significant difference between the 2 drugs

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Sangarlangkarn *et al.*, 1987, Thailand[41]	–	40 Patients undergoing lower abdomen or lower extremity surgery Lidocaine-glucose (gender not specified, mean 46.5 y ± 3.0) Meperidine (gender not specified, mean 42.8 y ± 3.9)	• Lidocaine-glucose (20) • Meperidine (20)	Sensory blockade; motor blockade; postoperative analgesia; complications	While intrathecal meperidine as a solo anesthetic agent may be useful due to lower cost, this benefit is offset by higher incidence of complications; there was no significant advantage over lidocaine-glucose
Sia *et al.*, 1997, Singapore[43]	Double-blinded randomized prospective trial	40 In-patients undergoing transurethral resection of prostate Bupivacaine (100%, mean 73.9 y ± 4.9) Meperidine (100%, mean 73.45 y ± 4.6)	• Bupivacaine (20) • Meperidine (20)	Blood pressure; heart rate; highest sensory block and time to reach it; degree of motor blockade	Intrathecal pethidine did not show any significant advantage over intrathecal bupivacaine
Souter *et al.*, 2005, US[18]	Case report	1 In-patient with severe refractory cancer pain (100%, 24 y)	• Meperidine (1)	–	Continuous intrathecal meperidine infusion was very effective in controlling refractory cancer pain
Swayze *et al.*, 1991, US[62]	–	20 Patients receiving labor analgesia (0%, age not specified)	• Meperidine (20)	VAS; patient satisfaction scores; time to pain relief and return of pain	"At follow-up, 14 of 18 patients rated satisfaction as excellent, with the remaining 4 rating it as good."
Tauzin-Fin *et al.*, 1992, France[33]	–	60 Patients undergoing endoscopic surgery of prostate or bladder tumor resection Meperidine (100%, mean 66.5 y ± 6.1) Meperidine plus prilocaine (100%, mean 67.9 y ± 5.9)	• Meperidine (30) • Meperidine plus prilocaine (30)	Sensory blockade and duration; motor blockade and duration; plasma meperidine levels	Adding prilocaine to meperidine improves the motor and sensory block during surgery in addition to altering meperidine kinetics but without producing major side effects

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Trivedi *et al.*, 1990, US[17]	Prospective study	16 Patients undergoing knee arthroscopy (62.5%, range 22-64 y)	• Meperidine (16)	Onset and extent of sensory and motor blockades	Low-dose meperidine as a spinal anesthetic appears to be a good option for ambulatory knee arthroscopy
Wadhwani *et al.*, 2013, UK[48]	Randomized controlled trial	50 Patients undergoing perineal surgery (gender and age not specified)	• Lignocaine (25) • Meperidine (25)	Analgesic requirements; pain scores; motor block; complications	Meperidine is useful for procedures that result in significant postoperative pain, though the side effect of urinary retention could delay discharge; the authors felt that a larger study to establish how often this complication occurs would be helpful
Yap *et al.*, 2016, US[49]	–	211 Patients undergoing cesarean section (0%, age not specified)	• Meperidine (66) • Fentanyl (145)	Antiemetic use; 24-hour postoperative opioid use	Intrathecal meperidine was associated with more nausea and vomiting than fentanyl, but also a decrease in postoperative opioid use; further prospective randomized controlled trials are needed to determine the risk-benefit for intrathecal meperidine
Yu *et al.*, 2002, China[50]	Prospective, randomized, double-blind, placebo-controlled trial	40 In-patients undergoing elective cesarean section Saline (0%, mean 33 y ± 6) Meperidine (0%, mean 33 y ± 5)	• Saline with bupivacaine (20) • Meperidine with bupivacaine (20)	Duration of effective analgesia; 24-hour morphine requirement	The addition of meperidine was associated with prolonged postoperative analgesia, but greater intraoperative nausea and vomiting; further studies are needed to determine if the nausea and vomiting can be reduced while maintaining increased duration of analgesia
Zabetian *et al.*, 2013, Iran[51]	Randomized double-blind placebo-controlled trial	70 In-patients undergoing cesarean section Placebo (0%, mean 27.12 y ± 4.25) Meperidine (0%, mean 28.52 y ± 7.30)	• Placebo (35) • Meperidine (35)	Shivering incidence and intensity	Using mini-dose intrathecal meperidine reduces severity and intensity of both intra- and postoperative shivering; further studies should be designed, but the authors suggest that a small dose of intrathecal meperidine should be used to prevent shivering in cesarean sections under spinal anesthesia

