

Summary Report

Hydromorphone hydrochloride

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Food and Drug Administration

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

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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 hydromorphone hydrochloride (hydromorphone HCl; UNII code: L960UP2KRW), 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 hydromorphone 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 hydromorphone 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 hydromorphone 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

Hydromorphone HCl was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA), Pentec Health, the Specialty Sterile Pharmaceutical Society (SSPS), and US Compounding Pharmacy.

Hydromorphone HCl was nominated for moderate to severe pain (including chronic, cancer, and postoperative pain) via epidural, intrathecal, intravenous, intramuscular, and subcutaneous injections from 0.01-100 mg/mL.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of hydromorphone HCl.⁶⁻¹³

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

- It may be necessary to compound a product with a greater concentration than commercially available, especially with epidural injections where volume is limited in the epidural space
- Compounded product may be the only product to effectively treat the indication for which it is intended
- Patient need for dosage form or strength, including greater concentration, that is not available commercially or patient sensitivities to dyes, fillers, preservatives or other excipients in manufactured products
- Manufacturer backorder
- If the FDA-approved, single-use only vials were used for compounding and the vial was punctured a second time or the vial's contents were used for more than one patient, then the compounding pharmacy would be using the product off-label
- Need for concentration-stable ready-to-use products for dose accuracy, minimization of sterility-breach risks, and avoidance of diluent bag evaporation implications
- Reducing risk of controlled substance diversion by providing product in a single sealed, precisely measured, concentrated solution with a ready-to-use formulation for infusion
- 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

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of hydromorphone 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 hydromorphone HCl; name variations of hydromorphone 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 hydromorphone 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 two concepts: hydromorphone HCl, and epidural or intrathecal administration (refer to Appendix 1 for full search strategies). Due to the availability of FDA-approved hydromorphone products for intravenous, intramuscular and/or subcutaneous injection, these ROA were not considered for the literature review. 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 25, 2020. In addition, the ECRI Guidelines Trust® repository was searched on March 25, 2020 for clinical practice guidelines that

recommended the use of hydromorphone 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 hydromorphone 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 hydromorphone 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 hydromorphone HCl. Studies in which hydromorphone 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 hydromorphone HCl; setting; total number of patients; number of patients who received hydromorphone HCl; patient population; indication for use of hydromorphone HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of hydromorphone HCl in a combination product; use and formulation of hydromorphone HCl in a compounded product; use of hydromorphone 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 hydromorphone 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 hydromorphone 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 hydromorphone HCl in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 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 3 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

- Hydromorphone HCl is available as an FDA-approved product in the nominated dosage form and ROA.
- Hydromorphone HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for hydromorphone HCl.
- Hydromorphone HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Ireland, and the UK.

Table 1. Currently approved products – US^a

| Active Ingredient | Concentration | Dosage Form | Route of Administration | Status | Approval Date ^b |
|-------------------|---------------|-------------|-------------------------|--------------|----------------------------|
| Hydromorphone HCl | 0.2-10 mg/mL | Injectable | Injection | Prescription | 04/25/2003 |

^aSource: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

^bIf 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 |
| Hydromorphone HCl | 1-100 g/mL | Injectable, Solution | Injection, Subcutaneous, Intramuscular, Intravenous | Abu Dhabi | Active | – |
| | | | | Australia | Schedule 8 – Controlled Drug | 09/09/2016 |
| | | | | Belgium | Medical prescription | 06/04/2009 |
| | | | | Canada | Marketed | 12/31/1995 |
| | | | | Ireland | Prescription-only non-renewable | 10/28/2005 |
| | | | | UK | Prescription-only medication | 11/19/2012 |

Abbreviations: “–”, not mentioned.

^aMedicine 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.

^bIf multiple approval dates and/or multiple strengths, then earliest date provided.

Results of literature review

Study selection

Database searches yielded 857 references; 1 additional reference was identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 638 titles and abstracts were screened. After screening, the full text of 217 articles was reviewed. Eighty-nine studies were included; after multiple reports of the same study were merged, there were 84 included studies. One hundred twenty-eight studies were excluded for the following reasons: wrong study design (71 studies); not nominated dosage form or ROA (30); hydromorphone HCl used as brand or proprietary product (10); hydromorphone HCl only mentioned briefly (6); wrong substance (6); duplicate study (4); used in FDA-approved form or ROA (1).

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

Characteristics of included studies

The 84 included studies were published between 1982 and 2019. There were 29 experimental studies, 25 observational studies, 30 descriptive studies, and 0 clinical practice guidelines. The 84 studies were conducted in the following countries: Canada, China, Italy, UK, and US.

A total of 12,468 patients participated in the 84 included studies. The number of patients in each study ranged from 1 to 3,736.

Outcome measures differed among the included studies and included: adverse events, duration of action, extubation, length of stay, need for rescue analgesics, pain scores, and patient and provider satisfaction.

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

Use of hydromorphone HCl

Eight thousand seven hundred twenty-four patients received hydromorphone HCl as a treatment for pain, administered epidurally and intrathecally in doses ranging from 2 mcg to 15,000 mcg. Duration of treatment ranged from once to 3 years.

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

Hydromorphone HCl was used as a compounded product but not as a combination product.

In 44 studies, the authors' concluding statement recommended the use of hydromorphone HCl.^{6,9,14-55} In 12 studies, the authors concluded that the use of hydromorphone was not recommended.⁵⁶⁻⁶⁷ In 15 studies, the authors concluded that the use of hydromorphone HCl required further studies.⁶⁸⁻⁸² In 13 studies, the authors' concluding statement did not address the use of hydromorphone HCl.⁸³⁻⁹⁵ Refer to Table 5 for a summary of authors' conclusions.

Pharmacology and historical use

In addition to the 84 included studies, 3 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of hydromorphone HCl. Hydromorphone is commercially available and FDA-approved for intravenous, intramuscular, and subcutaneous administration.

Hydromorphone HCl is a semisynthetic morphine derivative; it is more soluble than morphine in both aqueous and lipophilic media, has a shorter duration of action, and is approximately 5 times more potent than morphine via systemic administration.⁶

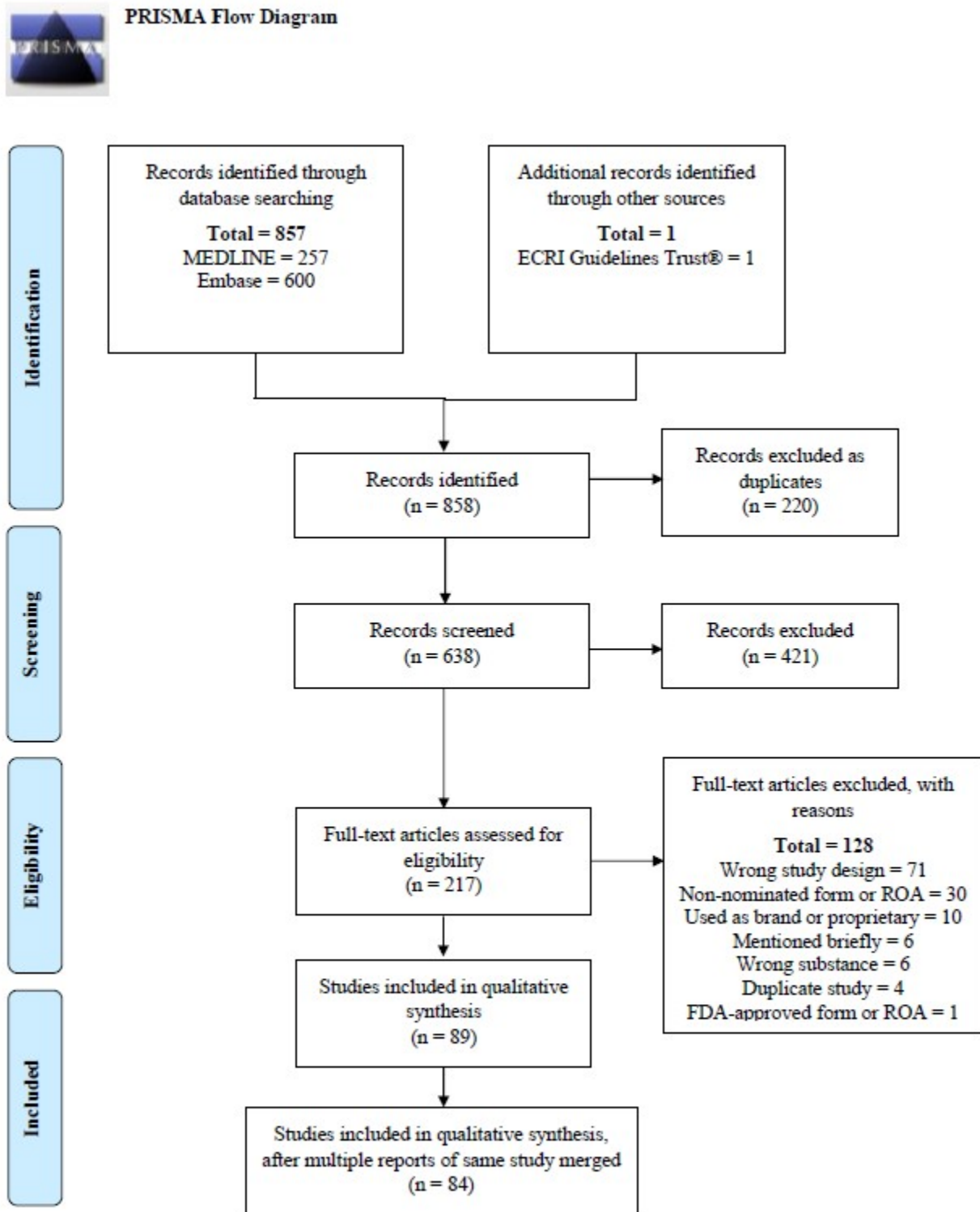
In epidural administration, lipophilic drugs demonstrate fewer side-effects and reduced risk of delayed respiratory depression, but the analgesic action is limited to segmental distribution and requires catheter placement at or near the level of surgery.²⁴ On the other hand, hydrophilic opioids have better analgesia that is not segmentally limited, but are associated with increased delayed respiratory depression, as well as other opioid-related side effects.²⁴ Several of the included studies noted that hydromorphone is less lipid soluble than fentanyl and less hydrophilic than morphine.^{24,63} Hydrophilic opioids, like morphine and hydromorphone, are commonly used in continuous epidural infusions, and “may provide more reliable neuraxial analgesia than the more lipophilic opioids such as fentanyl and sufentanil.”²⁵

