Summary Report

Clonidine hydrochloride

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

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

INTRODUCTION

This report was created to assist the US Food and Drug Administration (FDA) in its evaluation of the use of clonidine hydrochloride (clonidine HCl; UNII code: W76I6XXF06), 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 clonidine HCl is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted, and health care practitioners were consulted to identify how clonidine HCl has been used historically and currently.[1-3] Assessments 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 clonidine HCl and thereby assist the FDA in determining whether there is a need to include this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Clonidine HCl was nominated for inclusion on the 503B Bulks List by Fagron, the Outsourcing Facilities Association (OFA), Pentec Health, and the Specialty Sterile Pharmaceutical Society (SSPS). Clonidine HCl was nominated for use in combination with additional Active Pharmaceutical Ingredients (APIs) (refer to Table 8).

Clonidine HCl was nominated for the treatment of opioid-induced hyperalgesia via a 1- to 1.5-mg/mL injection. Clonidine HCl was also nominated to treat severe pain (such as neuropathic pain and birthing pain) as a solution for intrathecal injection in concentrations ranging from 1 to 10,000 mcg/mL. In addition, clonidine HCl was nominated for the treatment of an unknown medical condition, but clonidine is generally used to treat pain as a topical cream with a strength based on the prescriber's request (therapeutic dose 0.2%).

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of clonidine HCl.[6-26]

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

- The FDA-approved medications that contain clonidine HCl (tablets and patches) are not suitable for making sterile injection products due to the excipients.
- Individual finished products have considerable variance in the final API. The use of finished product has the potential to introduce unacceptable inaccuracies into the compounded medication.
- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Practitioners often prescribe doses that require higher strengths or concentrations than those available in FDA-approved products or use in combination with other medications.
- If the FDA-approved, single-use-only vials were used for compounding and the vial was punctured a second time, or its 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 numbers of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100% potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- In order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of clonidine HCl products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in the 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: the US, Canada, European Union (EU), the 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, the 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 clonidine HCl; name variations of clonidine HCl were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; and approval date. Information was recorded only for products with strengths, forms, and/or ROAs 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 clonidine HCl. The availability of OTC products (yes/no) in the US and their ROAs 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 3 concepts: clonidine HCl; injectable, intrathecal, or topical administration or form; and therapeutic or preventative use (refer to Appendix 1 for full search strategies). Results were limited to human studies in the English language. Searches were conducted on September 10, 2020. In addition, the ECRI Guidelines Trust® repository was searched on September 10, 2020, for clinical practice

guidelines that recommended the use of clonidine HCl and provided sufficient information on its dosing and administration.

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

Study selection

Studies were included if they used clonidine HCl 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. Studies were excluded if they were written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, preclinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if clonidine HCl was used as an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; an unspecified dosage form or ROA; used for an indication that was not nominated; mentioned briefly as a previously failed treatment or rescue treatment; or clonidine HCl was not used clinically. Studies in which clonidine HCl was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological, 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 clonidine HCl; setting; total number of patients; number of patients who received clonidine HCl; patient population; indication for the use of clonidine HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of clonidine HCl in a combination product; use and formulation of clonidine HCl in a compounded product; use of clonidine HCl compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances clonidine HCl was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use clonidine HCl. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided verbal informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase

compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (refer to Appendix 3 for complete survey and *Results of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

Survey

A survey was distributed to the members of professional medical associations to determine the use of clonidine HCl in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 3 for the complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted for project Year 3 surveys.

The survey was posted on the project website, and the survey link was distributed to the associations that agreed to participate (refer to Appendix 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 US 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

- Clonidine HCl is available as an FDA-approved product in the nominated dosage form and ROA. Clonidine HCl is also available as an FDA-approved oral extended-release suspension, extended-release tablet, tablet, and transdermal system.
- Clonidine HCl is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for clonidine HCl.
- Clonidine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Ireland, Latvia, New Zealand, and the UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Clonidine HCl	0.1-0.5 mg/mL	Injectable	Injection	Prescription	10/02/1996

[a]Source: US FDA. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*.
[b]If there are multiple approval dates and/or multiple strengths, then the earliest date is 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]
Clonidine HCl	0.15 mg/mL	Solution	Injection, intramuscular, intrathecal, intravenous, subcutaneous	Abu Dhabi	Active	—
				Australia	S4 – Prescription-only medicine	9/26/1991
				Belgium	Medical prescription	8/13/1972
				Ireland	Prescription-only (non-renewable)	4/01/1979
				Latvia	Prescription	10/31/2007
				New Zealand	Prescription	1/18/1973
				UK	Prescription-only medication	5/10/2006

Abbreviation: —, not provided.

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

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

Results of literature review

Study selection

Database searches yielded 4745 references; 9 additional references were identified from searching the ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 3405 titles and abstracts were screened. After screening, the full text of 1283 articles was reviewed. Initially, 490 studies were included; after multiple reports of the same study were merged, there were 470 included studies. A total of 793 studies were excluded for the following reasons: wrong study design (648 studies); FDA-approved dosage form or ROA (61); clonidine HCl only mentioned briefly (21); indication not nominated (15); clonidine HCl not used clinically (11); dosage form, ROA, or combination not nominated (11); unspecified dosage form or ROA (9); article retracted (5); duplicate study (4); unable to obtain full text (3); wrong substance (3); language other than English (2).

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

Characteristics of included studies

The 470 included studies were published between 1987 and 2020. There were 424 experimental studies, 19 observational studies, and 27 descriptive studies. The 470 studies were conducted in the following countries: Algeria, Australia, Belgium, Brazil, Canada, Chile, China, Croatia, Czech Republic, Denmark, Egypt, Estonia, Finland, France, Germany, Greece, India, Indonesia, Iran, Ireland, Israel, Italy, Japan, Lebanon, Mexico, Morocco, the Netherlands, Republic of Kosovo, Romania, Serbia and Montenegro, Singapore, Slovenia, South Korea, Spain, Sweden, Switzerland, Tunisia, Turkey, the UK, and the US.

A total of 44,537 patients participated in the 470 included studies. The number of patients in each study ranged from 6 to 328.

Outcome measures differed among the included studies and included: agitation, analgesia duration, analgesia efficacy, analgesia requirements, bispectral index, block characteristics, blood gases, carbon dioxide production, cutaneous silent period, cytometric bead array, electroencephalogram (EEG) power spectral analysis, functional status, hemodynamic parameters, hemodynamic stability, hyperalgesia, intraocular pressure, length of stay, neonatal Apgar score, occurrence of heavy bleeding, onset of analgesia, onset of blocks, opioid-induced myoclonus, oxygen consumption, pain scores, patient satisfaction, pulse oximetry, recovery times, sedation, shivering, side effects.

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

Use of clonidine HCl

In all studies, clonidine HCl was used for analgesia or anesthesia.

Clonidine HCl was received via infiltration by 95 patients. Clonidine HCl was administered in doses ranging from 0.5 mcg/kg to 6 mcg/kg or 150 mcg; the duration of treatment ranged from once to twice.

A total of 430 patients received clonidine HCl via intraarticular or periarticular injection. Clonidine HCl was administered in a one-time dose of 1 mcg/kg or in doses ranging from 80 to 150 mcg.

A total of 142 patients received clonidine HCl via intramuscular injection. Clonidine HCl was administered as a one-time dose ranging from 0.5 to 2 mcg/kg, or 25 to 300 mcg.

A total of 20 patients received clonidine HCl via intraperitoneal injection. Clonidine HCl was administered as a one-time dose of 1 mcg/kg.

A total of 5501 patients received clonidine HCl via intrathecal injection. Clonidine HCl was administered in doses ranging from 0.25 to 3 mcg/kg or 3.9 to 450 mcg; the duration of treatment ranged from 1 to 3 doses. Clonidine HCl was also administered in doses ranging from 5 to 1500 mcg/day, and the duration of treatment ranged from 3 months to 18 years.

A total of 2976 patients received clonidine HCl via intravenous injection. Clonidine HCl was administered in doses ranging from 0.25 to 60 mcg/kg or 30 to 600 mcg; the duration of treatment ranged from 1 to 5 times. Clonidine HCl was also administered as an infusion with doses ranging from 0.3 to 3 mcg/kg/hour or 7.5 mcg/hour; the duration of treatment was 4 hours to 90 days.

A total of 70 patients received clonidine HCl via irrigation administered as a one-time dose ranging from 150 to 250 mcg.

A total of 11,065 patients received clonidine HCl via perineural injection. Clonidine HCl was administered in doses ranging from 0.1 to 4 mcg/kg or 3.75 to 500 mcg; the duration of treatment ranged from 1 to 5 times. Clonidine HCl was also administered as an infusion with doses ranging from 0.2 to 2 mcg/kg/hour or 3 to 45 mcg/hour; the duration of treatment ranged from 48 hours to 9 days.

A total of 187 patients received clonidine HCL via subcutaneous injection. Clonidine HCl was administered as a one-time dose ranging from 1 to 2 mcg/kg or 10 to 150 mcg. Clonidine HCl was also administered in a dose of 300 mcg at a rate of 4 mL/hour for 48 hours.

A total of 182 patients received clonidine HCl via topical application. Clonidine HCl was administered as a one-time dose ranging from 200 to 500 mcg. Clonidine HCl was also administered in a dose of 3.9 mg/day or 3 times per day, and the duration of treatment ranged from 8 to 12 weeks.

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

Clonidine HCl was used as a compounded product but was not used in a combination product (refer to Tables 8-10).

In all studies, clonidine was used for analgesia or anesthesia. In 251 studies, the authors' concluding statement recommended the use of clonidine HCl via infiltration; intraarticular/periarticular, intramuscular, intraperitoneal, intrathecal, intravenous, perineural, or subcutaneous injection; irrigation; or topical administration.[6,20,27-276] In 77 studies, the authors did not recommend the use of clonidine HCl via infiltration; intramuscular, intrathecal, intravenous, periarticular, perineural, or subcutaneous injection; or topical administration.[277-352] In 52 studies, the authors' concluding statement was that further studies were necessary for the use of clonidine HCl via infiltration; intrathecal, intravenous, periarticular, perineural, or subcutaneous injection; or topical administration.[353-404] In 21 studies, the authors' concluding statement did not provide a conclusive recommendation regarding the use of clonidine HCl via intrathecal, intravenous, periarticular, perineural, or subcutaneous injection.[405-425] In 68 studies, the authors' conclusions did not address the use of clonidine HCl via intramuscular, intrathecal, intravenous, periarticular, or perineural injection.[426-493] There is 1 study protocol, but no results are available at this point in time.[494] Refer to Table 5 for a summary of authors' conclusions.

Pharmacology and historical use

Additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of clonidine HCl.

