Summary Report

Ketamine hydrochloride

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
ASHP	American Society of Health-System Pharmacists
CRPS	Complex regional pain syndrome
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HCl	Hydrochloride
IRB	Institutional Review Board
IV	Intravenous
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 US Food and Drug Administration (FDA) in its evaluation of the use of ketamine hydrochloride (ketamine HCl; UNII code: O18YUO0I83), 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 ketamine 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 ketamine 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 ketamine 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

Ketamine HCl was nominated for inclusion on the 503B Bulks List by Fagron Inc., Pentec Health, the Specialty Sterile Pharmaceutical Society (SSPS), and the US Compounding Pharmacy.

Ketamine HCl was nominated for pain management, sedation, the treatment of migraine, and the treatment of depression via a 10-100 mg/mL intranasal spray. Ketamine HCl was also nominated for the treatment of severe pain (including chronic pain, cancer pain, and postoperative pain) as an intrathecal solution with concentrations up to 3 mg/mL. In addition, ketamine HCl was nominated for general anesthesia and as an adjunct for procedural sedation via intramuscular and intravenous administration as a 1.25-50 mg/mL solution.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of ketamine HCl.[6-20]

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

- The FDA-approved injectable ketamine formulations contain a preservative that is not typically indicated for intranasal use; furthermore, nasal spray formulations should be customized to the patient and are typically more diluted than the commercially available solutions.
- Practitioners often prescribe doses that require higher strengths or concentrations than those available in FDA-approved products or use in combinations with other medications.
- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes, and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical-size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100-percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- 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.
- Practitioner or facility need for different strengths or forms or ready-to-use packaging.
- Manufacturer backorder.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of ketamine 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 ketamine HCl; name variations of ketamine 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 ketamine HCl. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: ketamine HCl; epidural or intrathecal administration; and therapeutic or preventative use for analgesia or anesthesia (refer to Appendix 1 for full search strategies). A literature review was not conducted for intravenous, intramuscular, or intranasal administration due to the availability of FDA-approved products for these ROAs. Results were limited to human studies in the English language. Searches were conducted on August 31, 2020. In addition, the ECRI Guidelines Trust® repository was searched on August 31, 2020, for clinical practice guidelines that recommended the use of ketamine HCl and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.3.3 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which ketamine 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, preclinical 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 ketamine HCl was used as a dosage form, ROA, or combination that was not nominated; an unspecified dosage form or ROA; or an indication that was not nominated; or if it had a nonclinical use or was mentioned briefly as a previous failed treatment. Studies in which ketamine 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 ketamine HCl; setting; total number of patients; number of patients who received ketamine HCl; patient population; indication for use of ketamine HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of ketamine HCl in a combination product; use and formulation of ketamine HCl in a compounded product; use of ketamine 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

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances ketamine HCl was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use ketamine HCl. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. 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 synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate, to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (refer to Appendix 2 for complete survey and *Results of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

Survey

A survey was distributed to the members of professional medical associations to determine the use of ketamine 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 Years 1 and 2 were not contacted to distribute the project Year 3 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

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

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Esketamine HCl	EQ 28 mg base	Spray	Nasal	Prescription	03/05/2019
Ketamine HCl	EQ 10-100 mg base/mL	Injectable	Injection	Prescription	Approved prior to 01/01/1982

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

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Esketamine HCl	25 mg/mL	Solution	Intramuscular, Intravenous	Belgium	Medical prescription	11/25/2014
	28 mg / 2 actuations 28 mg / dose 140 mg/mL	Solution, solution for injection, spray solution	Nasal	Abu Dhabi	Active	–
				Canada	Narcotic	06/11/2020
				EU	Authorized	12/18/2019
				Ireland	Prescription-only nonrenewable	12/18/2019
				New Zealand	Controlled	09/03/2015
Ketamine HCl	1-100 mg/mL	Infusion, injectable solution, solution, solution for injection	Injection, intramuscular, intravenous	Abu Dhabi	Active	–
				Australia	S8 – Controlled drug	02/14/2000
				Belgium	Medical prescription	02/28/1971
				Canada	Narcotic (CDSA I)	12/31/1972
				Hong Kong	Prescription-only medicine	06/14/1979
				Ireland	Prescription-only nonrenewable	04/01/1980
				Namibia	–	08/18/2004
				New Zealand	Controlled	02/19/1970
				Saudi Arabia	Prescription	–
				UK	Prescription-only medication	07/01/2003

Abbreviations: – , not provided; CDSA, Controlled Drugs and Substances Act; EU, European Union; UK, United Kingdom.
[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Results of literature review

Study selection

Database searches yielded 1895 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1308 titles and abstracts were screened. After screening, the full text of 297 articles was reviewed. Twenty-four studies were included; after multiple reports of the same study were merged, there were 22 included studies. Two hundred seventy-three studies were excluded for the following reasons: wrong study design (121 studies); FDA-approved dosage form or ROA (74); unspecified dosage form or ROA (62); non-nominated dosage form or ROA (8); ketamine HCl mentioned only briefly (3); language other than English (3); duplicate study (2).

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

Characteristics of included studies

The 22 included studies were published between 1996 and 2020. There were 20 experimental studies and 2 descriptive studies. The 22 studies were conducted in the following countries: Brazil, Egypt, India, Iran, Nepal, Saudi Arabia, Taiwan, Turkey, and US.

A total of 1434 patients participated in the 22 included studies. The number of patients in each study ranged from 1 to 180.

Outcome measures differed among the studies and included: onset and duration of analgesia; hemodynamic variables; need for rescue analgesia; onset and duration of sensory and motor blocks; pain-free period; pain intensity; adverse effects; vital signs.

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

Use of ketamine HCl

Six hundred forty-seven patients received ketamine HCl for analgesia or anesthesia, administered intrathecally in doses ranging from 0.5 mg to 100 mg.

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

Ketamine HCl was not used as a compounded product, nor was it used in a combination product (refer to Tables 8-10).

In 11 studies, the authors' concluding statement recommended the use of ketamine HCl for analgesia or anesthesia.[21-31] In 6 studies, the authors concluded that the use of ketamine HCl for analgesia or anesthesia was not recommended.[32-37] There were 2 studies in which the authors concluded that further studies were necessary regarding the use of ketamine HCl for analgesia or anesthesia.[38,39] In 2 studies, the authors' concluding statement did not address the use of ketamine HCl for analgesia or anesthesia.[40,41] One study did not provide a recommendation for the use of ketamine HCl, stating that its use led to faster onset of sensory and motor blockade, but when compared to fentanyl, the addition did not prolong spinal analgesia duration.[42] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 22 included studies, additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of ketamine HCl.