Intrathecal opioid administration offers benefits over epidural administration including faster onset and lower systemic diffusion.⁴⁰ 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 cerebrospinal fluid quickly, which results in them having an effect on fewer spinal levels.⁴⁰ More hydrophilic drugs, such as morphine and hydromorphone, have demonstrated a greater rostral spread and a significant effect across multiple spine levels in comparison.⁴⁰ 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.⁸⁰

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.⁹⁶ 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.⁹⁶

At the time of the last guidelines published by the PACC in 2017, the authors noted that “there is an ongoing investigative effort, with FDA oversight, by Mallinckrodt Pharmaceuticals (St. Louis, MO) to move [intrathecal] hydromorphone from a compounded to a branded, formally manufactured, FDA-approved product.”⁹⁶ The authors elaborated to say that this process will involve 2 clinical trials, the first one a controlled, two-arm, parallel group, randomized withdrawal study and the second an open-label single-arm safety study.⁹⁶⁻⁹⁸

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 ^{14,18,26,30,32,34,39,40,45,47,48,51-55,75,76,79,80,82-84,87,88,91-95} | 30 |
| Observational ^{6,9,15,17,19,21,23,27,29,37,38,41,43,44,50,60,62,64,69-71,73,81,86,90} | 25 |
| Experimental ^{16,20,22,24,25,28,31,33,35,36,42,46,49,56-59,61,63,65-68,72,74,77,78,85,89} | 29 |

Table 4. Number of studies by country

| Country | Number of Studies |
|--|-------------------|
| Canada ^{56,57,59} | 3 |
| China ^{31,36} | 2 |
| Italy ³⁵ | 1 |
| UK ⁸⁹ | 1 |
| US ^{6,9,14-30,32-34,37-55,58,60-88,90-95} | 77 |
| Total US: 77 | |
| Total Non-US Countries: 7 | |

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 |
|---|--|-----------------|---------------|-------------------------|---|
| Chronic refractory pain ^{6,9,14,23,26,27,39,47,52-55,73,75,76,78,79,82-84,87,90,93,95} | 250-15000 mcg/hour | 1000 mcg/mL | – | Epidural | 3 months until patient death Until patient death |
| | | | Solution | | |
| | Infusion 1-916.67 mcg/hour Bolus 550-750 mcg | 5-50,000 mcg/mL | – | Intrathecal | At least 2 weeks – almost 3 years |
| | | | Solution | | |
| Continuous epidural analgesia ^{15-18,21,22,24,32,34,43-45,50,61,64,67,69,85,88} | Loading 5-20 mcg/kg; 800-1500 mcg Infusion 0.5-4 mcg/kg/hour; 25-300 mcg/hour | 2.5-500 mcg/mL | Solution | Epidural | 5 hours – 5 days When able to transition to oral or enteral analgesics |
| PCEA ^{19,25,29,33,37,38,46,49,51,58,60,62,63,71,72,94} | Loading 5 mcg/kg; 225-3000 mcg Infusion 20-80 mcg/hour Lockout 5-150 mcg/10-30 minutes | 10-75 mcg/mL | Solution | Epidural | 24 hours – 4 days |
| | Infusion 16.4-30.8 mcg/kg/day Lockout 0.5-5 mL/15-60 minutes | | | | |
| Epidural analgesia ^{28,30,41,42,48,66,68,91,92} | 100-2000 mcg | 5-240 mcg/mL | – Solution | Epidural | 1-6 doses |
| Spinal analgesia ^{20,40,41,70,74,77,80,81,86} | 2-150 mcg | 100 mcg/mL | – Solution | Intrathecal | Once |
| Combined spinal-epidural analgesia ⁶⁵ | 10-14 mcg | – | Solution | Intrathecal | At least once |

Abbreviations: “–”, not mentioned; PCEA, patient-controlled epidural analgesia.
Study 41 was administered as both spinal and epidural analgesia.

Table 7. Dosage by indication – non-US countries

| Indication | Dose | Concentration | Dosage Form | Route of Administration | Duration of Treatment |
|--|---|----------------------|--------------------|--------------------------------|------------------------------|
| Continuous epidural analgesia ^{56,57} | Bolus 600 mcg Infusion 80-90 mcg/hour | 10-200 mcg/mL | Solution | Epidural | 48-72 hours |
| PCEA ^{35,89} | Infusion 60 mcg/hour Bolus 30 mcg/20 minutes | 4-10 mcg/mL | Solution | Epidural | 24 hours |
| Combined spinal-epidural analgesia ³¹ | 40-120 mcg/hour | 20-60 mcg/mL | Solution | Epidural | 48 hours |
| Epidural analgesia ⁵⁹ | 600 mcg | 100 mcg/mL | – | Epidural | Once |
| Spinal analgesia ³⁶ | 100 mcg | 1000 mcg/mL | Solution | Intrathecal | Once |

Abbreviations: “–”, not mentioned; PCEA, patient-controlled epidural analgesia.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

| Indication | Publication Year | Compounding Method | Dosage Form | Final Strength |
|---|------------------|---|-------------|----------------|
| Intrathecal infusion analgesia ^{23,78} | 2002-2018 | <ul style="list-style-type: none"> Intrathecal mixtures were prepared by Custom Care Pharmacy in Tampa, Florida | Solution | – |
| | | <ul style="list-style-type: none"> Compounded with bupivacaine in the same infusion bag by the hospital pharmacy | Solution | 5-10 mcg/mL |

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. Sixteen SMEs discussed hydromorphone HCl. Amongst these 16 SMEs, there were 9 medical doctors, 5 pharmacists, 1 nurse practitioner, and 1 dentist. The SMEs specialized and/or were board-certified in anesthesiology, compounding, emergency medicine and critical care, oncology and hematology, oral and maxillofacial surgery, pain medicine, palliative care, pediatric anesthesia, pharmacotherapy, and primary care and family practice, working in academia, academic medical center, hospital/health system, and pharmacy/pharmaceutical company. The SMEs had been in practice for 6 to 34 years.

A couple of anesthesiologist SMEs said that there is a movement to use less narcotics in patients, or to only use non-synthetic opioids. They said that they typically use Tylenol® (acetaminophen) preoperatively and ketamine and Precedex® (dexmedetomidine) intraoperatively. When they do use opioids, most of the anesthesiologist SMEs used fentanyl, morphine sulfate, or Dilaudid® (hydromorphone HCl) in their practice. One SME said that they never use morphine; they prefer fentanyl or hydromorphone HCl due to having a “cleaner profile” regarding histamine release and mutagenicity. They noted that one of the benefits of giving longer acting narcotics (such as hydromorphone HCl) is that the effect will persist into the postoperative period and cause less postoperative pain.

Intrathecal and epidural infusions are typically used for obstetrics. The service determines the formula, with mixtures typically including bupivacaine and some concentration of sufentanil or fentanyl. One SME who specialized in anesthesiology said that they have not used hydromorphone HCl via the epidural route since residency. They used it for post-operative pain control and the residency director thought that it was superior to other options. Another SME said that they used to use hydromorphone HCl in total epidurals for lower joint and abdominal procedures before they started doing transversus abdominis plane (TAP) block with Exparel® (liposomal bupivacaine). They have never used it via the intrathecal route but can see it being used that way so long as they used a preservative-free preparation. Another anesthesiologist noted that it can be given intramuscularly; in theory it should take longer to be absorbed and last longer than intravenous route.

Currently, anesthesiologists said that opioids, such as intravenous hydromorphone HCl, are utilized for postoperative pain control in the post anesthesia care unit (PACU) where ketamine and dexmedetomidine are unavailable. Several anesthesiologists said that intravenous morphine is administered if the patient has an allergy to hydromorphone HCl. One SME said that morphine sulfate is superior to hydromorphone HCl, but when hydromorphone HCl came off-patent, it ended up being used more often and intravenous morphine sulfate became second line.

One SME who specialized in oncology said that while oxycodone and morphine sulfate are similar drugs, they usually start with oxycodone unless insurance agencies will only pay for morphine first. They try to keep with the same long-acting drug that they used for the short-acting drug. They use fentanyl patches frequently, especially with patients who have head and neck cancer and cannot take things by mouth. They also said that they are using more methadone. The SME said that they love hydromorphone HCl as an oral drug, that it is very effective, but also more expensive than their other options. They generally use it with patients who have renal issues. Most hospice facilities will end up changing the medication to morphine unless the patient has had renal issues, so the SME tries to put patients on something that they can continue therapy with, so they are familiar with the drug. Another SME said that they go with whatever is on the patient’s formulary so they can minimize their copay.

One SME who specialized in palliative care said that a common “failing” with prescribers is that they move too quickly to using hydromorphone HCl. They use it often, especially for subcutaneous administration where they keep the volume down to <1-3 mL/hour. A greater concentration would be better, but the SME did not see that as a huge need. Furthermore, they try not to use neuraxial administration (such as intrathecal or epidural routes) if they can help it. They do inherit hospital patients who have implanted pumps; this is a problem because the patient is likely going to die in 3 weeks, the implanted pump will run dry in one week, it costs \$1000 to refill the pump, and the practitioners do not think the pump is really working in the first place. Another SME said that they have seen patients with hydromorphone HCl in an intrathecal pump. The problem with this is that it must be individually made because the concentration of the solution in the reservoir is patient specific. However, there is a lot of waste since they are only available as 2 mg vials; it is too much, and they end up throwing out three quarters of the bottle. They said it would be beneficial if smaller vials were available.