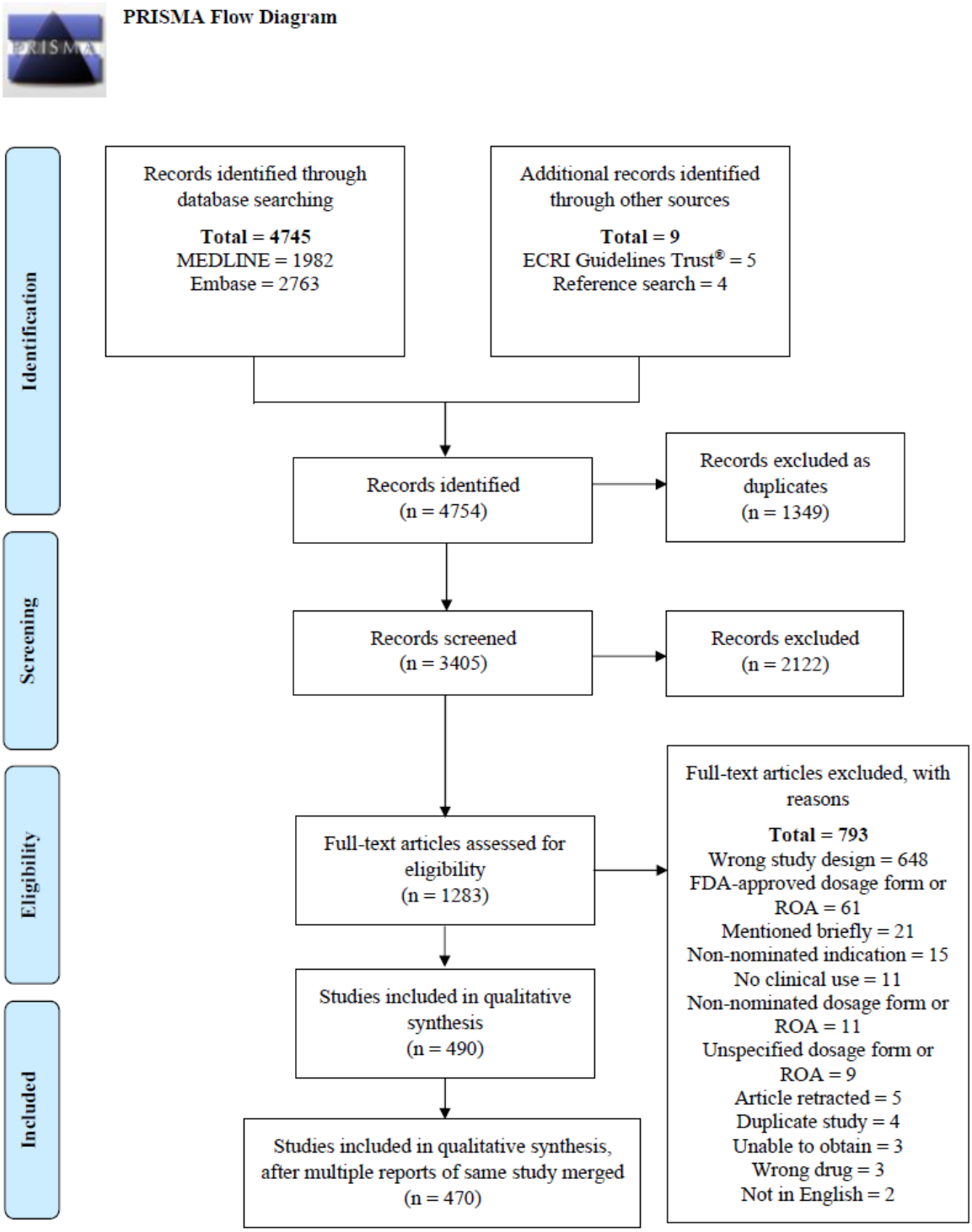
The recommended FDA indication for intrathecal drug therapy is moderate-to-severe trunk and limb pain and intractable pain that has been refractory to conservative treatment attempts. The Polyanalgesic Consensus Conference (PACC) noted that while there is interest in using intrathecal therapy to cover focal extremity pain, support in the literature is lacking, with only anecdotal reports.[495] 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.[495]

According to the PACC, intrathecal clonidine is usually administered to patients with neuropathic pain combined with an opioid, bupivacaine, and/or ziconotide, with the recommended starting dose of 20 to 100 mcg/day and a maximum dose of 600 mcg/day. The maximum concentration is 1000 mcg/mL. In their guidelines, the authors note that medications such as clonidine or baclofen are associated with significant withdrawal symptoms in cases of abrupt cessation or interruption of therapy. As a result, prescribers should prepare rescue strategies for this life-threatening situation.[495]

Despite the risks associated with the off-label use of intrathecal medications and compounded products (such as infusion system corrosion and device failure), it was suggested that "compounded medications were the de facto standard of care, and peer-reviewed literature exists to support the use of both on- and off-label medications."[495] An FDA safety communication from November 2018 advises caution and notes that compounded medicines "are not currently approved for use with implanted pumps for intrathecal infusion of pain medicine."[496] Potential safety issues associated with using a non-FDA-approved medication for intrathecal pump administration include pump failure, dosing errors, toxicity to the spinal cord and brain tissue, and the formation of granulomas at the catheter tip or infusion site.[496]

In the review conducted by the National Academies of Science Engineering and Medicine, its authors concluded that "there is insufficient evidence to suggest [the] effectiveness of topical clonidine to treat neuropathic pain conditions when applied to intact skin."[497]

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[76,117,165,169,172,173,194,205,207,211,257,353,372,379,385,399,426,439,445-447,450,451,453,463,475,493]	27
Observational[125-127,174,213,336,354,359,381,390,401-403,419,422,455,457,458,485]	19
Experimental[6,20,27-75,77-116,118-124,128-164,166-168,170,171,175-193,195-204,206,208-210,212,214-256,258-335,337-352,355-358,360-371,373-378,380,382-384,386-389,391-398,400,404-418,420,421,423-425,427-438,440-444,448,449,452,454,456,459-462,464-474,476-484,486-492,494]	424

Table 4. Number of studies by country

Country	Number of Studies
Algeria[124]	1
Australia[162,180,187,231,369,486]	6
Austria[132,149,256,293,295,367,412,425]	8
Belgium[85-88,107,128,157,232,233,262,272,290,323,332,428,443,461,481-483]	20
Brazil[28,43,44,63,103,104,139,156,158,215,283,296,326,338,343,362,413,417,460,469,480]	21
Canada[388]	1
Chile[75]	1
China[67,163,189,494]	4
Croatia[119]	1
Denmark[268,279,373,477]	4
Egypt[37,98,144,179,277,375]	6
Estonia[97]	1
Finland[177,185,193]	3
France[35,36,38,46,48-51,57-59,90,109-111,134,135,159-161,176,186,197,198,263,273,275,311,320,360,363,391,406,407,431-433,437,462]	39
Germany[56,129,131,152,344,350,378,392,404,418,454,490]	12
Greece[34,102,118,190,259,371,386,465]	8
India[20,30-33,39-42,45,47,52-55,62,70-73,78,80-83,91-93,105,112-114,120-123,130,136-138,141-143,146-148,150,151,153-155,166,167,181,188,191,195,196,199,201,202,209,210,212,214,217,219,220,224-229,234-239,244-248,250-252,255,258,264,266,269-271,276,278,280,284,289,292,304,305,313,314,316-319,321,322,325,329-331,333,335,339-342,345,346,348,356,361,368,393,396,398,408,423,424,427,430,438,456,459,470,473,474,478,479]	143
Indonesia[221]	1
Iran[133,222,223,351,376,377]	6
Ireland[168,328,365,472]	4
Israel[116]	1
Italy[64,66,68,69,79,89,170,171,192,337,366,374,441,442,444]	15
Japan[415]	1

Lebanon[27,145,182-184,267,288,466-468]	10
Mexico[349]	1
Morocco[178]	1
The Netherlands[260,261,302,327]	4
Republic of Kosova[108]	1
Romania[29,74]	2
Serbia and Montenegro[60]	1
Singapore[230]	1
Slovenia[421]	1
South Korea[208,395]	2
Spain[101,216,308,334,414]	5
Sweden[94-96,218,253,307,352,471]	8
Switzerland[61,106,249,287,291,299,300]	7
Tunisia[140,242,243,306,315,347,397,434]	8
Turkey[175,355,357,358,383,405]	6
United Kingdom (UK)[100,281,282,294,298,303,387,400,416,436]	10
United States (US)[6,65,76,77,84,99,115,117,125-127,164,165,169,172-174,194,200,203-207,211,213,240,241,254,257,265,274,285,286,297,301,309,310,312,324,336,353,354,359,364,370,372,379-382,384,385,389,390,394,399,401-403,409-411,419,422,426,429,435,439,440,445-453,455,457,458,463,464,475,476,484,485,487-489,491-493]	94
Multiple Countries • Czech Republic and the UK[420]	1
	Total US: 94 Total Non-US Countries: 376

Table 5. Summary of included studies

Refer to Appendix 2

Table 6. Dosage by indication – US

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Analgesia/anesthesia[6,65,76,77,84,99,115,117,125-127,164,165,169,172-174,194,200,203-207,211,213,240,241,254,257,265,274,285,286,297,301,309,310,312,324,336,353,354,359,364,370,372,379-382,384,385,389,390,394,399,401-403,409-411,419,422,426,429,435,439,440,445-453,455,457,458,463,464,475,476,484,485,487-489,491-493]	0.5 mcg/kg	0.5 mcg/kg/20 mL	—	Infiltration	Once
	1 mcg/kg	1 mcg/kg/30 mL	—	Intra-articular	Once
			Solution		
	0.5-2 mcg/kg; 25-100 mcg	0.5-2 mcg/kg/0.5-1 mL 5-100 mcg/mL	—	Intramuscular	Once
			Solution		
	1 mcg/kg; 15-300 mcg	6.25-150 mcg/mL	—	Intrathecal	Once or twice
			Solution		
	5-1500 mcg/day	28.4-500 mcg/mL	—		3 months – 18 years
			Solution		
	—	—	—	Intravenous	5 times over 6 months
	0.25-2 mcg/kg; 50-150 mcg	0.5-1 mcg/kg/1-50 mL	—		Once
			Solution		
	1 mcg/kg up to once weekly	1 mcg/kg/40-50 mL	Solution		6 weeks
	Loading 1 mcg/kg Infusion 0.3-0.4 mcg/kg/hour	—	—		90 days

	1-2 mcg/kg; 7.5-500 mcg	1 mcg/kg/30 mL 1.25-25 mcg/mL	— Solution	Perineural	At least once or twice
	50-100 mcg/6-12 weeks	2.5-8.33 mcg/mL	—		2-3 blocks
	3-4 mcg/hour	0.5 mcg/mL	—		9 days
	Infusion 8-10 mcg/hour Lockout 2-10 mcg/20-60 minutes	1-2 mcg/mL	Solution		3 days
	80 mcg	0.5-0.8 mcg/mL	— Suspension	Periarticular	Once
	1 mcg/kg	1 mcg/kg/mL	—	Subcutaneous	Once
	3.9 mg/day	0.1%-0.2%	Gel	Topical	8-12 weeks

Abbreviation: —, not provided.

Table 7. Dosage by indication – non-US countries

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Analgesia/anesthesia[20,27-64,66-75,78-83,85-98,100-114,116,118-124,128-163,166-168,170,171,175-193,195-199,201,202,208-210,212,214-239,242-253,255,256,258-264,266-273,275-284,287-296,298-300,302-308,311,313-323,325-335,337-352,355-358,360-363,365-369,371,373-378,383,386-388,391-393,395-398,400,404-408,412-418,420,421,423-425,427,428,430-434,436-438,441-444,454,456,459-462,465-474,477-483,486,490,494]	3-6 mcg/kg; 150 mcg	3 mcg/kg/10-100 mL 5 mcg/mL	—	Infiltration	Once or twice
			Solution		
	1 mcg/kg; 150 mcg	1 mcg/kg/30 mL 7.5 mcg/mL	—	Intra-articular	Once
			Solution		
	2 mcg/kg; 150-300 mcg	2 mcg/kg/5 mL 150 mcg/mL	—	Intramuscular	Once
			Solution		
	1 mcg/kg	1 mcg/kg/20 mL	—	Intraperitoneal	Once
	"30 γ"; "50 γ"[a]	—	—	Intrathecal	1-3 doses
	0.25-3 mcg/kg; 3.9-450 mcg	0.25-2 mcg/kg/0.2-4 mL 1.3-150 mcg/mL	—		
			Solution		
	37-310 mcg/day	150 mcg/mL	—		14-16 months
	"3+g/kg"[a]	—	—	Intravenous	Once
	150 mg[a]	150 mg/mL[a]	Solution		Once
	0.4-60 mcg/kg; 75-600 mcg	0.4-8 mcg/kg/1-200 mL 3.75-150 mcg/mL	—		Once
			Solution		
	1 mcg/kg/week; 30 mcg/week	1 mcg/kg/7 mL 3 mcg/mL	—		3-5 times
			Solution		

	0.3-3 mcg/kg/hour; 7.5 mcg/hour	1.5-3 mcg/mL	—		14-72 hours Until extubation
			Solution		
	Loading 1-8 mcg/kg Infusion 0.3-2 mcg/kg/hour Lockout 15-30 mcg/7-15 minutes	1-8 mcg/kg/5-100 mL 0.2-150 mcg/mL	—		4 hours to 7 days Duration of surgery
			Solution		
	150-250 mcg	10-16.7 mcg/mL	—	Irrigation	Once
	1 mcg/kg; 80 mcg	1 mcg/kg/100 mL 0.8-150 mcg/mL	—	Periarticular	Once
	Up to 150 mg[a]	5-7.5 mg/mL[a]	Solution	Perineural	Once
	0.1-4 mcg/kg; 3.75-150 mcg	0.1-2 mcg/kg/1-40 mL 0.67-75 mcg/mL	—		1-4 injections
			Solution		
	1 mcg/kg/week; 30 mcg/week	1 mcg/kg/7 mL	—		3-5 times
			Solution		
	0.2 mcg/kg/hour; 10-12 mcg/hour	1-2 mcg/mL	—		48-72 hours
			Solution		
	Loading 1-2 mcg/kg; 150 mcg Infusion 2 mcg/kg/hour; 5-45 mcg/hour Lockout 2-10 mcg/15-60 minutes	1 mcg/kg/25 mL 1-7.5 mcg/mL	—		48-72 hours
			Solution		
	1-2 mcg/kg; 10-150 mcg	1 mcg/kg/mL 16.7-150 mcg/mL	—	Subcutaneous	Once
			Solution		

	300 mcg at 4 mL/hour	—	—		48 hours
	200-500 mcg	0.04%-0.1%	Solution	Topical	Once
	Apply 3 times per day	0.1%	Gel		Up to 3 months

Abbreviation: —, not provided.
[a]As reported by the text.