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Zakeri *et al*., 2017, Iran[52]	Clinical trial study	93 Patients undergoing cesarean section Placebo (0%, mean 28.29 y ± 6.05) Midazolam (0%, mean 27.23 y ± 4.91) Meperidine (0%, mean 27.42 y ± 6.23)	Bupivacaine plus: • Placebo (31) • Midazolam (31) • Meperidine (31)	Nausea; pain scores; frequency of pain	While meperidine had a longer duration of analgesia, midazolam had fewer side effects; further studies are needed to determine the effects of intrathecal midazolam and meperidine

Abbreviations: "–", not mentioned; PCA, patient-controlled analgesia; VAS, visual analogue score.
[a]As defined by authors.

Appendix 3.1. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded meperidine hydrochloride. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer meperidine hydrochloride to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer meperidine hydrochloride by any of the following dosage forms and/or routes of administration? (check all that apply)

   - o Intrathecal injection
   - o None of the above

4. I prescribe or administer meperidine hydrochloride for the following conditions or diseases: (check all that apply)

   - o Anesthesia
   - o Moderate to severe pain
   - o Other (please explain) _____

5. I use meperidine hydrochloride with my patients as the following: (check all that apply)

   - o FDA-approved drug product
   - o Compounded drug product
   - o Other (please explain) _____

6. I use compounded meperidine hydrochloride because: (check all that apply)

   - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
   - o Patient allergies prevent me from using commercially available products. (please explain) _____
   - o Patient conditions prevent me from using commercially available products. (please explain) _____
   - o There are no commercially available products containing meperidine hydrochloride.
   - o Other (please explain) _____

7. Do you stock non-patient-specific compounded meperidine hydrochloride at your practice?

   - o Yes
   - o No
   - o I'm not sure

8. I obtain compounded meperidine hydrochloride from the following: (check all that apply)

   - o Compound myself at my practice
   - o Have the product compounded by an in-house pharmacy
   - o Purchase, or have a patient purchase, from a compounding pharmacy
   - o Purchase, or have a patient purchase, from an outsourcing facility
   - o Other (please explain) _____

9. What is your practice setting? (check all that apply)

   - o Physician office/private practice
   - o Outpatient clinic
   - o Hospital/health system
   - o Academic medical center
   - o Emergency room
   - o Operating room
   - o Other (please describe) _____

10. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 3.2. Survey instrument for Ambulatory Surgery Center Association

Welcome. We want to understand your clinical use of compounded drugs. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

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OMB Control No. 0910-0871
Expiration date: June 30, 2022

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503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you utilize a 503B outsourcing facility to acquire compounded drugs?
   - o Yes. If yes, why? _____
   - o No. If no, why not? _____

3. Do you obtain any of the following products from a 503B outsourcing facility? (check all that apply)

   - o I do not obtain any compounded drugs from 503B outsourcing facilities
   - o Amitriptyline / Ketoprofen / Oxymetazoline
   - o Budesonide
   - o Calcium gluconate
   - o Droperidol
   - o Epinephrine
   - o Epinephrine for ophthalmic administration
   - o Epinephrine / Lidocaine for ophthalmic administration
   - o Epinephrine / Bupivacaine / Fentanyl
   - o Fentanyl
   - o Flurbiprofen
   - o Flurbiprofen for ophthalmic administration
   - o Hydromorphone
   - o Ipamorelin
   - o Ketoprofen / Nifedipine
   - o Lidocaine / Epinephrine / Tetracaine HCl
   - o Meperidine
   - o Morphine
   - o Naloxone
   - o Neomycin
   - o Phentolamine

- o Promethazine
- o Remifentanil
- o Sufentanil
- o Tramadol
- o None of the above

4. What type of specialty procedures are performed in your facility? (check all that apply)

   - o Dental
   - o Dermatology
   - o Endoscopy
   - o Neurosurgery
   - o Obstetrics/gynecology
   - o Ophthalmology
   - o Otolaryngology
   - o Orthopedics
   - o Pain
   - o Plastics
   - o Podiatry
   - o Other (please describe) _____

Appendix 4. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.