One SME who specialized in pain management said that they do not do a lot of intrathecal pump administration anymore; they tend to see patients who have an intrathecal pump who want to switch to oral administration. As a result, they do not put patients on a pump unless they are committed to being on the pump without high doses of oral opioids. Typically, these are cancer patients, but they have non-cancer patients on the pumps as well.

One SME who works in primary care said that the opioids they prescribe most often are oxycodone, hydrocodone, methadone, and morphine. In their practice they typically use a combination of long and short-acting pain medications. They said that hydromorphone HCl is probably the most potent (milligram for milligram) of any of the opioids but is reasonably safe. It can be used with other adjunctive analgesics, and they have no issues seeing it used in combination for intrathecal or epidural ROA. In fact, they would feel better about hydromorphone HCl being in higher concentrations in intrathecal or epidural ROA than as a systemic administration, because it is such a potent medication. Another SME said that all opioids should come in a patch format, that they would be helpful for the outpatient population.

One dental SME said that they do not use hydromorphone HCl in their 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 SME stated that their hospital outsources ready-to-use hydromorphone PCAs; however, there was another SME who said that their hospital system has not been able to get patient-controlled analgesia (PCA) from outsourcing facilities the past few years due to opioid shortages. They need products in different concentrations than are commercially available for pediatric patients and use PCAs for pain relief, their high volume pediatric intensive care unit (PICU), and oncology patients. Additionally,

sometimes they need high concentrations of opioids due to some patients having volume restrictions. There are advantages to purchasing the opioids in ready-to-use syringes to keep on-hand in the nursing unit due to quick access and extended beyond use date (BUD). They would like to get hydromorphone HCl, along with morphine and fentanyl, from outsourcing facilities. With hydromorphone HCl, they must take a highly concentrated and large vial to get what they need, and it has a shorter BUD compared to outside sources.

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. One SME said that their outsourcing facility has been able to help hospitals with shortages related to the global coronavirus disease 2019 (COVID-19) pandemic, particularly around fentanyl, midazolam, and hydromorphone HCl. However, they have also been having a difficult time obtaining the FDA-approved hydromorphone HCl product, and said that if they were to run out, they could switch to making it from the API, but it would create an additional regulatory burden. The only time they would want to do that is if they cannot get an FDA-approved product any other way due to cost prohibitive requirements on current good manufacturing practice (cGMP). Additionally, a lot of health-system directors do not like buying sterile products produced from non-sterile API.

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 2.2 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. Five respondents (1.72% of 290 responses, where respondents were allowed to select multiple drug products) obtained hydromorphone 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 hydromorphone HCl prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded hydromorphone HCl

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded hydromorphone 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 |
| Remifentanyl | 4 |
| Sufentanyl | 2 |
| Tramadol | 2 |

| | |
|---|----|
| None of the above | 75 |
| Do not obtain any compounded drugs from 503B outsourcing facility | 74 |

^aSurvey respondents allowed to select multiple products.

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

| Procedure Type | Responses, n (N=686)^{a,b} |
|-----------------------|---|
| 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 |

^aSurvey respondents were allowed to select multiple procedure types.

^bNo respondents provided description for 'Other' procedure type

CONCLUSION

Hydromorphone HCl was nominated for inclusion on the 503B Bulks List via epidural, intrathecal, intravenous, intramuscular, and subcutaneous injections to treat moderate to severe pain (including chronic, cancer, and postoperative pain). Hydromorphone HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Ireland, UK, and US.

From the literature review and interviews, hydromorphone HCl is a semisynthetic morphine derivative and is approximately 5 times more potent than morphine with a shorter duration of action. Due to the more hydrophilic nature of the drug, hydromorphone HCl provides better analgesia but is associated with increased respiratory depression and other side effects. Intrathecal administration of opioids generally is associated with faster onset and lower systemic spread and hydrophilic agents such as hydromorphone HCl has a greater spread across multiple spinal levels. Similarly, to epidural administration, hydrophilic drugs are associated with a delayed, but longer duration of analgesia, as well as increased incidence of side effects. According to the 2017 PACC guidelines, there is an ongoing investigation to make intrathecal hydromorphone HCl an official FDA-approved product. However, the literature shows that hydromorphone HCl is currently being used via both epidural and intrathecal ROA.

Several SMEs who specialized in anesthesiology said that while they have used hydromorphone HCl for epidural administration in the past, they do not do so currently. Additionally, the anesthesiologists interviewed do not use hydromorphone HCl via spinal administration either, preferring intravenous routes. Oral hydromorphone HCl is used for oncology patients, with one SME saying that it is very effective, but also more expensive. Additionally, the practitioner tries to keep the patient on a therapy that can be continued if they go to a hospice facility, where the patient will be switched to morphine unless they have renal issues. One SME who worked in palliative care said that they think practitioners move too quickly to using hydromorphone HCl, instead of using the other options that are available. Additionally, they run into issues with intrathecal administration of hydromorphone HCl since the concentrations provided in the reservoir are patient-specific. SMEs in both palliative care and pain management said that they prefer to avoid intrathecal pump administration. In primary care practitioners, one SME said that they would feel better about hydromorphone being in higher concentrations in intrathecal or epidural ROA than as a systemic administration, because it is such a potent medication.

Zero people responded to the survey distributed via professional medical associations and available on the project website. Two hundred thirty people responded to the survey distributed via the ASCA. Five respondents reported obtaining hydromorphone 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 24, 2020
- Date last searched: March 25, 2020
- Limits: Humans (search hedge); English language
- Number of results: 257

| | | |
|----|-------------------------|--------|
| 1 | hydromorphone/ | 1278 |
| 2 | dih#dromorfin\$.tw. | 0 |
| 3 | dih#dromorph#n\$.tw. | 387 |
| 4 | dimorphon\$.tw. | 3 |
| 5 | h#dromorf#n\$.tw. | 1 |
| 6 | h#dromorph#n\$.tw. | 1594 |
| 7 | or/1-6 | 2455 |
| 8 | infusions, spinal/ | 152 |
| 9 | exp injections, spinal/ | 15963 |
| 10 | analgesia, epidural/ | 8126 |
| 11 | epidural space/ | 4476 |
| 12 | spinal\$.tw. | 263566 |
| 13 | intraspinal\$.tw. | 4982 |
| 14 | epidural\$.tw. | 41555 |
| 15 | extradural\$.tw. | 6694 |
| 16 | extra dural\$.tw. | 139 |
| 17 | peridural\$.tw. | 2057 |
| 18 | peri dural\$.tw. | 6 |
| 19 | caudal\$.tw. | 45099 |
| 20 | intracaudal\$.tw. | 11 |

| | | |
|----|------------------------------|---------|
| 21 | arachnoid\$.tw. | 8046 |
| 22 | subarachnoid\$.tw. | 35081 |
| 23 | intrathecal\$.tw. | 23476 |
| 24 | intra thecal\$.tw. | 74 |
| 25 | or/8-24 | 385734 |
| 26 | and/7,25 | 319 |
| 27 | exp animals/ not humans/ | 4682464 |
| 28 | 26 not 27 | 265 |
| 29 | limit 28 to english language | 257 |

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 25, 2020
- Limits: Humans (search hedge); English language
- Number of results: 600

| | | |
|----|---|-------|
| 1 | hydromorphone'/mj | 1854 |
| 2 | dihidromorfin*':ti,ab,tn | 0 |
| 3 | dihydromorfin*':ti,ab,tn | 0 |
| 4 | dihidromorphin*':ti,ab,tn | 0 |
| 5 | dihydromorphin*':ti,ab,tn | 509 |
| 6 | dihidromorphon*':ti,ab,tn | 0 |
| 7 | dihydromorphon*':ti,ab,tn | 6 |
| 8 | dimorphon*':ti,ab,tn | 8 |
| 9 | hidromorfin*':ti,ab,tn | 0 |
| 10 | hydromorfin*':ti,ab,tn | 0 |
| 11 | hidromorfon*':ti,ab,tn | 1 |
| 12 | hydromorfon*':ti,ab,tn | 4 |
| 13 | hidromorphin*':ti,ab,tn | 0 |
| 14 | hydromorphin*':ti,ab,tn | 38 |
| 15 | hidromorphon*':ti,ab,tn | 2 |
| 16 | hydromorphon*':ti,ab,tn | 2730 |
| 17 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 | 4143 |
| 18 | intraspinal drug administration'/de | 3443 |
| 19 | epidural drug administration'/de | 8848 |
| 20 | intrathecal drug administration'/de | 20957 |
| 21 | intracaudal drug administration'/de | 16 |
| 22 | epidural anesthesia'/exp | 33994 |

| | | |
|----|--|---------|
| 23 | spinal anesthesia'/de | 25573 |
| 24 | spinal*':ti,ab | 361878 |
| 25 | intraspinal*':ti,ab | 6715 |
| 26 | epidural*':ti,ab | 58651 |
| 27 | extradural*':ti,ab | 8870 |
| 28 | extra dural*':ti,ab | 238 |
| 29 | peridural*':ti,ab | 2985 |
| 30 | peri dural*':ti,ab | 12 |
| 31 | caudal*':ti,ab | 58144 |
| 32 | intracaudal*':ti,ab | 17 |
| 33 | arachnoid*':ti,ab | 12154 |
| 34 | subarachnoid*':ti,ab | 49560 |
| 35 | intrathecal*':ti,ab | 34633 |
| 36 | intra thecal*':ti,ab | 230 |
| 37 | #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 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 | 542048 |
| 38 | #17 AND #37 | 680 |
| 39 | [animals]/lim NOT [humans]/lim | 6008743 |
| 40 | #38 NOT #39 | 620 |
| 41 | #38 NOT #39 AND [english]/lim | 600 |

