Summary Report

Sufentanil citrate

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Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
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 sufentanil citrate (UNII code: S9ZFX8403R), 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 sufentanil citrate 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 sufentanil citrate 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 sufentanil citrate 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

Sufentanil citrate was nominated for inclusion on the 503B Bulks List by Pentec Health and the Specialty Sterile Pharmaceutical Society (SSPS).

Sufentanil citrate was nominated to treat severe pain (such as chronic non-malignant and cancer pain), for epidural and surgical analgesia, and for surgical anesthesia via a 0.4-3000mcg/mL solution for intrathecal, epidural, and intravenous injection.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of sufentanil citrate.[6-8]

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

- Practitioners often prescribe doses that require higher strengths or concentrations than those available in FDA-approved products or use in combinations with other medications.
- 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.
- 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 sufentanil citrate 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 sufentanil citrate; name variations of sufentanil citrate 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 sufentanil citrate. 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: sufentanil citrate, intrathecal administration, and therapeutic use for anesthesia or analgesia (refer to Appendix 1 for full search strategies). Due to the availability of FDA-approved sufentanil products for intravenous and epidural 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 31, 2020. In addition, the ECRI Guidelines Trust® repository was searched on March 31, 2020 for clinical practice guidelines that recommended the use of sufentanil citrate 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 sufentanil citrate 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 sufentanil citrate was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, combination that was not nominated; or as a rescue medication in a trial not designed to evaluate the effect of sufentanil citrate. Studies in which sufentanil citrate 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 sufentanil citrate; setting; total number of patients; number of patients who received sufentanil citrate; patient population; indication for use of sufentanil citrate; dosage form and strength; dose; ROA; frequency and duration of therapy; use of sufentanil citrate in a combination product; use and formulation of sufentanil citrate in a compounded product; use of sufentanil citrate 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 (SME) were conducted to understand how and in what circumstances sufentanil citrate 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 sufentanil citrate: 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 sufentanil citrate in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 3 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact

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

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

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

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

CURRENT AND HISTORIC USE

Results of background information

- Sufentanil citrate is available as an FDA-approved product in the nominated dosage form and ROA.
- Sufentanil citrate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for sufentanil citrate.
- Sufentanil citrate is available in the nominated dosage form and ROA in Abu Dhabi, Belgium, Canada, Hong Kong, Latvia, Namibia, and Saudi Arabia.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Sufentanil citrate	50 mcg/mL	Solution	Injection	Prescription	05/04/1984

[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]
Sufentanil citrate	5-50 mcg/mL	Solution for injection	Epidural, injection, intravenous	Abu Dhabi	Active	–
				Belgium	Medical Prescription	10/31/1978
				Canada	Narcotic (CDSA 1)	08/01/2001
				Hong Kong	Prescription only medicine	05/12/2005
				Latvia	Prescription	12/17/2018
				Namibia	–	02/22/1988
				Saudi Arabia	Prescription	–

Abbreviation: "– ", not mentioned.

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

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

Results of literature review

Study selection

Database searches yielded 899 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 581 titles and abstracts were screened. After screening, the full text of 399 articles was reviewed. Two hundred two studies were included; after multiple reports of the same study were merged, there were 200 included studies. One hundred ninety-seven studies were excluded for the following reasons: wrong study design (151 studies); sufentanil citrate used as brand or proprietary product (16); sufentanil citrate only mentioned briefly (14); duplicate study (4); wrong dosage form or ROA (3); language other than English (2); unable to obtain full text (2); sufentanil citrate used in FDA-approved formulation (2); wrong substance (2); sufentanil citrate used for an indication that was not nominated (1).

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

Characteristics of included studies

The 200 included studies were published between 1987 and 2019. There were 178 experimental studies, 15 observational studies, and 7 descriptive studies. The 200 studies were conducted in the following countries: Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Egypt, Finland, France, Germany, India, Iran, Italy, Korea, the Netherlands, Romania, Singapore, South Korea, Sweden, Switzerland, Taiwan, Tunisia, Turkey, and the US.

A total of 21,687 patients participated in the 200 included studies. The number of patients in each study ranged from 1 to 2560.

Outcome measures differed among the included studies and included: patient satisfaction; onset and duration of analgesia; time to sensory and motor blocks; need for rescue analgesia; pain scores; side effects; hemodynamic effects; neonatal Apgar scores; incidence of shivering; fetal heart rate changes.

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

Use of sufentanil citrate

Twelve thousand seven hundred seventy-eight patients received sufentanil citrate as a treatment for pain, administered via combined spinal-epidural and spinal injections, in doses ranging from 1 mcg to 150 mcg. Duration of treatment ranged from once to 5 years and 3 months. Forty patients received sufentanil citrate as a treatment for shivering, administered via a 2.5 mcg injection, once.

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

Sufentanil citrate was not used as a compounded product, nor was it used in a combination product.

In 104 studies, the authors' concluding statement recommended the use of sufentanil citrate for the treatment of pain and shivering via combined spinal-epidural and spinal anesthesia.[6,9-110] In 15 studies, the authors concluded that the use of sufentanil citrate was not recommended for the treatment of pain via combined spinal-epidural and spinal anesthesia.[111-126] In 16 studies, the authors concluded that further studies were necessary for the use of sufentanil citrate for the treatment of pain via combined spinal-epidural and spinal anesthesia.[127-142] In 65 studies, the authors did not provide a

conclusion recommending for or against the use of sufentanil for pain via combined spinal-epidural and spinal anesthesia.[143-207] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 200 included studies, 10 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of sufentanil citrate.

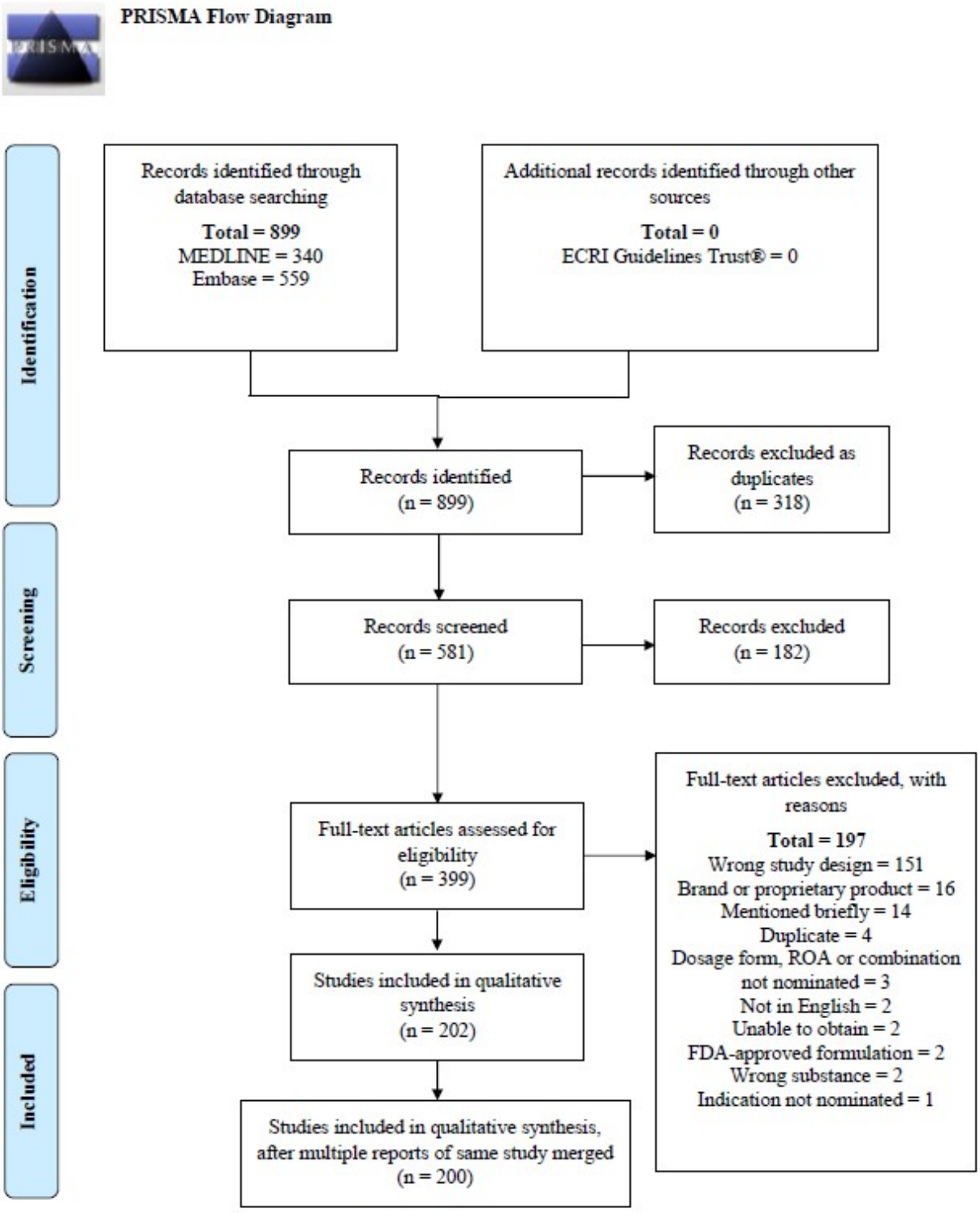
Sufentanil citrate is a piperidine derivative synthetic opioid that is more lipid soluble when compared to fentanyl, in addition to being more potent.[208,209] Potency ranges from 5-10 times higher for intravenous sufentanil citrate and 3-5 times higher for epidural administration.[210]

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.[211] 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.[211] 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."[212]

Intrathecal opioid administration offers benefits over epidural administration in faster onset and lower systemic spread.[213] As with epidural administration, the lipophilicity of the chosen opioid is an important consideration; more lipophilic drugs, such as fentanyl and sufentanil, are removed from the cerebrospinal fluid (CSF) very quickly, which results in them having an effect on fewer spinal levels.[213] More hydrophilic drugs, such as morphine and hydromorphone, have demonstrated a greater rostral spread and a significant effect across multiple spine levels in comparison.[213] 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, such as sufentanil citrate, have a faster onset of analgesia, but a shorter duration of action and decreased side effects.[214] Because the lipophilic opioids have a shorter duration of action (90-120 minutes), they are less suitable for most patients in labor; as a result, some practitioners use continuous spinal analgesia to permit "incremental drug injection to achieve a specific endpoint."[215]

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.[216] 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.[216]

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[38,137,138,153,161,170,184]	7
Observational[9,31,40,49,76,78,93,127,128,131,135,139,141,145,171]	15
Experimental[6,10-30,32-37,39,41-48,50-75,77,79-92,94-126,129,130,132-134,136,140,142-144,146-152,154-160,162-169,172-183,185-207]	178

Table 4. Number of studies by country

Country	Number of Studies
Austria[41,84]	2
Belgium[45,46,60,101,103,104,113,125,140,150,156,168,177,192,197-200]	18
Brazil[18-20,34,59,80,92,155,173,178,193-195]	13
Canada[21,28,117]	3
China[30,87,98,100,108,123,201-207]	13
Croatia[47,63,64,83,148]	5
Czech Republic[72]	1
Egypt[91,164,188]	3
Finland[66]	1
France[74,126,147,151,162,165,174,175]	8
Germany[22,61,97,190]	4
India[10-12,29,50,58,65,77,102,107,120]	11
Iran[13,14,32,52,53,90,106,112,115,143,146,189]	12
Italy[27,37,85,96,134,149,152,157,158,196]	10
Korea[15]	1
The Netherlands[17,55-57]	4
Romania[176]	1
Singapore[71,79,94,95,191]	5

South Korea[62,68,121]	3
Sweden[6,51,172,185]	4
Switzerland[16,43,44,73,133]	5
Taiwan[70]	1
Tunisia[166]	1
Turkey[23,35,36,119,142]	5
US[9,24-26,31,33,38-40,42,48,49,54,67,69,75,76,78,81,82,86,88,89,93,99,105,109-111,114,116,118,122,124,127-132,135-139,141,144,145,153,154,159-161,163,167,169-171,179-184,186,187]	66
	Total US: 66 Total Non-US Countries: 134

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
Combined spinal-epidural anesthesia[24-26,31,42,54,69,82,86,89,114,116,122,127,128,136,141,144,145,153,154,160,161,167,169,179-184,186]	1-50 mcg	2.5-50 mcg/mL	–	Intrathecal	Once
			Solution		
Spinal anesthesia[9,33,38-40,48,49,67,75,78,81,88,99,105,109-111,118,124,129,131,132,137,139,159,163,170,187]	1-50 mcg	2.5-50 mcg/mL	–	Intrathecal	1-4 doses
			Solution		
Chronic refractory pain[76,93,135,171]	0.5-3.0 mcg/hour	–	–	Intrathecal	0.8-14 years
	25-160 mcg/day	–	–		
Continuous spinal anesthesia[130,138]	Bolus 5 mcg Infusion 5-12 mcg/hour	1-2.5 mcg/mL	Solution	Intrathecal	Total dose infused 244 mcg For duration of labor until delivery, so long as pain relief is adequate

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Spinal anesthesia[6,10,12-20,22,27,29,32,35-37,41,43,44,47,50-53,55-59,61-64,66,68,70,72,74,77,79,80,83,90,91,96,97,102,106,107,112,113,115,117,119-121,133,142,143,146-150,152,157,165,173,174,176,185,188-190,192,196,201]	3 mL	–	–	Intrathecal	Once
	1.5-150 mcg 1 mg/kg	0.71-50 mcg/mL 1 mcg/kg/3-5 mL	– Solution		Once
	Bolus 1 mcg/kg Intermittent doses 5-10 mcg/kg	1 mcg/kg/3-5 mL	Solution		Through the duration of surgery
Combined spinal-epidural anesthesia[11,21,23,28,30,45,46,60,61,65,71,73,84,85,87,92,94,95,98,101,103,104,108,123,126,140,151,152,155,156,158,162,164,166,168,172,175,177,178,191,193-195,197-200,202-207]	1-10 mcg	0.75-50 mcg/mL	– Solution	Intrathecal	Once
Continuous spinal anesthesia[100,125,134]	Bolus 2-7.5 mcg Infusion 1-4 mcg/hour Lockout 1-2 mcg/5-15 minutes	2-4 mcg/mL	Solution	Intrathecal	Duration of labor 12-48 hours
Shivering[34]	2.5 mcg	–	–	Intrathecal	Once

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Thirteen SMEs discussed sufentanil citrate. Amongst these 13 SMEs, there were 8 medical doctors, 2 pharmacists, 1 nurse practitioner, and 2 dentists. The SMEs specialized and/or were board-certified in anesthesiology, dentistry, oral and maxillofacial surgery, pain medicine, palliative care, pharmacotherapy, pediatric anesthesia, and primary care and family practice, working in academia, academic medical center, hospital/health system, and private practice/clinic. The SMEs had been in practice for 6 to 34 years.

Several SMEs who specialized in anesthesiology said that they rarely use Sufenta® (sufentanil citrate); it is an older drug and was used a long time ago, but now practitioners mostly use Dilaudid® (hydromorphone) or morphine instead. One SME said that it is not on formulary at their hospital. Sufentanil citrate is about 10 times more potent than fentanyl and the commercial product requires dilution before being administered to patients. One SME said they have no experience with epidural or intrathecal sufentanil citrate. Another SME said that sufentanil citrate was mixed "on the fly", with the patient only being given 10 mcg at a time. It was tried for epidural administration, but because sufentanil citrate is more lipid-soluble than fentanyl, practitioners observed a more localized effect due to decreased spread. Therefore, despite sufentanil citrate having a faster onset of action, patients had a very dense level of analgesia right at the site of injection; as a result, one SME described it as a "bust." However, they said that there are still a lot of people who use sufentanil citrate instead of fentanyl and just give a relatively low dose due to increased potency. However, the SME said that they have seen sufentanil citrate run into issues with practicality when it comes to narcotic restrictions that allow nurses to get fentanyl on their own, but anesthesiologists had to be the ones to pull sufentanil citrate.

Several anesthesiologists 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, or hydromorphone in their practice. In their experience, opioids are utilized in the post anesthesia care unit (PACU) where ketamine and dexmedetomidine are unavailable. One SME said that their PACU typically uses hydromorphone unless the patient has an allergy; if the patient has an allergy, they use morphine instead.

One anesthesiologist said that most elective cesarean sections are done under spinal anesthesia with bupivacaine, fentanyl, or Duramorph® (morphine sulfate). Epidurals are only used for elective cesarean sections if a catheter is already in place from labor and before they remove the epidural catheter, they will add morphine so the patient can recover and be able to walk. Several anesthesiologists mentioned that there is a fair amount of waste with intrathecal and epidural administration; they only use a small amount and end up throwing the rest away.

One SME who specialized in dentistry said that they have not used sufentanil citrate. Another dentist said that some of their patients need to be asleep for dental procedures and the primary narcotic that they use is intravenous fentanyl; they also might use alfentanil or remifentanil if they want something with a faster metabolism. The SMEs said that they use nonsteroidal anti-inflammatory drugs (NSAIDs) and oral opioids for postoperative pain management. Typically, they use a combination that includes Tylenol®, such as Tylenol #2 or Tylenol #3 (acetaminophen and codeine), Norco® (acetaminophen and hydrocodone), or Percocet® (acetaminophen and oxycodone). They may also use NSAIDs such as etodolac or ibuprofen. One SME said that they occasionally use tramadol if a patient is unable to take another opioid due to an allergy; sometimes they also use morphine.