An anesthetic agent with potent analgesic properties, spinal ketamine was first used in a human population during war-related surgery in 1984.[35,43] Intrathecal ketamine HCl is active at the "phencyclidine site of the NMDA [*N*-methyl D-aspartate] receptor-gated calcium channel and inhibits the NMDA receptors noncompetitively." [35] Furthermore, ketamine HCl "acts at opiate, monoaminergic receptors and voltage-sensitive calcium channels."[35] According to 1 author, intrathecal ketamine "produced significant analgesia without interfering with cardiovascular and respiratory function. However, the occurrence of central side-effects and the short duration of surgical analgesia limited the usefulness of spinal ketamine."[35] Another author said that adverse effects of ketamine HCl as an anesthetic agent "are seen in the recovery phase of surgery and include psychomimetic events such as hallucinations, psychomotor agitation, mental confusion, euphoria, and fear."[32] However, the author added that the use of subarachnoid ketamine "with a low incidence of side effects, was possible because of the development of preservative-free S (+) ketamine."[32]

Several included studies noted that there is concern about intrathecal ketamine use due to preservatives, such as chlorobutanol and benzalkonium chloride. However, "preservative-free ketamine has been shown to be devoid of neurotoxic effects after both single and repeated administration."[35,38] Other factors, such as "the use of multiple drugs for a prolonged period and intrathecal catheters," may also add to neurological complications.[38]

In addition to being used as an anesthetic, ketamine has been investigated for use in cases of suicidal ideation among adults with psychiatric disorders. A 2020 systematic review and meta-analysis was conducted evaluating randomized controlled trials with either ketamine or esketamine.[44] The authors concluded that although "currently there is considerable uncertainty about the use of ketamine specifically as a treatment for suicidal ideas … current results of trials suggest that this drug may have a potential place in the clinical care of suicidal patients."[44] In these studies, ketamine was mostly administered via an intravenous route.[44]

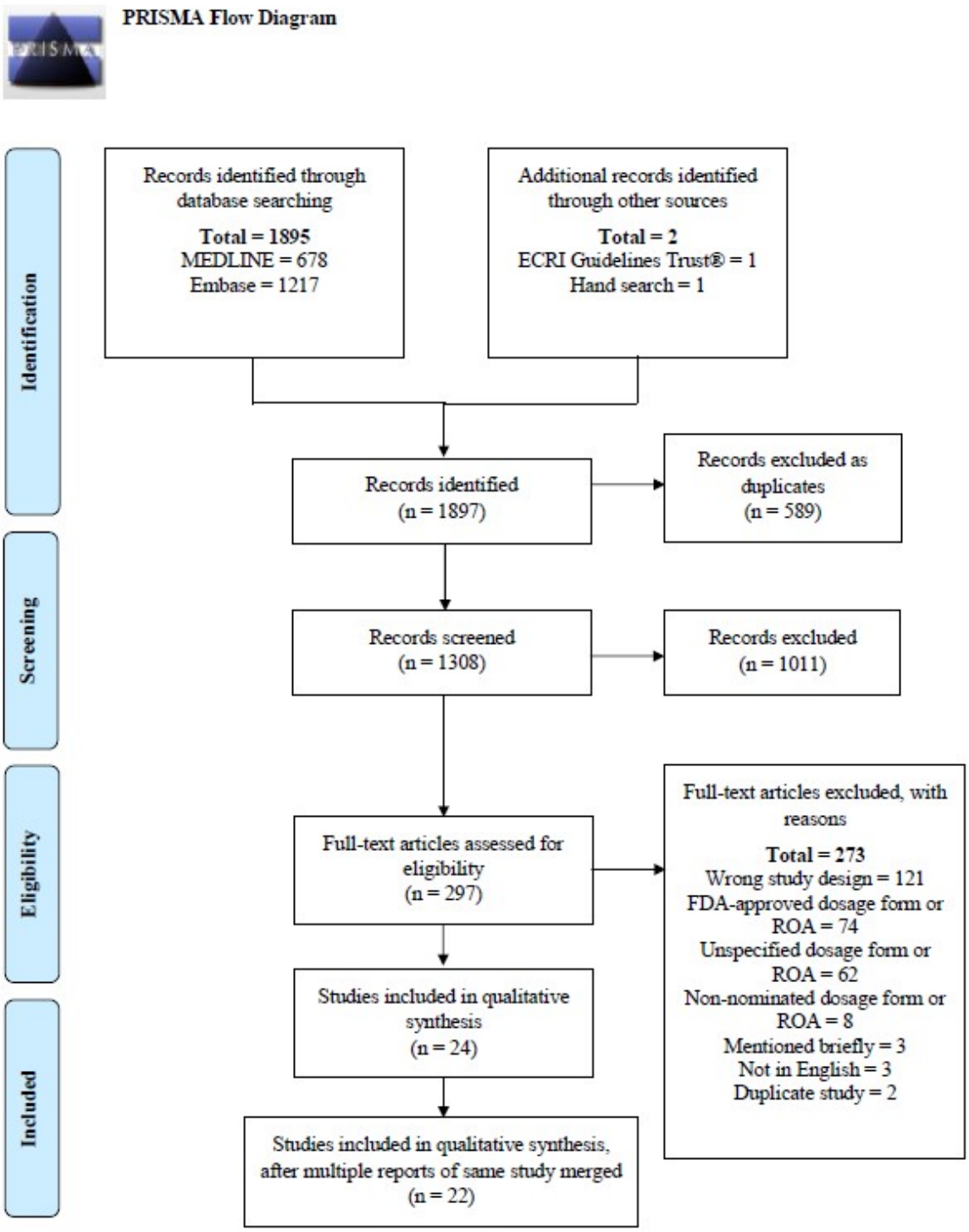
Furthermore, in March 2019, the S-enantiomer of ketamine (esketamine) was approved by the FDA as an intranasal therapy for treatment-resistant depression.[45] The authors of a 2020 narrative review commented that the interest in the S-enantiomer is linked to "evidence from relatively old studies in humans [which] showed that IV [intravenous] esketamine had better analgesic, intraoperative amnesia and anaesthetic properties, with less drowsiness, lethargy, cognitive impairment and psychotic emergent reactions, than the racemic mixture and R-enantiomer."[45] In addition, the researchers investigated intranasal administration to avoid the "inherent difficulties for both patients and clinicians" associated with intravenous esketamine, as well as the low bioavailability associated with oral esketamine.[45] The authors concluded that although the limited clinical trials show efficacy and safety in patients with treatment-resistant depression, "the optimum dose, duration and frequency of use are not fully understood."[45] And despite the convenience of the intranasal dosage form, the use of intranasal esketamine may be limited in practice due to cost and administrative regulation; additional long-term data is necessary.[45]

Both the FDA Drug Shortages list and the American Society of Health-System Pharmacists (ASHP) Current Drug Shortages list include ketamine HCl products.[46,47] Both lists included the ketamine injection (first posted to FDA on February 16, 2018, to ASHP on February 7, 2018).[46,47] The reasons

provided for these shortages included discontinuation of manufacturing, increased demand for the product, manufacturing delay, and "other."[46,47]

The ASHP has the Standardize 4 Safety initiative to develop national standardized concentrations for intravenous medications in both pediatric and adult patients.[48,49] For ketamine, the concentration standards for continuous infusions are 2 mg/mL and 10 mg/mL for pediatric patients, but only the 10 mg/mL concentration is commercially available.[48] ASHP states that there is the possibility of concentration and unit mismatch, depending on the pharmacy or outsourcing facility label.[48]

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[40,41]	2
Observational	0
Experimental[21-39,42]	20