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 | | | | | |
| Ackerman <i>et al.</i> , 2003, US ⁸³ | Retrospective chart audit | 15 In-patients with chronic pain states such as complex regional pain syndrome, neuropathic pain, and cancer pain (60%, range 26-86 y) | <ul style="list-style-type: none"> Intrathecal clonidine alone (15) Intrathecal clonidine with hydromorphone (3) Intrathecal clonidine with morphine (4) | Pain score | The utilization of intrathecal clonidine is limited in this patient population; duration of relief is typically less than 18 months |
| Adigun <i>et al.</i> , 2019, US ⁸⁴ | Case | 1 Patient with ongoing and difficult to diagnose axial pain (100%, 38 y) | <ul style="list-style-type: none"> Intrathecal pump with hydromorphone and baclofen (1) | – | It is safe to incorporate baclofen into an intrathecal solution with bolus dosing without resulting in weakness or side effects |
| Aglio <i>et al.</i> , 2018, US ⁶⁸ | Double-blind, placebo-controlled randomized trial | 99 In-patients undergoing either new or repeat decompressions or fusions of the spine Placebo (59.4%, mean 60 y ± 12.5) Hydromorphone (72.7%, mean 57 y ± 27) Epidural (47.1%, mean 59.5 y ± 19) | <ul style="list-style-type: none"> Placebo (32) Epidural hydromorphone only (33) Epidural hydromorphone with bupivacaine (34) | Presence of opioid sparing and rescue time | Preemptive analgesia with single-shot epidural injection of either hydromorphone alone or hydromorphone with bupivacaine is safe and effective but more work needs to be done to see if the immediate postoperative outcome improvement has a long-term effect |
| Aloia <i>et al.</i> , 2017, US | Randomized controlled trial | 140 In-patients undergoing major hepatopancreatobiliary (HPB) surgery Epidural (59%, median 56.3 y) Intravenous (44%, median 57.4 y) | <ul style="list-style-type: none"> Thoracic epidural analgesia (TEA) with PCEA (106) Intravenous patient-controlled analgesia (PCA; 34) | Area under the curve pain score during the first 48 hours after surgery | Patients have a superior experience in major HPB surgery with thoracic epidural analgesia; there is improved pain control, less narcotic use, and without increased length of stay or complications |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|--|-------------------------------------|--|---|---|--|
| Amsbaugh <i>et al.</i> , 2016, US ⁶⁹ | Retrospective analysis | 73 In-patients diagnosed with gynecologic cancer undergoing interstitial brachytherapy (ISBT) (gender not specified, 45 patients <60 y, 30 patients ≥60 y) | <ul style="list-style-type: none"> Epidural ropivacaine only (12) Epidural ropivacaine with fentanyl (14) Epidural ropivacaine with hydromorphone (45) | Pain scores, rescue medication, antiemetic and antipruritic use | Epidural analgesia provides safe and effective pain control for patients receiving ISBT; combined modality improves pain control and lessens oral and intravenous opioid requirements without increasing risk of adverse effects; randomized trials are needed to determine the optimal epidural analgesia |
| Amundson <i>et al.</i> , 2018, US | Single center, retrospective review | 77 In-patients undergoing living liver donation Control (52%, median 37 y) Abdominal wall block (55%, median 35y) | <ul style="list-style-type: none"> Control: intrathecal hydromorphone (48) Abdominal wall block: intrathecal hydromorphone plus abdominal wall blockade with liposomal bupivacaine (29) | Pain scores; opioid requirements; time to full diet; bowel activity | The addition of an abdominal wall blockade improved the postoperative pain control and decreased time to full diet and bowel activity; prospective, blinded, randomized clinical trials evaluating the blockade with liposomal bupivacaine when compared to free bupivacaine are needed |
| Anderson <i>et al.</i> , 2001, US ⁶ | Retrospective study | 37 Out-patients with chronic, non-malignant pain (37.8%, mean 64 y ± 12) | <ul style="list-style-type: none"> Continuous intrathecal hydromorphone (37) | Safety and effectiveness of continuous intrathecal hydromorphone | Long-term intrathecal hydromorphone can be a safe alternative for nonmalignant pain in patients who have failed morphine therapy due to side effects or inadequate pain relief |
| Aziz <i>et al.</i> , 2018, US ⁹⁹ Galica <i>et al.</i> , 2018, US ²³ | Retrospective chart review | 62 Out-patients with lumbar failed back surgery syndrome (48%, mean 64.23 y ± 12.08) | <ul style="list-style-type: none"> Intrathecal hydromorphone with bupivacaine trial, with implantation if successful (62) | Pain scores | Patients showed significantly improved pain intensity scores following permanent implant |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|------------------------------|---|--|--|---|
| Beatty <i>et al.</i> , 2013, US ⁷⁰ | Retrospective comparison | 114 In-patients after elective cesarean delivery Hydromorphone (0%, mean 30.1 y ± 5) Morphine (0%, mean 31.2 ± 4.6) | <ul style="list-style-type: none"> Intrathecal hydromorphone (38) Intrathecal morphine (76) | Presence of any opioid-related complication that requires treatment within 24 hours of intrathecal opioid administration | The analgesia and incidence of opioid-related side effects did not differ between the intrathecal opioids (hydromorphone 0.04 mg and morphine 0.1 mg); further research needed |
| Bentley <i>et al.</i> , 2014, US | Case series | 5 Patients with refractory cancer pain (40%, range 16-72 y) | <ul style="list-style-type: none"> Intrathecal morphine and bupivacaine (1) Intrathecal hydromorphone and bupivacaine (4) | – | – |
| Bhandari <i>et al.</i> , 2000, US ¹⁴ | Case report | 1 Out-patient with a history of Crohn's disease and chronic abdominal pain (0%, 25 y) | <ul style="list-style-type: none"> Intrathecal hydromorphone (1) | – | The patient's chronic abdominal pain was successfully managed with opioids through an intrathecal infusion device. |
| Brodsky <i>et al.</i> , 1990, US ⁸⁸ | Case report | 1 In-patient receiving postoperative analgesia for thoracotomy (0%, 59 y) | <ul style="list-style-type: none"> Continuous epidural hydromorphone (1) | – | – |
| Brodsky <i>et al.</i> , 1990, US ¹⁵ | Prospective | 44 In-patients receiving postoperative analgesia for thoracotomy (gender and age not specified) | <ul style="list-style-type: none"> Continuous epidural hydromorphone (1) | Pain score, complications and side effects | Continuous epidural hydromorphone can produce safe and predictable analgesia for patients after thoracotomy |
| Brookes <i>et al.</i> , 2011, UK | Randomized, open label study | 21 In-patients undergoing major abdominal surgery (gender and age not specified) | <ul style="list-style-type: none"> TEA with PCEA (8) Transversus abdominis plane block (TAPB), bilateral plus intravenous PCA (13) | Scores for pain, satisfaction, sedation, nausea, and pruritus | TAPB and TEA have comparable analgesia with high patient satisfaction; opioid consumption was significantly higher with TEA, possibly due to fixed basal delivery rates; TAPB may be a viable alternative to TEA for postoperative analgesia in abdominal surgery |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|--|--------------------------------------|---|--|--|--|
| Chaplan <i>et al.</i> , 1992, US ¹⁶ | Prospective randomized blinded study | 54 In-patients scheduled to undergo major thoracic, abdominal, or pelvic surgery Morphine (78%, mean 62 y ± 14) Hydromorphone (78%, mean 59 y ± 13) | <ul style="list-style-type: none"> • Continuous epidural morphine (27) • Continuous epidural hydromorphone (27) | Pain scores, pruritus and nausea | Epidural morphine and hydromorphone provide comparable analgesia; hydromorphone reduces the occurrence of moderate to severe pruritus on the first postoperative day |
| Choi <i>et al.</i> , 2014, Canada ⁵⁶ | Randomized controlled trial | 39 In-patients receiving epidural after undergoing lumbar spinal fusion Intervention (35%, mean 57 y ± 13) Placebo (33%, mean 59 y ± 13) | <ul style="list-style-type: none"> • Intervention: continuous epidural hydromorphone with bupivacaine (20) • Placebo: continuous epidural normal saline (19) | Cumulative opioid consumption during the first 48 hours post-operation | It is not yet warranted to use continuous epidural analgesia to reduce postoperative opioid consumption; the optimal regimen for pain after 1- or 2-level lumbar decompression and fusion is not yet determined |
| Choudhry <i>et al.</i> , 2016, US ¹⁷ | Retrospective review | 32 In-patients undergoing Nuss procedure and needing analgesia Thoracic epidural catheter (80%, mean 15 y ± 2.75) Chest wall catheter (82%, mean 15.06 y ± 2.2) | <ul style="list-style-type: none"> • Thoracic epidural catheter: hydromorphone and ropivacaine (15) • Chest wall catheter: ropivacaine (17) | Comparison of technique for pain management after Nuss procedure | Better analgesia on the day of surgery was provided through the thoracic epidural catheter; on subsequent days until discharge, the analgesia scores were comparable; other benefits of the chest wall catheter included being less labor intensive, fewer side effects, shorter time in the operating room, and a shorter hospital stay |
| Christian <i>et al.</i> , 2017, US ¹⁸ | Case report | 1 In-patient receiving postoperative analgesia after pheochromocytoma resection (0%, 54 y) | <ul style="list-style-type: none"> • Thoracic epidural hydromorphone (1) | – | Transversus abdominis plane block coupled with thoracic epidural opioid analgesia were able to provide adequate pain relief without the exacerbation of hypotension |
| Cohen <i>et al.</i> , 2017, US ¹⁹ | Retrospective | 178 In-patients undergoing hepatobiliary surgery (gender and age not specified) | <ul style="list-style-type: none"> • PCEA with bupivacaine and hydromorphone 10 mcg/mL (54) • PCEA with bupivacaine and hydromorphone 5 mcg/mL (124) | Length of stay; mobility within 12 hours | Hydromorphone at 5 mcg/mL is effective for analgesia when combined with bupivacaine; future prospective randomized studies are needed to confirm results |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|--|--|---|--|---|--|
| Colibaseanu <i>et al.</i> , 2019, US ²⁰ | Prospective, non-blinded randomized controlled trial | 200 In-patients undergoing colorectal surgery Intrathecal hydromorphone (55%, median 58 y) TAPB (57%, median 61 y) | <ul style="list-style-type: none"> Intrathecal hydromorphone (98) TAPB with liposomal bupivacaine (102) | Mean pain scores; morphine milligram equivalents administered within 48 hours after surgery | The intrathecal opioid administration provided better immediate postoperative pain control compared to TAPB; however, both resulted in low pain scores and should be considered in multimodal postoperative analgesic plans |
| Cramer, 2019, US ⁷¹ | Retrospective | 46 In-patients who underwent planned surgical intervention and utilized PCEA postoperatively Morphine (56%, range 6-17 y) Hydromorphone (57%, range 5-16 y) | PCEA with ropivacaine plus: <ul style="list-style-type: none"> Morphine (25) Hydromorphone (21) | Percentage of patients with pain scores <4 on postoperative days 0 and 1 using the Face, Legs, Activity, Cry, Consolability scale or verbal numerical scale | Ropivacaine and morphine PCEA may be superior to ropivacaine and hydromorphone PCEA when controlling pain in the initial 48 hours postoperatively; the largest benefit comparing morphine to hydromorphone is seen in the initial 24 hours after surgery |
| Deer <i>et al.</i> , 2009, US ⁹⁰ | Retrospective observational study | 16 Out-patients with severe nonmalignant pain (31.2%, mean 62 y) | Intrathecal ziconotide plus: <ul style="list-style-type: none"> Hydromorphone (7) Morphine (5) Fentanyl (3) Sufentanil (1) | Safety and tolerability of intrathecal ziconotide in combination with intrathecal opioids | — |
| Densmore <i>et al.</i> , 2010, US ²¹ | Retrospective review | 117 In-patients undergoing Nuss bar placement (75%, mean 12.9 y ± 4.8) | <ul style="list-style-type: none"> Morphine (51) Hydromorphone (46) Fentanyl (20) <p>Bupivacaine or ropivacaine were used in 94% of epidurals; clonidine in 20%</p> | Pain management strategy after Nuss procedure | Using a pain service-driven epidural administration of morphine or hydromorphone with local anesthetic can provide excellent analgesia for patients after Nuss procedure |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|--|---|---|---|---|---|
| Du Pen <i>et al.</i> , 2006, US ⁹ | Retrospective review | 24 Out-patients with intractable nonmalignant pain (50%, range 36-80 y) | <ul style="list-style-type: none"> Intrathecal hydromorphone (24) | Changes in pain after the start of intrathecal hydromorphone; pain interference from baseline to 3 months; dose changes over time | With the intervention, average pain scores decreased significantly; side-effect and pain-interference scores were essentially unchanged over time |
| Fuchs <i>et al.</i> , 1982, US ⁹¹ | – | 11 In-patients receiving epidural anesthesia for major vascular reconstruction operations (gender and age not specified) | <ul style="list-style-type: none"> Epidural hydromorphone or meperidine (5) Bupivacaine alone (4) | Pain relief | – |
| Gaeta <i>et al.</i> , 1995, US ²² | Randomized prospective double-blind study | 20 In-patients undergoing lateral thoracotomy and receiving postoperative analgesia Epidural hydromorphone (44%, mean 53.5 y ± 9.8) Intraleural bupivacaine (45%, mean 61.3 y ± 11.3) | <ul style="list-style-type: none"> Epidural hydromorphone (9) Intraleural bupivacaine (11) | Severity of pain using a visual analog pain scale (VAPS) | In the first 5 hours after thoracotomy, epidural hydromorphone is superior to intraleural bupivacaine for satisfactory pain outcomes |
| Galica <i>et al.</i> , 2016, US ¹⁰⁰ Hayek <i>et al.</i> , 2016, US ⁷³ Hayek <i>et al.</i> , 2015, US | Retrospective cohort | 57 Patients with failed back surgery syndrome (46%, mean 65.4 y) | <ul style="list-style-type: none"> Inpatient trial with intrathecal hydromorphone/bupivacaine, followed by intrathecal pump implantation with hydromorphone/bupivacaine (57) | Pain scores; oral opioid intake before and after implant; intrathecal opioid dose, type and rate at 6, 12 and 24 months | Intrathecal hydromorphone/bupivacaine effective for chronic pain of failed back surgery syndrome; dose escalation occurred over time |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|--|--|--|---|---|---|
| Ganapathy <i>et al.</i> , 2015, Canada ⁵⁷ | Randomized, open-label feasibility study | 50 In-patients undergoing open abdominal surgery TEA (33%, mean 48 y ± 12.2) Lateral to medial transversus abdominis plane block (LM-TAP; 38%, mean 61.7 y ± 10.8) | <ul style="list-style-type: none"> TEA with PCEA using bupivacaine and hydromorphone (24) LM-TAP block using ropivacaine (26) | Pain on verbal rating score with cough at 24 hours after operation | LM-TAP blocks can be a viable alternative compared to TEA, and can be initiated post-operation; further studies are needed to determine the role of LM-TAP in pain management following abdominal surgery |
| Gauger <i>et al.</i> , 2009, US ⁷² | Prospective, randomized | 38 In-patients scheduled to undergo surgery for idiopathic scoliosis PCEA (0%, mean 15.1 y ± 1.5) Intravenous PCA (21%, mean 14.7 y ± 1.8) | <ul style="list-style-type: none"> PCEA with bupivacaine and hydromorphone (19) Intravenous PCA with hydromorphone (19) | Patient-reported pain scores; severity of muscle spasms; patient satisfaction with analgesia; analgesic doses | Epidural catheters decreased the percentage of patients needing diazepam for spasms and may have improved analgesia in patients when compared to intravenous PCA; however, the high failure rate suggests that patients with epidural catheters should be checked to make sure they are receiving adequate blockade early on, and convert to intravenous analgesia if necessary |
| Goodarzi <i>et al.</i> , 1999, US ²⁴ | – | 90 In-patients scheduled for elective orthopedic surgery Morphine (53%, mean 13.3 y ± 3.4) Fentanyl (57%, mean 11.5 y ± 2.2) Hydromorphone (67%, mean 10 y ± 5.6) | <ul style="list-style-type: none"> Morphine (30) Fentanyl (30) Hydromorphone (30) | Pain scores; patient somnolence; nausea, vomiting, and other side effects | There was a comparable analgesic effect across the groups; hydromorphone had considerably less side effects than morphine |
| Gorback <i>et al.</i> , 1991, US ⁹² | Prospective analysis | 14 In-patients undergoing transsternal thymectomy for myasthenia gravis (28.6%, range 16-60 y) | <ul style="list-style-type: none"> Epidural hydromorphone (14) | Extubation profile | – |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|--|---|---|---|--|---|
| Grider <i>et al.</i> , 2011, US ⁵⁸ | Prospective, randomized double-blinded clinical trial | 75 In-patients presenting for thoracotomy (gender and age not specified) | <ul style="list-style-type: none"> • Epidural bupivacaine with hydromorphone • Epidural bupivacaine alone • OnQ® intercostal catheter with bupivacaine • Epidural plus OnQ® intercostal catheter, both with bupivacaine | Pain scores; incentive spirometry; pain during spirometry | OnQ® intercostal nerve block with continuous bupivacaine provided excellent postoperative analgesia; the thoracic epidural bupivacaine with hydromorphone produced superior analgesia and pulmonary function in comparison with intercostal continuous nerve block; the OnQ® intercostal nerve analgesia was equivalent to thoracic epidural analgesia with bupivacaine alone |
| Grider <i>et al.</i> , 2012, US ²⁵ | Prospective, randomized, double-blind trial | 75 In-patients undergoing thoracotomy for lung cancer (63%, range 46-75 y) | <ul style="list-style-type: none"> • Epidural bupivacaine and hydromorphone (25) • Epidural bupivacaine (25) • CPI with bupivacaine (25) | Pain scores both with and without incentive spirometry | TEA with bupivacaine and hydromorphone may provide enhanced analgesia compared to TEA or CPI with bupivacaine alone; increased basal rates required for analgesia in the bupivacaine-only group resulted in increased hypotension when compared to the group with hydromorphone; CPI with local anesthetic appears to produce acceptable analgesia for post-thoracotomy pain |
| Gulati <i>et al.</i> , 2013, US | Case series | 5 Patients with severe chronic or cancer pain (60%, range 48-61 y) | <ul style="list-style-type: none"> • Epidural hydromorphone trial followed by intrathecal pump (3) • Epidural morphine trial followed by intrathecal pump (2) | Pain scores, opioid consumption monitored daily during trial | A combined spinal-epidural can be used to compare the first-line medications for intrathecal delivery – ziconotide and morphine (or hydromorphone) |
| Halpern <i>et al.</i> , 1996, Canada ⁵⁹ | Randomized controlled double-blind study | 46 In-patients after undergoing cesarean section Hydromorphone (0%, mean 34 y ± 3.6) Morphine (0%, mean 33 y ± 4.3) | <ul style="list-style-type: none"> • Epidural hydromorphone (24) • Epidural morphine (22) | Pain scores, incidence of nausea and pruritus | Hydromorphone showed no clinical benefit for postoperative analgesia after cesarean section when compared to morphine |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|--|-------------------------------|--|---|---|--|
| Harper <i>et al.</i> , 2019, US ²⁶ | Case report | 1 Out-patient with squamous cell carcinoma of the tongue (0%, 59 y) | <ul style="list-style-type: none"> Intrathecal hydromorphone delivery system (1) | Pain control, need for rescue analgesics | Intrathecal drug delivery can improve patient quality of life, though care should be taken to prevent respiratory depression |
| Hayek <i>et al.</i> , 2012, US ²⁷ | – | 32 Out-patients with failed back surgery syndrome (gender not specified, mean 62.6 y ± 8) | <ul style="list-style-type: none"> Intrathecal pump with patient therapy manager (32) | Pain scores, oral opioid consumption, patient therapy manager usage | The use of intrathecal hydromorphone and bupivacaine infusion gives patients pain relief while attenuating opioid escalation |
| Henderson <i>et al.</i> , 1987, US ²⁸ | Double-blind comparison study | 30 In-patients who had undergone elective cesarean section under lumbar epidural analgesia (0%, age not specified) | <ul style="list-style-type: none"> Intramuscular hydromorphone (15) Epidural hydromorphone (15) | – | Epidural hydromorphone had a longer duration of action when compared to intramuscular hydromorphone |