One SME who specialized in oncology said that they were not familiar with the use of sufentanil citrate. 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.

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 they do not know anything about sufentanil citrate. 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. Another SME said that all opioids should come in a patch format, which would be helpful for the outpatient population.

Several SMEs in palliative care said that they do not use sufentanil citrate in their patients. 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" and 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.

As far as compounded anesthetics are concerned, one SME who specialized in anesthesiology said that they use single ingredient drugs in anesthesia; they had no experience with compounding multiple powders together. Furthermore, they rarely mix products in the same syringe stating that this is frowned upon due to potential compatibility concerns. The exception would be regional or epidural anesthesia where they might add fentanyl or morphine to a local anesthetic to reduce the number of injections. Several SMEs who specialized in anesthesiology talked about using prefilled syringes that were produced by a third party and added that the Anesthesia Patient Safety Foundation (APSF) and the Joint Commission prefer that anesthesiologists use prefilled syringes; drawing up each product increases the potential for error and sterility concerns and that prefilled syringes offer less waste and fewer errors, though it is also more expensive. One SME said that epidural infusions are typically compounded by the hospital pharmacy, though perioperative antibiotics are either prepared by the pharmacy or the anesthesiologist themselves in the operating room. Another SME said that they see compounded drugs as convenient, but the only real application would be for epidural mixes. Everything else is typically mixed by the anesthesiologists themselves before administration. One of the anesthesiologists said that they have had problems with drugs being on shortage. In some cases, they can adjust, for example if fentanyl is on backorder, then they can use morphine and alter their technique. Other drugs, such as backordered

propofol, do not have alternatives. They noted that outsourcing facilities typically have a 2-3-month lead-in time between when the drug goes on shortage and when they are able to produce the product.

Several anesthesiologist SMEs said that they could not think of a situation where they would want to use a higher concentration opioid than what is already commercially available. One SME who specialized in dentistry said that compounded drugs for dentistry typically are topical local anesthetics. 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. Two respondents (0.7% of 290 responses, where respondents were allowed to select multiple drug products) obtained sufentanil citrate 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 sufentanil citrate was prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded sufentanil citrate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded sufentanil citrate

No respondents to survey distributed via professional medical associations

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

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

Table 16. Products obtained from a 503B outsourcing facility

Product	**Responses, n (N=290)[a]**
Amitriptyline / Ketoprofen / Oxymetazoline	1
Budesonide	2
Calcium gluconate	2
Droperidol	2
Epinephrine	11
Epinephrine for ophthalmic administration	16
Epinephrine / Lidocaine for ophthalmic administration	31
Epinephrine / Bupivacaine / Fentanyl	3

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

[a]Survey respondents allowed to select multiple products.

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

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

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

CONCLUSION

Sufentanil citrate was nominated for inclusion on the 503B Bulks List as an intrathecal, epidural, and intravenous injection to treat severe pain (such as chronic non-malignant and cancer pain) and for epidural analgesia and surgical analgesia/anesthesia. Sufentanil citrate is available in the nominated dosage form and ROA in Abu Dhabi, Belgium, Canada, Hong Kong, Latvia, Namibia, Saudi Arabia, and the US.

From the literature review and interviews conducted, sufentanil citrate is a more potent and lipid soluble formulation of fentanyl. It has been administered as an injection for spinal anesthesia, chronic refractory pain, and shivering. The SMEs who specialized in anesthesiology said that they rarely use sufentanil citrate in their practice. It has the same benefits and issues as fentanyl except it is more potent. One SME said that sufentanil citrate has increased restrictions regarding the healthcare professionals who are permitted to access it. Because sufentanil citrate is a more lipophilic opioid, practitioners see a very localized effect when it is administered via epidural administration. Practitioners who specialized in dentistry, oncology, primary care, and palliative care said that they do not use sufentanil citrate in their patients, preferring other opioids instead.

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. Two respondents reported obtaining sufentanil citrate 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 30, 2020
- Date last searched: March 31, 2020
- Limits: Humans (search hedge); English language
- Number of results: 340

1	sufentanil/	1827
2	fentan#l$ sulfat$.tw.	1
3	fentan#l$ sulphat$.tw.	0
4	fentathi#n#l$.tw.	5
5	fentatien#l$.tw.	1
6	su?fentan#l$.tw.	2755
7	or/1-6	2990
8	infusions, spinal/	152
9	injections, spinal/	12461
10	subarachnoid space/	4341
11	peridural$.tw.	2058
12	peri dural$.tw.	6
13	arachnoid$.tw.	8049
14	subarachnoid$.tw.	35089
15	intrathecal$.tw.	23461
16	intra thecal$.tw.	74
17	or/8-16	70913
18	exp anesthesia/ and analgesia/	7640
19	exp pain/	390118
20	pain management/	33018

21	dt.fs.	2190714
22	ad.fs.	1397027
23	tu.fs.	2196516
24	pc.fs.	1267521
25	an?esth$.tw.	370983
26	analges$.tw.	121050
27	pain$.tw.	677140
28	or/18-27	5348484
29	and/7,17,28	432
30	exp animals/ not humans/	4683966
31	29 not 30	387
32	limit 31 to english language	340

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 31, 2020
- Limits: Humans (search hedge); English language
- Number of results: 559

1	sufentanil'/mj	2504
2	fentanil* sulfat*':ti,ab,tn	0
3	fentanyl* sulfat*':ti,ab,tn	1
4	fentanil* sulphat*':ti,ab,tn	0
5	fentanyl* sulphat*':ti,ab,tn	1
6	fentathianil*':ti,ab,tn	0
7	fentathianyl*':ti,ab,tn	0
8	fentat$ienil*':ti,ab,tn	8
9	fentat$ienyl*':ti,ab,tn	7
10	su$fentanil*':ti,ab,tn	3624
11	su$fentanyl*':ti,ab,tn	210
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	4343
13	intrathecal drug administration'/de	20957
14	subarachnoid space'/de	8060
15	peridural*':ti,ab	2986
16	peri dural*':ti,ab	12
17	arachnoid*':ti,ab	12163
18	subarachnoid*':ti,ab	49595
19	intrathecal*':ti,ab	34656
20	intra thecal*':ti,ab	230
21	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	106303
22	anesthesia'/exp	385676

23	analgesia'/exp	169756
24	pain'/exp	1365007
25	drug dose':lnk	622349
26	drug administration':lnk	1723493
27	drug therapy':lnk	3854477
28	prevention':lnk	1161898
29	an$esth*':ti,ab	538171
30	analges*':ti,ab	178297
31	pain*':ti,ab	1038314
32	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	6707628
33	#12 AND #21 AND #32	702
34	[animals]/lim NOT [humans]/lim	6011079
35	#33 NOT #34	638
36	#33 NOT #34 AND [english]/lim	559

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					
Abboud *et al.*, 1996, US[9]	–	17 In-patients undergoing labor (0%, mean 24.9 y ± 5.3)	• Intrathecal (IT) sufentanil (17)	Maternal satisfaction of analgesia; onset and duration of analgesia	"In conclusion, results from our study indicate that intrathecal sufentanil appears to be very effective in providing labor analgesia and is more suitable for patients with short duration of labor, since it seems to be associated with acute tolerance which needs further investigation."
Abdollahpour *et al.*, 2015, Iran[143]	Double-blind, randomized clinical trial	75 In-patients undergoing elective caesarean section Saline (0%, mean 28.6 y ± 6.06) Midazolam (0%, mean 28.12 y ± 5.29) Sufentanil (0%, mean 28.76 y ± 3.97)	Bupivacaine plus: • Saline (25) • Midazolam (25) • Sufentanil (25)	Time to achieve/recovery of sensory/motor blocks; time to request for opium	"The findings show that adding sufentanil or midazolam to bupivacaine shortens the onset of spinal anesthesia and increases the time duration of anesthesia; however it does not change the motor block recovery time. Adding sufentanil delays the first request for narcotic analgesics while adding midazolam leads to a decrease in nausea and hypotension. Adding sufentanil or midazolam does not have any deleterious effect on infants' Apgar scores. However, increases shiver in patients."
Abouleish *et al.*, 2000, US[144]	Double-blind, randomized study	48 In-patients in early labor Normal saline (0%, mean 23.5 y ± 5.2) Dextrose (0%, mean 25.3 y ± 6.3)	Sufentanil plus • Normal saline (24) • Dextrose (24)	Duration and quality of analgesia	Dextrose plus intrathecal sufentanil reduced pruritus without effecting the duration or the quality of analgesia
Abouleish *et al.*, 1994, US[127]	Open-label, non-randomized trial	38 In-patients in advanced labor (0%, mean 28 y ± 5)	• Isobaric bupivacaine and sufentanil (38)	Onset and duration of analgesia and motor blockade	Further studies are needed to evaluate optimal dosing regimens, side effect profiles, and effects on labor progress

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Agrawal *et al.*, 2009, India[10]	–	60 In-patients undergoing caesarean section under spinal anesthesia Group I (0%, mean 27.4 y ± 4.49) Group II (0%, mean 25.9 y ± 3.32) Group III (0%, mean 25.65 y ± 2.5)	• Group I: bupivacaine (20) • Group II: bupivacaine plus fentanyl (20) • Group III: bupivacaine plus sufentanil (20)	Time of onset; analgesia; side effects; need for rescue analgesia; duration of analgesia; fetal outcome	"Addition of opioid to Bupivacaine is an effective measure to prolong the duration of post operative analgesia as well as to improve the quality of sub-arachnoid block. Use of sufentanil is superior to Fentanyl in terms of onset of block and increased duration of analgesia."
Akkamahadevi *et al.*, 2012, India[11]	Randomized, prospective, single-blind study	60 In-patients in spontaneous labor Sufentanil (0%, mean 23.46 y) Fentanyl (0%, mean 22.02 y)	Bupivacaine in IT and epidural routes plus: • Sufentanil (30) • Fentanyl (30)	Pain scores; patient satisfaction; duration of analgesia	"We conclude that combined spinal epidural using sufentanil and fentanyl achieved high patient satisfaction and excellent labour analgesia without serious maternal or neonatal side-effects. Sufentanil provided a significantly longer duration of labour analgesia compared with fentanyl."
Albright and Forster, 1999, US[145]	Retrospective computerized analysis	In-patients who received major regional anesthesia (gender and age not specified) Number of patients not reported	• IT sufentanil ± bupivacaine plus epidural bupivacaine and fentanyl • Epidural lidocaine with epinephrine or 2-chloroprocaine	IT sufentanil side effects requiring treatment with nalbuphine or naloxone	Combined spinal-epidural anesthesia is safe and efficacious
Albright and Forster, 1997, US[128]	Retrospective computerized analysis	2560 In-patients who received combined spinal-epidural (CSE) analgesia and cesarean delivery (gender and age not specified)	• CSE with sufentanil and bupivacaine for spinal (1217) • Systemic or no medication (1140)	Incidence of emergency cesarean delivery	"The conflicting results of this retrospective study of 2,560 deliveries at a low-risk maternity center when compared with case reports from a tertiary care center suggest that further studies are necessary in different practice settings and patient populations to determine the incidence, significance, and appropriate management of fetal distress following CSE analgesia."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Alimian *et al.*, 2017, Iran[146]	Double-blind randomized clinical trial	105 In-patients who are candidates for elective cesarean section (0%, mean 37 y ± 7)	Sufentanil plus: • Hyperbaric bupivacaine 8 mL (35) • Hyperbaric bupivacaine 9 mL (35) • Hyperbaric bupivacaine 10 mL (35)	Spinal anesthesia hemodynamic parameters; sensory and motor block	Lower doses of bupivacaine are more reasonable for spinal anesthesia
Arkoosh *et al.*, 1998, US[129]	Prospective, randomized, double-blind study	50 In-patients requesting analgesia for spontaneous labor Sufentanil 1 mcg (0%, mean 24 y ± 6) Sufentanil 2 mcg (0%, mean 26 y ± 8) Sufentanil 3 mcg (0%, mean 28 y ± 7) Sufentanil 5 mcg (0%, mean 24 y ± 6) Sufentanil 10 mcg (0%, mean 24 y ± 7)	• Sufentanil 1 mcg (10) • Sufentanil 2 mcg (10) • Sufentanil 3 mcg (10) • Sufentanil 5 mcg (10) • Sufentanil 10 mcg (10)	ED50 (effective dose) and ED95; fetal and neonatal outcomes	IT sufentanil produces reliable analgesia, but further studies are needed to determine if side-effects are dose related and to compare it to other labor analgesics
Arkoosh *et al.*, 2008, US[130]	Prospective, randomized, multicenter trial	429 In-patients in spontaneous or induced labor Continuous IT (0%, mean 28.97 y ± 5.57) Continuous epidural (0%, mean 28.94 y ± 6.23)	Bupivacaine and sufentanil via: • Continuous IT (329) • Continuous epidural (100)	Incidence of neurologic complications	Continuous IT analgesia had better early analgesia, less motor blockade, more pruritus, and higher maternal satisfaction, but the catheter was significantly more difficult to remove; larger studies are needed to better define rate of permanent neurologic complications and optimal analgesic regimens

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Arkoosh *et al.*, 1994, US[111]	Prospective, randomized, double-blind study	30 In-patients in labor Fentanyl (0%, mean 28 y ± 8) Sufentanil (0%, mean 26 y ± 5)	Morphine plus: • Fentanyl (15) • Sufentanil (15)	Time from injection to request for additional analgesia; time to delivery; method of delivery; Apgar scores	"In conclusion, we have demonstrated that there is little difference between the quality and duration of labor analgesia produced by subarachnoid administration of either sufentanil 10 mcg or fentanyl 25 mcg with morphine 0.25 mg. Both produce adequate analgesia but this analgesia cannot be relied on to persist throughout labor until delivery."
Arya *et al.*, 2011, India[12]	Prospective, randomized clinical trial	40 Out-patients undergoing outpatient gynecological surgery General anesthesia (0%, mean 26.7 y ± 11.9) Selective spinal anesthesia (0%, mean 29.9 y ± 11.3)	• General anesthesia (20) • Selective spinal anesthesia with sufentanil and lignocaine (20)	Recovery time to awaken, extubation, and orientation; time from the end of surgery to exiting the operating room, straight leg raising, deep knee bend, and reaching a modified Aldrete score >9; discharge time	"In conclusion, selective spinal anaesthesia using lignocaine (10 mg) along with sufentanyl (10 mcg) can be used as an alternative to general anaesthesia with propofol for short duration outpatient gynaecological laparoscopic procedures with faster recovery without any added adverse effects."
Asenhnoune *et al.*, 2005, France[147]	Prospective, randomized study	38 In-patients undergoing elective urologic lower abdominal or lower limb surgery Small dose (68.4%, mean 64 y ± 16) Large dose (68.4%, mean 60 y ± 20)	Sufentanil plus: • Small dose bupivacaine (19) • Large dose bupivacaine (19)	Heart rate; systolic and diastolic blood pressure; mean arterial pressure; cardiac output	Use of small dose bupivacaine may prevent cardiovascular side effects
Bacak Kocman *et al.*, 2010, Croatia[148]	Randomized study	34 In-patients scheduled for transurethral urologic surgery (gender and age not specified)	Sufentanil plus: • Hyperbaric levobupivacaine 5 mg (17) • Hyperbaric levobupivacaine 7 mg (17)	Sensory and motor block; time to first analgesic request	Hyperbaric levobupivacaine 5 mg plus sufentanil provides adequate sensory block and results in similar cardiovascular stability, and less intensive motor block, and faster motor recovery compared to levobupivacaine 7 mg