Table 4. Number of studies by country

Country	**Number of Studies**
Brazil[32]	1
Egypt[21,22,27]	3
India[23,28,34,35,38]	5
Iran[25,26,36]	3
Nepal[42]	1
Saudi Arabia[33]	1
Taiwan[30]	1
Turkey[29,31,37,39]	4
United States[24,40,41]	3
	Total US: 3 Total Non-US Countries: 19

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication: Pain					
Abd El-Rahman et al, 2018, Egypt[21]	Randomized, double-blind study	90 Inpatients scheduled for major abdominal cancer surgery • Morphine (gender not specified, mean 41.50 y ± 3.90) • Ketamine (gender not specified, mean 41.23 y ± 4.12) • Morphine and ketamine (gender not specified, mean 41.70 y ± 3.80)	All patients received intrathecal hyperbaric bupivacaine plus: • Intrathecal morphine (30) • Intrathecal ketamine (30) • Intrathecal morphine and ketamine (30)	Total dose of intravenous PCA morphine consumption	"Adding intrathecal ketamine 0.1mg/kg to morphine 0.3mg in patients who underwent major abdominal cancer surgery reduced the total postoperative morphine consumption in comparison with either drug alone, with an overall good postoperative analgesia in all groups, with no side effects apart from sedation."
Basuni, 2016, Egypt[22]	Prospective double-blind study	50 Inpatients undergoing elective lower segment transverse incision cesarean section • Ketamine-midazolam-bupivacaine (0%, mean 29.7 y ± 3.8) • Fentanyl-bupivacaine (0%, mean 28.5 y ± 4.5)	Spinal anesthesia with a combination of either: • Ketamine, midazolam, and bupivacaine (25) • Fentanyl and bupivacaine (25)	Hemodynamic variables, pain-free period	"Intrathecal low-dose ketamine combined with midazolam and low-dose bupivacaine stabilizes hemodynamics and prolongs postoperative analgesia without significant side-effects in parturients undergoing CS [cesarean section]."
Carpi et al, 2020, Brazil[32]	Double-blind, randomized clinical trial	80 Inpatients scheduled to undergo elective abdominal hysterectomy • Morphine (0%, median 45.0 y [IQR 39.5; 48.0]) • Ketamine (0%, median 45.0 y [IQR 40.0; 49.5])	Spinal anesthesia with bupivacaine, sufentanil, and: • Morphine (40) • Ketamine (40)	Pain intensity at rest	"Compared with ketamine, intrathecal morphine obtained better postoperative analgesia up to 12 hours after surgery, with a higher incidence of pruritus without any significant change in other variables."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Gantasala et al, 2019, India[23]	Randomized comparative study	60 Inpatients scheduled for elective lower abdominal surgeries under subarachnoid block • Bupivacaine (46.7%, mean 40.3 y ± 7.8) • Bupivacaine and ketamine (36.7%, mean 43.4 y ± 7.8)	Intrathecal bupivacaine with either: • Normal saline (30) • Ketamine (30)	Duration of postoperative analgesia	"Ketamine, when added to bupivacaine intrathecally, decreased onset and prolonged the duration of sensory block. It also prolonged the post-operative analgesia with better haemodynamic stability than bupivacaine alone."
Govindan et al, 2001, US[24]	Double-blind randomly controlled study	60 Inpatients scheduled for surgeries (gender and age not specified)	• Intrathecal ketamine 75 mg (not reported) • Intrathecal ketamine 75 mg with epinephrine (not reported) • Intrathecal ketamine 100 mg (not reported) • Intrathecal ketamine 100 mg with epinephrine (not reported)	Onset and duration of sensory and motor blocks	"In conclusion, intrathecal ketamine can be used clinically in selected patients to produce adequate anesthesia for lower abdomen and lower extremities. Increasing the dosage of ketamine and addition of epinephrine prolongs the duration of spinal anesthesia."
Hussain et al, 2012, Saudi Arabia[33]	Prospective, open-label, parallel assignment, randomized, single-center trial	80 Inpatients admitted for lower limb and perianal surgery • Ketamine (87.5%, mean 49.4 y ± 19) • Midazolam (80%, mean 45.8 y ± 18)	Intrathecal bupivacaine with either: • Ketamine (40) • Midazolam (40)	Onset of action, vital signs, pain assessment, postoperative analgesia time	"Intrathecal midazolam with bupivacaine provides very good and prolonged post-operative analgesia compare to intrathecal ketamine with bupivacaine."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kataria et al, 2018, India[34]	Prospective, randomized, double-blind study	90 Inpatients scheduled for surgery under spinal anesthesia • Nalbuphine (76.67%, mean 35.7 y ± 12.26) • Ketamine (83.33%, mean 36.37 y ± 2.70) • Normal saline (73.33%, mean 34.07 y ± 11.90)	Intrathecal hyperbaric bupivacaine with: • Nalbuphine (30) • Ketamine (30) • Normal saline (30)	Duration of analgesia, sensory onset, hemodynamic stability, side effects	"Both the groups were effective in providing adequate anesthesia and analgesia along with good hemodynamic stability, but bupivacaine with nalbuphine group was better than ketamine group and bupivacaine alone group with respect to the prolonged duration of analgesia, prolonged duration of sensory block with early onset, and lesser side effects."
Kathirvel et al, 2000, India[35]	–	30 Inpatients scheduled for intracavitary brachytherapy applicator insertion for carcinoma of the cervix under spinal anesthesia • Bupivacaine (0%, mean 52.3 y ± 11.9) • Bupivacaine with ketamine (0%, mean 48.6 y ± 10.7)	• Intrathecal bupivacaine (15) • Intrathecal bupivacaine with ketamine (15)	Spinal block onset, maximum sensory level, duration of blockade, hemodynamic variables, postoperative analgesic requirements, adverse events	"We conclude that intrathecal racemic ketamine has local anaesthetic-sparing effects. However, the high incidences of adverse events and poor patient satisfaction limit the clinical use of spinal racemic ketamine 25 mg as an adjunct to spinal bupivacaine."
Khezri et al, 2013, Iran[25]	Randomized, double-blind, placebo-controlled study	60 Inpatients scheduled for cesarean section under spinal anesthesia • Ketamine (0%, mean 27.22 y ± 5.81) • Control (0%, mean 26.55 y ± 6.05)	Intrathecal bupivacaine with either: • Ketamine (30) • Control (30)	Time to first analgesic request and requirement in the first 24 hours after surgery, onset and duration of sensory and motor blockades, adverse effects	"In conclusion, based on the data found in our study, it could be concluded that intrathecal ketamine 0.1 mg/kg with spinal bupivacaine caused a prolonged intraoperative anesthesia, increased the time to the first analgesic request, and decreased the total analgesic consumption in the first 24 postoperative hours as compared with the control group following elective cesarean delivery."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Khezri et al, 2011, Iran[36]	Prospective randomized double-blind clinical trial	87 Inpatients scheduled for elective cesarean section under spinal anesthesia (0%, age not specified)	Spinal bupivacaine with: • Saline (not reported) • Ketamine (not reported) • Midazolam (not reported)	Onset of sensory and motor block, hemodynamic parameters, duration of analgesia	"Applying combination of midazolam and bupivacaine provides better results in onset time of sensory and motor blocks and postoperative analgesia."
Khezri et al, 2016, Iran[26]	Prospective randomized double-blind study	90 Inpatients scheduled for cesarean section under spinal anesthesia • Ketamine (0%, mean 30.43 y ± 3.70) • Fentanyl (0%, mean 30.20 y ± 5.41) • Placebo (0%, mean 29.16 y ± 5.11)	Intrathecal bupivacaine with either: • Ketamine (30) • Fentanyl (30) • Placebo (30)	Time to first analgesic request, postoperative analgesic requirement, onset and duration of sensory and motor blockade, adverse effects	"Addition of ketamine or fentanyl to spinal bupivacaine were equally effective in pain control after cesarean section and therefore, based on the specific conditions of patients, ketamine at concentrations mentioned earlier, could be a proper alternative to achieve postoperative analgesia."