Table 8. Number of studies by combination

	Combination Formula	**Number of Studies**
Nominated	Clonidine HCl 0.2% / Amantadine HCl 8% / Amitriptyline HCl 2% / Baclofen 4% / Clonidine HCl 0.2% / DMSO 5% / Gabapentin 5% / Ketoprofen 10% / Lidocaine HCl monohydrate 5% – topical cream	0

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

Indication	**Compounding Method**	**Dosage Form**	**Final Strength**
Analgesia/Anesthesia[377,388]	• Clonidine was dissolved in hydroalcoholic solution. • Gelling agent carbomer 941 was added while stirring. • Triethanolamine was slowly added until clonidine gel formed.	Gel	0.1%
	• Pentoxifylline and clonidine were mixed together in a vehicle containing anhydrous ethanol, polyethylene glycol 400, propylene glycol, and oleyl alcohol.	Solution	0.04%-0.1%

Results of interviews

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Ten SMEs discussed clonidine HCl. Among these 10 SMEs, there were 9 medical doctors and 1 nurse practitioner. The SMEs specialized and/or were board-certified in anesthesiology, neurology, oncology, ophthalmology, and pain medicine, working in academic medical institutions, outpatient practice, and community hospitals. The SMEs had been in practice for 8 to 38 years. Additional information was collected as part of the Expanded Information Initiative project, referred to as Phase 3, in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

While the literature review identified studies in which clonidine HCl was used to extend the duration of a block as part of a retrobulbar injection, 6 SMEs who specialized in ophthalmology were not familiar with the use of clonidine HCl in this manner. Retrobulbar injections will "numb the eye completely," and while they used to be done in cataract surgery, "we don't do much now for cataract surgery." This can be attributed to the shortened duration of cataract surgery, "so you don't need the anesthesia." Additionally, "most cataract surgeons like to have the patient be able to move their eyes a little bit because they can improve the access to the cataract at the time of surgery." While retrobulbar blocks are not used in cataract surgery, "they are still done for many retinal procedures." A retrobulbar or peribulbar block is used frequently prior to retinal procedures in surgeries that will last longer than the anesthesia that a lidocaine block would provide.

Retrobulbar injections are also associated with several risks and complications, including "diplopia; there's risk of hitting the muscle, risk of even globe perforation, injecting into the retina, even blindness is a potential risk, or even if you inject it into the optic nerve, you can get even death." One SME stated that retrobulbar blocks for cataract surgery are deviating from the standard of care, commenting, "I would testify against somebody for doing retrobulbar blocks." Now, "the trend has been to be going more topical." After the administration of topical drops, a small incision is made in the eye, and an intraocular injection of a small amount that "numbs the structures inside the eye, but it doesn't numb the muscles" can be made at the time of surgery. This injection is still considered a topical application but allows for "ultra-local" anesthesia to be administered.

One SME discussed the use of intrathecal clonidine to treat pain in patients with multiple sclerosis. The SME stated that while they have used clonidine in this manner, it has only been for a few patients, typically those unable to tolerate other medications. The SME used the commercially available product in doses ranging from 100 to 500 mcg a day.

Another SME stated that they do not use intravenous clonidine to treat pain but have used clonidine as part of an implanted intrathecal pump. A patient that is started on an intrathecal pump "has failed all conservative therapy." The pump typically contains a local anesthetic in conjunction with other substances unless the patient has an allergy to the drug class. Patients are typically trialed on a medication prior to insertion of a pump to ensure that the dose is appropriate and the patient is not experiencing any side effects. During the trial, the patient is kept in the hospital, and "you mirror the implantation of the pump" by administering the drug via a catheter into the intrathecal space. The SME has also used oral clonidine when discontinuing or weaning someone off an opioid to prevent withdrawal. The SME stated that using clonidine for opioid-induced analgesia would make sense because the patient could go into withdrawal as you reduce the dose of an opioid, and clonidine would be beneficial to prevent or stop withdrawal.

One SME discussed the use of clonidine HCl as part of a topical pain product. The SME stated that topical formulations are never first-line options and are only used if the patient asks for a product they do not have to take by mouth or has tried topical lidocaine or Voltaren® (diclofenac) gel with no relief. When determining the appropriate formulation, the different pain pathologies a patient presents with will guide the selection of ingredients. Typically, each formulation has 3 or 4 APIs, allowing the use of multiple mechanisms of action to treat the patient's pain or to treat pain of multiple etiologies (eg, neuropathic and inflammatory). Clonidine can be added to the formulation for patients with myofascial pain and high blood pressure. Another SME stated that, if the multi-ingredient topical product that was nominated worked, it would be great for the treatment of neuropathic pain "because generally neuropathic pain is a pretty specific area," continuing that a topical product "would work really well there."

Topical formulations are beneficial in patients with comorbidities that prevent the use of oral medications. The SME provided the example of a patient with arthritis and kidney disease who is thus unable to take an oral nonsteroidal anti-inflammatory drug (NSAID). The SME stated, "if you can get everything in a topical form and they don't have to take it orally, obviously that would be best for the patient if it actually works for them," continuing that they prefer to minimize the number of oral medications a patient takes to avoid unwanted side effects.

One SME stated, "I have had patients on it [clonidine] for pain; I've never had it work. They usually come to me on it, and I take them off it."

One SME who specialized in anesthesiology stated that they did not have any experience using clonidine but mentioned that it could be used to prolong a peripheral block, although the SME uses Precedex® for this indication. The SME also commented that clonidine can be used as an antihypertensive but not as much for anesthesia.

As part of Phase 3, 1 nominator provided additional information regarding the multi-ingredient product contained within the clonidine HCl nomination.

Clonidine HCl 0.2% / amantadine HCl 8% / amitriptyline HCl 2% / baclofen 4% / gabapentin 5% / ketoprofen 10% / lidocaine HCl monohydrate 5% / DMSO 5% will be compounded as a topical cream to treat neuropathic pain applied multiple times throughout the day for multiple days. This is used by practitioners as a non–patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: silicon dioxide, methylparaben, titanium dioxide, talc, lactose, mineral oil, magnesium stearate, propylene glycol, hypromellose, and propylparaben, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants. Their hazardous concerns are classified as allergen, human endocrine disruptor, human immune toxicant or allergen, expected to be toxic or harmful, and possible human carcinogen. Clonidine HCl is added for its analgesic effects, amantadine for pain management, amitriptyline for its ability to inhibit both serotonin and noradrenaline reuptake, baclofen to treat spasticity, gabapentin to mediate pain, ketoprofen for its anti-inflammatory properties, and lidocaine HCl for its analgesic properties. This product is needed because it will result in a clinical difference for patients as it does not include the harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event, refer to Table 16 for characteristics of the facilities the participants represented. A prequestionnaire was also distributed to participants; refer to Tables 16-19 for results of the prequestionnaire.

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

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

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

Another theme for deciding what products to purchase from an outsourcing facility focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover, leading to several participants turning to outsourcing facilities to obtain products intended for use in these areas. Participants stated that they evaluate the volume of product needed and the frequency with which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant explained, "We look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the

patient demand, then those are the items that we're going to look to potentially move out." Another participant stated that, while they do not obtain a lot of products from outsourcing facilities, "When we do purchase from 503Bs, typically it would be if we just don't have the capacity to keep up with what the demand is." One participant also commented that they would obtain labor-intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 (COVID-19) pandemic has also impacted the operations of hospitals, as noted by one participant who stated that "it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital" and another who stated, "Without 503B, we would've been in significant trouble." One participant commented that "even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when." Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making, with one participant stating, "It is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready-to-use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing."

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

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

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining them from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products used. However, the products used in a facility are often developed in-house over decades based on physician and nurse requests and, more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, "These practices had evolved somewhat disparately. Even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines." This has led to challenges obtaining certain products from outsourcing facilities. As another participant said, "I think we made 9 different epidural concentrations, all driven by anesthesia, and they want what they want, and

503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn't going to go through the expense of adding that to their product list." The participant explained, "Similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses on where things are placed, they said, 'No, we can't have it,' and 'that's too big! It won't fit! We want it in this format,' and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck insourcing." Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that "3% saline, for instance, is sold in a 500-mL bag, but the clinical guideline is a 150-mL bolus. We're either going to draw that out, or we're sending it to the ER with stickers all over it saying only give 150 [mL]." The participant also mentioned that "it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose; is it a unit dose, or isn't it?"

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

A few participants commented on the use of APIs by outsourcing facilities. One commented that as long as they are conducting end-product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. Another participant explained that as long as buyers are familiar with the regulations and know what to look for, there should be no issues with purchasing products compounded starting from APIs. Another participant stated that as more outsourcing facilities began using APIs, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using APIs if there is a shortage, stating, "I think the FDA has really looked closely at APIs, and they're slowly pushing the 503B outsourcers to a sterile-to-sterile." Only 1 participant commented that they prefer sterile-to-sterile. Another participant stated that all the companies they use are sterile-to-sterile.

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. So, there is a need for this product to be compounded from APIs as a preservative-free product. One participant stated that "if there's not a preservative-free containing option, it really should be something that should be able to be compounded from bulk... especially for the pediatric patient population." However, another participant from a children's hospital stated they have never needed to use an outsourcing facility for preservative-free products. Preservative-free is also an issue for ophthalmic products; however, one participant observed

this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products, but when they reviewed the facilities, they did not pass their internal quality standards; 1 facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross-reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because they "would have to build a separate clean room with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house are not worth it.

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

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions regarding specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum. This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded alum in-house from nonsterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that a sterile alum powder is available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating, "I've talked to that company, but I've had some concerns for them because they don't sell it as a drug. The owner was selling you a chemical; we're selling you a bulk API. It's just sterile. They were fuzzy and I never followed up, but when I asked about their process for verifying the sterility, as you would with a sterile product—we do USP [United States Pharmacopeia] <71> Sterility Testing—they couldn't really give me an answer. They just say they tested for sterility." The participants commented that alum is only needed a few times a year. However, as one participant observed, "When you need it, it's an emergency," and another noted

that it "is a challenge for anybody who has the cyclophosphamide-induced hemorrhagic cystitis." As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility, but "more times than not, they go unused and expire." Another stated that they do not keep it in stock because there is a minimum purchase, and there are only a few cases a year for whom they need to use alum. The participant had it stat shipped when needed. Another participant stated, "We had a meeting with the head of urology who was baffled why they're even ordering it. He was like, 'this is…old, really old. I don't even know why we're using it' and basically approved for us to not even make it anymore for now."