| Hong <i>et al.</i> , 2016, US ²⁹ | Retrospective review | 56 In-patients with idiopathic scoliosis who underwent posterior spinal fusion (17.9%, mean 14.7 y ± 2.0) | <ul style="list-style-type: none"> Epidural hydromorphone (56) | Pain scores; sedation scores; narcotic use; use of adjuvant medications; hours to first ambulation and first oral intake; respiratory rate; SpO ₂ values; need for any respiratory interventions; length of stay; any adverse events | Hydromorphone epidurals are a reasonable alternative to intravenous PCA for pain control with postoperative posterior spinal fusion when looking at analgesia, side-effect profile, and length of stay |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|--|-----------------------------|---|--|---|---|
| Hong <i>et al.</i> , 2017, US ⁶⁰ | Retrospective review | 40 In-patients with idiopathic scoliosis who underwent elective posterior spinal fusion surgery Intrathecal morphine (10%, mean 13.3 y ± 2.3) Epidural hydromorphone (10%, mean 13.5 y ± 1.7) | <ul style="list-style-type: none"> Intrathecal morphine (20) Epidural hydromorphone (20) | Pain scores; opioid use after postoperative day 1; adverse events | In comparison to epidural hydromorphone, patients who received intrathecal morphine were able to directly move to oral opioids, walk sooner, have their Foley catheters removed sooner, and have a shorter length of stay |
| Horan <i>et al.</i> , 1985, US ³⁰ | Case report | 1 In-patient after esophagogastrostomy (100%, 60 y) | <ul style="list-style-type: none"> Epidural hydromorphone (1) | – | Postoperative analgesia was obtained with epidural hydromorphone |
| Hu <i>et al.</i> , 2019, China ³¹ | Randomized | 150 In-patients who underwent cesarean section under combined spinal-epidural anesthesia Group A (0%, mean 25.6 y ± 5.6) Group B (0%, mean 24.7 y ± 6.3) Group C (0%, mean 26.2 y ± 4.6) | Ropivacaine plus: <ul style="list-style-type: none"> Group A: Hydromorphone 2 mg (50) Group B: Hydromorphone 4 mg (50) Group C: Hydromorphone 6 mg (50) | Pain scores, Ramsay sedation scale score | Epidural hydromorphone has a good analgesic effect in the early stage after cesarean section; 6 mg hydromorphone is more effective |
| Hutchins <i>et al.</i> , 2018, US ⁶¹ | Randomized controlled trial | 48 In-patients who had open pancreatic surgery Paravertebral (48%, mean 67.9 y ± 11.5) Epidural (61%, mean 63.6 y ± 9) | <ul style="list-style-type: none"> Bilateral paravertebral catheters with ropivacaine (26) Epidural catheter with hydromorphone and bupivacaine (27) | Pain scores; oral opioid use; length of stay | Continuous thoracic paravertebral blocks are a potential alternative to thoracic epidurals in patients undergoing an upper abdominal procedure |
| Jason Lowry <i>et al.</i> , 2001, US ³² | Case series | 10 In-patients who underwent spinal fusion by open thoracotomy (40%, mean 15.3 y ± 1.5) | <ul style="list-style-type: none"> Continuous epidural with ropivacaine and hydromorphone (10) | Pain scores | This technique was shown to be safe and effective for postoperative analgesia after anterior spinal surgery |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
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| Jules-Elysee <i>et al.</i> , 2014, US ¹⁰¹ Jules-Elysee <i>et al.</i> , 2015, US ³³ | Randomized, double-blind placebo-controlled study | 84 In-patients undergoing total hip arthroplasty Periarticular injection (49%, mean 63.7 y ± 8.5) PCEA (56%, mean 64.8 y ± 7.1) | <ul style="list-style-type: none"> Periarticular injection (PAI) with bupivacaine, morphine, methylprednisolone, and cefazolin plus clonidine patch and epidural saline infusion (41) PCEA with bupivacaine and hydromorphone plus placebo patch and pill (43) | Readiness for discharge | PAI did not decrease time to discharge and was associated with higher pain scores and greater opioid consumption; PAI had lower Opioid-Related Symptom Distress Scale (ORSDS) scores than PCEA; both interventions had similar quality of recovery scores and patient satisfaction; PAI may be an acceptable alternative when PCEA is not available or too costly |
| Konen <i>et al.</i> , 1999, US ³⁴ | Case report | 1 In-patient with Rett's syndrome who was scheduled to undergo spine stabilization (0%, 14 y) | <ul style="list-style-type: none"> Epidural hydromorphone with bupivacaine (1) | Behavioral pain score; sedation | Rett's syndrome is associated with respiratory impairment, that may exacerbate respiratory side effects of epidural opioids; the infusion of low concentrations of local anesthetics may be advisable in these patients |
| Lee <i>et al.</i> , 2009, Italy ³⁵ | – | 79 In-patients undergoing total knee replacement (gender not specified, range 25-75 y) | PCEA with ropivacaine and: <ul style="list-style-type: none"> Hydromorphone (39) Fentanyl (40) | Pain scores | The PCEA with hydromorphone showed better pain control compared to fentanyl; however, adverse effects seemed to occur more often and must be prevented |
| Li <i>et al.</i> , 2018, US ⁶² | Retrospective comparative study | 56 In-patients who had undergone posterior spinal fusion for scoliosis Intrathecal morphine (21%, mean 14.8 y ± 1.7) Epidural (21%, mean 14.4 y ± 1.7) | <ul style="list-style-type: none"> Intrathecal morphine transitioned to oral medication post-surgery (28) Epidural hydromorphone (28) | Pain; opioid dosage | Intrathecal morphine and oral analgesics provide safe and effective pain control and routine postoperative admission to the intensive care unit (ICU) is not necessary |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
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| Li <i>et al.</i> , 2019, China ³⁶ | Randomized | 1500 In-patients undergoing cesarean section Control (0%, mean 28.7 y ± 5.5) Observation (0%, mean 29.2 y ± 5.7) | <ul style="list-style-type: none"> Control: intrathecal bupivacaine and sufentanil (750) Observation: intrathecal bupivacaine and hydromorphone (750) | Pain scores | When compared with sufentanil, intrathecal hydromorphone has a longer analgesia duration and effect and is safer; it is ideal for obstetric analgesia |
| Liu <i>et al.</i> , 2011, US ¹⁰² Liu <i>et al.</i> , 2011, US ³⁷ | Prospective survey | 1000 In-patients undergoing total hip replacement Bupivacaine with hydromorphone (44%, mean 64 y ± 12) Bupivacaine with clonidine (44%, mean 65 y ± 12) | <ul style="list-style-type: none"> PCEA with bupivacaine and hydromorphone (500) PCEA with bupivacaine and clonidine (500) | Pain scores; side effects; provider satisfaction | The authors returned to previous standard solution of bupivacaine and hydromorphone for PCEA after total hip replacement |
| Liu <i>et al.</i> , 2010, US ³⁸ | Prospective survey | 3736 In-patients undergoing elective major lower extremity orthopedic surgery (40%, mean 64 y ± 14) | <ul style="list-style-type: none"> PCEA with bupivacaine and hydromorphone (3736) | Pain scores, side effects | PCEA with bupivacaine and hydromorphone provides safe and effective postoperative analgesia in patients undergoing orthopedic surgery |
| Liu <i>et al.</i> , 1995, US ⁶³ | Randomized, double-blind study | 16 In-patients undergoing prostatectomy Epidural (100%, mean 60 y ± 8) Intravenous (100%, mean 59 y ± 11) | <ul style="list-style-type: none"> PCEA with hydromorphone (8) Intravenous PCA with hydromorphone | Pain scores, sedation, side effects, gastrointestinal function, hydromorphone consumption | PCEA did not result in significant benefits for postoperative analgesia, recovery of gastrointestinal function, or hospitalization duration |
| Loomba <i>et al.</i> , 2012, US ³⁹ | Case report | 1 Out-patient with complex regional pain syndrome (100%, 44 y) | <ul style="list-style-type: none"> Switched from intrathecal morphine via infusion pump to hydromorphone due to hiccups (1) | Patient-reported pain relief; resolution of hiccups | Patients should be aware of hiccups as a rare side effect with intrathecal morphine |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|--|-------------------------------|---|---|---|---|
| Lotto <i>et al.</i> , 2007, US ⁴⁰ | Case reports | 2 In-patients presenting for subthalamic deep brain stimulation for Parkinson's disease (100%, range 71-78 y) | <ul style="list-style-type: none"> 3 doses of intrathecal fentanyl followed by 1 dose of intrathecal hydromorphone (1) Single dose of intrathecal hydromorphone (1) | Patient-reported pain control | This technique allowed patients to tolerate deep brain stimulation who otherwise would not be able to |
| Lynde <i>et al.</i> , 2016, US ⁷⁴ | Up-down sequential allocation | 20 In-patients undergoing elective cesarean delivery (0%, range 19-40 y) | <ul style="list-style-type: none"> Intrathecal injection containing bupivacaine, fentanyl, and hydromorphone <p>Each dose of hydromorphone was determined using up-down sequential allocation method</p> | Pain score | Additional research is needed to examine the ED ₉₅ of intrathecal hydromorphone and to compare hydromorphone to morphine for efficacy and side effects |
| Macres <i>et al.</i> , 2000, US ⁷⁵ | Case report | 1 Patient with erythromelalgia (0%, 82 y) | <ul style="list-style-type: none"> Intrathecal pump with hydromorphone and clonidine (1) | Pain score | Intrathecal hydromorphone and clonidine can be used for analgesia in a patient with secondary erythromelalgia; further research in the pathophysiology and treatment is warranted |
| Marroquin <i>et al.</i> , 2017, US ⁴¹ | Retrospective chart review | <p>1020 In-patients who underwent cesarean delivery</p> <p>Intrathecal morphine (0%, mean 30.8 y ± 5.62)</p> <p>Intrathecal hydromorphone (0%, mean 30.8 y ± 6.16)</p> <p>Epidural morphine (0%, mean 28.6 y ± 5.68)</p> <p>Epidural hydromorphone (0%, mean 29.9 y ± 6.82)</p> | <ul style="list-style-type: none"> Intrathecal morphine (450) Intrathecal hydromorphone (387) Epidural morphine (81) Epidural hydromorphone (102) | Time to first postoperative opioid for pain; total opioid consumption in the first 24 hours postoperative | Neuraxial hydromorphone is a reasonable alternative to neuraxial morphine; hydromorphone provides long-acting analgesia with a reasonable side effect profile |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
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| Martinez <i>et al.</i> , 2017, US ⁷⁶ | Case series | 6 Out-patients with refractory epigastric pain from chronic pancreatitis (50%, mean 45.3 y ± 10) | Intrathecal pump with: <ul style="list-style-type: none"> Hydromorphone and bupivacaine (4) Hydromorphone (1) Hydromorphone, bupivacaine, and clonidine (1) | Pain score; morphine equivalents; hospitalizations from pre-pump placement to post-placement | Intrathecal pump therapy is promising as an alternative treatment for chronic pancreatitis-induced pain; larger scale studies are needed to evaluate efficacy and risks |
| Mhyre <i>et al.</i> , 2008, US ⁴² | Randomized controlled trial | 7 In-patients with single-gestation uncomplicated pregnancies (0%, age not specified) | Epidural bupivacaine plus: <ul style="list-style-type: none"> Hydromorphone (2) Fentanyl (5) | Pain score | While epidural hydromorphone can provide rapid onset of labor analgesia, it requires sufficient dosing of co-administered local anesthetic |
| Mhyre <i>et al.</i> , 2013, US ⁷⁷ | Double-blind, randomized controlled trial | 67 In-patients with singleton term pregnancies who anticipated neuraxial analgesia and vaginal delivery Hydromorphone (0%, mean 28.6 y ± 5.1) Control (0%, mean 28.6 y ± 5.3) | Intrathecal bupivacaine plus: <ul style="list-style-type: none"> Hydromorphone (35) Control (32) | Pain score; duration of spinal analgesia | Further research is needed to determine if intrathecal hydromorphone 100 mcg changes the dose of intrathecal bupivacaine that is necessary to induce labor analgesia within 20 minutes |
| Michaud <i>et al.</i> , 2007, US ⁴³ | Case-control | 62 In-patients who underwent belt lipectomy Epidural (14%, age not specified) Non-epidural (15%, age not specified) | <ul style="list-style-type: none"> Epidural analgesia with bupivacaine or ropivacaine combined with hydromorphone (35) Non-epidural analgesia (27) | Pain scores; average daily and total parenteral and/or oral opioids | Epidural analgesia provides superior pain control compared to patient-controlled analgesia and on-demand opioids |
| Mironer <i>et al.</i> , 2002, US ⁷⁸ | Double-blind, randomized crossover, multicenter study | 24 Out-patients receiving intrathecal opioid treatment for chronic intractable nonmalignant pain (42%, range 39-85 y) | <ul style="list-style-type: none"> Intrathecal morphine ± bupivacaine (19) Intrathecal hydromorphone ± bupivacaine (5) | Pain scores; satisfaction with treatment on Quality of Life questionnaire | The short-term use of an opioid with bupivacaine in intrathecal pumps appears to be safe; however, the addition of bupivacaine to the opioids does not produce a significant analgesic effect at the commonly used dosages |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
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| Moman <i>et al.</i> , 2019, US ⁷⁹ | Case report | 1 Patient with recurrent metastatic squamous cell tongue cancer (0%, 59 y) | <ul style="list-style-type: none"> Intrathecal hydromorphone infusion (1) | Patient-reported pain; use of oral analgesics | Targeted drug delivery via high cervical intrathecal infusion may be effective to treat severe pain associated with head and neck cancer; experimental studies are necessary |
| Moore <i>et al.</i> , 2013, US ⁴⁴ | Retrospective cohort | 72 In-patients presenting for selective dorsal rhizotomy Epidural (65%, mean 6.06 y ± 3.78) Systemic (61%, mean 6.63 y ± 4.02) | <ul style="list-style-type: none"> Epidural analgesia with ropivacaine and hydromorphone and parenteral ketorolac (31) Systemic analgesia with fentanyl and diazepam (41) | Pain scores recorded by nursing staff | Epidural ropivacaine and hydromorphone and intravenous ketorolac produces superior analgesia; the epidural regimen is associated with fewer episodes of respiratory depression, reduced costs, and elimination of mandatory postoperative ICU care |
| New <i>et al.</i> , 2014, US ⁴⁵ | Case series | 7 In-patients with Sickle Cell Disease receiving epidural analgesia (14%, mean 15.4 y ± 3.7) | <ul style="list-style-type: none"> Fentanyl and bupivacaine; then changed to morphine (1) Fentanyl, bupivacaine, and clonidine; then changed to fentanyl and clonidine (1) Fentanyl and clonidine (1) Fentanyl and bupivacaine (1) Hydromorphone, bupivacaine, and clonidine; then changed to bupivacaine and clonidine (1) Hydromorphone, bupivacaine, and clonidine; then changed to hydromorphone and clonidine (1) | Pain scores; 24-hour morphine equivalent both pre- and post-epidural | The authors suggest that epidural analgesia may reduce Sickle Cell Disease-related, opioid-related, and pain-related morbidity, and facilitate opioid weaning in the selected patients |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|--|--|---|--|--|---|
| Nguyen <i>et al.</i> , 2016, US ⁶⁴ | Prospective case-matched observational study | 90 In-patients undergoing elective surgery (29%, mean 52 y +/- 13) | <ul style="list-style-type: none"> Epidural hydromorphone (30) Epidural fentanyl (60) | Pain at rest and during activity; need for intravenous opioids or increase in infusion rate; blood pressure and other epidural-related complications | Fentanyl was favored over hydromorphone for epidural use due to better intraoperative urine output, fewer repeated episodes of hypotension, and less excessive sedation and unresponsiveness |
| O'Reilly-Shah <i>et al.</i> , 2018, US ⁶⁵ | Phase II clinical trial | 20 In-patients presenting for labor analgesia Success (0%, mean 26.1 y ± 3.5) Not success (0%, mean 24.9 y ± 3.8) | <ul style="list-style-type: none"> Combined spinal-epidural analgesia with hydromorphone administered at doses according to Dixon's up-and-down sequential allocation method (20) | Pain scores; side effects | Because of prolonged time to onset, the authors do not recommend hydromorphone in favor of sufentanil or fentanyl |
| Parker <i>et al.</i> , 2002, US ⁶⁶ | Randomized, double-blind study | 44 In-patients who requested epidural labor analgesia Control (0%, mean 26 y ± 7) Hydromorphone (0%, mean 27 y ± 6) | Epidural fentanyl plus: <ul style="list-style-type: none"> Saline (22) Hydromorphone (22) | Pain scores; motor block | "Adding hydromorphone 300 µg does not prolong the analgesic duration. When performing an ambulatory epidural in early labour, after a lidocaine and epinephrine test dose, we found no advantage in adding hydromorphone 300 µg to fentanyl." |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|--------------------------------|---|--|---|--|
| Parker <i>et al.</i> , 1992, US ⁴⁶ | Prospective double-blind study | 170 In-patients scheduled to undergo elective cesarean delivery Group 1 (0%, mean 28 y ± 6) Group 2 (0%, mean 28 y ± 5) Group 3 (0%, mean 28 y ± 6) Group 4 (0%, mean 28 y ± 4) | <ul style="list-style-type: none"> Group 1: Hydromorphone PCEA (43) Group 2: PCEA hydromorphone with basal infusion (46) Group 3: PCEA hydromorphone and bupivacaine (42) Group 4: PCEA hydromorphone and bupivacaine with basal infusion (39) | Pain score; nurse-assessed side effects | Efficacy of hydromorphone PCEA was not improved with the addition of bupivacaine or the basal infusion after cesarean delivery |
| Patel <i>et al.</i> , 2013, US ⁹⁴ | Case report | 1 In-patient with Multiple Sclerosis presenting for cystectomy and ileal conduit (0%, 46 y) | <ul style="list-style-type: none"> PCEA with hydromorphone (1) | Pain control; neurological deficits | In patients with baseline neurological deficits, the benefits of epidural analgesia need to be considered against the risk of difficulty in evaluating for new or progressive neurological deficits; patient education and extensive risk/benefit discussion is very important |
| Rauch, 2011, US ⁸⁰ | Case report | 1 In-patient scheduled for cesarean delivery (0%, 22 y) | <ul style="list-style-type: none"> Intrathecal hydromorphone (1) | Patient-reported pain; need for additional pain medications | Hydromorphone's higher lipid solubility means that the common side effects of intrathecal opioids are less intensive and shorter in duration than those of morphine; the author encourages more research regarding this use |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|---|--|---|---|---|
| Rauch, 2012, US ⁸¹ | Retrospective chart review | 226 In-patients who received a spinal anesthetic for post-cesarean pain management Hydromorphone (0%, mean 29.2 y ± 6.6) Fentanyl (0%, mean 29.0 y ± 6.5) Local anesthetic only (0%, mean 28.1 y ± 6.4) | <ul style="list-style-type: none"> Intrathecal hydromorphone (143) Intrathecal fentanyl (63) Local anesthetic only (20) | Pain scores measured over 24 hours | Intrathecal hydromorphone does not only appear to be safe, but also more effective than other intrathecal opioids for providing intraoperative and postoperative pain management of patients undergoing cesarean delivery; further research is needed, including a prospective, randomized controlled trial comparing intrathecal hydromorphone to intrathecal morphine |
| Ruan <i>et al.</i> , 2007, US ⁴⁷ | Case report | 1 Out-patient with severe low back pain and left-sided leg pain due to degenerative lumbar disc disease, lumbar spinal stenosis and lumbar radiculitis (0%, 65 y) | <ul style="list-style-type: none"> Patient-controlled epidural morphine trial and intrathecal pump implantation switched from morphine to hydromorphone (1) | Patient-reported pain; side effects | The mechanism of intrathecal morphine inducing hiccups needs further investigation |
| Singh <i>et al.</i> , 1997, US ⁴⁹ | Randomized, double-blind placebo-controlled study | 62 In-patients undergoing thoracotomies (gender not specified) Group 1 (mean 66 y ± 5) Group 2 (mean 64 y ± 9) Group 3 (mean 63 y ± 8) | <ul style="list-style-type: none"> Epidural hydromorphone (23) Epidural hydromorphone and bupivacaine (20) Epidural hydromorphone and intravenous ketorolac (19) | Pain scores; total hydromorphone requirement over preceding 24 hours; number of complaints of non-incisional pain; requests for rescue medication | The addition of intravenous ketorolac reduced the incidence of non-incisional pain and the hydromorphone requirement compared with PCEA hydromorphone alone; bupivacaine supplementation was not effective to reduce the incidence of non-incisional pain |
| Sucato <i>et al.</i> , 2005, US ⁵⁰ | Retrospective chart review | 613 In-patients who had surgical treatment for idiopathic scoliosis CEA (16%, mean 14.5 y ± 1.2) Patient-controlled analgesia (18%, mean 14.6 y ± 1.1) | <ul style="list-style-type: none"> CEA with hydromorphone and bupivacaine (413) Patient-controlled analgesia with intravenous morphine or meperidine (200) | Pain scores | Both interventions provided good postoperative pain management; however, CEA has improved pain control with less fluctuations and less maximum pain; regardless of intervention, close vigilance is necessary to maintain patient safety |