Mohamed et al, 2016, Egypt[27]	Double-blind, randomized, controlled trial	90 Inpatients scheduled for major abdominal cancer surgery • Dexmedetomidine (gender not specified, mean 44.43 y ± 4.05) • Ketamine (gender not specified, mean 44.20 y ± 4.20) • Dexmedetomidine and ketamine (gender not specified, mean 44.63 y ± 3.84)	Intrathecal bupivacaine plus: • Dexmedetomidine (30) • Ketamine (30) • Dexmedetomidine and ketamine (30)	Hemodynamics, pain score, time to first request of analgesia, total PCA morphine consumption, sedation score, adverse effects	"In conclusion, the combination of intrathecal dexmedetomidine and ketamine provided superior postoperative analgesia, prolonged the time to first request of rescue analgesia, and reduced the total consumption of PCA morphine, without serious side effects compared to either drug alone."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Murali Krishna et al, 2008, India[38]	Prospective, randomized, double-blind study	60 Inpatients scheduled for lower limb surgery • Normal saline (85%, mean 41.0 y ± 11.7) • Ketamine (70%, mean 39.3 y ± 10.9) • Ketamine and midazolam (90%, mean 34.1 y ± 10.9)	Intrathecal bupivacaine plus: • Normal saline (20) • Ketamine (20) • Ketamine and midazolam (20)	Onset and duration of sensory and motor block, duration of pain-free period, total rescue analgesic requirement, central or neurologic complication	"A low dose of midazolam and ketamine with bupivacaine intrathecally results in prolonged analgesia and less haemodynamic fluctuations. However, the safety of this combination needs to be proved before its use in clinical practice."
Peniche et al, 2017, US[50] Peniche et al, 2017, US[51] Peniche et al, 2018, US[40]	Case	1 Patient with a history of COPD, scoliosis post-multiple spine surgeries, implantation of spinal cord stimulator and intrathecal pump (0%, 70 y)	• Intrathecal pump with a mixture of hydromorphone, ketamine, bupivacaine, and clonidine (1)	Pain control	"This case highlights the importance of close communication among all providers and understanding the difference in IT versus systemic opioid kinetics in the management of postoperative pain management. We are currently developing hospital policy for safe and appropriate care of inpatients with IT-PCA."
Samantaray and Hanumantha Rao, 2006, India	Prospective, randomized, double-blind study	30 Inpatients scheduled for various urological procedures • Ketamine (93.3%, mean 44.2 y ± 7.3) • Midazolam and ketamine (100%, mean 43.9 y ± 6.7)	• Intrathecal ketamine (15) • Intrathecal ketamine and midazolam (15)	Sensory and motor blockade, duration of pain relief	"To summarize, our study showed that IT midazolam along with ketamine not only prolongs the duration of ketamine analgesia but also provide a greater degree of motor blockade with a reduced incidence of psychomimetic reaction. The utility of IT ketamine as a sole anesthetic agent is limited owing to its side effect but there is definitive benefit of using two separate classes of anesthetics for subarachnoid block in clinical practice with minimum side effects."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Shrestha et al, 2013, Nepal[42]	Prospective, randomized, double-blind study	100 Inpatients scheduled for elective or semiurgent cesarean delivery • Ketamine (0%, mean 24.66 y ± 5.278) • Fentanyl (0%, mean 23.96 y ± 4.286)	Intrathecal bupivacaine plus: • Ketamine (50) • Fentanyl (50)	Onset of sensory block, degree of motor block, total duration of analgesia	"Addition of preservative free ketamine led to faster onset of sensory and motor blockade, although it did not prolong the duration of spinal analgesia compared to addition of fentanyl in parturients undergoing caesarean section with spinal anaesthesia."
Su et al, 2014, US[41]	Case report	1 Patient with severe inversion deformity and limited range of motion complicated by CRPS (0%, 48 y)	• Intrathecal baclofen and ketamine pump (1)	Pain control	"Amputation is a viable option for uncontrolled CRPS and may be a very effective last resort. Our patient elected to undergo amputation for recovery of function despite expected increase in pain. Our patient exceeded our expectations during her acute inpatient rehabilitation stay and continues to meet her functional goals in home PT and OT."
Togal et al, 2004, Turkey[29]	–	40 Patients with prostate hypertrophy undergoing transurethral prostate resection under spinal anesthesia • Bupivacaine plus S(+) ketamine (100%, mean 70.0 y ± 4.6) • Bupivacaine (100%, mean 68.0 y ± 4.8)	• Intrathecal bupivacaine plus S(+) ketamine (20) • Intrathecal bupivacaine (20)	Spinal block onset time, maximum sensory level, duration of blockade, hemodynamic variables, postoperative analgesic requirements, adverse events	"Intrathecal S(+) ketamine administered with a low dose of bupivacaine provides shorter motor and sensory block onset time, shorter duration of action and less motor blockade in elderly males."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Unlugenc et al, 2006, Turkey[37]	Prospective, randomized, double-blind, controlled study	90 Inpatients undergoing cesarean section • Saline (0%, mean 28.8 y) • Ketamine (0%, mean 29.7 y) • Fentanyl (0%, mean 30.2 y)	Intrathecal bupivacaine followed by: • Saline (30) • S(+) ketamine (30) • Fentanyl (30)	Onset and duration of sensory and motor block, time to reach maximal dermatomal level of sensory block, duration of spinal analgesia	"There is thus no strong rationale for using IT S(+) ketamine as an adjuvant to spinal bupivacaine and it cannot be recommended at the present time."
Yang et al, 1996, Taiwan[30]	Double-blind crossover study	20 Inpatients with primary cancer diagnosis (50%, range 22-69 y)	• Intrathecal morphine (20) • Intrathecal morphine and ketamine (20)	Pain intensity and frequency	"The present study demonstrates that ketamine enhances the analgesic effect of morphine, thus reducing the dose of intrathecal morphine."
Yektaz, 2011, Turkey[39]	–	180 Patients who underwent spinal anesthesia (gender and age not specified)	Intrathecal bupivacaine 15 mg plus: • Normal saline (20) • Bupivacaine 2.5 mg (20) • Ketamine (20) • Fentanyl (20) • Sufentanil (20) • Dexmedetomidine (20) • Neostigmine (20) • Midazolam (20) • Droperidol (20)	Side effects, time to first pain, characteristics of spinal anesthesia	"No differences in the time to the first pain were found between intrathecal adjuvant agents. Their effects on the characteristics of spinal anesthesia are similar. Each adjuvant agent causes specific side effects. However, postoperative analgesic requirement was not considered in our study, and dose-finding studies (which are performed to determine the adjuvant agent doses that cause minimal and maximal side effects) were not performed. Further studies should be performed to evaluate those factors."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Yentür et al, 2004, Turkey[31]	Randomized, double-blind, and placebo controlled	45 Inpatients scheduled for orthopedic surgery by unilateral spinal anesthesia • Normal saline (53.3%, mean 39.8 y ± 15.6) • Morphine (46.7%, mean 43.0 y ± 15.6) • Morphine and ketamine (60%, mean 40.6 y ± 20.8)	Spinal bupivacaine plus: • Normal saline (15) • Morphine (15) • Morphine and ketamine (15)	Motor and sensory block levels	"Subanalgesic doses of morphine and ketamine added to 0.5% HB extended the sensory block period but not the motor block in unilateral spinal anaesthesia."