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

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

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

While none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities do not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility, they also compound a proprietary formulation in-house. This participant observed that "it is complicated to do in-house. We do it on a Baxa 1200 or 2400, either one, compounder. Then we send it up to [*sic*] for pH and potassium testing. Obviously, then we're confined to <797> beyond-use dates versus longer beyond-use-dates that we get from the 503B." Another participant commented that cardioplegic solutions are managed by the perfusion department, not the pharmacy, and they use the del Nido solution as well as 3 other formulations.

The participants also discussed challenges when utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because "it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to… It just isn't worth the dating that they gave us or can give us." Another commented that they obtain very little product from outsourcing facilities due to "the amount of work for vetting and continually validating quality of these 503B outsourcing facilities." The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an

outsourcing facility, followed by continuous reviewing of FDA quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant explained, "Traditionally, we've found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some other smaller 503Bs where we've had agreements for certain products to take it off our plate, and then lo and behold they're shut down, or closed, or whatever it may be." Minimum purchase amounts were also reported as a concern, with one participant stating, "What we see consistently is the 503Bs, they want us to commit to giving them a certain volume but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities utilizing APIs to compound narcotics. One participant commented that this often worsens drug shortages due to the Drug Enforcement Administration (DEA) quotas placed on the quantity that can be produced. The participant stated, "They [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year after year and then chasing our tail. Also, we may actually want to tell 503Bs they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products, because it actually induces the shortage in many ways."

Results of survey

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

Among respondents, 0 (0%) used clonidine HCl.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 3.3 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 16 for respondent characteristics. Among the respondents, 35 (81% of 43 total respondents) used outsourcing facilities to obtain drug products, 4 (9%) did not use outsourcing facilities, and 4 (9%) did not respond to this question.

Twenty-seven respondents (19% of 143 responses, where respondents were allowed to select multiple reasons) who obtained drug products from outsourcing facilities due to a need for ready-to-use products, and 20 respondents (14%) obtained drug products from outsourcing facilities due to drug shortages (refer to Table 17).

Fourteen respondents (31% of 45 total responses, where respondents were allowed to select multiple types) who obtained nonsterile products from outsourcing facilities, and 31 (69%) obtained sterile products from outsourcing facilities. Refer to Table 18 for the categories of products obtained from outsourcing facilities.

Zero respondents (0% of 108 responses, where respondents were allowed to select multiple drug products) obtained clonidine HCl from a 503B outsourcing facility (refer to Table 19).

Table 11. Characteristics of survey respondents

No survey respondents provided this information

Table 12. Compounded products prescribed or administered

Product	Responses, n (N = 1)
Acetylcysteine	0
Bupivacaine hydrochloride	0
Clonidine hydrochloride	0
Tetracaine hydrochloride	0
Triamcinolone acetonide	1
Tropicamide	0
None of the above	0

Table 13. Conditions for which clonidine HCl was prescribed or administered

No survey respondents provided this information

Table 14. Reasons for using compounded clonidine HCl

No survey respondents provided this information

Table 15. Use of non–patient-specific compounded clonidine HCl

No survey respondents provided this information

Table 16. Demographics of prequestionnaire respondents' facilities

Type of Facility	Responses, n (N = 102)[a]
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4

Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N = 39)**
< 50	4
50-99	3
100-199	1
200-299	4
300-399	5
400-599	3
> 600	19

[a]Respondents were allowed to select more than 1 type of facility.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, and oncology.

Table 17. Reasons for obtaining products from outsourcing facilities

Categories	Responses, n (N = 143)[a]
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10

Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other[b]	8

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

Table 18. Categories of products obtained from outsourcing facilities

Categories	**Responses, n (N = 142)[a]**
Cardioplegic solutions	14
Dermatologic preparations	6
Dialysate solutions	0
Fluids	8
Ophthalmic preparations	10
Patient-controlled analgesia	20
Ready-to-use anesthesia syringes	25
Ready-to-use antibiotic syringes and/or bags	14
Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other[b]	6

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

Table 19. Products obtained from an outsourcing facility

Product	Responses, n (N = 108)[a]
Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0
Atropine	9
Baclofen	4
Betamethasone	0
Biotin	0
Bupivacaine	8
Calcium chloride	1
Caffeine sodium benzoate	0
Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0
Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4

Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0
Potassium chloride	0
Potassium phosphate	0
Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6
Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0
None of the above	8

[a]Respondents were allowed to select multiple products.

CONCLUSION

Clonidine HCl was nominated for inclusion on the 503B Bulks List as a solution for injection to treat opioid-induced hyperalgesia, a solution for intrathecal injection to treat severe pain, and as a topical cream to treat pain. Clonidine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Ireland, Latvia, New Zealand, the UK, and the US.

From the literature review, 470 studies were included. The included studies used clonidine HCl as a solution for infiltration, intraarticular injection, intramuscular injection, intraperitoneal injection, intrathecal injection, intravenous injection, irrigation perineural injection, periarticular injection, and subcutaneous injection, as well as a topical gel and solution for anesthesia and analgesia. In 251 studies, the authors recommended the use of clonidine HCl, and in 77 studies, the authors did not recommend the use of clonidine HCl. The remaining studies either stated that additional studies were needed, or no conclusive recommendations were provided.

From the interviews, 10 SMEs discussed the use of clonidine HCl. Of the SMEs who specialized in ophthalmology, 6 were not familiar with using clonidine to extend the duration of a retrobulbar block. One SME had used the commercially available clonidine product as an intrathecal injection to treat pain in patients with multiple sclerosis but stated they have only done this for a few patients who were unable to tolerate other medications. One SME mentioned that clonidine is an ingredient that can be added into topical pain medications, and another stated that if the nominated multi-ingredient product worked, it would be useful to treat neuropathic pain since this is typically a localized type of pain. One SME has also used clonidine with other medications as part of an implantable pain pump for patients that have failed all other treatment options. One SME commented that clonidine is not used frequently in anesthesiology.

As part of Phase 3, additional information was provided by 1 nominator regarding the multi-ingredient product contained within the clonidine HCl nomination. Clonidine HCl 0.2% / amantadine HCl 8% / amitriptyline HCl 2% / baclofen 4% / gabapentin 5% / ketoprofen 10% / lidocaine HCl monohydrate 5% / DMSO 5% will be compounded as a topical cream to treat neuropathic pain.

From the survey responses, 0 out of 1 respondent used clonidine HCl. From the prequestionnaire, 0 respondents obtained clonidine HCl from a 503B outsourcing facility.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other nonindexed citations and daily from 1946 to September 9, 2020
- Date last searched: September 10, 2020
- Limits: Humans (search hedge); English language
- Number of results: 1982

1	clonidine/	13,253
2	clonidin$.tw.	14,787
3	chlofazolin$.tw.	2
4	chlophazolin$.tw.	2
5	chlophelin$.tw.	2
6	clinidin$.tw.	17
7	clofelin$.tw.	140
8	clomidin$.tw.	1
9	clondin$.tw.	9
10	or/1-9	18,306
11	exp administration, intravenous/	143,297
12	administration, topical/	38,476
13	administration, cutaneous/	22,117
14	infusions, parenteral/	26,254
15	infusions, intra-arterial/	9715
16	infusions, spinal/	160
17	infusions, subcutaneous/	1092
18	injections/	42,641
19	injections, intra-arterial/	9183
20	injections, intramuscular/	31,040

21	injections, spinal/	12,581
22	injections, subcutaneous/	32,745
23	microinjections/	16,209
24	skin absorption/	11,705
25	exp nerve block/	22,479
26	topical$.tw.	105,876
27	transcutaneous$.tw.	14,488
28	epicutaneous$.tw.	2015
29	((cutanous$ or dermal$ or skin) adj3 (absorb$ or absorpt$ or appl$)).tw.	11,309
30	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	12,242
31	subcutaneous$.tw.	166,851
32	intravenous$.tw.	341,580
33	intra venous$.tw.	579
34	intravascular$.tw.	47,940
35	intra vascular$.tw.	304
36	intraarterial$.tw.	6161
37	intra arterial$.tw.	16,232
38	intramuscular$.tw.	52,609
39	intra muscular$.tw.	719
40	extradural$.tw.	6773
41	extra dural$.tw.	142
42	peridural$.tw.	2065
43	peri dural$.tw.	6
44	caudal$.tw.	45,786
45	intracaudal$.tw.	11
46	intrathecal$.tw.	23,893

47	intra thecal$.tw.	76
48	perineural$.tw.	7566
49	peri neural$.tw.	64
50	extraneural$.tw.	1153
51	extra neural$.tw.	117
52	((gangli$ or nerv$ or paracervical$ or plexus or transvers$ abdomin$) adj2 block$).tw.	21,956
53	emulsions/	18,003
54	exp gels/	52,189
55	liniments/	123
56	ointments/	12,797
57	skin cream/	1037
58	emulsion?.tw.	33,284
59	gel?.tw.	308,821
60	liniment?.tw.	145
61	ointment?.tw.	11,882
62	salve?.tw.	341
63	paste?.tw.	12,532
64	unguent$.tw.	113
65	lotion?.tw.	2318
66	cream?.tw.	19,024
67	or/11-66	1,418,357
68	drug therapy/	30,585
69	de.fs.	2,995,589
70	dt.fs.	2,232,857
71	ad.fs.	1,418,564
72	tu.fs.	2,231,286

73	pc.fs.	1,292,135
74	exp “anesthesia and analgesia”/	233,699
75	exp pain/	397,244
76	exp pain management/	34,343
77	therap$.tw.	2,803,718
78	treat$.tw.	5,536,094
79	prevent$.tw.	1,429,383
80	prophyla$.tw.	165,597
81	an?esth$.tw.	377,026
82	analges$.tw.	123,887
83	pain$.tw.	697,966
84	sedat$.tw.	59,042
85	or/68-84	11,580,890
86	and/10,67,85	3843
87	exp animals/ not humans/	4,732,434
88	86 not 87	2238
89	limit 88 to english language	1982

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: September 10, 2020
- Limits: Humans (search hedge); English language
- Number of results: 2763

1	‘clonidine’/mj	18,584
2	‘clonidin*’:ti,ab,tn	18,530
3	‘chlofazolin*’:ti,ab,tn	4
4	‘chlophazolin*’:ti,ab,tn	11
5	‘chlophelin*’:ti,ab,tn	3
6	‘clinidin*’:ti,ab,tn	49
7	‘clofelin*’:ti,ab,tn	131
8	‘clomidin*’:ti,ab,tn	7
9	‘clondin*’:ti,ab,tn	23
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	25,801
11	‘parenteral drug administration’/de	2175
12	‘intramuscular drug administration’/de	71,729
13	‘intravascular drug administration’/exp	418,783
14	‘perineural drug administration’/de	289
15	‘subcutaneous drug administration’/de	100,834
16	‘topical drug administration’/de	82,855
17	‘cutaneous drug administration’/de	669
18	‘injection’/exp	247,856
19	‘intrathecal drug administration’/de	20,971
20	‘intracaudal drug administration’/de	21
21	‘skin absorption’/de	8062
22	‘topical treatment’/de	13,116

23	‘nerve block’/exp	43,105
24	‘topical*’:ti,ab	150,100
25	‘transcutaneous*’:ti,ab	19,563
26	‘epicutaneous*’:ti,ab	3417
27	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	17,999
28	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18,371
29	‘subcutaneous*’:ti,ab	251,728
30	‘intravenous*’:ti,ab	492,475
31	‘intra venous*’:ti,ab	1463
32	‘intravascular*’:ti,ab	68,880
33	‘intra vascular*’:ti,ab	696
34	‘intramuscular*’:ti,ab	75,845
35	‘intra muscular*’:ti,ab	1286
36	‘intraarterial*’:ti,ab	30,269
37	‘intra arterial*’:ti,ab	22,965
38	‘extradural*’:ti,ab	9122
39	‘extra dural*’:ti,ab	242
40	‘peridural*’:ti,ab	3002
41	‘peri dural*’:ti,ab	12
42	‘caudal*’:ti,ab	59,296
43	‘intracaudal*’:ti,ab	23
44	‘intrathecal*’:ti,ab	35,532
45	‘intra thecal*’:ti,ab	242
46	‘perineural*’:ti,ab	12,280
47	‘peri neural*’:ti,ab	191
48	‘extraneural*’:ti,ab	1684