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Bakhshaei *et al.*, 2010, Iran[13]	Prospective, randomized double-blind, controlled trial	90 In-patients scheduled for elective cesarean section Normal saline (0%, mean 24.2 y ± 6.3) Sufentanil 5 mcg (0%, mean 26.4 y ± 8.4) Sufentanil 10 mcg (0%, mean 22.8 y ± 6.8)	Hyperbaric lidocaine plus: • Normal saline (30) • Sufentanil 5 mcg (30) • Sufentanil 10 mcg (30)	Heart rate; non-invasive arterial blood pressure; respiratory rate; oxygen saturation; sensory level to pinprick; degree of motor block	Adding 10 mcg sufentanil to lidocaine provided more effective analgesia with minimal side effects
Bameshki *et al.*, 2010, Iran[14]	Randomized, single-blinded study	50 In-patients awaiting transhiatal esophagectomy IT (40%, mean 57.9 y ± 12.7) Intravenous (IV; 60%, mean 66.2 y ± 10.4)	Sufentanil via: • IT (25) • IV (25)	Intraoperative sufentanil consumption; Visual analogue scale (VAS); morphine requirements for postoperative analgesia	"Preoperative IT [intrathecal] sufentanil can be used as a booster to achieve rapid and effective analgesia not only during the operation but also during the immediate postoperative period."
Bang *et al.*, 2012, Korea[15]	Randomized, double-blind study	105 In-patients undergoing cesarean section Saline (0%, mean 33.1 y ± 2.5) Sufentanil 2.5 mcg (0%, mean 32.3 y ± 3.8) Sufentanil 5 mcg (0%, mean 33.4 y ± 3.8)	• Saline (35) • Sufentanil 2.5 mcg (35) • Sufentanil 5 mcg (35)	Maximum level of sensory and motor block; level of intraoperative sedation; quality of intraoperative analgesia; the duration of effective analgesia	Sufentanil 2.5 mcg provides adequate analgesia both intraoperatively and postoperatively with minimal adverse effects
Bettex *et al.*, 2002, Switzerland[16]	Prospective, randomized study	24 In-patients with normal cardiopulmonary function who were scheduled for elective cardiac surgery Continuous IV sufentanil (100%, mean 57.2 y ± 9.4) IT sufentanil (81.8%, mean 53.5 y ± 11.4)	• Continuous IV sufentanil (13) • IT sufentanil and morphine (11)	Duration of intubation; postoperative analgesia requirements; postoperative spirometry	"In low-risk patients undergoing coronary artery bypass graft or valve surgery, combined intrathecal sufentanil and morphine with a target controlled infusion of propofol satisfies the goals of fast-track cardiac surgery."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Birnbach *et al.*, 2001, US[131]	Comparative (cohort) study	35 Patients at >36 weeks gestation who were candidates for external cephalic version (ECV) Subarachnoid analgesia (0%, mean 28.5 y ± 7) No subarachnoid analgesia (0%, mean 28.7 y ± 4.8)	• Subarachnoid analgesia with sufentanil (20) • No subarachnoid analgesia (15)	Procedure pain (visual analog scale); patient satisfaction (10-point scale)	ECV success rates increased after administration of spinal analgesia, though findings may not be generalizable to other institutions; further studies are needed to answer questions about the incidence of rare ECV complications
Borgdorff *et al.*, 2004, the Netherlands[17]	Prospective, randomized, blinded study	40 In-patients having major abdominal surgery IT sufentanil (73.7%, mean 55 y ± 9) IV sufentanil (57.9%, mean 56 y ± 4)	• IT sufentanil (20) • IV sufentanil (20)	Response of the hormones of the hypothalamic-pituitary-adrenal axis, catecholamines, and blood glucose	"The data show that large-dose ITS [intrathecal sufentanil] prevents the intraoperative hormonal stress response in comparison with balanced anesthesia…This technique improves post-operative analgesia when compared with balanced anesthesia."
Borgia *et al.*, 2010, Italy[149]	Prospective, randomized, double blind, controlled trial	30 In-patients undergoing caesarean section (0%, age not specified)	IT bupivacaine and sufentanil plus: • Morphine • Magnesium sulfate	Postoperative analgesic requirements	IT magnesium sulfate can be considered a good adjuvant agent with rapid onset of analgesia and absence of opioid-related side effects
Bosmans *et al.*, 2009, Belgium[150]	Prospective, randomized, double-blinded study	60 Out-patients undergoing knee arthroscopy Ropivacaine (50%, mean 51.7 y) Lidocaine (56.7%, mean 45.5 y)	Sufentanil plus: • Ropivacaine (30) • Lidocaine (30)	Onset, offset and level of sensory and motor block; time to ambulation, urination and discharge	"Both intrathecal local anesthetics can be used in the ambulatory setting."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Bouvet *et al.*, 2011, France[151]	Prospective randomized double-blind dose–response study	85 In-patients undergoing elective caesarean delivery (0%, range 19-43 y)	Sufentanil and morphine plus levobupivacaine at dose of: • 6 mg (17) • 8 mg (17) • 10 mg (17) • 12 mg (17) • 14 mg (17)	Success or failure of the IT block; ED50 and ED95 of IT levobupivacaine	In combination with IT sufentanil and IT morphine, the ED95 of IT levobupivacaine is 12.9 mg
Braga Ade *et al.*, 2014, Brazil[18]	Prospective, randomized, double-blind study	64 In-patients scheduled for cesarean section Fentanyl (0%, mean 31.56 y ± 6.05) Sufentanil (0%, mean 29.40 y ± 6.46)	Bupivacaine plus: • Fentanyl (32) • Sufentanil (32)	Sensory block latency; maximum sensory block level, maximum motor block degree; time for motor regression; duration of analgesia; level of consciousness in the intraoperative period	Sufentanil and fentanyl with spinal bupivacaine were equally effective in the intraoperative period without fetal adverse effects; sufentanil provided a longer duration of both analgesia and motor block
Braga Ade *et al.*, 2003, Brazil[19]	Prospective, randomized, double-blind controlled trial	80 In-patients scheduled for elective caesarean section Group 1 (0%, mean 28.7 y ± 6.5) Group 2 (0%, mean 27.6 y ± 5.7) Group 3 (0%, mean 26.3 y ± 5.6) Group 4 (0%, mean 26.0 y ± 5.5)	• Group 1: bupivacaine (20) • Group 2: bupivacaine plus sufentanil 2.5 mcg (20) • Group 3: bupivacaine plus sufentanil 5 mcg (20) • Group 4: bupivacaine plus sufentanil 7.5 mcg (20)	Block onset; maximum sensory block level, motor block degree; duration of analgesia	Combining sufentanil with bupivacaine was effective, with a more rapid onset of analgesia and prolonged postoperative pain relief; pruritus was more common with higher doses

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Braga Ade *et al.*, 2010, Brazil[20]	Clinical, randomized, double-blind	40 In-patients undergoing elective cesarean sections Group 1 (0%, mean 30.05 y ± 5.436) Group 2 (0%, mean 28.90 y ± 6.78)	• Group 1: 4 mL of hyperbaric bupivacaine and sufentanil solution (20) • Group 2: 3 mL of hyperbaric bupivacaine and sufentanil solution (20)	Sensory block latency; maximum sensory block level; maximal motor block degree; time for motor regression; duration of analgesia	"Four milliliter of anesthetic solution composed of hyperbaric bupivacaine, 10 mg, associated with 5 mcg of sufentanil was more effective than 3 ml of the same solution, providing better intra- and postoperative analgesia without maternal-fetal repercussions."
Breen *et al.*, 1999, Canada[21]	Randomized, double-blind study	40 In-patients in early labor CSE analgesia (0%, mean 31.5 y ± 4.6) Epidural (0%, mean 29.8 y ± 5.1)	• CSE analgesia with IT sufentanil (21) • Epidural lidocaine with fentanyl (19)	Duration of analgesia	"In summary, we found that intrathecal sufentanil 10 mcg provides a more rapid onset of more profound analgesia than epidural lidocaine (45 mg + 12 mcg epinephrine) followed by 100 mcg epidural fentanyl. The initial ability to ambulate is better with intrathecal sufentanil and pruritions is more common."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Bremerich *et al.*, 2007, Germany[22]	Randomized, double-blind study	60 In-patients scheduled for elective caesarean section Bupivacaine plus fentanyl 10 mcg (0%, mean 31 y ± 3) Bupivacaine plus fentanyl 20 mcg (0%, mean 33 y ± 4) Bupivacaine plus sufentanil 5 mcg (0%, mean 29 y ± 4) Levobupivacaine plus fentanyl 10 mcg (0%, mean 31 y ± 5) Levobupivacaine plus fentanyl 20 mcg (0%, mean 32 y ± 3) Levobupivacaine plus sufentanil 5 mcg (0%, mean 32 y ± 3)	Bupivacaine plus: • Fentanyl 10 mcg (10) • Fentanyl 20 mcg (10) • Sufentanil 5 mcg (10) Levobupivacaine plus: • Fentanyl 10 mcg (10) • Fentanyl 20 mcg (10) • Sufentanil 5 mcg (10)	Sensory and motor block characteristics; duration of complete and effective analgesia	The most appropriate anesthetic regiment was levobupivacaine plus sufentanil 5 mcg
Brizzi *et al.*, 2005, Italy[152]	A prospective and randomized study	100 In-patients undergoing cesarean section (0%, age not specified)	Levobupivacaine and sufentanil via: • CSE anesthesia (50) • Spinal anesthesia (50)	Motor block; interoperative discomfort	Sequential CSE anesthesia may be an important step forward in regional anesthesia
Buser *et al.*, 2007, US[153]	Case report	1 In-patient presenting for labor with Marfan's syndrome (0%, 22 y)	• CSE with IT sufentanil and epidural infusion of ropivacaine and sufentanil (1)	Hemodynamic instability; pulse oximetry; fetal heart rate	CSE anesthesia may be particularly helpful in patients with Marfan's syndrome undergoing labor

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Cakirca *et al.*, 2019, Turkey[23]	Double-blind prospective study	45 In-patients undergoing elective cesarean section Saline (0%, mean 27.8 y ± 7.4) Fentanyl (0%, mean 25.5 y ± 5.2) Sufentanil (0%, mean 27.4 y ± 7.1)	Levobupivacaine plus: • Saline (15) • Fentanyl (15) • Sufentanil (15)	Hemodynamic parameters, sensory and motor blockade levels, VAS pain scores, the time to the first analgesic requirement and adverse events	The addition of fentanyl and sufentanil to levobupivacaine was able to increase the quality of both anesthesia and analgesia
Camann *et al.*, 1992, US[25]	Randomized, double-blind study	24 In-patients undergoing active labor IT sufentanil (0%, mean 29 y ± 6) Epidural sufentanil (0%, mean 29 y ± 4) IV sufentanil (0%, mean 31 y ± 3)	• IT sufentanil (9) • Epidural sufentanil (8) • IV sufentanil (7)	VAS	IT sufentanil provided effective analgesia, while the same dose given via other routes failed to do so
Camann *et al.*, 1993, US[26]	Randomized, blinded study	40 In-patients undergoing active labor Sufentanil (0%, mean 28 y ± 5) Sufentanil plus epinephrine (0%, mean 29 y ± 5)	• Sufentanil (20) • Sufentanil plus epinephrine (20)	VAS	IT sufentanil provided rapid-onset analgesia, though with short duration; epinephrine did not prolong duration, but increased occurrence of side effects

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Camann *et al.*, 1998, US[24]	Dose-response	100 In-patients undergoing labor Group 1 (0%, mean 28 y ± 1.5) Group 2 (0%, mean 33 y ± 1.8) Group 3 (0%, mean 32 y ± 1.8) Group 4 (0%, mean 26 y ± 2) Group 5 (0%, mean 29 y ± 3) Group 6 (0%, mean 29 y ± 2.5) Group 7 (0%, mean 30 y ± 1.5) Group 8 (0%, mean 30 y ± 1.2) Group 9 (0%, mean 29 y ± 1.2)	• Group 1: IT sufentanil 2 mcg (11) • Group 2: IT sufentanil 5 mcg (8) • Group 3: IT sufentanil 10 mcg (13) • Group 4: epidural bupivacaine 5 mg (10) • Group 5: epidural bupivacaine 12.5 mg (11) • Group 6: epidural bupivacaine 25 mg (13) • Group 7: IT sufentanil 1 mcg plus epidural bupivacaine 2.5 mg (11) • Group 8: IT sufentanil 2.5 mcg plus epidural bupivacaine 6.25 mg (12) • Group 9: IT sufentanil 5 mcg plus epidural bupivacaine 12.5 mg (11)	VAS; duration of analgesia; ED50	Combinations of epidural bupivacaine with IT sufentanil can provide effective analgesia during labor
Campanella *et al.*, 2009, Italy[27]	Prospective, observational, randomized, controlled, single-blind study	92 In-patients undergoing caesarean delivery (0%, range 17-40 y)	• Levobupivacaine (31) • Levobupivacaine plus sufentanil (30) • Levobupivacaine plus sufentanil and clonidine (31)	Duration of analgesia and motor block	Levobupivacaine plus sufentanil and clonidine optimized the postoperative analgesia

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Campbell *et al.*, 1997, Canada[28]	Prospective, randomized, double-blind study	39 In-patients undergoing labor Epinephrine (0%, mean 25.5 y ± 4.8) Saline (0%, mean 27.5 y ± 6.3)	IT sufentanil and bupivacaine plus: • Epidural epinephrine (20) • Saline (19)	Duration of analgesia; VAS; somnolescence; motor block; sensory block	Addition of epinephrine significantly prolonged labor analgesia without causing adverse effects; IT sufentanil and bupivacaine provided rapid labor analgesia, with or without epinephrine
Campbell *et al.*, 1995, US[154]	Prospective, randomized, double-blind study	52 In-patients undergoing labor Bupivacaine (0%, mean 28.9 y ± 5.5) Sufentanil (0%, mean 29.5 y ± 7.2) Bupivacaine plus sufentanil (0%, mean 28.6 y ± 7.1)	• Bupivacaine (14) • Sufentanil (14) • Bupivacaine plus sufentanil (15)	Duration of analgesia; VAS; somnolescence; motor block; sensory block	Addition of bupivacaine to IT sufentanil significantly prolonged the duration of labor analgesia
Cardoso *et al.*, 2006, Brazil[155]	Randomized, prospective, double-blind study	26 In-patients receiving labor analgesia Clonidine (0%, mean 25.1 y ± 4.5) Without clonidine (0%, mean 27.4 y ± 4.7)	• IT clonidine, sufentanil, and bupivacaine (13) • IT sufentanil and bupivacaine (13)	Quality of analgesia; side effects	Addition of clonidine did not improve quality or prolong analgesic effect, but neither did it increase side effects
Chandra *et al.*, 2008, India[29]	Randomized blind study	60 In-patients with pregnancy-induced hypertension and presenting for elective caesarian delivery (0%, age not specified)	• Bupivacaine (20) • Bupivacaine and fentanyl (20) • Bupivacaine and sufentanil (20)	Quality of intraoperative analgesia; side effects; hemodynamic variables	The addition of sufentanil or fentanyl improved the quality of the spinal block, though the duration of action was longer with sufentanil
Chen *et al.*, 2010, China[30]	Prospective, randomized, double-blinded, up-down sequential allocation study	64 In-patients scheduled for elective caesarian delivery Ropivacaine plus sufentanil (0%, mean 28 y ± 3) Ropivacaine (0%, mean 28 y ± 3)	• Ropivacaine plus sufentanil (32) • Ropivacaine (32)	Onset and efficacy of analgesia; motor block; side effects; hypotension	The addition of IT sufentanil decreased the ED50 for spinal ropivacaine, with a lower incidence of shivering compared to ropivacaine alone

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Cohen *et al.*, 1993, US[31]	–	108 In-patients in active labor (0%, mean 28 y ± 6)	• IT sufentanil	Analgesia; hemodynamic changes; sensory and motor block; side effects	Intrathecal sufentanil produced rapid analgesia onset and the authors speculate that the effects result from a local anesthetic action from the opioid
Coppejans and Vercauteren, 2006, Belgium[156]	Prospective randomized double-blind study	91 In-patients undergoing elective caesarian section Bupivacaine (0%, mean 31 y ± 4) Ropivacaine (0%, mean 32 y ± 4) Levobupivacaine (0%, mean 32 y ± 5)	Sufentanil plus: • Bupivacaine (30) • Ropivacaine (30) • Levobupivacaine (30)	Sensory and motor block; need for epidural supplementation; hypotension severity; neonatal outcome	New local anesthetics may be used effectively for intrathecal anesthesia
Courtney *et al.*, 1992, US[132]	Randomized, double-blinded fashion	37 In-patients scheduled for elective caesarian delivery Sufentanil 0 mcg (0%, mean 29.1 y ± 6.7) Sufentanil 10 mcg (0%, mean 32.2 y ± 4.4) Sufentanil 15 mcg (0%, mean 32.6 y ± 1.3) Sufentanil 20 mcg (0%, mean 34.7 y ± 5.1)	• Sufentanil 0-20 mcg (37)	Onset and duration of sensory and motor anesthesia; duration of effective analgesia; intraoperative parenteral opioid requirements; side effects	All doses of sufentanil provided prolonged postoperative analgesia with significant pruritus; further investigations are needed to assess clinically significant respiratory depression
Culebras *et al.*, 2007, Switzerland[133]	Prospective randomized double-blind study	77 Patients undergoing elective colorectal surgery (50.6%, age not specified)	• Morphine (38) • Morphine plus sufentanil (39)	Sufentanil and morphine consumption; pain relief; patient satisfaction; side effects	Further studies should be done to investigate the effectiveness of intrathecal sufentanil with IT morphine to determine a dose-response pattern within non-toxic intrathecal sufentanil dosage ranges