Abbreviations: –, not provided; COPD, chronic obstructive pulmonary disease; CRPS, complex regional pain syndrome; CS, cesarean section; HB, hyperbaric bupivacaine; IQR, interquartile range; IT, intrathecal; OT, occupational therapy; PCA, patient-controlled analgesia; PT, physical therapy.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Analgesia/Anesthesia[24,40,41]	119-339 mcg/day	195 mcg/mL	–	Intrathecal	–
	75-100 mg	25-33.3 mg/mL			Once

Abbreviation: –, not provided.

Table 7. Dosage by indication – non-US countries

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Analgesia/Anesthesia[21-23,25-39,42]	0.1 mL/kg	–	–	Intrathecal	Once
	0.05-1.5 mg/kg 0.5-50 mg	0.025-0.5 mg/kg/mL 3.57-50 mg/mL	–		
	2 mg/day	–	–		–

Abbreviation: –, not provided.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Four SMEs discussed ketamine HCl. Among these 4 SMEs, there were 3 medical doctors and 1 nurse practitioner. The SMEs specialized and/or were board-certified in anesthesiology, oncology, and pain medicine, working in academic medical institutions and community hospitals. The SMEs had been in practice for 12 to 25 years. Additional information was collected as part of the Expanded Information Initiative, referred to as Phase 3—a project in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

Two SMEs commented that ketamine is commonly used in IV interoperatively and postoperatively for acute pain management. One SME stated that in pediatric patients, they evaluate the expected level of postoperative pain and include ketamine in the regimen when there is mild to moderate, moderate to severe, or severe pain expected. The SME stated that low-dose infusions of ketamine can also be used. Another SME mentioned that the specific procedure will determine the dose administered, stating that for most procedures 10-20 mg is used, but for joint surgeries, in order to reduce the amount of narcotics needed, 50 mg is administered. Ketamine can also be used to induce anesthesia, which is especially useful in trauma patients who are also hypotensive, as well as on patients in post-anesthesia care units (PACUs) who are decompensating. Ketamine can also cause sedation, so it can be used in difficult patients who are undergoing blocks or in those with a low pain threshold. The SME stated that intramuscular ketamine is often used in pediatric patients because they tend not to cooperate for an IV. However, ketamine should be avoided in patients with seizure disorders and in those who are extremely hypertensive. In addition, ketamine is a dissociative anesthetic, so it would not be used in a patient with psychosis. Ketamine can cause salivation and bradycardia, and historically ketamine has been used in combination with atropine as a "ketamine dart." The atropine helps to prevent bradycardia, as well as to dry up the saliva.

For pain management, one SME has seen ketamine used in topical compounded pain products, but they have not used it as an intrathecal injection. They commented that there is not a lot of literature about ketamine use via an intrathecal route, and considering the dissociative adverse effects (e.g., hallucinations, psychosis), this is not something that they would use with a patient. If a patient was referred to them after having done well while trialed on intrathecal ketamine, the SME would be willing to implant the intrathecal pump. However, this SME has not done any intrathecal ketamine trials themselves. The SME added that physicians who use IV ketamine for complex regional pain syndrome (CRPS) speak of needing round-the-clock nursing supervision to ensure that adverse effects do not occur, and these physicians use benzodiazepines to prevent such adverse effects.

One SME stated that they do not use ketamine.

As part of Phase 3, 1 nominator provided additional information regarding the products that will be compounded using ketamine HCl.

Ketamine HCl will be compounded as a 10 mg/mL solution for injection as a one-time dose for use as anesthesia. This product is used by practitioners as a non-patient-specific compounded product in operating rooms and surgery centers. It is needed because the preparation and distribution of in-process sterilized solutions for injection—which are packaged in labeled, ready-to-use syringes—enhances the safety for patients who require these formulations during surgery or other medical procedures. Prescribers prefer the compounded alternative of the commercially available formulations to avoid the risk of contamination when a syringe is drawn up into a vial, and to avoid the risk of misidentification of a drug product after that product is drawn up into an unlabeled syringe. By externalizing error-prone risks to a

more controlled, regulated, and sterile setting, patient safety is greatly enhanced. Furthermore, ensuring that the identification and dosage strengths of medications are clearly visible with labels meeting Institute for Safe Medication Practices (ISMP) standards, while removing the need for rapid mathematical calculation in high-acuity situations, also enhances patient safety.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event; refer to Table 15 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants; refer to Tables 15-18 for results of the prequestionnaire.

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtained varied from less than 1% to the majority of compounded products used at one participant's facility. A participant stated, "we have this method that we use where if we can buy it commercially ready to administer, we do that. If we can't buy it in that format, then we buy it in a vial, for example, that can be snapped into a Mini-Bag Plus, because we're a Baxter house, as a second preference. If we can't buy it in either of those two formats and we can get it from a 503B, then we do that. And our last resort is compounding internally." Two participants commented that they will not outsource a product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from 1 outsourcing facility, minimizing the impact to the participant's facility.

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, like emergency departments and operating rooms. Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use dates compared to products compounded in-house, allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented that "we're always going to outsource a PCA [patient-controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an automated dispensing cabinet, stating that "operationally, if you have a stat medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a 5-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing <797> right, it's 5 minutes. It's 4 minutes to tube it. It's 3 minutes to make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals as they face a unique need in that they are already having to perform a lot of manipulations to products due to a lack of concentrations or sizes available. One participant commented that "at baseline, already, we manipulate about 80% of what we dispense to patients" and another stated that "there's a number of drugs that require additional manipulation to get them to a concentration that's appropriate for kids." One participant stated that "we're trying to minimize compounding, expedite actual therapies to patients in that setting [operating room], minimize manipulations as much as possible." Similarly, in the emergency department, one participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor and another commented that "we absolutely buy as many pressor drips as we can." One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require

manipulation prior to administration to be purchased as syringes from outsourcing facilities, stating that "they would prefer to have a syringe form."