| Author, Year, Country | Study Type^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
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| Shulman <i>et al.</i> , 1987, US ⁴⁸ | Case series | 21 In-patients who received epidural hydromorphone for post-thoracotomy pain relief (gender not specified, range 18-76 y) | <ul style="list-style-type: none"> Epidural hydromorphone (21) | Duration of action; amount of supplemental intravenous morphine | In the authors' clinical experience, epidural hydromorphone provided excellent pain relief with fewer side effects when compared to epidural morphine |
| Swisher <i>et al.</i> , 2019, US ⁵¹ | Case report | 1 In-patient presenting for pneumonectomy (100%, 51 y) | <ul style="list-style-type: none"> Thoracic epidural hydromorphone (1) | Pain scores at rest | Opioid-only thoracic epidural is a novel option for postoperative rescue analgesia; provides adequate analgesia without excessive additional opioid use and minimized risks of local anesthetic systemic toxicity |
| Tanelian <i>et al.</i> , 1989, US ⁵² | Case report | 1 Patient with neurogenic and nociceptive pain due to Pancoast tumor (100%, 45 y) | <ul style="list-style-type: none"> Implanted epidural catheter with external pump for hydromorphone administration (1) | Pain scores | With oral carbamazepine and epidural hydromorphone, the patient had complete pain relief for 3 months, until his death |
| Tanelian <i>et al.</i> , 1989, US ⁵³ | Case report | 1 Patient with metastatic cecum adenocarcinoma (0%, 46 y) | <ul style="list-style-type: none"> Implanted epidural catheter with external pump for hydromorphone and bupivacaine administration (1) | Pain scores | Though epidural hydromorphone was not enough to obtain adequate pain relief alone, a lower dose administered with bupivacaine was effective; the authors commented that their observations awaits further investigation in controlled studies |
| Trainor <i>et al.</i> , 2016, US ⁵⁴ | Case report | 1 Out-patient with pain related to metastatic squamous cell carcinoma of the lung (100%, 70 y) | <ul style="list-style-type: none"> Intrathecal drug delivery device with hydromorphone and bupivacaine (1) | Patient-reported pain scores | Intrathecal opioids are effective for cancer-related pain while avoiding side effects; the authors recommend that intrathecal drug delivery devices be considered earlier in the treatment of cancer-related pain |