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Dabbagh *et al.*, 2009, Iran[32]	Double-blind, randomized, placebo-controlled clinical trial	80 Patients undergoing coronary artery bypass graft surgery (gender and age not specified)	• Sufentanil • Sufentanil plus bupivacaine	Hemodynamic variables; need for inotropic agents	IT sufentanil with bupivacaine appears to be more hemodynamically stable than intrathecal sufentanil alone
Dahlgren *et al.*, 1997, Sweden[6]	–	80 In-patients presenting for elective caesarian section Placebo (0%, mean 30.3 y ± 3.9) Fentanyl (0%, mean 30 y ± 3.3) Sufentanil 2.5 mcg (0%, mean 31.3 y ± 5) Sufentanil 5 mcg (0%, mean 34.9 y ± 5)	Hyperbaric bupivacaine plus: • Placebo (20) • Fentanyl (20) • Sufentanil 2.5 mcg (20) • Sufentanil 5 mcg (20)	Duration of analgesia; need for antiemetic; pruritus; umbilical cord gases; Apgar scores	The addition of either IT fentanyl or sufentanil to bupivacaine reduced the need for antiemetics and increased duration; pruritus was almost always attributed to sufentanil and was dose dependent; sufentanil had a slightly longer duration of action
D'Ambrosio *et al.*, 2010, Italy[157]	–	60 Patients undergoing major orthopedic surgery (gender and age not specified)	Sufentanil plus: • Levobupivacaine (not reported) • Ropivacaine (not reported) • Bupivacaine (not reported)	Hemodynamic variables; motor block	All 3 local anesthetics provided a stable hemodynamic; ropivacaine produced a shorter sensory-motor block offset, but the quality was comparable to the others
D'Ambrosio *et al.*, 2013, Italy[158]	Randomized, double blind, prospective trial	70 In-patients undergoing elective caesarian section by Stark method Levobupivacaine 0.25% (0%, mean 31.7 y ± 5.1) Levobupivacaine 0.5% (0%, mean 29.8 y ± 4.8)	Sufentanil plus: • Levobupivacaine 0.25% (35) • Levobupivacaine 0.5% (35)	Intraoperative effectiveness; hemodynamic effects; anesthetic recovery time; patient satisfaction	The lower concentration of levobupivacaine may be a suitable alternative for levobupivacaine 0.50%

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
D'Ambrosio *et al.*, 2011, Italy[217] D'Ambrosio *et al.*, 2015, Italy[134]	Prospective, randomized, double-blind, controlled study	32 In-patients undergoing elective total knee or hip replacement	Sufentanil plus: • Levobupivacaine 0.125% (not reported) • Levobupivacaine 0.0625% (not reported)	Pain	Further studies are needed, but the authors said that the postoperative infusion of levobupivacaine plus sufentanil was useful for postoperative pain
D'Angelo *et al.*, 1994, US[33]	Randomized double-blind design	50 In-patients undergoing labor Sufentanil (0%, mean 24 y ± 4.5) Bupivacaine (0%, mean 25 y ± 4.5)	• Sufentanil (25) • Bupivacaine (25)	Pain; motor blockade; hemodynamic variables; length of labor; type of delivery	IT sufentanil resulted in more rapid analgesia compared to epidural bupivacaine and caused no motor blockade, which may be advantageous
D'Angelo *et al.*, 2001, US[159]	Double-blinded technique	30 In-patients undergoing labor Control (0%, mean 25 y ± 4) Neostigmine (0%, mean 29 y ± 6)	Spinal bupivacaine, clonidine, and sufentanil plus: • Control (15) • Neostigmine (15)	Pain; hemodynamics; fetal heart rate; nausea; pruritus; sedation; motor and sensory block; maternal oxygen saturation	Spinal neostigmine produces severe nausea and is not associated with prolonging the duration of spinal analgesia
D'Angelo *et al.*, 1999, US[160]	Double-blinded design	30 In-patients undergoing labor Control (0%, mean 26 y ± 5) Intervention (0%, mean 25 y ± 6)	Spinal sufentanil and bupivacaine plus: • Control (15) • Clonidine (15)	Pain; nausea; pruritus; sedation; motor block; hemodynamics	Spinal clonidine prolongs analgesia without producing serious adverse effects; additional studies are needed for spinal clonidine
D'Angelo *et al.*, 1998, US[161]	Case report	1 In-patient presenting for vaginal delivery with a history of myasthenia gravis (0%, 27 y)	• CSE analgesia with sufentanil (1)	Analgesia; muscle weakness	CSE analgesia helps to provide analgesia while minimizing motor block

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
de Figueiredo Locks, 2012, Brazil[34]	Prospective blinded, randomized clinical trial	80 In-patients undergoing cesarean section Bupivacaine, morphine, and sufentanil (0%, mean 26.8 y ± 5.8) Bupivacaine and morphine (0%, mean 27.4 y ± 6.6)	• Bupivacaine, morphine, and sufentanil (40) • Bupivacaine and morphine (40)	Incidence of shivering	The addition of sufentanil to bupivacaine and morphine in spinal anesthesia provides a decrease in shivering incidence
Demiraran *et al.*, 2006, Turkey[35]	Prospective, randomized, double-blind, controlled trial	100 In-patients scheduled for elective cesarean section Placebo (0%, mean 27.8 y ± 6.2) Sufentanil 1.5 mcg (0%, mean 28 y ± 5.5) Sufentanil 2.5 mcg (0%, mean 30.4 y ± 6.2) Sufentanil 5 mcg (0%, mean 29.5 y ± 6.4)	Bupivacaine plus: • Placebo (25) • Sufentanil 1.5 mcg (25) • Sufentanil 2.5 mcg (25) • Sufentanil 5 mcg (25)	Pain; fetal bradycardia; pruritus	Adding sufentanil 1.5-2.5 mcg to bupivacaine provided adequate anesthesia, good postoperative analgesia, and a lower incidence of pruritus compared to higher doses
Derakhshan *et al.*, 2018, Iran[112]	Randomized, double-blind, clinical trial	96 Patients undergoing lower limb orthopedic surgery Bupivacaine (51.5%, mean 39.86 y ± 9.41) Bupivacaine plus epinephrine (54.5%, mean 37.75 y ± 9.2) Bupivacaine plus sufentanil (53.3%, mean 43.03 y ± 9.41)	• Bupivacaine (33) • Bupivacaine plus epinephrine (30) • Bupivacaine plus sufentanil (33)	Onset of and recovery from sensory and motor block; pain score	Adding epinephrine or sufentanil to bupivacaine did not prolong sensory and motor blockades compared to bupivacaine alone
Doger *et al.*, 2011, Turkey[36]	–	40 Patients undergoing transurethral resection of the prostate (TURP; gender and age not specified)	• IT bupivacaine (20) • IT bupivacaine and sufentanil (20)	Hemodynamic parameters; recovery time	"Due to the fact that less motor block was observed and the recovery period was shorter, the combination of bupivacaine + sufentanil might be more appropriate for patients undergoing TURP."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Donadoni *et al.*, 1987, Belgium[113]	–	38 Patients undergoing urologic surgery Sufentanil (89.5%, range 51-88 y) Placebo (95%, range 40-81 y)	• Sufentanil plus lignocaine (19) • Placebo plus lignocaine (19)	Quality and duration of analgesia; ventilation rate; hemodynamic variables; side effects	The only benefit was a longer analgesic interval in the sufentanil group, but there were no significant reductions in need for analgesic supplementation; results did not show any beneficial effect in spinal sufentanil 7.5 mcg
Draisci *et al.*, 2009, Italy[37]	Prospective, randomized, double-blind, controlled trial	64 In-patients scheduled for elective caesarian section IT morphine (0%, mean 34.5 y ± 5) Subcutaneous morphine (0%, mean 30 y ± 5)	IT sufentanil plus: • IT morphine (32) • Subcutaneous morphine (32)	Pain; side effects; use of rescue analgesics	Administration of spinal sufentanil and morphine was effective and provided longer pain relief, despite a higher occurrence of side effects
Duale *et al.*, 2003, France[162]	Prospective, randomized, double-blinded study	53 In-patients undergoing elective caesarian section with CSE (0%, range 28-35.5 y)	Spinal bupivacaine and sufentanil plus: • Epidural morphine (28) • IT morphine (25)	Pain; requests for rescue analgesia; time to discharge	The epidural morphine protocol was more effective than the IT morphine
Dunn *et al.*, 1998, US[114]	Randomized	70 In-patients in early labor IT sufentanil (0%, mean 26.7 y ± 4.6) Epidural sufentanil (0%, mean 27.4 y ± 5)	• IT sufentanil (35) • Epidural sufentanil (35)	Onset, length, and intensity of analgesia; motor blockade; side effects	Cost and increased incidence and severity of pruritus make the authors favor epidural technique over intrathecal sufentanil
Eaton, 1998, US[38]	Case reports	3 Out-patients with aortic stenosis who underwent extracorporeal shockwave lithotripsy (ESWL; 0%, range 54-77 y)	• IT sufentanil (3)	Time to discharge; hemodynamics	IT sufentanil appears to be of good value in this patient population
Eaton *et al.*, 1997, US[39]	–	40 Out-patients undergoing ESWL Sufentanil (65%, mean 51.3 y ± 15.8) Lidocaine (65%, mean 55.4 y ± 19.7)	• Sufentanil (20) • Lidocaine (20)	Pain; requests for additional analgesia; time to discharge	Sufentanil was as safe and efficacious as lidocaine, and had improved hemodynamic stability and was associated with more rapid discharge

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Eaton and Kristensen, 1997, US[40]	Retrospective	20 Out-patients undergoing ESWL (70%, mean 56.5 y ± 12.5)	• Sufentanil (20)	Analgesia adequacy; need for additional sedation; time to discharge	"Subarachnoid sufentanil is a safe and effective technique for lithotripsy. A prospective study to compare it with other methods is justified."
Eberle *et al.*, 1998, US[163]	–	305 In-patients undergoing labor Epidural with measured left uterine displacement (0%, mean 28.5 y ± 7.3) Epidural with left lateral decubitus (0%, mean 29.1 y ± 6.3) Sufentanil with measured left uterine displacement (0%, mean 27.0 y ± 6.1) Sufentanil with left lateral decubitus (28.3 y ± 6.6)	• Epidural with measured left uterine displacement (68) • Epidural with left lateral decubitus (73) • Sufentanil with measured left uterine displacement (73) • Sufentanil with left lateral decubitus (81)	Fetal heart rate changes	There was no difference in prolonged fetal deceleration between epidural bupivacaine and intrathecal sufentanil
Eissa *et al.*, 2004, Egypt[164]	Controlled, randomized, double blind trial	40 Patients in early labor (0%, age not specified)	• IT ropivacaine (20) • IT sufentanil (20)	Duration and quality of analgesia; side effects	IT ropivacaine provides effective short duration analgesia; side effects are comparable between ropivacaine and sufentanil
Eschertzhuber *et al.*, 2008, Austria[41]	Prospective, randomized, single-blinded	46 In-patients undergoing dorsal spinal fusion due to idiopathic scoliosis Low dose morphine (gender not specified, mean 15 y ± 2) High dose morphine (gender not specified, mean 15 y ± 2) Control (gender not specified, mean 15 y ± 1)	• Low dose morphine and sufentanil (14) • High dose morphine and sufentanil (14) • Control (14)	Duration of surgery; intraoperative hemodynamics; end tidal sevoflurane concentrations; complications; intraoperative blood loss; use of rescue analgesia; time to extubation	Low dose IT morphine and sufentanil provided a blood-sparing effect, sufficient postoperative analgesia, and showed side-effects that were comparable to the control group not receiving intrathecal opioids

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Fabiano *et al.*, 2012, US[135]	Retrospective review	5 Patients with post-herpetic neuralgia (60%, range 61-83 y)	• IT morphine and bupivacaine (1) • IT morphine (1) • IT sufentanil, bupivacaine, and clonidine (1) • IT sufentanil and bupivacaine (1) • IT sufentanil (1)	Pain	Continuous intrathecal opioid administration may be an option in refractory post-herpetic neuralgia, but further study is warranted
Farzi *et al.*, 2017, Iran[115]	Double-blind clinical trial	99 In-patients undergoing elective cesarean section Fentanyl (0%, mean 28.66 y ± 5.77) Sufentanil (0%, mean 29.67 ± 5.5) Placebo (0%, mean 30.09 y ± 4.45)	• Fentanyl (33) • Sufentanil (33) • Placebo (33)	Duration of analgesia; complications	Adding fentanyl or sufentanil to intrathecal bupivacaine increased duration of analgesia while maintaining hemodynamic stability; fentanyl appears to be preferred due to similar duration of analgesia to sufentanil, but a faster return of motor block and ambulation
Ferouz *et al.*, 1997, US[42]	Randomized, prospective, double-blind study	40 In-patients undergoing labor with the lateral opening of a pencil-point needle either up or down Dextrose up (0%, mean 29 y ± 8) Dextrose down (0%, mean 30 y ± 8) Saline up (0%, mean 30 y ± 6) Saline down (0%, mean 27 y ± 7)	• Sufentanil in dextrose (20) • Sufentanil in saline (20)	Pain relief; side effects	Intrathecal sufentanil has better labor analgesia when administered with saline compared to dextrose
Fleron *et al.*, 2003, France[165]	Prospective, randomized study	217 Patients undergoing elective aortic surgery Control (88%, mean 66 y ± 10) IT (89%, mean 67 y ± 11)	• Control (112) • IT sufentanil and morphine (105)	Complications; mortality; pain; morphine use	There was no change in the incidence of major cardiovascular, respiratory, and renal complications between the 2 groups

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Fournier *et al.*, 2000, Switzerland[43]	–	42 Patients scheduled for elective total hip replacement Sufentanil (33%, mean 80 y ± 5) Fentanyl (48%, mean 79 y ± 6)	• Sufentanil (21) • Fentanyl (21)	Onset, quality, and duration of action; postoperative requirements; hemodynamic changes; adverse effects	Both IT fentanyl and IT sufentanil produced excellent analgesia with low incidence of adverse effects
Fournier *et al.*, 2005, Switzerland[44]	Randomized, double-blind study	40 Patients undergoing elective total hip replacement IT sufentanil (35%, mean 79 y ± 6) IV sufentanil (40%, mean 81 y ± 8)	• IT sufentanil (20) • IV sufentanil (20)	Quality, onset, and duration of analgesia; adverse effects	The IT sufentanil provided better quality and longer duration of analgesia compared to IV sufentanil
Frikha *et al.*, 2007, Tunisia[166]	Prospective study	40 In-patients undergoing labor Sufentanil (0%, mean 29 y ± 3) Tramadol (0%, mean 29 y ± 5)	Bupivacaine with: • IT sufentanil (20) • IT tramadol (20)	Duration of analgesia; frequency of adverse maternal and fetal side effects	IT sufentanil combined with bupivacaine provided rapid-onset analgesia; tramadol had longer-lasting analgesia
Gage *et al.*, 1997, US[167]	–	66 In-patients undergoing labor Dextrose lateral position (0%, mean 25 y ± 6) Sufentanil-dextrose lateral position (0%, mean 25 y ± 5) Sufentanil-dextrose sitting position (0%, mean 25 y ± 4) Sufentanil-saline lateral position (0%, mean 27 y ± 6) Sufentanil-saline sitting position (0%, mean 26 y ± 6)	• Dextrose lateral position (6) • Sufentanil-dextrose lateral position (15) • Sufentanil-dextrose sitting position (15) • Sufentanil-saline lateral position (15) • Sufentanil-saline sitting position (15)	Pain scores; sensory block height; side effects	Dextrose should not be added to intrathecal sufentanil when it is administered to patients who are sitting

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Gaiser *et al.*, 1998, US[116]	Randomized, double-blind study	55 In-patients in active labor Fentanyl 25 mcg (0%, mean 22.4 y ± 3) Fentanyl 37.5 mcg (0%, mean 22.3 y ± 7.6) Fentanyl 50 mcg (0%, mean 22 y ± 6.2) Sufentanil 5 mcg (0%, mean 23.4 y ± 5.7) Sufentanil 10 mcg (0%, mean 22.8 y ± 6.6) Sufentanil 15 mcg (0%, mean 23 y ± 6.2)	• Fentanyl 25 mcg (9) • Fentanyl 37.5 mcg (10) • Fentanyl 50 mcg (8) • Sufentanil 5 mcg (10) • Sufentanil 10 mcg (10) • Sufentanil 15 mcg (8)	Duration of analgesia, contraction pain, degree of pruritus, maternal blood pressure, maternal heart rate, fetal heart rate, Apgar scores, and neurologic and adaptic capacity scores	The duration of analgesia as well as pruritus was longer with sufentanil than fentanyl; based on shorter duration of pruritus and lower cost, the authors use fentanyl for intrathecal injection in labor analgesia
Gambling *et al.*, 1998, US[136]	Randomized study	1223 In-patients undergoing labor CSE (0%, mean 21.7 y ± 4.9) IV (0%, mean 22.4 y ± 4.9)	• CSE with IT sufentanil and epidural bupivacaine plus fentanyl (616) • IV meperidine (607)	Operative delivery rates; pain scores; side effects	"Combined spinal-epidural analgesia during labor does not increase the cesarean delivery rate for dystocia in healthy parturient patients at full term, regardless of parity. However, an unexpected increase in the number of cesarean deliveries for profound fetal bradycardia after intrathecal sufentanil was observed. Further investigation is warranted."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Gautier *et al.*, 1998, Belgium[45]	–	98 In-patients undergoing labor Clonidine 15 mcg (27 y ± 2) Clonidine 30 mcg (29 y ± 3) Sufentanil 2.5 mcg (0%, mean 30 y ± 6) Sufentanil 2.5 mcg plus clonidine 15 mcg (0%, mean 29 y ± 5) Sufentanil 2.5 mcg plus clonidine 30 mcg (0%, mean 30 y ± 4) Sufentanil 5 mcg (0%, mean 27 y ± 2) Sufentanil 5 mcg plus clonidine 15 mcg (0%, mean 31 y ± 4) Sufentanil 5 mcg plus clonidine 30 mcg (0%, mean 30 y ± 5)	• Clonidine 15 mcg (10) • Clonidine 30 mcg (10) • Sufentanil 2.5 mcg (13) • Sufentanil 2.5 mcg plus clonidine 15 mcg (13) • Sufentanil 2.5 mcg plus clonidine 30 mcg (13) • Sufentanil 5 mcg (12) • Sufentanil 5 mcg plus clonidine 15 mcg (13) • Sufentanil 5 mcg plus clonidine 30 mcg (13)	Maximum pain relief and duration of analgesia; hemodynamic changes; side effects	The duration of analgesia is significantly increased when clonidine 30 mcg is combined with sufentanil 2.5 or 5 mcg
Gautier *et al.*, 1997, Belgium[168]	Double-blind, randomized study	42 In-patients undergoing labor Control (0%, mean 27.4 y ± 4.4) Epinephrine (0%, mean 28.6 y ± 2.9)	Sufentanil and bupivacaine plus: • Control (21) • Epinephrine (21)	Analgesia efficacy; hemodynamic changes; side effects	Adding epinephrine to the mixture allowed for high-quality analgesia with a low sensory block and no motor block; the authors noted that this combination required 3 drugs and 2 of them to be diluted, which introduces the possibility of drug preparation error
Gautier *et al.*, 2003, Belgium[46]	Prospective study	90 In-patients undergoing elective cesarean section Bupivacaine (0%, mean 29 y ± 5) Levobupivacaine (0%, mean 30 y ± 4) Ropivacaine (0%, mean 30 y ± 6)	IT sufentanil plus: • Bupivacaine (30) • Levobupivacaine (30) • Ropivacaine (30)	Analgesia efficacy; hemodynamic changes; side effects	Mixing bupivacaine with sufentanil is an appropriate choice for performing cesarean sections under spinal analgesia