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover, leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency with which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant stated that, while they do not obtain a lot of products from outsourcing facilities, "when we do purchase from 503Bs, typically it would be if we just don't have the capacity to keep up with what the demand is." One participant also commented that they will obtain labor-intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 (COVID-19) pandemic has also impacted the operations of hospitals, as noted by one participant who stated that "it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital" and another who expressed that "without 503B, we would've been in significant trouble." One participant commented that "even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when." Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making, with one participant stating "it is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready-to-use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing."

In addition to the evaluation of the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established cleanroom and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use date that can be assigned to these products and, as the participant stated, "We obviously need to provide product with much [more] extensive beyond-use dating than we can provide." Several participants also commented that they do not perform high-risk compounding in-house and therefore, all of these products are outsourced. There are challenges with midsize hospitals being able "to operationalize testing compounds we make for extended stability." One participant stated, "We might make our own syringes if we could get extended dating, but I believe my operations colleagues don't always know how to do this and adhere to the letter of the law."

One participant also commented on the impact that The Joint Commission has had on pushing pharmacies to obtain products from outsourcing facilities. The 2018 medication management standard MM.05.01.07 was intended to move IV admixture preparation out of the nursing unit. This forced pharmacies to consider strategies to make IV admixtures available for use on the floor. Additionally, NPSG.03.04.01 states that all medications and solutions should be adequately labeled, including in the operating room and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used within 1 hour, which may be problematic if syringes are drawn up at the beginning of the day and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers, stating that "predatory pricing on premixes is present in the market."

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products used. However, the products used in a facility are often developed in-house over decades based on physician and nurse requests, and more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, "these practices had evolved somewhat disparately. Even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines." This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, "I think we made 9 different epidural concentrations, all driven by anesthesia, and they want what they want, and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn't going to go through the expense of adding that to their product list." The participant also said that "similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, 'no, we can't have it, and that's too big, it won't fit, we want it in this format' and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing." Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that "3% saline, for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We're either going to draw that out or we're sending it to the ER with stickers all over it saying only give 150 [mL]." The participant continued that "it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose: is it a unit dose, or isn't it?"

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that "most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end," and another stated, "I can only think of one time in recent history where we went to an outsourcer." One participant commented that "503Bs can't accept the additional volume if it's a true shortage. If you're not with them pre-shortage, you're not going to get products when you need it during the shortage" continuing that "typically in a shortage, you learn to live without them. You have to." Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that "what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of Health-System Pharmacists] and the FDA allow." This "adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages."

A few participants commented on the use of API by outsourcing facilities. One commented that as long as they are conducting end-product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. As long as buyers are familiar with regulations and know what to look for, another participant commented, there should not be any issues with purchasing products compounded starting from API. Another participant stated that as more outsourcing facilities began using API, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using API if there is a shortage, stating, "I think the FDA has really looked closely at API, and they're slowly pushing the 503B

outsourcers to a sterile-to-sterile." Only 1 participant commented that they prefer sterile-to-sterile. Another participant stated that the companies they use are all sterile-to-sterile.

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. So, there is a need for this product to be compounded from API as a preservative-free product. One participant stated that "if there's not a preservative-free containing option, it really should be something that should be able to be compounded from bulk . . . especially for the pediatric patient population." However, another participant from a children's hospital said that they have never needed to use an outsourcing facility for preservative-free products. Preservative-free is also an issue for ophthalmic products; however, one participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products, but when they reviewed the facilities, they did not pass their internal quality standards; one facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross-reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because "they would have to build a separate cleanroom with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house are not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-Tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of commercially available products. The participant stated that they purchase low-dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that while the evidence does not support many of the ingredients used in topical pain products, "However, there are select patients. It's very rare that taking that cream away from them actually causes more harm than good." A few participants commented that there is a gap in the market for nonsterile products, with one stating, "I think that there is a large opportunity for more nonsterile products to be produced by 503Bs." Another stated that as their facility grows and acquires more outpatient clinics, they receive a lot of questions regarding obtaining products for office use. The participant noted that they often have to refer these clinics to outsourcing facilities but stated "there's not many 503Bs [that] are doing the nonsterile for clinic use." As a result, the inpatient pharmacy is often asked to take on this role but "you don't have the space or the staff to do that."

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions regarding specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum.

This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded alum in-house from nonsterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating that "I've talked to that company, but I've had some concerns for them because they don't sell it as a drug. The owner was selling you a chemical, we're selling you a bulk API. It's just sterile. They were fuzzy and I never followed up, but when I asked about their process for verifying the sterility, as you would with a sterile product—we do USP <71> Sterility Testing—they couldn't really give me an answer. They just say they tested for sterility." The participants commented that alum is only needed a few times a year. However, as one participant observed, "When you need it, it's an emergency," and another noted that it "is a challenge for anybody who has cyclophosphamide-induced hemorrhagic cystitis." As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility but "more times than not, they go unused and expire." Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for which they need to use alum. The participant had it stat shipped when needed. Another participant stated that "we had a meeting with the head of urology who was baffled, why they're even ordering it. He was like, 'this is . . . old, really old. I don't even know why we're using it' and basically approved for us to not even make it anymore for now."

Two participants commented on the use of glycerin at their facility. One stated that they purchase it from a 503A because they were not able to find an outsourcing facility that provides this product. The participant commented that glycerin is used in 3 different concentrations at their facility, 1 for ophthalmic use, 1 for neurologic use in trigeminal neuralgia, and 1 for instilling into "a very specific kind of pump that's used to deliver a very specific kind of chemotherapy." When there are breaks in the chemotherapy regimen, the pump has to be filled with something and by using glycerin "it can go 3 months or something like that, so it's a huge patient satisfier to have that concentration available." The participant also commented that since they have been unable to find an outsourcing facility that compounds the concentration needed for trigeminal neuralgia, they have patients who have been waiting years for treatment. The other participant stated that they compound it in-house but said that it is not done very frequently. The participant commented that it is very difficult to sterilize due to the thickness of the product.

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis, with one commenting that "our nephrologists like it in place of heparin for some patients to keep the ports patent or so they don't have to go to alteplase or some of the other drugs." There is a commercially available product; however, it is only available as a 500 mL bag and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use date is limited to 12 to 24 hours depending on storage, which results in waste.

One participant stated that they obtain papaverine from outsourcing facilities for use in urology as Bimix (papaverine/phentolamine) and Trimix (papaverine/phentolamine/alprostadil).

While none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities did not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility, they also compound a proprietary formulation in-house. This participant observed that "it is complicated to do in-house. We do it on a Baxa

1200 or 2400, either one, compounder. Then we send it up to [*sic*] for pH and potassium testing. Obviously, then we're confined to <797> beyond-use dates versus longer beyond-use dates that we get from the 503B." Another participant commented that cardioplegic solutions are managed by the perfusion department, not pharmacy, and they use del Nido solution as well as 3 other formulations.