| Author, Year, Country | Study Type ^a | Patient Population (% male, age) | Intervention/Comparator (# of patients) | Primary Outcome Measure | Authors' Conclusions |
|--|------------------------------|---|--|---|--|
| Turchaninov <i>et al.</i> , 2015, US ⁶⁷ | Prospective randomized study | 36 In-patients undergoing major abdominal surgery (gender and age not specified) | <ul style="list-style-type: none"> TAPB with liposomal bupivacaine (19) Epidural analgesia with hydromorphone and bupivacaine (17) | Pain on NRS; total daily opioid requirements; length of hospital stay | TAPB with liposomal bupivacaine appears to offer adequate pain control, despite higher initial postoperative pain scores; it is associated with a low risk profile and fewer contraindications than epidural placement |
| Udeshi <i>et al.</i> , 2013, US ⁵⁵ | Case report | 1 Patient with sickle cell disease (0%, 19 y) | <ul style="list-style-type: none"> Hydromorphone via intrathecal drug delivery system with Personal Therapy Manager bolus (1) | Patient-reported pain relief; use of oral pain medication | The intrathecal drug delivery system was effective in the patient and benefit was also shown with the Personal Therapy Manager to help monitor and adjust therapy |
| Urits <i>et al.</i> , 2019, US | Case report | 1 Patient with colon cancer (100%, 58 y) | <ul style="list-style-type: none"> Intrathecal pump placement with hydromorphone and bupivacaine (1) | Patient-reported pain | Retrograde placement of an intrathecal catheter may be effective for treating site-specific analgesia |
| Warner <i>et al.</i> , 2018, US ⁸² | Case report | 1 Patient with fibromyalgia, chronic migraines, and systemic amyloidosis (100%, 58 y) | <ul style="list-style-type: none"> Hydromorphone via intrathecal drug delivery system with Personal Therapy Manager bolus (1) | Pain scores | Systemic amyloidosis is associated with severe neuropathic pain and is difficult to treat; Scrambler therapy or an implanted intrathecal drug delivery system resulted in analgesic benefit and improved quality of life; future studies are necessary |