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Goluza *et al.*, 2010, Croatia[47]	Randomized, prospective pilot study	20 Patients scheduled for ureteroscopic lithotripsy (gender not specified, range 31-68 y)	• Sufentanil and levobupivacaine (10) • Levobupivacaine (10)	Efficacy and duration of sensory and motor blocks	Adding IT sufentanil to levobupivacaine is a safe and effective method of spinal anesthesia
Goodarzi, 1998, US[48]	–	80 Patients undergoing spinal fusion for idiopathic scoliosis Group A (17.5%, mean 14.8 y ± 1.2) Group B (12.5%, mean 13.13 y ± 3.01)	• Group A: IT morphine and sufentanil (40) • Group B: control (40)	Blood pressure; anesthetic requirement; intraoperative blood loss; postoperative pain control	IT opioids may be used safely for anesthesia during major operations
Goodarzi *et al.*, 1996, US[49]	–	10 Patients undergoing spinal fusion (20%, mean 14.1 y ± 1.2)	• IT morphine and sufentanil (10)	Somatosensory-evoked potentials; hemodynamic changes	IT opioids have no effect on somatosensory-evoked potentials
Grieco *et al.*, 1993, US[169]	Double-blind, randomized protocol	41 In-patients undergoing labor Sufentanil (0%, mean 27.62 y ± 3.66) Sufentanil plus epinephrine (0%, mean 26.23 y ± 6.64) Sufentanil plus morphine (0%, mean 27.64 y ± 4.59)	• Sufentanil (13) • Sufentanil plus epinephrine (13) • Sufentanil plus morphine (15)	Duration of analgesia; maternal and fetal effects	While both epinephrine and morphine prolong labor analgesia with sufentanil, the longer duration of pain relief from morphine is associated with increased side effects – therefore, IT morphine is not recommended for labor analgesia
Gupta *et al.*, 2013, India[50]	Prospective, randomized, double-blind study	90 Patients scheduled for elective endoscopic urologic surgery Bupivacaine (73%, mean 62.67 y ± 11.28) Bupivacaine plus sufentanil (73%, mean 64.6 y ± 10.16) Bupivacaine plus fentanyl (73%, mean 61.43 y ± 9.05)	• Bupivacaine (30) • Bupivacaine plus sufentanil (30) • Bupivacaine plus fentanyl (30)	Efficacy and duration of sensory and motor blocks; side effects; hemodynamic changes	Bupivacaine and sufentanil for spinal anesthesia were associated with a lower occurrence of hemodynamic instability, as well as better quality and prolonged duration compared to fentanyl

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Hamilton and Cohen, 1995, US[170]	Series of 6 cases	6 In-patients undergoing analgesia (0%, range 26-35 y)	• Sufentanil (6)	Sensory block; side effects	Caution should be used with potent IT opioids, and careful monitoring
Harsten *et al.*, 1997, Sweden[51]	Randomized, double-blind and controlled trial	58 In-patients undergoing labor Bupivacaine (0%, mean 26.7 y ± 4.1) Sufentanil (0%, mean 26.4 y ± 3.9)	• Bupivacaine • Sufentanil	Onset of anesthesia; side effects; hemodynamic changes	IT sufentanil produces more rapid and profound analgesia than epidural bupivacaine
Hashemnejad *et al.*, 2018, Iran[52]	Randomized	200 Patients undergoing active labor (0%, age not specified)	• Sufentanil (100) • No techniques (100)	Delivery tools using; birth weight; Apgar score	The authors recommend using sufentanil to reduce vaginal labor pain
Hassani *et al.*, 2014, Iran[53]	Double-blind randomized clinical trial	90 Patients undergoing elective orthopedic surgery on lower extremities (75.6%, mean 32 y ± 15)	Bupivacaine plus: • Sufentanil (30) • Fentanyl (30) • Placebo (30)	Maximum sensational block; vital signs changes; pain evaluation; side effects	When compared to other regular and lipophilic opioids, sufentanil is recommended for spinal anesthesia along with bupivacaine
Hassenbusch *et al.*, 1995, US[171]	Prospective consecutive series	18 Out-patients with exclusively neuropathic pain (gender not specified, range 30-77 y)	• IT morphine (7) • IT sufentanil (11)	Pain relief	While long-term IT opioid infusions may have efficacy in treating neuropathic pain, but require higher infusion doses
Hein *et al.*, 2010, Sweden[172]	Randomized, double-blind placebo-controlled trial	82 In-patients undergoing labor Placebo (0%, range 22-37 y) Morphine 50 mcg (0%, range 22-38 y) Morphine 100 mcg (0%, range 20-40 y)	Bupivacaine and sufentanil plus: • Placebo (28) • Morphine 50 mcg (28) • Morphine 100 mcg (26)	Onset; maternal and neonatal side effects; maternal satisfaction	Adding morphine to bupivacaine and sufentanil did not significantly increase analgesia duration
Henderson *et al.*, 2001, Canada[117]	Randomized, double-blind trial	12 Out-patients scheduled to undergo gynecologic laparoscopic procedures (0%, range 32-72 y)	• IT lidocaine plus sufentanil (7) • IT sufentanil (5)	Duration of analgesia; time to motor recovery; side effects	IT sufentanil is inferior to IT lidocaine plus sufentanil for anesthesia

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Herman *et al.*, 1997, US[54]	–	60 In-patients undergoing labor Sufentanil 2.5 mcg (0%, mean 26.4 y ± 4.7) Sufentanil 5 mcg (0%, mean 26.2 y ± 5.6) Sufentanil 7.5 mcg (0%, mean 25.2 y ± 4) Sufentanil 10 mcg (0%, mean 25.5 y ± 3.7) Sufentanil 12.5 mcg (0%, mean 29.4 y ± 5.6) Sufentanil 15 mcg (0%, mean 24.3 y ± 5.3)	• Sufentanil 2.5 mcg (10) • Sufentanil 5 mcg (10) • Sufentanil 7.5 mcg (10) • Sufentanil 10 mcg (10) • Sufentanil 12.5 mcg (10) • Sufentanil 15 mcg (10)	Pain; fetal effects; side effects	The ED50 and ED95 for intrathecal sufentanil were 2.6 and 8.9 mcg, respectively
Honet *et al.*, 1992, US[118]	Prospective, double-blind study	60 In-patients undergoing labor Fentanyl (0%, mean 27 y ± 7) Meperidine (0%, mean 26 y ± 6) Sufentanil (0%, mean 28 y ± 7)	• Fentanyl (20) • Meperidine (20) • Sufentanil (20)	Average first dose to make a patient comfortable; the duration of the first dose of opioid analgesia; duration of effective opioid analgesia; VAS; nausea	Intermittent spinal injection with fentanyl, meperidine, or sufentanil provides adequate labor analgesia for the first stage; however, meperidine may have advantages over the others due to more reliable analgesia
Houweling *et al.*, 1992, the Netherlands[55]	–	24 Patients undergoing elective resection and bifemoral grafting for aorto-iliac occlusive disease Epidural (67%, mean 59.9 y ± 8.9) IT (50%, mean 64.1 y ± 7.9)	• Epidural sufentanil (12) • IT sufentanil (12)	Hemodynamic changes; duration of surgery; blood loss; urine production; duration of analgesia	Both epidural and IT sufentanil analgesia can produce comparable and stable hemodynamics

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Houweling *et al.*, 1993, the Netherlands[56]	–	60 Patients scheduled for elective bifemoral grafting for abdominal aneurysms IV (75%, mean 65 y ± 5.7) Epidural (75%, mean 63.2 y ± 8) IT (85%, mean 67.8 y ± 9.2)	• IV sufentanil (20) • Epidural sufentanil (20) • IT sufentanil (20)	Hemodynamic changes; duration of surgery; blood loss; urine production; duration of analgesia	IT sufentanil produced the most stable heart rate compared to the other ROA
Houweling and Joosten, 1993, the Netherlands[57]	–	36 Patients scheduled for abdominal aortic surgery Morphine (89%, mean 63 y ± 8.1) Sufentanil (94%, mean 68 y ± 8.5)	• IT morphine (18) • IT sufentanil (18)	Hemodynamic changes; duration of analgesia; postoperative complications	Both opioids provided adequate analgesia; hemodynamic differences were minimal in the post-revascularization period
Jain *et al.*, 2018, India[58]	Prospective randomized clinical study	60 In-patients undergoing cesarean section Bupivacaine (0%, mean 22.16 y ± 2.71) Bupivacaine plus sufentanil (0%, mean 23.93 y ± 2.68)	• Bupivacaine (30) • Bupivacaine plus sufentanil (30)	Onset of sensory and motor block; level of sedation; pulse; blood pressure; side effects	Adding sufentanil to IT bupivacaine shortens the onset and prolongs duration of sensory and motor blockade
Juliao and Lauretti, 2000, Brazil[59]	Randomized double-blind study	72 In-patients undergoing abdominal gynecological surgery Control (0%, mean 45 y ± 7) Sufentanil (0%, mean 43 y ± 10) Clonidine (0%, mean 41 y ± 7) Sufentanil plus clonidine (0%, mean 41 y ± 8)	• Control: saline (17) • Sufentanil (18) • Clonidine (17) • Sufentanil plus clonidine (20)	Sensory block; duration of anesthesia; time to rescue analgesia; side effects	Adding low doses of IT clonidine prolonged extension of sensory block, motor block, and analgesia duration; intrathecal clonidine combined with sufentanil provided slightly superior analgesia compared to both the control and sufentanil groups

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Karaman *et al.*, 2006, Turkey[119]	Prospective, randomized and double-blind study	54 In-patients undergoing cesarean section Morphine (0%, mean 29.5 y ± 6) Sufentanil (0%, mean 30.2 y ± 4.7)	Bupivacaine plus: • Morphine (27) • Sufentanil (27)	Time and efficacy of sensory block; time to resolution of motor block; neonatal effects; hemodynamic effects; sedation; side effects	Adding sufentanil or morphine to bupivacaine provided safe and effective anesthesia; morphine increased duration of postoperative analgesia compared to sufentanil without increasing side effects
Kartawiadi *et al.*, 1996, Belgium[60]	Randomized trial	63 In-patients presenting for vaginal delivery CSE (0%, mean 28.2 y ± 4.2) Epidural (0%, mean 29.07 y ± 3.9)	Bupivacaine, sufentanil, and epinephrine via: • CSE analgesia (32) • Epidural analgesia (31)	Onset and duration of analgesia; side effects	Compared with epidural analgesia, CSE injection provided excellent pain relief with a more rapid onset and longer duration
Kaufner *et al.*, 2016, Germany[61]	Prospective randomized trial	179 In-patients undergoing elective cesarean section Intrathecal (0%, mean 31 y ± 5.4) Epidural (0%, mean 31.7 y ± 6.3) Patient-controlled epidural analgesia (PCEA; 0%, mean 31.7 y ± 6.3)	IT sufentanil and bupivacaine plus: • IT morphine (60) • Epidural morphine (59) • PCEA ropivacaine and sufentanil (60)	Pain relief	IT opioid bolus administration had more efficacy in reducing pain after cesarean section
Kaur *et al.*, 2011, India[120]	Randomized, double-blind study	90 Patients undergoing elective endoscopic urological surgeries Bupivacaine (93%, mean 61.33 y ± 17.22) Bupivacaine plus sufentanil (90%, mean 59.33 y ± 15.58) Bupivacaine plus butorphanol (90%, mean 61.1 y ± 17.63)	• Bupivacaine (30) • Bupivacaine plus sufentanil (30) • Bupivacaine plus butorphanol (30)	Level and duration of sensory block; hemodynamic effects; side effects	Combining butorphanol with bupivacaine is especially beneficial in geriatric patients with co-morbid conditions

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Kim *et al.*, 2015, South Korea[62]	Prospective, randomized, double-blind study	52 Patients undergoing TURP Fentanyl (100%, mean 73.1 y ± 6.1) Sufentanil (100%, mean 71.7 y ± 5.2)	Bupivacaine plus: • Fentanyl (26) • Sufentanil (26)	Pain; need for postoperative analgesia; satisfaction level	Intrathecal sufentanil was found to be superior to fentanyl for postoperative analgesia
Kim *et al.*, 2009, South Korea[121]	–	70 Patients undergoing transurethral prostatectomy (100%, range 58-85 y)	Bupivacaine plus: • Fentanyl (35) • Sufentanil (35)	Onset and duration of the sensory block; degree of the motor block; side-effects; perioperative analgesic requirements	Sufentanil was superior to fentanyl regarding spinal block quality; however, both sufentanil and fentanyl were able to provide adequate anesthesia without hemodynamic instability
Krobot *et al.*, 2011, Croatia[63]	Prospective, randomized, double-blind study	40 Patients undergoing arthroscopic knee surgery Fentanyl (70%, mean 40 y ± 19) Sufentanil (60%, mean 37 y ± 16)	Bupivacaine plus: • Fentanyl (20) • Sufentanil (20)	Sensory and motor block; hemodynamic data; side-effects; time to first analgesic	Both fentanyl and sufentanil provided adequate sensory block when added to bupivacaine, as well as resulting in similar motor block, cardiovascular stability, and first micturition time; bupivacaine-sufentanil was found to be superior due to prolonged first analgesic time and significantly longer postoperative analgesia duration
Krobot *et al.*, 2011, Croatia[64]	Prospective, randomized, double-blind study	40 Patients undergoing hip fracture repair (gender not specified, range 75-92 y)	• Levobupivacaine (20) • Levobupivacaine plus sufentanil (20)	Sensory and motor block; hemodynamic changes; side effects; time to first analgesic	Levobupivacaine plus sufentanil provided a similar sensory block and postoperative analgesia, but faster motor recovery and more stable cardiovascular profile compared to levobupivacaine
Kumar *et al.*, 2011, India[65]	Double-blind prospective study	50 Patients undergoing lower limb surgery Bupivacaine (64%, mean 69 y ± 5.25) Bupivacaine plus sufentanil (68%, mean 68.88 y ± 5.01)	• Bupivacaine (25) • Bupivacaine plus sufentanil (25)	Sensory and motor block; hemodynamic changes; side effects; duration of analgesia	Low-dose sufentanil allows for local anesthetic dose to be safely and significantly lowered, which allows for avoiding hemodynamic fluctuation and prolonging duration of sensory analgesia

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Kuukasjärvi *et al.*, 2019, Finland[66]	–	80 In-patients in early labor (0%, age not specified)	Spinal: • Sufentanil (20) • Fentanyl (20) Epidural • Sufentanil (20) • Fentanyl (20)	Analgesia at 20 minutes	"Both spinal and epidural sufentanil and fentanyl provide analgesia in early labor. At 20 minutes the analgesic effect of epidural sufentanil and fentanyl was 63% and 60% of the respective spinal analgesic effect. Epidural administration of sufentanil or fentanyl can be considered if intrathecal injection is not desired"
Lau *et al.*, 1999, US[122]	Prospective, randomized, double-blinded study	60 Patients undergoing ESWL Sufentanil 15 mcg (100%, mean 49 y ± 12) Sufentanil 15 mcg (100%, mean 53 y ± 17) Sufentanil 17.5 mcg (100%, mean 56 y ± 13) Sufentanil 20 mcg (100%, mean 52 y ± 11)	• Sufentanil 12.5 mcg (15) • Sufentanil 15 mcg (15) • Sufentanil 17.5 mcg (15) • Sufentanil 20 mcg (15)	Pain relief; propofol use; side effects	15 mcg of IT sufentanil is the optimal dose for performing ESWL
Lau *et al.*, 1997, US[67]	Prospective, randomized, double-blind study	22 Out-patients undergoing ESWL Sufentanil (64%, mean 50 y ± 14) Lidocaine (45%, mean 53 y ± 17)	• IT sufentanil (11) • IT lidocaine (11)	Intraoperative and postoperative pain; recovery time; antiemetic requirements; side effects; sedation	IT sufentanil 20 mcg is a safe and effective alternative drug for ESWL; the only adverse effect noted was pruritus, which was easily managed