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because "it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to. . . . It just isn't worth the dating that they gave us or can give us." Another commented that they obtain very little product from outsourcing facilities due to "the amount of work for vetting and continually validating quality of these 503B outsourcing facilities." The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that "[t]raditionally, we've found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some other smaller 503Bs where we've had agreements for certain products to take it off our plate, and then lo and behold they're shut down, or closed, or whatever it may be." Minimum purchase amounts were also reported as a concern with one participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration places on the quantity that can be produced. The participant stated that "they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year after year and then chasing our tail. Also, we may actually want to tell 503Bs they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products because it actually induces the shortage in many ways."

Results of survey

One person responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

The 1 respondent used ketamine HCl, but not in the nominated ROA/dosage forms.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.2 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 15 for respondent characteristics. Among respondents, 35 (81% of 43 total respondents) utilized outsourcing facilities to obtain drug products, 4 (9%) did not utilize outsourcing facilities, and 4 (9%) did not respond to this question.

Twenty-seven respondents (19% of 143 responses, in which respondents were allowed to select multiple reasons) obtained drug products from outsourcing facilities due to a need for ready-to-use products, and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 16).

Fourteen respondents (31% of 45 total responses, in which respondents were allowed to select multiple types) obtained nonsterile products from outsourcing facilities, and 31 (69%) obtained sterile products from outsourcing facilities. Refer to Table 17 for the categories of products obtained from outsourcing facilities.

Fourteen respondents (13% of 108 responses, in which respondents were allowed to select multiple drug products) obtained ketamine HCl from a 503B outsourcing facility (refer to Table 18).

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	Responses, n (N=1)
Doctor of Medicine (MD)	0
Doctor of Osteopathic Medicine (DO)	0
Doctor of Medicine in Dentistry (DMD/DDS)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	0
Naturopathic Doctor (ND)	0
Nurse Practitioner (NP)	0
Physician Assistant (PA)	0
Other[a]	1
Practice Setting	**Responses, n (N=1)**
Physician office or private practice	0
Outpatient clinic	0
Hospital or health system	0
Academic medical center	1
Emergency room	0
Operating room	0

[a]Respondent had a PhD in pharmacology.

Table 12. Conditions for which ketamine HCl prescribed or administered

No survey respondents provided this information

Table 13. Reasons for using compounded ketamine HCl

No survey respondents provided this information

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

No survey respondents provided this information

Table 15. Demographics of prequestionnaire respondents' facilities

Type of Facility	**Responses, n (N=102)[a]**
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4
Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N=39)**
< 50	4
50-99	3
100-199	1

200-299	4
300-399	5
400-599	3
> 600	19

[a]Respondents allowed to select more than one type of facility.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, oncology.

Table 16. Reasons for obtaining products from outsourcing facilities

Categories	**Responses, n (N=143)[a]**
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other[b]	8

[a]Respondents allowed to select multiple categories.
[b]Respondents reported staffing shortages, need for extended dating, volume of product used, standardization projects as additional reasons for utilizing outsourcing facilities.

Table 17. Categories of products obtained from outsourcing facilities

Categories	**Responses, n (N=142)[a]**
Cardioplegic solutions	14
Dermatologic preparations	6

Dialysate solutions	0
Fluids	8
Ophthalmic preparations	10
Patient-controlled analgesia	20
Ready-to-use anesthesia syringes	25
Ready-to-use antibiotic syringes and/or bags	14
Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other[b]	6

[a]Respondents allowed to select multiple categories.
[b]Respondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost anti-seizure medications, antiviral medications, topical pain, and oral tablets/capsules.

Table 18. Products obtained from an outsourcing facility

Product	**Responses, n (N=108)[a]**
Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0
Atropine	9
Baclofen	4
Betamethasone	0
Biotin	0
Bupivacaine	8
Calcium chloride	1
Caffeine sodium benzoate	0

Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0
Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4
Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0
Potassium chloride	0
Potassium phosphate	0
Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6

Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0
None of the above	8

[a]Respondents were allowed to select multiple products.

CONCLUSION

Ketamine HCl was nominated for inclusion on the 503B Bulks List as an intranasal spray, intrathecal injection, intramuscular injection, and intravenous injection for pain management, sedation, treatment of migraine, treatment of depression, and as general anesthesia. Ketamine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, the EU, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, the UK, and the US.

From the literature review, 22 studies were included. Ketamine HCl was used as an intrathecal injection for analgesia or anesthesia in all of the included studies. In 11 studies, the authors recommended the use of ketamine HCl for analgesia or anesthesia. In 6 studies, the authors concluded that the use of ketamine HCl for analgesia or anesthesia was not recommended. There were 2 studies in which the authors concluded that further studies were necessary regarding the use of ketamine HCl for analgesia or anesthesia. In 2 studies, the authors' concluding statement did not address the use of ketamine HCl for analgesia or anesthesia. One study did not provide a recommendation for the use of ketamine HCl, stating that its use led to faster onset of sensory and motor blockade, but when compared to fentanyl, the addition did not prolong spinal analgesia duration.

In the interviews, 2 of the SMEs stated that ketamine is commonly used intravenously, or either interoperatively or postoperatively. One SME commented that there is not a lot of literature that supports using IT ketamine, and with the dissociative adverse effects, this is not something that the SME would initiate in a patient. When managing CRPS with IV ketamine, around-the-clock nursing is needed to try to avoid unwanted adverse effects, as well as the need to add benzodiazepines. One of the SMEs did not use ketamine.

In the survey responses, 1 of 1 respondent used ketamine HCl, but not in the nominated ROA/dosage forms.

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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 nonindexed citations and daily 1946 to August 28, 2020
- Date last searched: August 31, 2020
- Limits: Humans (search hedge); English language
- Number of results: 678

1	ketamine/	12,503
2	ketamin$.tw.	18,537
3	or/1-2	20,167
4	infusions, spinal/	160
5	exp injections, spinal/	16,127
6	epidural space/	4518
7	spinal$.tw.	268,841
8	intraspinal$.tw.	5058
9	epidural$.tw.	42,248
10	extradural$.tw.	6769
11	extra dural$.tw.	142
12	peridural$.tw.	2064
13	peri dural$.tw.	6
14	caudal$.tw.	45,753
15	intracaudal$.tw.	11
16	arachnoid$.tw.	8170
17	subarachnoid$.tw.	35,759
18	intrathecal$.tw.	23,858
19	intra thecal$.tw.	76
20	or/4-19	391,986

21	exp anesthesia/	191,709
22	exp analgesia/	44,114
23	exp pain/	396,652
24	pain management/	34,213
25	drug therapy/	30,572
26	ad.fs.	1,417,133
27	de.fs.	2,992,723
28	dt.fs.	2,230,036
29	tu.fs.	2,228,819
30	pc.fs.	1,290,187
31	an?esth$.tw.	376,647
32	analges$.tw.	123,701
33	pain$.tw.	696,618
34	therap$.tw.	2,798,841
35	treat$.tw.	5,527,202
36	prevent$.tw.	1,427,059
37	prophyla$.tw.	165,367
38	or/21-37	11,553,773
39	and/3,20,38	1387
40	exp animals/ not humans/	4,729,286
41	39 not 40	808
42	limit 41 to english language	678

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: August 31, 2020
- Limits: Humans (search hedge); English language
- Number of results: 1217