49	‘extra neural*’:ti,ab	163
50	((gangli* OR nerv* OR paracervical* OR plexus OR ‘transvers* abdomin*’) NEAR/2 block*):ti,ab	33,491
51	‘gel’/exp	77,538
52	‘liniment’/de	251
53	‘lotion’/de	2872
54	‘ointment’/exp	18,662
55	‘paste’/de	2524
56	‘salve’/de	166
57	‘cream$’:ti,ab	29,771
58	‘emulsion$’:ti,ab	45,291
59	‘liniment$’:ti,ab	234
60	‘lotion$’:ti,ab	4014
61	‘ointment$’:ti,ab	21,630
62	‘paste$’:ti,ab	15,028
63	‘salve$’:ti,ab	477
64	‘unguent*’:ti,ab	240
65	‘gel$’:ti,ab	363,135
66	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65	2,289,371
67	‘drug therapy’/de	745,726
68	‘add on therapy’/de	18,947
69	‘drug dose’:lnk	626,181
70	‘drug administration’:lnk	1,760,155
71	‘drug therapy’:lnk	3,935,840
72	‘prevention’:lnk	1,179,551

73	‘anesthesiological procedure’/exp	855,999
74	‘pain’/exp	1,404,106
75	‘therap*’:ti,ab	4,216,165
76	‘treat*’:ti,ab	8,016,848
77	‘prevent*’:ti,ab	1,941,020
78	‘prophyla*’:ti,ab	264,110
79	‘an$esth*’:ti,ab	547,830
80	‘analges*’:ti,ab	182,583
81	‘pain*’:ti,ab	1,071,001
82	‘sedat*’:ti,ab	94,519
83	#67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82	14,538,158
84	#10 AND #66 AND #83	5431
85	[animals]/lim NOT [humans]/lim	6,086,394
86	#84 NOT #85	3363
87	#84 NOT #85 AND [english]/lim	2763