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Lauretti *et al.*, 1999, Brazil[173]	Placebo-controlled, double-blinded design	56 Patients undergoing minor arthroscopic procedures Control (67%, mean 28 y ± 13) Sufentanil (47%, mean 39 y ± 17) Nitroglycerin (38.5%, mean 37 y ± 20) Sufentanil plus nitroglycerin (53%, mean 42 y ± 22)	IT bupivacaine plus: • Control: transdermal placebo (13) • IT sufentanil (15) • Transdermal nitroglycerin (13) • IT sufentanil plus transdermal nitroglycerin (15)	Pain; time to first analgesic medication; use of analgesics; side effects	Transdermal nitroglycerin prolonged spinal sufentanil analgesia
Lee *et al.*, 2011, South Korea[68]	–	72 In-patients undergoing cesarean section Control (0%, mean 33.2 y ± 2.5) Fentanyl (0%, mean 33.3 y ± 2.9) Sufentanil (0%, mean 32 y ± 3.7)	IT bupivacaine plus: • Control (24) • Fentanyl (24) • Sufentanil (24)	Maximal level of sensory and motor block; quality of intraoperative analgesia; duration of effective analgesia; side effects	Adding fentanyl or sufentanil to spinal analgesia provides adequate intraoperative analgesia; further studies are required to determine optimal doses
Leighton *et al.*, 1996, US[69]	Prospective study	147 In-patients in active labor (0%, age not specified)	• Epidural bupivacaine (77) • IT sufentanil via 27-gauge needle plus epidural bupivacaine (33) • IT sufentanil via 24-gauge needle plus epidural bupivacaine (37)	Dermatomal spread of epidural bupivacaine; sensory blockade; respiratory measures	With IT sufentanil, epidural bupivacaine was able to anesthetize more dermatomes
Li *et al.*, 2019, China[123]	Randomized	1500 In-patients undergoing cesarean section Sufentanil (0%, mean 28.7 y ± 5.5) Hydromorphone (0%, mean 29.2 y ± 5.7)	IT bupivacaine plus: • Sufentanil (750) • Hydromorphone (750)	Pain on VAS	When compared with sufentanil, IT hydromorphone has a longer analgesia duration and effect and is safer; it is ideal for obstetric analgesia

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Lilot *et al.*, 2013, France[174]	Prospective, comparative, randomized, and single-blinded trial	65 Patients undergoing traumatic femoral neck surgery Ropivacaine 6 mg (18%, mean 86 y ± 6) Ropivacaine 8 mg (12%, mean 85 y ± 7) Ropivacaine 10 mg (33%, mean 84 y ± 6) Ropivacaine 12 mg (12%, mean 83 y ± 4)	IT sufentanil plus: • Ropivacaine 6 mg (17) • Ropivacaine 8 mg (17) • Ropivacaine 10 mg (15) • Ropivacaine 12 mg (16)	Sensory and motor block; dose of epinephrine; incidence of very severe hypotension; duration of surgery; patient satisfaction	"Further study is needed to determine the impact of unilateral spinal anesthesia with hypobaric ropivacaine on outcome in elderly patients undergoing hip fracture surgery."
Lin *et al.*, 1998, Taiwan[70]	–	41 In-patients undergoing elective caesarian section (0%, age not specified)	• Bupivacaine (19) • Bupivacaine plus sufentanil (19)	Hypotension; chest discomfort; need for analgesic	"The addition of intrathecal sufentanil to 0.5% bupivacaine for spinal anesthesia improved perioperative discomfort and significantly reduced the demand of post-operative analgesia but on the other hands, it tended to increase perioperative hypotension and cause mild pruritus."
Lo *et al.*, 1999, Singapore[71]	–	59 In-patients undergoing labor Control (0%, mean 27.8 y ± 2.3) Fentanyl (0%, mean 28.1 y ± 3.5) Sufentanil (0%, mean 27.1 y ± 3.9)	Bupivacaine plus: • Control (20) • Fentanyl (19) • Sufentanil (20)	Analgesia; hypotension; nausea and vomiting; motor blockade	"In combined spinal epidural for labour analgesia, adding sufentanil 10 mcg to intrathecal bupivacaine 2.5 mg provided fast onset and good analgesia for a longer duration compared with adding fentanyl 10 mcg and with plain bupivacaine."
Malek and Kurzova, 2004, Czech Republic[72]	–	63 Patients undergoing surgical repair of hip fracture Fentanyl (29%, mean 70.1 y ± 5.9) Sufentanil (38%, mean 72.9 y ± 8) Control (29%, mean 74.1 y ± 9.3)	Bupivacaine plus: • Fentanyl (21) • Sufentanil (21) • Control: saline (21)	Duration of analgesia; time to request of analgesia; side effects	IT fentanyl and sufentanil both significantly prolonged the time to first request for analgesia; sufentanil appeared to have longer analgesia and less postoperative nausea and vomiting

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Mardirosoff and Dumont, 1999, Switzerland[73]	Randomized, double-blinded, placebo-controlled study	105 In-patients undergoing labor Control (0%, mean 30 y ± 3) Sufentanil 2.5 mcg (0%, mean 29 y ± 6) Sufentanil 5 mcg (0%, mean 27 y ± 5)	IT bupivacaine and epinephrine plus: • Control (35) • Sufentanil 2.5 mcg (35) • Sufentanil 5 mcg (35)	Duration of analgesia; side effects	Sufentanil 2.5 mcg had an advantage over sufentanil 5 mcg; not only did it provide the same quality and duration of analgesia, it had reduced pruritus
Marks and Atchabahian, 2017, US[137]	Case report	1 Patient undergoing a total knee arthroplasty (100%, 46 y)	• IT sufentanil and bupivacaine (1)	Hemodynamic changes; pain scores; motor function	Further studies should be done evaluating the reliability of using a spinal solution of low dose local anesthetic in combination with an opioid for total knee arthroplasty
Mason *et al.*, 2001, France[74]	Double-blind randomized study	30 In-patients undergoing thoracotomy (70%, range 31-85 y)	• Control (15) • Sufentanil and morphine (15)	Pain rating; need for analgesic; spirometric data	Combining IT sufentanil and morphine produces rapid-onset analgesia for 24 hours
Meininger *et al.*, 2003, US[75]	Prospective, randomized, double-blidn study	100 In-patients undergoing elective caesarian section Mepivacaine (0%, mean 31.7 y ± 5.8) Mepivacaine plus fentanyl 5 mcg (0%, mean 32.7 y ± 5) Mepivacaine plus fentanyl 10 mcg (0%, mean 33.4 y ± 5.9) Mepivacaine plus sufentanil 2.5 mcg (0%, mean 31.4 y ± 3.6) Mepivacaine plus sufentanil 5 mcg (0%, mean 32 y ± 6.4)	• Mepivacaine (20) • Mepivacaine plus fentanyl 5 mcg (20) • Mepivacaine plus fentanyl 10 mcg (20) • Mepivacaine plus sufentanil 2.5 mcg (20) • Mepivacaine plus sufentanil 5 mcg (20)	Sensory, motor, and analgesic block; hemodynamic variables; neonatal outcomes	Adding IT fentanyl or sufentanil improved the postoperative analgesia, with sufentanil providing longest duration of complete and effective analgesia
Mercier *et al.*, 1998, France[175]	Prospective, randomized, double-blind study	50 In-patients undergoing labor Sufentanil plus clonidine (0%, mean 28 y ± 4) Sufentanil (0%, mean 28 y ± 3)	• Sufentanil plus clonidine (24) • Sufentanil (26)	Duration of analgesia	Adding clonidine to IT sufentanil extended labor analgesia duration without increasing motor blockade

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Mirea *et al.*, 2013, Romania[176] Mirea *et al.*, 2012, Romania[218]	Prospective, randomized study	60 Patients undergoing orthopedic surgery (gender not specified, >65 y)	IT bupivacaine and sufentanil administered at: • Moderate speed (20) • Slow speed (20) • Fast speed (20)	Blood pressure; ephedrine use	"Low speed of local anaesthetic injection reduced the incidence and severity of hypotension and also the need of vasopressor agent during spinal anaesthesia for orthopaedic surgery in elderly patient."
Missant *et al.*, 2004, Belgium[177]	Double blind, randomized trial	38 In-patients undergoing labor Ropivacaine plus sufentanil (0%, mean 30.1 y ± 4.5) Ropivacaine plus sufentanil and clonidine (0%, mean 29.9 y ± 4.9)	• Ropivacaine plus sufentanil (20) • Ropivacaine plus sufentanil and clonidine (18)	Onset and duration of analgesia; blood pressure; ephedrine requirements; heart rate; side effects	Routine administration of spinal clonidine to sufentanil and ropivacaine is not recommended
Monsivais and Monsivais, 2014, US[76]	Pre-designed cohort review	12 Patients with chronic, intractable, non-malignant pain (58%, range 38-79 y)	• IT sufentanil pump (12)	Pain scales	IT sufentanil therapy may be acceptable in cases that have failed surgical and standard pain interventions;
Motiani *et al.*, 2010, India[77]	Prospective, randomized double-blind study	90 Patients undergoing elective, major orthopedic surgery Sufentanil (73%, mean 37.1 y ± 13.5) Fentanyl (77%, mean 37.3 y ± 15.6) Control (77%, mean 39.1 y ± 12.9)	Bupivacaine plus: • Sufentanil (30) • Fentanyl (30) • Control: saline (30)	Onset and duration of sensory and motor block; pain scores; side effects	The addition of sufentanil or fentanyl lead to earlier onset and prolonged duration of sensory block compared to bupivacaine alone
Nakamura *et al.*, 2009, Brazil[178]	Randomized trial	40 In-patients undergoing labor CSE (0%, mean 21.4 y ± 4.4) Epidural (0%, mean 19.9 y ± 3.6)	• CSE with sufentanil plus bupivacaine (20) • Epidural with ropivacaine (20)	Pain scores; duration of analgesia; latency times; sensory and motor blockade; Apgar score	"EA [Epidural] and CSE analgesia relieved maternal pain during obstetric analgesia, but CSE mothers had pruritus and a longer labor. Newborns of mothers who received epidural analgesia showed the best neurological and adaptive capacity score."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Nelson *et al.*, 2001, US[78]	Retrospective chart and operating room log review	63 Patients undergoing shockwave lithotripsy Sufentanil (55%, mean 53.1 y ± 15) Lidocaine (55%, mean 46.5 y ± 13.2)	• Sufentanil (25) • Lidocaine plus other agents (38) Note – some of the patients who received lidocaine also received sufentanil, but this number is not known	Treatment success rate; treatment time; fluoroscopy time; time to ambulation and voiding postoperatively	Using IT sufentanil for anesthesia during shockwave lithotripsy is associated with better outcomes
Nelson *et al.*, 1999, US[179]	Four-phase study	106 In-patients undergoing labor (0%, age not specified)	Phase I • Neostigmine 5 mcg (6) • Neostigmine 10 mcg (6) • Neostigmine 20 mcg (6) Phase II • Sufentanil (20) Phase III • Sufentanil plus neostigmine (20) Phase IV • Sufentanil (20) • Sufentanil plus neostigmine (20)	Analgesic effect; side effects; maternal and neonatal effects	IT neostigmine reduces the ED50 for IT sufentanil
Nelson *et al.*, 2002, US[180]	–	75 In-patients undergoing labor Phase I (0%, age not reported) Phase II: • Fentanyl (0%, mean 25 y ± 6) • Sufentanil (0%, mean 25 y ± 5)	Phase I • Fentanyl (20) Phase II • Fentanyl (29) • Sufentanil (26)	Pain relief; side effects; block height; maternal hemodynamics; fetal heart rate	While intrathecal sufentanil is more potent compared to fentanyl, it is also more expensive and has a greater risk of dosing error

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Ngiam and Chong, 1998, Singapore[79]	–	55 In-patients undergoing non-emergency caesarian section Fentanyl plus bupivacaine (0%, mean 31.2 y ± 4.6) Sufentanil plus bupivacaine (0%, mean 31.2 y ± 6.4) Bupivacaine (0%, mean 31.9 y ± 4.6)	• Fentanyl plus bupivacaine (18) • Sufentanil plus bupivacaine (20) • Bupivacaine (17)	Duration of analgesia; need for intraoperational analgesics; incidence of desaturation; side effects	Adding sufentanil or fentanyl to bupivacaine prolonged duration of effective analgesia and improved intraoperative analgesia; fentanyl was associated with more pruritus and episodes of desaturation
Nielsen *et al.*, 1996, US[181]	Prospective	129 In-patients undergoing labor IT sufentanil (0%, mean 24.5 y ± 6.3) Epidural bupivacaine (0%, mean 26.9 y ± 6.3)	• IT sufentanil (65) • Epidural bupivacaine (64)	Fetal heart tracing (FHT) characteristics; obstetrical outcomes	"These results support the conclusion that the incidence of clinically significant FHT abnormalities and hypotension is equivalent in patients receiving ITS [intrathecal sufentanil] when compared to EB [epidural bupivacaine] within the first hour of administration."
Nigro Neto *et al.*, 2014, Brazil[80]	Prospective, randomized, not blinded study	40 Patients undergoing elective coronary artery bypass grafting with cardiopulmonary bypass Control (68%, mean 56 y ± 7.2) Sufentanil (66%, mean 58 y ± 6.7)	• Control (19) • Sufentanil (21)	Changes in hemodynamic data; inotropic support; hypotension	IT sufentanil provides more hemodynamic stability
Norris *et al.*, 2001, US[182]	Prospective, quasi-randomized, clinical trial	2183 In-patients undergoing labor Epidural (0%, mean 24.6 y ± 6.2) CSE (0%, mean 24.6 y ± 6.2)	• Epidural sufentanil and bupivacaine (1112) • CSE with IT sufentanil ± bupivacaine (1071)	Mode of delivery	CSE analgesia is not associated increased rate of complications; either technique can provide safe and effective analgesia in labor

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Norris *et al.*, 1998, US[81]	Randomized, double-blind	54 In-patients undergoing labor Sufentanil 5 mcg (0%, mean 27 y ± 6) Sufentanil 10 mcg (0%, mean 26 y ± 7)	• Sufentanil 5 mcg (27) • Sufentanil 10 mcg (27)	Pain severity; side effects; sedation; maternal blood pressure and oxygen saturation; end-tidal CO_2	Both doses provide adequate labor analgesia, and are associated with measurable side effects
Norris *et al.*, 1994, US[183]	–	1022 In-patients admitted for vaginal delivery Epidural (0%, mean 27.3 y ± 0.3) CSE (0%, mean 28.4 y ± 0.3) General or spinal anesthesia only (0%, mean 26.5 y ± 0.7)	• Epidural (400) • CSE with either meperidine or sufentanil (506) • General or spinal anesthesia only (98) 358 Patients who received CSE received IT sufentanil	Major anesthetic complications	CSE anesthesia is a safe and effective alternative to epidural blockades
O'Keefe and Rich, 1996, US[82]	–	30 In-patients undergoing labor (0%, age not specified)	• Bupivacaine plus sufentanil (30)	Quality and duration of pain relief	The study solution produced rapid pain relief that may be a valuable option for laboring women
Oremus *et al.*, 2009, Croatia[83]	–	40 Patients scheduled for surgical hip fracture repair (gender not specified; range 71-91 y)	• Levobupivacaine • Levobupivacaine plus sufentanil and glucose	Block quality; hemodynamic stability	The addition of glucose and sufentanil provided equivalent spinal analgesia with greater hemodynamic stability when compared to levobupivacaine alone
Ortner *et al.*, 2010, Austria[84]	Two-phase, double-blind, randomized and prospective study	115 In-patients undergoing analgesia Sufentanil (0%, mean 28.8 y ± 5.9) Ropivacaine (0%, mean 28.8 y ± 4.9) Ropivacaine plus sufentanil 1.6 mcg (0%, mean 29.9 y ± 3.8) Ropivacaine plus sufentanil 2.2 mcg (0%, mean 28.2 y ± 4.1)	• Sufentanil (25) • Ropivacaine (30) • Ropivacaine plus sufentanil 1.6 mcg (30) • Ropivacaine plus sufentanil 2.2 mcg (30)	Effectiveness; motor block; sensory level; side effects	"Our results indicate that it is favorable to add sufentanil at a low dose of 1.6 mcg to ropivacaine for i.t. labor analgesia."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Palmer, 2001, US[138]	Case report	1 In-patient presenting for exploratory laparotomy and tumor debulking (0%, 47 y)	• Sufentanil (1)	Pain	A continuous IT sufentanil infusion may be considered for use in appropriate patients and circumstances, though greater experience is necessary
Parpaglioni *et al.*, 2009, Italy[85]	Prospective, double-blind, sequential allocation study	180 In-patients scheduled for elective caesarean section Levobupivacaine (0%, mean 33.82 y ± 4.3) Ropivacaine (0%, mean 34.83 y ± 3.69) Levobupivacaine and sufentanil (0%, mean 34.46 y ± 3.97) Ropivacaine and sufentanil (0%, mean 33.25 y ± 4.51)	• Levobupivacaine (45) • Ropivacaine (45) • Levobupivacaine and sufentanil (45) • Ropivacaine and sufentanil (45)	Onset time; effectiveness; duration of block	Adding sufentanil reduced the minimum local anesthetic dose of both local anesthetics, did not significantly affect potency ratio, and resulted in enhanced spinal anesthesia
Pellegrini, 1997, US[184]	Case report	1 In-patient undergoing labor (0%, 24 y)	• Sufentanil in combination with bupivacaine (1)	Pain	The CSE technique resulted in good analgesia with no increase in labor duration; "A word of caution is warranted because this is a report of only one case in which excellent analgesia was attained with no significant incidence of side effects. The results from this one case study were remarkable and may not be completely achieved with every case."
Pham *et al.*, 1996, US[86]	Randomized, double-blind study	40 In-patients undergoing early labor IT sufentanil (0%, mean 30.1 y ± 5.1) Epidural bupivacaine (0%, mean 33.0 y ± 3.4)	• IT sufentanil plus saline epidural (20) • IT saline plus bupivacaine epidural (20)	Hemodynamic changes; side effects	There were no significant hemodynamic changes with either method; both appear to provide effective pain relief, but should monitor maternal blood pressure