Abbreviations: “–”, not mentioned; CEA, continuous epidural analgesia; CPI, continuous paravertebral infusion; ICU, intensive care unit; LM-TAP, lateral to medial transversus abdominis plane block; PAI, periarticular injection; PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; TAPB, transversus abdominis plane block; TEA, thoracic epidural analgesia.

^aAs defined by authors.

Appendix 3.1. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded hydromorphone 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) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

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

- Yes
- No

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

- Epidural injection
- Intrathecal injection
- None of the above

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

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

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

- FDA-approved drug product
- Compounded drug product
- Other (please describe) _____

6. I use compounded hydromorphone hydrochloride because: (check all that apply)
- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
 - Patient allergies prevent me from using commercially available products. (please explain) _____
 - Patient conditions prevent me from using commercially available products. (please explain) _____
 - There are no commercially available products containing hydromorphone hydrochloride.
 - Other (please explain) _____
7. Do you stock non-patient-specific compounded hydromorphone hydrochloride at your practice?
- Yes
 - No
 - I'm not sure
8. I obtain compounded hydromorphone hydrochloride from the following: (check all that apply)
- Compound myself at my practice
 - Have the product compounded by an in-house pharmacy
 - Purchase, or have a patient purchase, from a compounding pharmacy
 - Purchase, or have a patient purchase, from an outsourcing facility
 - Other (please explain) _____
9. What is your practice setting? (check all that apply)
- Physician office/private practice
 - Outpatient clinic
 - Hospital/health system
 - Academic medical center
 - Emergency room
 - Operating room
 - Other (please describe) _____
10. What degree do you hold? (check all that apply)
- Doctor of Medicine (MD)
 - Doctor of Osteopathic Medicine (DO)
 - Doctor of Medicine in Dentistry (DMD/DDS)
 - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
 - Naturopathic Doctor (ND)
 - Nurse Practitioner (NP)
 - Physician Assistant (PA)
 - 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

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) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription) | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

2. Do you utilize a 503B outsourcing facility to acquire compounded drugs?

- Yes. If yes, why? _____
- No. If no, why not? _____

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

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

- Remifentanyl
- Sufentanyl
- Tramadol
- None of the above

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

- Dental
- Dermatology
- Endoscopy
- Neurosurgery
- Obstetrics/gynecology
- Ophthalmology
- Otolaryngology
- Orthopedics
- Pain
- Plastics
- Podiatry
- 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 (AAAAI) | 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 |

^aAssociations that declined in Year 1 were not contacted in Year 2.