Appendix 2.1. Table 5. Summary of included studies

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication: Analgesia/Anesthesia					
Abdel Hay et al, 2018, Lebanon[27]	Randomized, double-blind, clinical trial	225 Patients undergoing lumbar spinal fusion, lumbar laminectomy, lumbar microdiskectomy, or cervical laminectomy • Control (52%, mean 55.43 y ± 15.71) • Clonidine (42%, mean 53.93 y ± 14.24)	Peripheral nerve block with bupivacaine plus: • Control (109) • Clonidine (116)	Postoperative area under the curve for pain, rescue morphine consumption	"The addition of clonidine to local preincisional field block with bupivacaine resulted in better and prolonged postoperative analgesia in posterior lumbar spine surgeries, an effect that was more pronounced in patients with no preoperative spinal pain."
Abdo et al, 2010, US[353]	—	1 Patient with a history of relapsing and remitting multiple sclerosis presenting with neuropathic pain nonresponsive to other therapies (0%, 44 y)	• 2 lumbar sympathetic blocks with bupivacaine and clonidine separated by 6 weeks (1)	Reduction or resolution in symptoms and pain	"To our knowledge, this is the first case describing the use of sympathetic blockade for the treatment of neuropathic extremity pain in a patient with MS. Sympathectomy has been used to treat other types of neuropathic pain. Although further experience is necessary, it appears that sympathetic blocks provide another option for a difficult clinical situation."
Abosedira, 2008, Egypt[277]	Prospective, randomized, double-blind study	40 Patients scheduled for elective upper limb body surface surgery under a Bier block • Clonidine (33%, mean 39.0 y ± 17) • Dexmedetomidine (40%, mean 43.0 y ± 7.0)	Intravenous (IV) Bier block with lidocaine plus: • Clonidine (not reported) • Dexmedetomidine (not reported)	Quality of anesthesia, postoperative sedation	"This study reveals that adding dexmedetomidine to lidocaine during Bier's block is better than adding clonidine."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Abrão et al, 2012, Brazil[28]	Randomized, controlled study	60 Patients scheduled for upper limb surgery under axillary block (gender and age not specified)	Axillary plexus block with adrenaline, lidocaine 40 mL, and: • Clonidine (15) • Saline (15) Axillary plexus block with adrenaline, lidocaine 20 mL, and: • Clonidine (15) • Saline (15)	Duration of analgesia, duration of sensory and motor block, pain scale	"Clonidine produced better effects than enhancing volume of local anesthetic in brachial plexus block."
Acalovschi et al, 1997, Romania[498] Acalovschi et al, 1997, Romania[29]	—	45 Patients scheduled for orthopedic surgery under spinal anesthesia • Meperidine (60%, mean 43 y ± 14) • Meperidine plus epinephrine (46.7%, mean 54 y ± 17) • Meperidine plus clonidine (60%, mean 42 y ± 16)	• Meperidine (15) • Meperidine and epinephrine (15) • Meperidine and clonidine (15)	Onset and duration of sensory and motor block, hemodynamic responses, duration of analgesia, degree of sedation, side effects	"We conclude that coadministration of epinephrine or clonidine with meperidine enhances the duration and degree of spinal anesthesia and that adding clonidine prolongs the duration of postoperative analgesia."
Acharya et al, 2018, India[30]	Randomized, double-blind, controlled trial	92 Patients undergoing elective lower segment cesarean section • Levobupivacaine (0%, mean 25.3 y ± 3.22) • Levobupivacaine plus clonidine (0%, mean 25.8 y ± 3.18)	Bilateral transversus abdominis plane (TAP) block with either: • Levobupivacaine (46) • Levobupivacaine and clonidine (46)	Duration of postoperative analgesia	"We conclude that the addition of clonidine 1 mcg/kg to 20 mL levobupivacaine 0.25% in TAP block bilaterally for cesarean section provides 17-19 h of postoperative analgesia, decreases postoperative analgesic requirement, and increases maternal comfort compared to 20 mL of levobupivacaine 0.25% alone with minimal side effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ackerman et al, 2003, US[354]	Retrospective chart audit	15 Patients receiving treatment of chronic pain states, including complex regional pain syndrome (CRPS), neuropathic pain, and cancer pain (60%, range 26-86 y)	• Single-shot intrathecal (IT) clonidine (13) • Short-term IT clonidine infusion (13) • Long-term IT clonidine infusion (10) • Long-term IT clonidine infusion with IT opioid (8) All patients received a trial of single-shot and/or short-term infusion of clonidine	Reduction in pain scores	"We agree with the polyanalgesia consensus statement that clonidine is not a first tier intrathecal analgesic agent, but does have a role in the treatment of patients who fail intrathecal opioid therapy. Further research on the influence of catheter position within the intrathecal space (e.g., does clonidine work segmentally, requiring infusion at specific spinal segmental levels), as well as identifying the ideal ratio of clonidine to opioid is needed to maximize the effectiveness of IT clonidine analgesic therapy."
Adnan et al, 2005, Turkey[355]	Prospective, randomized, double-blind, controlled design	28 Patients with chronic renal failure (CRF) scheduled for construction of arteriovenous fistulae with axillary block • Control (26.7%, mean 43 y ± 18) • Clonidine (38.5%, mean 47 y ± 13)	Axillary block with lidocaine plus: • Saline control (15) • Clonidine (13)	Patient and block characteristics, hemodynamic parameters, sedative and analgesic requirements	"In conclusion, our study shows that 150 mcg of clonidine as an adjuvant for lidocaine in axillary block for arteriovenous fistula construction in CRF patients increases the duration of block, decreases both heart rates and blood pressures and provides sedation, thus improving the quality of blockade overall...A dose-response study with smaller doses than 150 mcg of clonidine would be warranted in order to reduce the prolonged sedative effects of clonidine in ambulatory patients. Thus, further studies will obviously address the dose-response effects of clonidine and local anaesthetic combination in order to obtain the maximum beneficial doses for axillary brachial plexus block [in] patients with CRF."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Agarwal et al, 2014, India[31]	Prospective, randomized, double-blind study	60 Patients undergoing lower limb orthopedic surgeries • Without clonidine (100%, mean 68.8 y ± 8.4) • Clonidine 15 mcg (100%, mean 66.1 y ± 5.6) • Clonidine 30 mcg (100%, mean 66.3 y ± 5.7)	Spinal anesthesia with hyperbaric bupivacaine and: • No clonidine (20) • Clonidine 15 mcg (20) • Clonidine 30 mcg (20)	Sensory block levels	"In elderly patients, clonidine when used intrathecally in doses of 15 mcg or 30 mcg with hyperbaric bupivacaine significantly potentiated the sensory blocks levels and duration of analgesia without affecting the trend of systolic blood pressure. Clonidine in doses of 30 mcg however facilitated the ascent of sensory level block to unexpectedly higher dermatomes for a longer time."
Agrawal et al, 2016, India[278]	—	120 Patients scheduled for elective fixation of long bone fractures of the lower limb under spinal anesthesia • Dexmedetomidine (77.5%, mean 44.3 y ± 12.2) • Clonidine (82.5%, mean 42.7 y ± 12.8) • Normal saline (57.5%, mean 44.6 y ± 15.9)	• IV dexmedetomidine (40) • IV clonidine (40) • Normal saline (40)	Motor and sensory blockade characteristics	"IV α2 agonists are useful adjuvants for prolongation of the duration of spinal block. IV dexmedetomidine produces a better clinical profile compared to clonidine."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Agrawal et al, 2014, India[356]	Randomized, controlled trial	105 Patients undergoing laparoscopic cholecystectomy under general anesthesia with endotracheal intubation • Midazolam (68.6%, mean 41.77 y ± 11.63) • Clonidine (74.3%, mean 38.89 y ± 12.73) • Normal saline (74.3%, mean 41.26 y ± 11.09)	• IV midazolam (35) • IV clonidine (35) • IV normal saline (35)	Bispectral index, sedation, propofol dose needed	"To conclude, midazolam and clonidine pretreatment provides adequate sedation, has dose sparing effect on propofol, partially blunts hemodynamic responses and decreases PONV [postoperative nausea and vomiting]. In addition, clonidine also demonstrated superiority in reducing postoperative shivering. However, considering the fact that different route, dosing, combinations and time interval between premedication and intubation might affect the efficacy of drugs; hence, further studies are recommended to find out the optimal dose and route to get the best results."
Ahmed et al, 2017, India[32]	Prospective, randomized, double-blind study	328 Patients scheduled for abdominal hysterectomy • Bupivacaine (0%, mean 44.3 y ± 7.3) • Bupivacaine and clonidine (0%, mean 44.0 y ± 6.5) • Bupivacaine and fentanyl (0%, mean 41.44 y ± 7.6) • Bupivacaine, clonidine, and fentanyl (0%, mean 43.7 y ± 6.2)	Spinal anesthesia with: • Bupivacaine (82) • Bupivacaine and clonidine (82) • Bupivacaine and fentanyl (82) • Bupivacaine, clonidine, and fentanyl (82)	Level of sensory block, onset and duration of motor block, postoperative analgesia, pain score, sedation score, adverse effects	"We found that combination of intrathecal clonidine and fentanyl along with bupivacaine increases the total duration of analgesia without significant side effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Akin et al, 2010, Turkey[357]	Randomized, double-blind, controlled study	60 Patients undergoing inguinal hernia repair or orchidopexy surgery • Normal saline (gender not specified, mean 4.1 y ± 2) • Caudal clonidine (gender not specified, mean 4.1 y ± 2) • IV clonidine (gender not specified, mean 4.4 y ± 2)	Caudal levobupivacaine plus: • Normal saline IV (20) • Caudal clonidine (20) • IV clonidine (20)	Time to first rescue analgesia, number of patients not requiring rescue analgesia after receiving caudal block	"In conclusion, caudal clonidine, 2 mcg × kg^{-1}, results in increased duration of analgesia when added to levobupivacaine without increasing the frequency of adverse effects. Comparing the action of caudal to intravenous clonidine, it seems that clonidine given caudally is probably exerting its analgesic effect through a direct spinal site of action; however, further studies are required to support this mechanism of action."
Alayurt et al, 2004, Turkey[358]	—	60 Patients undergoing ambulatory hand surgery with IV regional anesthesia (IVRA) • Saline (53.3%, mean 32 y ± 13) • Sufentanil (60%, mean 31 y ± 13) • Tramadol (46.7%, mean 31 y ± 11) • Clonidine (46.7%, mean 33 y ± 14)	IV lignocaine plus either: • Saline (15) • Sufentanil (15) • Tramadol (15) • Clonidine (15)	Hemodynamic variables, tourniquet pain, sedation scores, need for rescue analgesia	"Further investigations are needed to determine the efficacy and safety of clonidine in IVRA."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ali et al, 2014, India[33]	Prospective, randomized, double-blind study	60 Patients undergoing various orthopedic surgeries on the upper extremities under supraclavicular brachial plexus block • Placebo (50%, mean 39 y ± 15) • Clonidine (55%, mean 33 y ± 12)	Peripheral nerve block with ropivacaine plus: • Placebo (30) • Clonidine (30)	Quality of sensory and motor blockade, duration of postoperative analgesia, intra- and post-operative complications	"Addition of 75 mcg of clonidine to ropivacaine, for brachial plexus block, should be considered for a prolonged upper limb surgery and for decreasing the post-operative rescue analgesic requirements."
Allen and Horn, 2012, US[426]	—	1 Patient presenting for surgical repair of sternoclavicular joint dislocation (0%, 63 y)	• Single-shot interscalene nerve block with ropivacaine and clonidine in divided doses (1)	Resolution of pain	"However, the interscalene block proved completely effective at eliminating the patient's pain, even without superficial cervical plexus blockade. This suggests the sternoclavicular joint is, like much of the remainder of the clavicle, innervated by the brachial plexus, specifically C5 and C6 nerve roots, and not by the superficial cervical plexus or thoracic roots."
Altan et al, 2005, Turkey[405]	Placebo-controlled, double-blind study	60 Patients undergoing spinal surgery • Control (55%, mean 40.75 y) • Magnesium sulfate (65%, mean 42.25 y) • Clonidine (65%, mean 44.94 y)	IV induction and infusion of either: • Control (20) • Magnesium sulfate (20) • Clonidine (20)	Level of anesthesia through bispectral index	"In conclusion, both clonidine and magnesium sulphate lowered propofol consumption and attenuated the haemodynamic response to tracheal intubation. Clonidine was associated with bradycardia and hypotension and magnesium sulphate caused a delay in recovery."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Andersen et al, 2017, Denmark[279]	Paired, blinded, randomized trial	21 Healthy volunteers receiving bilateral adductor canal blocks (ACB; 100%, mean 23 y ± 2)	Each patient received both interventions, one in each thigh, with ACB containing ropivacaine and either: • Saline (21) • Clonidine (21)	Duration of sensory block	"Administering clonidine perineurally as an adjuvant to ropivacaine in an ACB did not prolong the duration of sensory block in a setup controlling for systemic effects of clonidine."
Andersen et al, 2015, US[359]	—	180 Patients who underwent unilateral hip arthroscopy (gender and age not specified)	• Lumbar plexus psoas compartment block and sciatic block with bupivacaine, epinephrine, and clonidine (141) • General anesthesia without regional anesthesia (39)	Pain score, opioid consumption	"The anesthesiologist's decision to perform either the Labat or parasacral sciatic nerve blockade should be based upon personal preference and patient's anatomic characteristics. Randomized controlled studies are needed to further assess the value of regional analgesic blocks in patients undergoing hip arthroscopy."
Andreotti et al, 2012, Greece[34]	—	45 Patients scheduled to undergo elective orthopedic surgery (gender and age not specified)	Spinal anesthesia (SA) with levobupivacaine and: • Fentanyl (15) • Tramadol (15) • Tramadol and clonidine (15)	Analgesia duration	"Tramadol and clonidine added to levobupivacaine for SA significantly prolong the pain free period when compared to fentanyl or tramadol alone."
Andrieu et al, 2007, France[35]	Double-blind, randomized, controlled study	87 Patients undergoing elective total thyroidectomy (17.2%, range 24-79 y)	Bilateral superficial cervical plexus block with either: • Saline (29) • Ropivacaine (29) • Ropivacaine and clonidine (29)	Nefopam requirement during first 24 hours after surgery	"The use of ropivacaine and clonidine improves intraoperative analgesia. Our data suggest that it is possible to manage pain after thyroid surgery with regional anaesthesia and acetaminophen."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Andrieu et al, 2009, France[36]	—	50 Patients undergoing radical prostatectomy (RP; 100%, range 55.7-67.2 y)	• Control (16) • IT morphine (17) • IT morphine and clonidine (17) All patients received postoperative patient-controlled analgesia (PCA) with IV morphine	Need for postoperative rescue analgesia	"In conclusion, our prospective randomized study showed a reduction in IV morphine consumption and pain intensity with the administration of IT morphine with or without clonidine. The increase in the duration of analgesia by clonidine and the absence of major side effects make IT morphine plus clonidine a useful technique for the management of pain after RP."