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Qian *et al.*, 2008, China[87]	Randomized trial	80 In-patients undergoing elective caesarean delivery Ropivacaine plus sufentanil (0%, mean 28.6 y ± 3.2) Ropivacaine (0%, mean 29.9 y ± 2.8)	• Ropivacaine plus sufentanil (40) • Ropivacaine (40)	Hypotension; nausea; duration of analgesia	Adding sufentanil to ropivacaine produced effective spinal anesthesia with significantly less hypotension, vomiting and shivering, as well as a shorter duration of motor blockade and longer-lasting analgesia than ropivacaine alone
Rane *et al.*, 2003, Sweden[185]	Double-blind, placebo-controlled randomized study	25 In-patients undergoing labor (0%, age not specified)	• IT adenosine plus sufentanil (13) • IT sufentanil (12)	Duration of analgesic effect; pain relief	"Adding 500 mcg of adenosine to 10 mcg of sufentanil could not provide any prolongation of labour pain relief."
Riley *et al.*, 2002, US[186]	–	73 In-patients undergoing labor (0%, age not specified)	IT sufentanil via: • Sprotte® spinal needle (36) • Gertie Marx® spinal needle (37)	Flow of cerebral spinal fluid through spinal needle; pain	The longer Gertie Marx® needle had a higher success rate for obtaining cerebral spinal fluid via CSE
Riley *et al.*, 1997, US[88]	–	45 In-patients in the first stage of labor Sufentanil 10 mcg/mL (0%, mean 31 y ± 7.7) Sufentanil 10 mcg/2 mL (0%, mean 31 y ± 3.9) Sufentanil 10 mcg/3 mL (0%, mean 32 y ± 3.9)	• Sufentanil 10 mcg/mL (15) • Sufentanil 10 mcg/2 mL (15) • Sufentanil 10 mcg/3 mL (15)	Pain; blood pressure; sensory changes	IT sufentanil provides rapid analgesia, but the volume of diluent was unimportant with regards to analgesia or side effects within the ranges tested
Riley *et al.*, 1997, US[187]	–	20 In-patients undergoing labor Bupivacaine (0%, mean 33 y ± 5) Sufentanil (0%, mean 28 y ± 6)	• Spinal bupivacaine for cesarean section (10) • Spinal sufentanil for labor analgesia (10)	Vasodilation	"In summary, we found that intrathecal sufentanil does not cause a clinically significant sympathectomy. The blood pressure decreases observed after intrathecal sufentanil administration are most likely due to pain relief."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Ross *et al.*, 2003, US[89]	–	28 In-patients undergoing labor Cocaine-positive (0%, mean 28.9 y ± 6.4) Control (0%, mean 22.3 y ± 4.0)	IT sufentanil in 2 patient populations: • Cocaine-positive (12) • Control (16)	Duration of analgesia; pain	"We conclude that intrathecal sufentanil produces a similar quality but shorter duration of analgesia in cocaine-abusing parturients compared with nonabusing parturients."
Sadeghi *et al.*, 2016, Iran[90]	Randomized, double-blinded clinical trial	60 Patients scheduled for elective lower limb orthopedic surgery Group 1 (100%, mean 34.4 y ± 10.8) Group 2 (100%, mean 35.7 y ± 8.3) Group 3 (100%, mean 40.3 y ± 9.3) Group 4 (100%, mean 36.8 y ± 5.8)	• Group 1: no history of opium use with IT bupivacaine plus saline (15) • Group 2: no history of opium use with IT bupivacaine plus sufentanil (15) • Group 3: history of chronic opium use with IT bupivacaine plus saline (15) • Group 4: history of chronic opium use with IT bupivacaine plus sufentanil (15)	Duration of sensory and motor blockade of spinal anesthesia; onset of sensory and motor blockade	"Addition of 5 mcg intrathecal sufentanil to hyperbaric bupivacaine in chronic opioid users lengthened the sensory and motor duration of blockade to be equivalent to blockade measured in non-addicts."
Said-Ahmed, 2006, Egypt[91]	Prospective randomized controlled study	60 Patients undergoing surgical repair of femur neck fracture (gender not specified, ≥70 y)	• Spinal bupivacaine plus fentanyl (20) • Spinal bupivacaine plus sufentanil (20) • Spinal bupivacaine (20)	Incidence of hypotension	"In this study bupivacaine minidose associated with either fentanyl or sufentanil provided satisfactory anesthesia and caused markedly less hypotension than plain bupivacaine, nearly eliminating the need for vasopressor support."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Said-Ahmed *et al.*, 2008, Egypt[188]	Randomized controlled double-blind clinical study	80 Patients undergoing repair of femur fracture (gender and age not specified)	Ropivacaine and sufentanil plus: • Normal saline (not reported) • Magnesium sulphate (not reported)	Onset and duration of sensory block; highest level of	"We conclude that intrathecal addition of magnesium sulphate (50 mg) to spinal anesthesia induced by ropivacaine-sufentanil significantly delayed the onset of both motor and sensory blockade but also prolonged the duration of anesthesia without additional side effects."
Salem *et al.*, 2007, Brazil[92]	–	52 In-patients undergoing labor CSE (0%, 20.6 y ± 4.1) Epidural (0%, mean 22.6 y ± 6.6)	• CSE with bupivacaine and IT sufentanil (28) • Epidural with ropivacaine and epidural sufentanil (24)	Side effects; sedation; pain; Apgar score	Sufentanil, administered via IT or epidural routes, had similar effects in the duration of labor after analgesia and newborn Apgar scores
Salimi *et al.*, 2014, Iran[189]	Randomized clinical trial	80 In-patients undergoing labor Sufentanil plus midazolam (0%, 27.7 y ± 3.2) Sufentanil (0%, mean 27.3 y ± 3.1)	• Sufentanil plus midazolam (40) • Sufentanil (40)	Duration of analgesia	IT midazolam could significantly enhance analgesia as an opioid adjunct
Scanlan and Backus, 1996, US[124]	Randomized, prospective, single center trial	36 In-patients undergoing spontaneous labor (0%, age not specified)	• IT sufentanil • Epidural bupivacaine	Incidence of surgical births; duration of labor; side effects	Epidural analgesia is an effective mode of pain relief
Schewe *et al.*, 2009, Germany[190]	Prospective, randomized study	132 In-patients scheduled for elective caesaran section IT (0%, mean 32 y ± 5) Epidural (0%, mean 33 y ± 5)	• IT sufentanil and bupivacaine (62) • Epidural sufentanil and ropivacaine (63)	Regional analgesic consumption; intraoperative and postoperative pain	"In parturients undergoing elective caesarean section, postoperative use of epidural ropivacaine via patient-controlled epidural analgesia is similar after spinal and epidural anaesthesia. Spinal anaesthesia is, however, accompanied with less postoperative pain, use of additional analgesics and side-effects."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Seemann *et al.*, 2012, US[93]	Archival (retrospective) study	97 Out-patients in a tertiary pain management program (45.4%, mean 58.77 y ± 14.88)	• IT sufentanil pump (49) • IT fentanyl pump (48) 37 of the patients initially receiving IT fentanyl were switched to sufentanil	Pain, patient satisfaction	Fentanyl and sufentanil may be effective alternatives to morphine in intrathecal delivery devices; sufentanil was found to be marginally more effective and more patients receiving sufentanil reported being satisfied with their care
Sia, 2000, Singapore[191]	Randomized, double-blinded, controlled study	48 In-patients undergoing labor (0%, age not specified)	IT sufentanil and bupivacaine plus: • Clonidine 0 mcg (16) • Clonidine 15 mcg (16) • Clonidine 30 mcg (16)	Duration of analgesia; blood pressure; motor and sensory block; sedation	The optimal dose of clonidine to enhance sufentanil-bupivacaine is 15 mcg
Sia *et al.*, 1999, Singapore[94]	Randomized, double-blinded, controlled study	42 In-patients in established labor Sufentanil 10 mcg plus bupivacaine 2.5 mg (0%, mean 27.0 y ± 4.83) Sufentanil 5 mcg plus bupivacaine 1.24 mg (0%, mean 28.3 y ± 4.72)	• Sufentanil 10 mcg plus bupivacaine 2.5 mg (21) • Sufentanil 5 mcg plus bupivacaine 1.24 mg (21)	Hypotension; analgesic effectiveness and duration	While the degree of analgesia was comparable, the larger dose showed superiority for a faster onset of action and a longer duration of analgesia
Sia *et al.*, 1998, Singapore[95]	Controlled, double-blind prospective trial	50 In-patients undergoing labor Sufentanil (0%, mean 27.5 y ± 4.9) Sufentanil plus bupivacaine (0%, mean 28.2 y ± 4.6)	• Sufentanil (25) • Sufentanil plus bupivacaine (25)	Incidence of hypotension; pain; criteria for walking	"The quality of analgesia in all subjects in the study was excellent. Side effects were more common in the IT sufentanil-bupivacaine combination group."
Sortino *et al.*, 2009, Italy[96]	–	30 In-patients undergoing labor (0%, age not specified)	• Sufentanil 3-6 mcg (30)	Fetal heart rate; efficacy and duration of analgesia; side effects	"Reduction of the dose of sufentanil during intrathecal analgesia seems to be effective for pain without developing non reassuring fetal heart traces."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Spaas *et al.*, 2009, Belgium[192]	Prospective, randomized, double-blinded study	90 In-patients undergoing knee arthroscopy (gender and age not specified)	• General anesthesia (30) • Bupivacaine plus sufentanil (30) • Lidocaine plus sufentanil (30)	Postoperative analgesia; onset and recovery of motor and sensory function; voiding; ambulation and discharge times	Patients receiving IT anesthesia for knee arthroscopy were discharged sooner with lidocaine than with bupivacaine
Standl *et al.*, 2001, Germany[97]	Prospective, randomized, double-blind, placebo-controlled	90 In-patients undergoing elective lower limb surgery Sufentanil (35%, mean 64 y ± 16) Bupivacaine (60%, mean 57 y ± 17) Mixture (40%, mean 59 y ± 18) Placebo (55%, mean 61 y ± 17) Sufentanil part 2 (50%, mean 67 y ± 14)	• Sufentanil (20) • Bupivacaine (20) • Mixture of sufentanil and bupivacaine (20) • Placebo (20) • Sufentanil part 2 (10)	Pain relief; motor block; hemodynamic and respiratory response	"Sufentanil injected through microspinal catheters provided profound pain relief without impairing motor function when compared with bupivacaine. However, close monitoring remains mandatory in this setting."
Stocche *et al.*, 2001, Brazil[193]	Prospective, randomized and blind study	30 In-patients undergoing labor Sufentanil (0%, mean 22.7 y ± 6.3) Bupivacaine (0%, mean 22.5 y ± 7.4)	• Sufentanil (15) • Bupivacaine (15)	Cortisol (CPC) and oxytocin (OPC) plasma concentrations; pain	"In the conditions of this study, epidural bupivacaine analgesia was associated to stable plasma cortisol and oxytocin concentrations. Conversely, intrathecal sufentanil promoted a more intense analgesia and decreased OPC and CPC."
Stocche *et al.*, 2001, Brazil[194]	Randomized, open-label	30 In-patients undergoing labor Sufentanil (0%, mean 22.7 y ± 6.3) Bupivacaine (0%, mean 22.5 y ± 7.4)	• Sufentanil (15) • Bupivacaine (15)	Release of oxytocin and cortisol; analgesia effectiveness	"Intrathecal sufentanil analgesia decreases plasma concentrations of oxytocin and cortisol in women with labor pain during the first stage of labor, but epidural bupivacaine only reduced the cortisol concentration."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Sun *et al.*, 2011, China[98]	Prospective double-blind and randomized controlled trial	144 In-patients undergoing cesarean delivery (0%, age not specified)	Ropivacaine and dextrose admixture plus: • Control (36) • Sufentanil 2.5 mcg (36) • Sufentanil 5.0 mcg (36) • Sufentanil 7.5 mcg (36)	Pain; duration of complete analgesia; effectiveness of anesthesia; duration and effectiveness of motor block	"In conclusion, the addition of 5 mcg sufentanil to 11.25 mg ropivacaine appears to be optimal, as it increases the efficacy of spinal analgesia without increasing the incidence of side effects."
Swenson *et al.*, 1995, US[99]	Randomized, double-blind study.	15 In-patients undergoing lower abdominal surgery Sufentanil (0%, mean 38.2 y ± 9.6) Control (0%, mean 34.0 y ± 4.5)	• Sufentanil (6) • Control (9)	End-tidal isoflurane concentration	"Prior administration of intrathecal sufentanil significantly decreases the isoflurane requirement in surgical patients, in addition to its previously demonstrated rapid onset and receptor efficacy."
Swenson *et al.*, 1994, US[139]	Retrospective examination	10 In-patients undergoing cardiopulmonary bypass surgery (80%, mean 51 y ± 12.9)	• Sufentanil plus morphine (10)	Systolic blood pressure; end-tidal isoflurane concentration; time to extubation	The combination of sufentanil and morphine provided stable hemodynamics and allowed early extubation in most patients; controlled prospective studies are needed to determine whether this combination offers advantages over existing methods and to determine optimal intrathecal sufentanil dose
Tebaldi *et al.*, 2008, Brazil[195]	Randomized, prospective study	22 In-patients undergoing labor Hyperbaric bupivacaine (0%, mean 23 y ± 3) Isobaric bupivacaine (0%, mean 27 y ± 8)	IT sufentanil and clonidine plus: • Hyperbaric bupivacaine (11) • Isobaric bupivacaine (11)	Quality of analgesia; mean arterial pressure; side effects	"Under the conditions of the present study, the association of a small dose of clonidine (30 mcg) with sufentanil caused a higher incidence of hypotension when the isobaric solution of the local anesthetic was used. For all other side effects, both hyperbaric and isobaric solutions showed similar behavior."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Tian *et al.*, 2013, China[100]	Controlled, prospective clinical trial	80 In-patients undergoing labor Sufentanil (0%, mean 28.51 y ± 2.24) Control (0%, mean 28.21 y ± 2.26)	• Sufentanil (40) • Control (40)	Intraparietal temperature, VAS score during labor	Continuous sufentanil spinal labor anesthesia is safe and effective, though associated with increased incidence of maternal fever; future studies should be conducted to investigate the pathogenesis and prognosis of the maternal fever
Troisi *et al.*, 2012, Italy[196]	Randomized study	40 Out-patients undergoing elective anorectal surgery (gender and age not specified)	Sufentanil plus: • Prilocaine (20) • Bupivacaine (20)	Intraoperative outcomes; mean recovery; discharge time; postoperative pain; urinary retention	"This study demonstrates the superiority of the combination of low-dose hyperbaric prilocaine and sufentanyl for spinal anaesthesia in ambulatory anorectal surgery. It is an excellent alternative to bupivacaine because of faster attainment and resolution block, greater haemodynamic stability, earlier deambulation, reduced risk of urinary retention and early patients discharge."
Van de Velde *et al.*, 2007, Belgium[197]	Double-blind, randomized trial	450 In-patients undergoing labor Bupivacaine (0%, mean 29.0 y ± 5.2) Ropivacaine (0%, mean 30.2 y ± 4.5) Levobupivacaine (0%, mean 29.9 y ± 4.3)	Intrathecal sufentanil plus: • Bupivacaine (145) • Ropivacaine (142) • Levobupivacaine (146)	Pain; sensory and motor block; neonatal outcomes	"This full dose-response study suggests that ropivacaine and levobupivacaine are of similar potency, whereas bupivacaine is more potent than both other drugs."
Van de Velde *et al.*, 1999, Belgium[101]	Randomized, prospective, clinical trial	110 In-patients undergoing labor Epidural (0%, mean 30 y ± 7.4) CSE (0%, mean 29 y ± 7.4)	Combination of bupivacaine, epinephrine, and sufentanil via: • Epidural (55) • CSE (55)	Heart rate; blood pressure; pain; onset time	"We conclude that CSE analgesia results in excellent pain relief during labor with immediate gratification as compared to epidural analgesia."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Van de Velde *et al.*, 2004, Belgium[140]	Double-blind, double placebo-controlled trial	300 In-patients undergoing analgesia (0%, range 26-33 y)	• Epidural bupivacaine, sufentanil, and epinephrine plus spinal saline (100) • Spinal sufentanil, epinephrine, and bupivacaine plus epidural saline (100) • Spinal sufentanil plus epidural saline (100)	Occurrence of new non-reassuring fetal heart rate abnormalities or uterine hyperactivity	"The present data corroborate previous recommendations of caution when performing CSE using a large dose (7.5 mcg or more) of spinal sufentanil because of the risk of uterine hyperactivity and [fetal heart rate] abnormalities."
Veena *et al.*, 2010, India[102]	Randomized clinical trial	60 In-patients undergoing caesarean section Bupivacaine (0%, mean 27.4 y ± 4.49) Bupivacaine plus sufentanil (0%, mean 25.65 y ± 2.5) Bupivacaine plus morphine (0%, mean 25.75 y ± 3.19)	IT bupivacaine plus: • Control (20) • Sufentanil (20) • Morphine (20)	Analgesia duration and onset; need for rescue analgesics; side effects	"Addition of small doses of sufentanil or morphine to intrathecal bupivacaine is suitable for use in caesarean section, providing rapid onset and prolonged analgesia but with some side effects like pruritis and somnolence."
Vercauteren *et al.*, 1998, Belgium[103]	Double-blind, randomized trial	98 In-patients scheduled for elective or semi-urgent cesarean section (0%, range 21-39 y)	IT sufentanil plus: • Plain bupivacaine (48) • Hyperbaric bupivacaine (49)	Quality of block; incidence of side effects	"A small dose of hyperbaric bupivacaine 0.5% combined with sufentanil used intrathecally during cesarean section offered a more reliable cephalad spread of the spinal block than the glucose-free combination, which was reflected in a lower incidence of hypotension and nausea."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Vercauteren *et al.*, 1998, Belgium[125]	Randomized, double-blind	45 In-patients undergoing major orthopaedic surgery under spinal anesthesia Sufentanil (33.3%, range 65-83 y) Bupivacaine (7.14%, range 65-82 y) Mixture (20%, range 65-84 y)	• Sufentanil (15) • Bupivacaine (14) • Mixture (15)	Pain, drug consumption, motor block, sedation, side effects, blood pressure, heart rate	Using solo sufentanil was associated with more nausea and vomiting than solo bupivacaine, and while the mixture provided advantages in analgesic quality and dose requirements, there was a high incidence of nausea and vomiting; further studies are needed to test other drug combinations
Vercauteren *et al.*, 2001, Belgium[198]	Randomized, double blinded study	75 In-patients undergoing labor Levobupivacaine (0%, mean 29 y ± 5) Bupivacaine (0%, mean 30 y ± 5)	IT sufentanil and epinephrine plus: • Levobupivacaine (37) • Bupivacaine (38)	Duration and quality of analgesia; side effects	"Intrathecal levobupivacaine has a similar clinical profile as racemic bupivacaine, but at equal doses it produced less motor block."
Vercauteren *et al.*, 2001, Belgium[199]	–	45 In-patients in early spontaneous labor Epinephrine (0%, mean 29.0 y ± 7) Control (0%, mean 29.5 y ± 6)	IT bupivacaine and sufentanil plus: • Epinephrine (23) • Control (22)	Pain; motor block; obstetric and neonatal outcomes	"It was concluded that epinephrine in a dose as low as 2.25 mcg significantly prolonged the duration of intrathecal analgesia of bupivacaine-sufentanil by 15 minutes."
Vercauteren *et al.*, 1997, Belgium[104]	Randomized double-blind	75 In-patients undergoing labor Sufentanil (0%, mean 29.3 y ± 4.6) Sufentanil plus bupivacaine (0%, mean 29.2 y ± 4.5) Sufentanil plus bupivacaine and epinephrine (0%, mean 27.4 y ± 3.7)	• Sufentanil (25) • Sufentanil plus bupivacaine (25) • Sufentanil plus bupivacaine and epinephrine (25) The standard epidural combination was sufentanil, bupivacaine, and epinephrine	Analgesia onset; duration; side effects; total drug requirement	"It is concluded that intrathecal injection of the standard epidural mixture offers effective and long-lasting analgesia. This may avoid side-effects and complications, manipulations of drugs with the risk for contamination, spilling of drugs and loss of time."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Vercauteren *et al.*, 2009, Belgium[200]	Randomized, double-blind study	100 In-patients undergoing elective caesarean section (0%, age not specified)	Sufentanil plus • Bupivacaine (50) • Levobupivacaine (50)	Motor block; rate of epidural supplementation; hemodynamic outcomes; neonatal outcomes	"Low dose spinal anesthesia allows the post-anesthetic care unit to be bypassed by caesarean section patients, enabling fast initiation of breast feeding. The use of levobupivacaine may induce less profound motor block while recovery is faster than with bupivacaine."
Vernis *et al.*, 2004, France[126]	Prospective, blinded, randomized study	113 In-patients in active labor CSE (0%, mean 27.6 y ± 4.2) Epidural (0%, mean 28.8 y ± 4.8)	• CSE: IT bupivacaine plus sufentanil (54) • Epidural: bupivacaine, epinephrine, and sufentanil (59)	Pain; motor block; use of additional analgesia; side effects; satisfaction	"The combined spinal-epidural technique provided more effective analgesia during labour than epidural analgesia alone but offered no other advantage. It induced more adverse effects and this should be considered before routinely using the combined spinal-epidural technique."
Viscomi *et al.*, 1996, US[105]	Open-label, nonrandomized trial	32 In-patients in spontaneous active labor (0%, mean 30.1 y ± 4.6)	Spinal sufentanil and bupivacaine via: • Single shot (15) • Double-needle (17)	Effective duration; side effects; motor block	"In parturients with cervical dilation of 7 cm or more, subarachnoid Sufentanil-bupivacaine produces rapid analgesia with an effective duration of approximately 130 minutes."
Viscomi *et al.*, 1997, US[141]	Prospective cohort observational study	41 In-patients undergoing labor Early labor (0%, mean 28.7 y ± 5.2) Advanced labor (0%, mean 30.5 y ± 4.0)	IT sufentanil and bupivacaine in: • Early labor (18) • Advanced labor (23)	Duration of effective analgesia; labor outcome; Apgar scores	"In summary, the duration of analgesia using intrathecal sufentanil is significantly shorter when administered in advanced labor compared with administration in early labor. Future comparisons of labor analgesic techniques should closely control for this difference."
Vosoughian, 2017, Iran[106]	–	60 In-patients undergoing hip surgery (gender and age not specified)	• Bupivacaine 5 mg plus sufentanil 10 mcg • Bupivacaine 10 mg plus sufentanil 5 mcg • Bupivacaine 15 mg	Hypotension	"Adding sufentanil as an adjuvant and decreasing the dose of intrathecal hyperbaric bupivacaine may help maintain a stable hemodynamic during lower limb surgery in the elderly."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Vyas *et al.*, 2010, India[107]	Randomized prospective double blind	60 In-patients undergoing elective cesarean section Sufentanil (0%, mean 27.33 y ± 3.99) Control (0%, mean 27.13 y ± 4.30)	IT bupivacaine plus: • Sufentanil (30) • Control (30)	Sensory and motor block characteristics; intraoperative hemodynamic variables; postoperative analgesia; Apgar score	"The addition of Sufentanil (5 mcg) intrathecally provides improved postoperative analgesia and haemodynamic stability with minimal side effects."
Wang *et al.*, 2015, China[201]	Randomized, double-blinded, placebo-controlled trial	60 In-patients undergoing transurethral resection of the prostate for benign prostatic hypertrophy Oxycodone (100%, mean 67.4 y ± 10.8) Placebo (100%, mean 69.1 y ± 8.3)	IT sufentanil and bupivacaine plus: • IV oxycodone (30) • Placebo (30)	Postoperative pain; analgesic requirements; side effects	"Preemptive intravenous oxycodone was an efficient and safe method to decrease postoperative pain and reduce tramadol analgesia in patients under low-dose dilute bupivacaine spinal anesthesia combined with intrathecal sufentanil."
Wang *et al.*, 2014, China[202]	Prospective, randomized, double-blind study	40 In-patients undergoing cesarean delivery Low dose (0%, mean 28.1 y ± 4.5) Conventional dose (0%, mean 28.1 y ± 4.8)	IT sufentanil plus: • Low dose bupivacaine followed by epidural lidocaine (20) • Conventional dose bupivacaine followed by epidural saline (20)	Time to T6 block; time to delivery; need for intraoperative epidural supplementation	"Intrathecal bupivacaine 5 mg with immediate 2% epidural lidocaine 5 mL provided comparable onset and efficacy of anesthesia as bupivacaine 10 mg with immediate epidural normal saline 5 mL for cesarean delivery."
Wang *et al.*, 2007, China[108]	Double-blind, randomized, prospective study	90 In-patients undergoing elective Caesarean section (0%, range 21-38 y)	IT bupivacaine plus: • IT sufentanil (30) • IV sufentanil (30) • Control (30)	Intraoperative pain	"Our result suggests that the IT combination of bupivacaine with a small dose of sufentanil is an appropriate choice for Caesarean section under spinal anaesthesia."
Waxler *et al.*, 2004, US[109]	Prospective, randomized, double-blind study	49 In-patients undergoing rectal surgery Lidocaine (66.6%, mean 42 y ± 13) Lidocaine plus sufentanil (82.1%, mean 39 y ± 13)	• IT lidocaine (21) • IT lidocaine plus sufentanil (28)	Recovery time; time to ambulation; time to discharge; adverse events	"IT lidocaine (15 mg) and sufentanil resulted in a shorter time to ambulation compared to [intrathecal] lidocaine (50 mg) alone and provided excellent anesthesia despite its disadvantage of pruritus."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Wong *et al.*, 2000, US[110]	Prospective, randomized, blinded study	170 In-patients undergoing labor induction Control (0%, mean 33 y ± 5) Sufentanil 2.5 mcg (0%, mean 35 y ± 5) Sufentanil 5 mcg (0%, mean 33 y ± 4) Sufentanil 7.5 mcg (0%, mean 33 y ± 4) Sufentanil 10 mcg (0%, mean 34 y ± 4)	IT bupivacaine combined with: • Control (34) • Sufentanil 2.5 mcg (34) • Sufentanil 5 mcg (34) • Sufentanil 7.5 mcg (34) • Sufentanil 10 mcg (34)	Analgesia effectiveness; time to rescue dose; side effects	"In conclusion, this study has shown that 2.5 mcg sufentanil combined with 2.5 mg bupivacaine provides satisfactory labor analgesia in parous patients who underwent induced labor and is associated with a lower incidence of nausea and vomiting and less severe pruritus that is 7.5 or 10.0 mcg. Sufentanil doses higher than 2.5 mcg provide no added benefit."
Xiao *et al.*, 2016, China[203]	Prospective, double-blinded, placebo-controlled trial	60 In-patients scheduled for elective cesarean delivery Magnesium (0%, mean 25 y ± 3) Control (0%, mean 26 y ± 3)	IT bupivacaine and sufentanil plus: • Magnesium sulfate (30) • Control (30)	Time to onset; duration of analgesia; subjective pain; arterial pressure; side effects	"In parturients with severe pre-eclampsia undergoing caesarean delivery, the addition of intrathecal magnesium sulfate to low-dose of bupivacaine and sufentanil prolongs the duration of analgesia and reduces the postoperative analgesic requirements without additional side effects."
Xiao *et al.*, 2015, China[205]	Randomized, double-blinded, dose-ranging study	200 In-patients undergoing elective cesarean section Bupivacaine 4 mg (0%, mean 30 y ± 3) Bupivacaine 6 mg (0%, mean 29 y ± 4) Bupivacaine 8 mg (0%, mean 30 y ± 4) Bupivacaine 10 mg (0%, mean 31 y ± 4)	IT sufentanil plus: • Bupivacaine 4 mg (50) • Bupivacaine 6 mg (50) • Bupivacaine 8 mg (50) • Bupivacaine 10 mg (50)	Success or failure of spinal anesthesia	"Our study showed that the ED50 and ED95 of intrathecal bupivacaine for severely preeclamptic patients undergoing elective cesarean delivery was 5.67 mg and 8.82 mg, respectively. In addition, decreasing the dose of intrathecal bupivacaine could reduce the incidence of maternal hypotension."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Xiao *et al.*, 2015, China[206]	Randomized, double-blinded, dose-ranging study	75 In-patients undergoing cesarean delivery with scarred uterus Ropivacaine 6 mg (0%, mean 32.3 y ± 5.2) Ropivacaine 8 mg (0%, mean 29.5 y ± 3.1) Ropivacaine 10 mg (0%, mean 29.3 y ± 3.3) Ropivacaine 12 mg (0%, mean 31.1 y ± 4.5) Ropivacaine 14 mg (0%, mean 32.5 y ± 5.2)	IT sufentanil plus: • Ropivacaine 6 mg (15) • Ropivacaine 8 mg (15) • Ropivacaine 10 mg (15) • Ropivacaine 12 mg (15) • Ropivacaine 14 mg (15)	Success or failure of spinal anesthesia	"When a CSEA [combined spinal-epidural anesthesia] technique use in patients with scarred uterus for an elective cesarean delivery, the ED50 and ED95 of intrathecal hyperbaric ropivacaine along with 5 mcg sufentanil were 8.28 mg and 12.24 mg, respectively. In addition, this local anesthetic is unsuitable for emergent cesarean delivery, but it has advantages for ambulatory patients."
Xiao *et al.*, 2017, China[204]	Prospective, double blinded, randomized, dose-response trial	60 In-patients undergoing cesarean delivery Magnesium (0%, mean 25 y ± 3) Control (0%, mean 26 y ± 3)	IT bupivacaine and sufentanil plus: • Magnesium sulfate (30) • Control (30)	Effective anesthesia; subjective pain; hypotension; sensory and motor block; side effects	"Intrathecal magnesium sulfate (50 mg) did not reduce the dose requirement of intrathecal bupivacaine, but can extend the duration of spinal anesthesia with no obvious additional side effects."
Yektaz, 2011, Turkey[142]	–	180 Patients undergoing spinal anesthesia (gender and age not specified)	IT bupivacaine 15 mg plus: • Control (20) • Bupivacaine 2.5 mg (20) • Ketamine (20) • Fentanyl (20) • Sufentanil (20) • Dexmedetomidine (20) • Neostigmine (20) • Midazolam (20) • Droperidol (20)	Intraoperative and postoperative 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…were not performed. Further studies should be performed to evaluate those factors."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Zheng *et al.*, 2015, China[207]	Prospective, randomized, double-blind investigation	80 In-patients undergoing elective cesarean section Ropivacaine 7.5 mg (0%, mean 28 y ± 3) Ropivacaine 9.0 mg (0%, mean 28 y ± 4) Ropivacaine 10.5 mg (0%, mean 29 y ± 4) Ropivacaine 12 mg (0%, mean 30 y ± 5)	IT sufentanil plus: • Ropivacaine 7.5 mg (20) • Ropivacaine 9.0 mg (20) • Ropivacaine 10.5 mg (20) • Ropivacaine 12 mg (20)	Analgesic effectiveness; sensory and motor block; subjective pain; side effects	"The results show that the ED95 of intrathecal hyperbaric ropivacaine coadministered with sufentanil 5 mcg for cesarean delivery was 11.4 mg."