1	'ketamine'/mj	17,238
2	'ketamin*':ti,ab,tn	26,642
3	#1 OR #2	29,725
4	'intraspinal drug administration'/de	3461
5	'epidural drug administration'/de	8892
6	'intrathecal drug administration'/de	20,970
7	'intracaudal drug administration'/de	21
8	'epidural space'/de	6443
9	'spinal*':ti,ab	370,570
10	'intraspinal*':ti,ab	7008
11	'epidural*':ti,ab	59,761
12	'extradural*':ti,ab	9119
13	'extra dural*':ti,ab	242
14	'peridural*':ti,ab	3002
15	'peri dural*':ti,ab	12
16	'caudal*':ti,ab	59,231
17	'intracaudal*':ti,ab	23
18	'arachnoid*':ti,ab	12,348
19	'subarachnoid*':ti,ab	51,055
20	'intrathecal*':ti,ab	35,508
21	'intra thecal*':ti,ab	242
22	#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 OR #17 OR #18 OR #19 OR #20 OR #21	544,572

23	‘anesthesia’/exp	392,609
24	‘analgesia’/exp	174,467
25	‘pain’/exp	1,401,413
26	‘drug therapy’/de	744,687
27	‘drug dose’:lnk	625,874
28	‘drug administration’:lnk	1,757,254
29	‘drug therapy’:lnk	3,929,231
30	‘prevention’:lnk	1,178,117
31	‘an$esth*’:ti,ab	547,174
32	‘analges*’:ti,ab	182,334
33	‘pain*’:ti,ab	1,069,041
34	‘therap*’:ti,ab	4,208,504
35	‘treat*’:ti,ab	8,002,301
36	‘prevent*’:ti,ab	1,937,390
37	‘prophyla*’:ti,ab	263,747
38	#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 OR #37	14,364,515
39	#3 AND #22 AND #38	2165
40	[animals]/lim NOT [humans]/lim	6,081,128
41	#39 NOT #40	1444
42	#39 NOT #40 AND [english]/lim	1217

Appendix 2.1. Survey instrument for professional medical associations

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

2. Do you prescribe or administer ketamine hydrochloride to your patients?
    - Yes
    - No
3. Do you prescribe or administer ketamine hydrochloride by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Intranasal spray
    - Intrathecal injection
    - None of the above
4. I prescribe or administer ketamine hydrochloride for the following conditions or diseases: (check all that apply)
    - Depression
    - General anesthesia
    - Migraine
    - Pain
    - Sedation
    - Other (please explain) _____
5. I prescribe or administer ketamine hydrochloride in combination with other active pharmaceutical ingredients as a multi-ingredient product.
    - Yes
    - No
6. I prescribe or administer ketamine hydrochloride with my patients as the following: (check all that apply)
    - FDA-approved drug product
    - Compounded drug product
    - Other (please explain) _____
7. I use compounded ketamine 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) _____
- I am not aware of any commercially available products containing ketamine hydrochloride
- Other (please explain) _____

8. Do you stock non-patient-specific compounded ketamine hydrochloride at your practice?
   - Yes
   - No
   - I'm not sure
9. I obtain compounded ketamine 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) _____
10. 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) _____
11. 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 2.2. Survey instrument for pharmacy roundtable prequestionnaire

1. Please select all that apply regarding the facility with which you are affiliated.
    - Academic medical center
    - Acute care hospital
    - Children's hospital
    - Community hospital
    - Critical access hospital
    - Dialysis center
    - Federal government hospital
    - Health system
    - Inpatient rehabilitation center
    - Long-term acute care hospital
    - Outpatient surgery center
    - Rural hospital
    - Skilled nursing facility
    - Specialty hospital, please identify specialty(ies)
    - Trauma center
    - Urban hospital
2. Please select the number of beds in the facility with which you are affiliated.
    - < 50
    - 50-99
    - 100-199
    - 200-299
    - 300-399
    - 400-599
    - > 600
3. Do you use an outsourcing facility (503b facility) to obtain any products used in your facility? A list of FDA registered outsourcing facilities can be found at https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilites.
    - Yes
    - No
4. Why do you use an outsourcing facility to obtain product(s)? Please select all that apply
    - Backorders
    - Convenience
    - Cost
    - Need for concentrations not commercially available
    - Need for preservative-free products
    - Need for ready-to-use products
    - No FDA-approved products available
    - No onsite compounding facility
    - Onsite compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

- Fluids
- Ophthalmic preparations
- Patient-controlled analgesia
- Ready-to-use anesthesia syringes
- Ready-to-use antibiotic syringes and/or bags
- Ready-to-use electrolyte solutions
- Ready-to-use vasopressor solutions
- Total parenteral nutrition solutions
- Other, please identify _____

7. From the list below, please select the drug(s) that you obtain as either a single ingredient or multi-ingredient product from an outsourcing facility.
    - Acetylcysteine
    - Adenosine
    - Aluminum potassium sulfate
    - Aspartic acid
    - Atenolol
    - Atropine
    - Baclofen
    - Betamethasone
    - Biotin
    - Bupivacaine
    - Calcium chloride
    - Caffeine sodium benzoate
    - Cholecalciferol
    - Chromium chloride
    - Clonidine
    - Dexamethasone sodium phosphate
    - Diclofenac
    - Gentamicin
    - Glycerin
    - Hydroxyzine
    - Ketamine
    - Levocarnitine
    - Lidocaine
    - Lorazepam
    - Magnesium sulfate
    - Manganese chloride
    - Methylprednisolone
    - Midazolam
    - Mupirocin
    - Norepinephrine
    - Ondansetron
    - Phytonadione
    - Potassium chloride
    - Potassium phosphate
    - Prilocaine
    - Proline
    - Propranolol
    - Ropivacaine
    - Sodium chloride
    - Sodium citrate

- Sodium phosphate
- Tetracaine
- Triamcinolone acetonide
- Tropicamide
- None of the above

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Anesthesiology	Society of Cardiovascular Anesthesiologists	Declined – failed to respond
Cardiology	American Academy of Cardiovascular Perfusion	Declined
	American Board of Cardiovascular Perfusion	Declined – failed to respond
	American Society of Extracorporeal Technology	Declined – failed to respond
Dermatology	American Academy of Dermatology	Declined – failed to respond
Naturopathy	American Association of Naturopathic Physicians	Agreed
Nephrology	American Society of Diagnostic and Interventional Nephrology	Declined
Ophthalmology	American Academy of Ophthalmology	Declined – failed to respond
	American Society of Cataract and Refractive Surgery	Agreed
	American Society of Retina Specialists	Declined
Podiatry	American Podiatric Medical Association	Agreed
Psychiatry	The International Society for Electroconvulsive Therapy and Neurostimulation	Agreed
Rheumatology	American College of Rheumatology	Agreed
Surgery	American Association of Neurological Surgeons	Declined – failed to respond
	American Association for Thoracic Surgery	Declined – failed to respond
	American College of Surgeons	Declined – failed to respond
	American Society for Reconstructive Microsurgery	Declined – failed to respond
Urology	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction	Declined
Wound Care	Association for the Advancement of Wound Care	Declined – failed to respond

[a]Associations that declined in Year 1 and/or Year 2 were not contacted in Year 3.