Anis et al, 2011, Egypt[37]	Randomized, controlled study	60 Patients undergoing hip surgery • No lumbar plexus block (45%, mean 31.55 y ± 7.29) • Saline (60%, mean 32.81 y ± 5.88) • Clonidine (50%, mean 31.91 y ± 5.02)	• No lumbar plexus block (20) Lumbar plexus block with bupivacaine and: • Saline (20) • Clonidine (20)	Postoperative pain, sedation, hemodynamics, analgesic consumption, local anesthetic side effects, serum cortisol level	"The study showed that posterior lumbar plexus block was an effective postoperative analgesic technique in patients undergoing hip surgeries and that adding clonidine in a concentration of 2.5 mcg/mL to bupivacaine 0.25% has resulted in decreasing the postoperative analgesic requirements."
Anouar et al, 2016, France[38]	Prospective, randomized, double-blind, clinical trial	40 Patients undergoing elective circumcision • Clonidine (100%, mean 30 months ± 3.12) • Placebo (100%, mean 25.2 months ± 5)	Dorsal penile nerve block with bupivacaine and: • Clonidine (20) • Placebo (20)	Success of block	"Clonidine can be used in dorsal penile nerve block to improve and to prolong its analgesic effects after male circumcision."
Arora et al, 2017, India[280]	Randomized, controlled trial	40 Patients between 2 and 10 years old scheduled to undergo inguinal hernia repair (gender and age not specified)	TAP block with either: • Ropivacaine (not reported) • Ropivacaine and clonidine (not reported)	Need for rescue analgesia, time to first analgesic in postoperative period, pain score, adverse effects	"Addition of clonidine to ropivacaine for TAP block did not result in any significant increase in duration of analgesia or improvement in quality of analgesia as seen by pain scores."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Arora et al, 2016, India[39]	Prospective, double-blind study	75 Patients undergoing lower limb surgery under spinal anesthesia • Saline (52%, mean 35.65 y ± 8.85) • Buprenorphine (44%, mean 35.9 y ± 8.63) • Clonidine (48%, mean 36.8 y ± 7.98)	Spinal anesthesia with heavy bupivacaine plus: • Saline (25) • Buprenorphine (25) • Clonidine (25)	Onset, duration of sensory and motor block, effect on hemodynamics, level of sedation, duration of postoperative analgesia, adverse effects	"Administration of buprenorphine and clonidine intrathecally does potentiate the duration of analgesia, sensory and motor block. The study suggests that combination of two or more drugs from different group (e.g., opioid and α2 agonist) can give better analgesia and less chance of side effects."
Arora et al, 2018, India[40]	—	75 Patients scheduled to undergo lower limb surgeries • Saline (60%, mean 40.04 y ± 14.67) • Clonidine 15 mcg (68%, mean 45.12 y ± 16.82) • Clonidine 30 mcg (64%, mean 46.00 y ± 18.07))	Spinal anesthesia with bupivacaine and: • Saline (25) • Clonidine 15 mcg (25) • Clonidine 30 mcg (25)	Hemodynamic parameters, onset and duration of sensory block, highest dermatomal level of sensory block, motor block onset, time to complete motor block recovery, mean time to request of first analgesic, side effects	"The addition of intrathecal clonidine 15 mcg to small dose bupivacaine increased the spread, duration of analgesia, and produced effective spinal anesthesia with stable hemodynamics and did not prolong postoperative motor block."
Arora et al, 2015, India[427]	Prospective, randomized, placebo-controlled study	90 Patients diagnosed with carcinoma of the breast and scheduled for breast surgery • Control (0%, mean 44.10 y ± 8.495) • Clonidine 1 mcg/kg (0%, mean 44.67 y ± 10.196) • Clonidine 2 mcg/kg (0%, mean 44.33 y ± 8.507)	IV administration of: • Control (30) • Clonidine 1 mcg/kg (30) • Clonidine 2 mcg/kg (30)	Hemodynamic response	"We conclude that minimal dose of IV clonidine 1 mcg kg^{-1} caused maximum attenuation of pressor response with minimal side effects like hypotension and sedation."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Aunac et al, 2002, Belgium[428]	—	39 Patients undergoing thyroidectomy • Saline (15.4%, mean 65 y ± 15) • Ropivacaine (15.4%, mean 60 y ± 11) • Ropivacaine and clonidine (23.1%, mean 72 y ± 18)	Bilateral combined deep and superficial cervical block with: • Saline (13) • Ropivacaine (13) • Ropivacaine and clonidine (13)	Opioid and nonopioid analgesic requirements	"We conclude that combined deep and superficial cervical plexus block is an effective technique to alleviate pain during and immediately after thyroidectomy."
Bailey et al, 2019, US[429]	Randomized, therapeutic trial	78 Patients undergoing anterior cruciate ligament (ACL) reconstruction with patellar tendon autograft • Femoral nerve blockade (FNB; 52.6, mean 24.4 y ± 8.8) • Adductor canal nerve blockade (57.5%, mean 21.0 y ± 7.3)	Ropivacaine with clonidine via: • Ultrasound-guided FNB (38) • Ultrasound-guided ACB (40)	Average pain score, morphine equivalent units consumed, quadriceps surface electromyography, straight leg raise, ability to ambulate without assistive devices	"Based on previous evidence and the results of this study, we recommend the use of ACB over FNB for the analgesic management of patients undergoing ACL reconstruction with patellar tendon autograft."
Bajwa et al, 2017, India[41]	Prospective, randomized study	100 Patients undergoing elective lower abdominal surgery • Clonidine (53%, mean 44.76 y ± 14.20) • Fentanyl (47%, mean 42.53 y ± 15.43)	IT hyperbaric bupivacaine plus either: • Clonidine (50) • Fentanyl (50)	Onset and duration of sensory and motor block, sedation score, hemodynamic parameters, total analgesia time, and potential side effects	"Addition of clonidine to intrathecal bupivacaine offers longer duration of postoperative analgesia than fentanyl but with higher sedation. Both the drugs offer similar surgical conditions and prolongs postoperative analgesia (clonidine more than fentanyl), so we suggest fentanyl as better choice when sedation is not desirable and clonidine is recommended when sedation is acceptable."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bajwa et al, 2012, India[42]	Randomized, clinical study	100 Patients who underwent emergency cesarean section • Bupivacaine (0%, mean 26.8 y ± 4.7) • Bupivacaine and clonidine 30 mcg (0%, mean 28.2 y ± 3.9) • Bupivacaine and clonidine 37.5 mcg (0%, mean 27.6 y ± 3.5) • Bupivacaine and clonidine 45 mcg (0%, mean 28.8 y ± 3.4)	Spinal block with either: • Bupivacaine (25) • Bupivacaine and clonidine 30 mcg (25) • Bupivacaine and clonidine 37.5 mcg (25) • Bupivacaine and clonidine 45 mcg (25)	Onset of analgesia, sensory and motor blockade levels, maternal heart rate and blood pressure, neonatal Apgar scores, postoperative block characteristics, adverse events	"The addition of 45 mcg, 37.5 mcg, and 30 mcg of clonidine to hyperbaric bupivacaine results in more prolonged complete and effective analgesia, allowing reduction of up to 18% of the total dose of hyperbaric bupivacaine. From the results of this study, 37.5 mcg of clonidine seems to be the optimal dose."
Baker et al, 2004, Austria[425]	Prospective, randomized, double-blind study	30 Patients undergoing hip surgery after traumatic hip fractures • Isobaric (gender not specified, mean 76 y ± 6) • Hyperbaric (gender not specified, mean 81 y ± 11)	IT administration of either: • Isobaric clonidine (15) • Hyperbaric clonidine (15)	Hemodynamics, IV fluid administration, pain scores, sedation scores, clonidine cerebrospinal fluid levels	"We conclude that increasing the baricity of IT clonidine solution in the conditions of our experiment reduces hemodynamic side effects but also analgesia from IT administered clonidine."
Balaraju et al, 2013, India[430]	Randomized, single-blind study	60 Patients undergoing functional endoscopic sinus surgery (gender and age not specified)	• Oral clonidine (not reported) • IV clonidine (not reported)	Heart rate, mean arterial pressure, postoperative sedation, analgesic requirements	"Conclusion: the administration of both oral clonidine and IV clonidine results in improved perioperative haemodynamic stability which are comparable in its effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Baptista et al, 2008, Brazil[43]	—	80 Patients undergoing hemorrhoidectomy Epidural anesthesia: • Ropivacaine (31.6%, mean 50.0 y ± 7.3) • Ropivacaine and clonidine (42.8%, mean 46.3 y ± 10.3) Subarachnoid anesthesia: • Bupivacaine (31.6%, mean 43.1 y ± 14.1) • Bupivacaine with clonidine (42.8%, mean 49.8 y ± 11.6)	Epidural anesthesia: • Ropivacaine (19) • Ropivacaine and clonidine (21) Subarachnoid anesthesia: • Bupivacaine (19) • Bupivacaine and clonidine (21)	Pain intensity	"The subarachnoid anesthesia with a 0,5% bupivacaine with clonidine, showed better analgesia than epidural anesthesia with a 0,75% ropivacaine with or without clonidine, though all proved to be safe and efficient."
Barioni et al, 2002, Brazil[44]	Randomized, double-blind study	60 Patients scheduled for unilateral ophthalmologic surgery with peribulbar blockade • Control (33.3%, mean 64 y ± 13) • Peribulbar clonidine (33.3%, mean 69 y ± 12) • Oral clonidine (53.3%, mean 60 y ± 15) • Peribulbar and oral clonidine (60%, mean 64 y ± 11)	• Control (15) • Peribulbar clonidine (15) • Oral clonidine (15) • Peribulbar and oral clonidine (15)	Anesthesia, analgesia, blood cortisol, adverse effects	"In conclusion, in spite of the higher intraoperative blood cortisol levels, peribulbar clonidine enhanced anesthesia and analgesia without increasing the frequency of adverse effects, and 30 mcg was considered to be a safe dose. Both oral and peribulbar administration of clonidine offered anxiolytic effect, suggesting a role for clonidine in ophthalmic surgery."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Batra et al, 2010, India[45] Subramanyam et al, 2010, India[499]	Prospective, randomized, double-blind study	61 Patients undergoing elective lower abdominal surgery • Bupivacaine (86.7%, mean 6.3 months ± 3.5) • Bupivacaine and fentanyl (73.3%, mean 7.2 months ± 4) • Bupivacaine and clonidine (81.3%, mean 5.7 months ± 2.6) • Bupivacaine, clonidine, and fentanyl (80%, mean 6.30 months ± 3.5)	Spinal anesthesia with: • Bupivacaine (15) • Bupivacaine and fentanyl (15) • Bupivacaine and clonidine (16) • Bupivacaine, clonidine, and fentanyl (15)	Height of sensory blockade, sedation score, reactivity score, propofol requirements	"Our study show[ed] that the requirement of propofol sedation reduces with intrathecal adjuvants. The reduction was significant with the addition of clonidine and clonidine–fentanyl combination as opposed to bupivacaine alone or with fentanyl. There was no significant difference in propofol infusion requirement with the use of bupivacaine alone or with fentanyl."
Beaussier et al, 2005, France[46]	Prospective, randomized, double-blind study	40 Patients scheduled for unilateral inguinal herniorrhaphy under monitored anesthesia care • Ropivacaine and clonidine (100%, mean 44 y ± 17) • Ropivacaine (100%, mean 49 y ± 17)	Ilioinguinal-iliohypogastric block (IIHB) with: • Ropivacaine and clonidine (20) • Ropivacaine (20)	Pain intensity, first request of supplemental analgesics	"In conclusion, the benefit of adding clonidine 75 mcg to ropivacaine 225 mg (7.5 mg/mL) for IIHB in adult patients having surgery for inguinal hernia repair is to reduce motion pain on the third postoperative day. This benefit must be balanced with an increasing risk of orthostatic hypotension in the immediate postoperative period."
Bedi et al, 2017, India[47]	Prospective, randomized, double-blind, systemic, placebo-controlled trial	84 Patients undergoing lower end humerus fracture fixation (75%) • Perineural clonidine (mean 40.36 y ± 15.08) • IV clonidine (mean 39.71 y ± 12.69) • Placebo (mean 38.07 y ± 15.63)	All received supraclavicular brachial plexus block with bupivacaine and: • Perineural clonidine (28) • IV clonidine (28) • Placebo (28)	Onset and duration of sensorimotor block, hemodynamic variables, duration of analgesia, level of sedation and adverse effects	"We therefore recommend that clonidine in a dose of 2 mcg/kg can safely and effectively be used as an adjuvant to supraclavicular brachial plexus block for fixation of fractures of lower end of humerus."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Benhamou et al, 1998, France[48]	Multicenter trial	78 Patients scheduled for elective cesarean section • Saline (0%, mean 31 y ± 5) • Clonidine (0%, mean 30 y ± 5) • Clonidine and fentanyl (0%, mean 31 y ± 6)	Spinal anesthesia with hyperbaric bupivacaine plus: • Saline (26) • Clonidine (26) • Clonidine and fentanyl (26)	Analgesic efficacy	"In conclusion, this study demonstrates improved intraoperative analgesia by adding clonidine to bupivacaine. By using a small dose of intrathecal clonidine, side effects were not increased. The combination of clonidine and fentanyl further improved analgesia."
Bernard et al, 1991, France[431]	Double-blind, randomized study	32 Patients scheduled to undergo elective total hip replacement • Clonidine (43.7%, mean 57 y ± 13) • Placebo (56.3%, mean 56 y ± 9)	Oral and IV administration of: • Clonidine (16) • Placebo (16)	Hemodynamic parameters	"Our results suggest that: 1) preoperative clonidine may improve the haemodynamic profile associated with anaesthetic discontinuation, but 2) IV infusion (0.3 $mcg*kg^{-1}*h^{-1}$) did not prolong this effect during the early postoperative period in the face of the sympathetic nervous discharge of recovery."
Bernard, 2006, France[49]	Prospective, randomized, double-blind study	20 Patients scheduled for hand surgery under brachial plexus block • Perineural clonidine (40%, mean 48 y ± 9) • Intramuscular (IM) clonidine (30%, mean 49 y ± 10)	Axillary brachial plexus block with bupivacaine and lidocaine plus either: • Perineural clonidine and IM saline (10) • Perineural saline and IM clonidine (10)	Sensory blockade	"In summary, clonidine is an efficient adjunct to local anesthetics for the axillary brachial nerve blocks."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bernard et al, 1993, France[50]	Double-blind, randomized study	24 Patients undergoing scoliosis correction • Morphine (41.7%, mean 29 y ± 12) • Clonidine and fentanyl (50%, mean 31 y ± 15)	• IT morphine (12) • IV clonidine and fentanyl (12)	Pain and sedation scores, hemodynamic data, blood gases	"In conclusion, this study confirms that intrathecal morphine administration at the end of extensive spinal surgery may provide relatively good postoperative analgesia. In spite of the low morphine doses used, major respiratory depression occurred during the first postoperative hours. Thus, systemic clonidine combined with low-dose fentanyl may be considered as a possible approach to postoperative pain treatment in the recovery room or intensive care unit, avoiding ventilatory depression at equipotent analgesic levels but resulting in sedation and moderate hypotension."