Abbreviations: "–", not mentioned; CSE, combined spinal-epidural; ED, effective dose; ECV, external cephalic version; ESWL, extracorporeal shockwave lithotripsy; FHT, fetal heart tracing; IT, intrathecal; IV, intravenous; PCEA, patient-controlled epidural analgesia; ROA, route of administration; TURP, transurethral resection of the prostate; VAS, visual analogue scale.

[a]As defined by authors.

Appendix 3.1. Survey instrument for professional medical associations

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

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

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

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

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

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

1. How familiar are you with the following terms?

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

2. Do you prescribe or administer sufentanil citrate to your patients?

   - o Yes
   - o No

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

   - o Intrathecal injection
   - o None of the above

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

   - o Severe pain
   - o Surgical anesthesia
   - o Other (please explain) _____

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

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

6. I use compounded sufentanil citrate because: (check all that apply)

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

7. Do you stock non-patient-specific compounded sufentanil citrate at your practice?

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

8. I obtain compounded sufentanil citrate from the following: (check all that apply)

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

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

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

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

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

Appendix 3.2. Survey instrument for Ambulatory Surgery Center Association

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

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

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

Thank you,

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

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

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

1. How familiar are you with the following terms?

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

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

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

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

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

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

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

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

Appendix 4. Survey distribution to professional associations

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

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

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

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