Bernard et al, 1991, France[360]	—	50 Patients undergoing extensive spinal surgery • Clonidine (52%, mean 27 y ± 3) • Placebo (32%, mean 29 y ± 5)	IV administration of either: • Clonidine (25) • Placebo (25)	Pain score, morphine requirement	"In conclusion, intravenous clonidine may be considered as a possible approach to postoperative pain treatment in patients recovering from major surgery and admitted to intensive care units. In the presence of low-dose morphine, IV clonidine can provide long-lasting stable analgesia and absence of ventilatory depression. One limitation of this technique may be a clinically significant decrease in blood pressure, especially if filling pressure is inadequate. Further studies are needed to substantiate the efficacy of this technique."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bernard et al, 1995, France[406]	Double-blind, randomized study	24 Patients scheduled for scoliosis correction • IV (gender not specified, mean 24 y ± 11) • Epidural (gender not specified, mean 18 y ± 7)	Clonidine as PCA via either: • IV (12) • Epidural (12)	Pain, clonidine requirements, sedation, hemodynamics	"We conclude that analgesia can be achieved postoperatively by both epidural and intravenous clonidine administration. The epidural route is associated with significant reductions in self-administered clonidine dose, and thus in the plasma clonidine concentration, and the level of sedation. Reduction in sedative, but not hemodynamic effects, could be evidence in favor of the epidural rather than the intravenous route when clonidine is given as the sole postoperative analgesic."
Bernard et al, 1993, France[432]	Double-blind manner	45 Patients undergoing scoliosis surgery (gender not specified, range 15-45 y)	IV administration of either: • Fentanyl (15) • Clonidine and fentanyl (15) • Clonidine, fentanyl, and dopamine (15)	Pain score, number of rescue analgesia boluses, hemodynamics, arterial blood gas tensions, pH	"In the presence of low-dose K [ketoprofen] and for similar pain relief, C [clonidine] reduced the dose of F and thus improved postoperative blood gas tensions. D [dexmedetomidine] in a dose of 7.5 mcg/kg/min lessened hypotension induced by C and did not modify pain relief. However, the large difference between the half-lives of C (12-14 h) and D (2-4 min) and a possible development of catecholamine-dependent hemodynamic state may result in severe cardiovascular depression after abrupt discontinuation of D. Thus, we conclude that D should not routinely be introduced in pain treatments including C, but only in the case of hypotension."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bernard et al, 1994, France[407]	Double-blind, randomized study	32 Patients scheduled for scoliosis correction surgery • Fentanyl (43.8%, mean 22.6 y ± 2.9) • Fentanyl and clonidine (37.5%, mean 24.4 y ± 2.8)	IV administration of either: • Fentanyl (16) • Fentanyl and clonidine (16)	Oxygen saturation, respiratory rate, supplemental analgesia demands, pain, sedation, hemodynamics	"We conclude that clonidine can prolong the risk of opioid respiratory depression, and that fentanyl doses should be extensively reduced when clonidine is given to achieve balanced postoperative analgesia."
Bernard and Macaire, 1997, France[51]	Double-blind fashion	56 Patients scheduled for carpal tunnel repair (gender not specified, range 24-80 y)	Brachial plexus block plus lidocaine and: • Saline (14) • Clonidine 30 mcg (14) • Clonidine 90 mcg (14) • Clonidine 300 mcg (14)	Sensory and motor functions, adequacy of surgical block, postoperative pain intensity, side effects	"This study suggests that a small dose of clonidine enhances the quality of the peripheral blocks from lidocaine and limits the classical α2-agonist side effects to sedation."
Bhar et al, 2016, India[52]	Prospective, randomized, double-blind study	150 Patients scheduled for abdominal hysterectomy • Control (0%, mean 44.6 y ± 7.1) • Neostigmine (0%, mean 48.7 y ± 6.6) • Clonidine (0%, mean 47.1 y ± 5.2)	IT bupivacaine plus either: • Control (50) • Neostigmine (50) • Clonidine (50)	Sensory and motor block, surgical condition, duration of spinal analgesia, side effects	"We can conclude from this study that both intrathecal clonidine and neostigmine improve the bupivacaine-induced subarachnoid block. However, clonidine provides better surgical condition with fewer incidences of nausea and vomiting compared to neostigmine. Clonidine is the adjuvant of choice to bupivacaine for abdominal hysterectomy."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bharti et al, 2010, India[500] Bharti et al, 2013, India[361]	Randomized, double-blind study	56 Patients undergoing open cholecystectomy (73.2%, range 34-70 y)	Wound infiltration with bupivacaine plus either: • Control (20) • IV clonidine (17) • Infiltration clonidine (19)	Postoperative analgesic requirement, side effects	"In conclusion, clonidine when administered in wound infiltration with bupivacaine provides effective postoperative analgesia as on IV administration but had fewer side-effects. Therefore, clonidine 3 mcg kg^{-1} with bupivacaine can be used for surgical site infiltration as part of a multimodal analgesia technique in patients undergoing open cholecystectomy. However, further studies are required to evaluate its efficacy in different surgical procedures."
Bharti et al, 2002, India[53]	Randomized, blinded, controlled study	24 Patients scheduled for elective cataract surgery (70.8%, range 40-70 y)	Peribulbar block with lignocaine, hyaluronidase, and either: • Normal saline (12) • Clonidine (12)	Onset and duration of lid akinesia, globe anesthesia and akinesia, time to first analgesic medication, total analgesic requirement	"Our study suggests that addition of clonidine 1 mcg/kg to the local anaesthetic mixture significantly increases the duration of peribulbar block, improves the quality of analgesia and patient comfort. Side-effects were negligible."
Bhatnagar et al, 2006, India[54]	Prospective, randomized, double-blind study	28 Patients scheduled to undergo thoracotomy for carcinoma of the esophagus • Bupivacaine (gender not specified, mean 44 y ± 18) • Bupivacaine and clonidine (gender not specified, mean 38 y ± 21)	Continuous paravertebral intercostal nerve block with either: • Bupivacaine (14) • Bupivacaine and clonidine (14)	Hemodynamic parameters, pain and sedation scores, pulmonary function tests	"In conclusion, clonidine, when used as an adjunct to bupivacaine for continuous intercostal block using a paravertebral catheter, improves analgesic efficacy after thoracotomy. Hypotension occurred more frequently among patients receiving clonidine, but this responded well to treatment. Sedation was the major adverse effect of clonidine that interferes with its clinical application."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bhattacharjee et al, 2015, India[408]	Prospective, randomized, double-blind study	90 Patients undergoing elective cesarean section • Control (0%, mean 29.83 y ± 6.438) • Clonidine (0%, mean 28.23 y ± 5.697) • Fentanyl (0%, mean 29.90 y ± 5.346)	IT administration of bupivacaine plus either: • Normal saline (30) • Fentanyl (30) • Clonidine (30)	Peak sensory block level, time to reach peak block level, time to 2-segment regression, maximum degree of motor block, side effects, perioperative analgesic requirements, time to first analgesic request	"It can be concluded from the present study that perioperative analgesia for caesarean section was prolonged by the addition of 75 mcg of clonidine and 25 mcg fentanyl to bupivacaine. However, prolongation of perioperative analgesia was more with fentanyl compared to clonidine, which also had unwanted side effects like nausea, vomiting and hypotension."
Bhushan et al, 2012, India[55]	Prospective, double-blind, randomized, controlled study	60 Patients undergoing lower segment cesarean section • Clonidine 60 mcg (0%, mean 24.7 y ± 3.15) • Clonidine 30 mcg (0%, mean 22.9 y ± 2.75) • Clonidine 15 mcg (0%, mean 23.4 y ± 3.50)	IT bupivacaine plus either: • Clonidine 60 mcg (20) • Clonidine 30 mcg (20) • Clonidine 15 mcg (20)	Duration of effective analgesia	"Addition of 60 mcg clonidine to intrathecal bupivacaine provides longer duration of postoperative analgesia than 15 mcg or 30 mcg but with more sedation. We get fairly good analgesia with less sedation in 15 mcg and 30 mcg clonidine and are better options when sedation is not desirable."
Biboulet et al, 2004, France[433]	Prospective, randomized, double-blind study	45 Patients scheduled for elective total hip arthroplasty (THA; 55.6%, range 28-77 y)	• PCA with morphine (14) Nerve block with bupivacaine and clonidine via either: • Femoral nerve block (16) • Psoas compartment block (15)	Morphine consumption	"PCA is an efficient and safe analgesia technique. FNB and PCB [Psoas compartment block] should not be used routinely after total-hip arthroplasty."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bock et al, 2002, Germany[56]	—	72 Patients undergoing minor surgery (87.5%, range 3.0-8.3 y)	Caudal bupivacaine plus either: • Caudal clonidine 1 mcg/kg (18) • Caudal clonidine 3 mcg/kg (18) • IV clonidine (18) • Control (18)	Incidence of postanesthetic agitation	"We, therefore, also used midazolam for preoperative anxiolysis. However, on the basis of our results we recommend the use of clonidine after induction of anaesthesia."
Bollag et al, 2012, Brazil[362] Bollag et al, 2012, Brazil[501]	Double-blind, randomized, controlled trial	81 Patients undergoing cesarean delivery • Placebo (0%, mean 30.5 y ± 6.7) • Bupivacaine and sodium chloride (0%, mean 31.8 y ± 4.5) • Bupivacaine and clonidine (0%, mean 29.5 y ± 6.7)	TAP block with either: • Placebo (30) • Bupivacaine and sodium chloride (25) • Bupivacaine and clonidine (26)	Wound hyperalgesia index	"Adding clonidine to a TAP block with bupivacaine did not affect wound hyperalgesia index and it did not improve short-term or long-term pain scores in women undergoing elective cesarean delivery. Further studies are warranted to determine the benefits of antihyperalgesic adjuvants in TAP solutions for specific individuals at risk for chronic pain."
Bonnet et al, 1990, France[57]	—	20 Patients recovering from peripheral orthopedic or perineal surgery • Epidural (EP; 20%, mean 45.5 y ± 20.8) • Intramuscular (30%, mean 52.3 y ± 17.9)	Clonidine administered via either: • Epidural (10) • IM (10)	Pain score	"In conclusion, EP and IM clonidine (2 mcg/kg) appears to produce satisfactory analgesia in postoperative patients recovering from peripheral orthopedic or perineal surgery. Similarities in quality and duration of analgesia and side effects of EP and IM clonidine suggest that these routes of administration may share some mechanisms of action."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bonnet et al, 1989, France[58]	—	44 Patients scheduled for orthopedic surgery • Isotonic saline (64.3%, mean 45.6 y ± 15.2) • Clonidine 75 mcg (46.7%, mean 40.8 y ± 21.9) • Clonidine 150 mcg (40%, mean 49.6 y ± 18.2)	Spinal anesthesia with hyperbaric tetracaine plus either: • Isotonic saline (14) • Clonidine 75 mcg (15) • Clonidine 150 mcg (15)	Sensory and motor blockade, pain intensity, sedation level, heart rate, respiratory rate, blood pressure	"Clonidine appears to be an alternative to epinephrine to prolong the duration of hyperbaric tetracaine spinal anesthesia in humans, confirming data reported with spinal bupivacaine. The effect of clonidine is dose dependent."
Bonnet et al, 1990, France[59]	—	36 Patients scheduled for orthopedic surgery • Group 1 (62.5%, mean 47.6 y ± 22.6) • Group 2 (60%, mean 51.4 y ± 18.1) • Group 3 (80%, mean 46.5 y ± 12.0) • Group 4 (25%, mean 54.3 y ± 17.8)	Premedication with oral diazepam and spinal anesthesia with bupivacaine plus either: • Group 1: Isotonic saline (8) • Group 2: Clonidine (10) Spinal anesthesia with bupivacaine and isotonic saline with oral premedication of either: • Group 3: Clonidine 150 mcg (10) • Group 4: Clonidine 300 mcg (8)	Duration of sensory and motor block	"In conclusion, the administration of oral clonidine as premedication fails to prolong the local anesthetic block during spinal anesthesia; by contrast we have confirmed that spinal clonidine is an effective adjunct to spinal bupivacaine."
Bonnet et al, 1989, France[363]	—	30 Patients scheduled to undergo orthopedic surgery • Saline (60%, mean 39.4 y ± 19.0) • Clonidine (73.3%, mean 40.4 y ± 15.0)	Spinal anesthesia with isobaric bupivacaine plus either: • Saline (15) • Clonidine (15)	Duration of sensory and motor block	"We conclude that the addition of clonidine to isobaric bupivacaine for spinal anesthesia prolongs sensory block and enhances its quality without important side effects. The results of this study in a limited number of patients suggest that spinal clonidine prevents tourniquet pain when associated with bupivacaine, although this requires confirmation in a much larger study."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Boussofara et al, 2006, Tunisia[434]	Double-blind, randomized trial	110 Patients scheduled to undergo elective lower extremity surgery • Saline (54.5%, mean 51 y ± 19) • Midazolam (50.9%, mean 49 y ± 20)	Spinal anesthesia with bupivacaine, clonidine, plus either: • Saline (55) • Midazolam (15)	Motor and sensory block levels and duration, sedation levels, postoperative analgesia, time of first pain relief request	"Addition of midazolam to an intrathecal B-C mixture does not potentiate postoperative analgesia but prolongs the motor blockade."
Brkovic et al, 2005, Serbia and Montenegro[60]	Double-blind study	40 Patients scheduled for surgical removal of impacted or partially impacted lower third molars • Epinephrine (30%, mean 23.5 y ± 0.8) • Clonidine (25%, mean 24.2 y ± 1.1)	Inferior alveolar nerve block with lidocaine plus either: • Epinephrine (20) • Clonidine (20)	Onset, duration, and intensity of local anesthesia, need for postoperative pain medicine, hemodynamic parameters	"The presented data suggest that clonidine could be a useful and safe alternative to epinephrine for intraoral block anaesthesia."
Brown et al, 2004, US[364]	Randomized, masked, clinical trial	99 Patients scheduled to undergo elective radical retropubic prostatectomy • Control (100%, mean 61.0 y ± 7.5) • Intrathecal (100%, mean 61.6 y ± 7.0)	• Control (50) • IT administration of bupivacaine, clonidine, and morphine (49)	Pain, postoperative functional status	"The benefits of improved immediate analgesia and decreased morphine requirements resulting from intrathecal analgesia must be weighed against factors such as pruritus, increased intraoperative requirement for fluids and vasopressors, and resources needed to implement this modality. Further studies are needed to determine the significance of the decrease in duration of hospital stay."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Brunschwiler et al, 1998, Switzerland[61]	—	36 Patients undergoing knee replacement • Placebo (33.3%, mean 81 y ± 1) • Morphine (16.7%, mean 78 y ± 3) • Clonidine (50%, mean 79 y ± 6)	Spinal anesthesia with bupivacaine plus either: • Placebo (12) • Morphine (12) • Clonidine (12)	Maximal sensory level and degree of motor block, duration of surgical analgesia and anesthesia	"In elderly patients 0.15 mg clonidine but not 0.15 mg morphine prolonged surgical analgesia when added to 10 mg plain bupivacaine."
Burlacu et al, 2006, Ireland[365]	—	52 Patients undergoing breast cancer surgery (gender not specified, range 27-77 y)	• Control (14) Paravertebral analgesia (PVA) with levobupivacaine plus either: • Normal saline (13) • Fentanyl (13) • Clonidine (12)	Cumulative morphine consumption	"In conclusion, this study shows that paravertebral fentanyl and clonidine in combination with diluted levobupivacaine (0.05%) are effective analgesics, as demonstrated by a significant decrease in supplemental postoperative morphine consumption. At the doses used, the addition of fentanyl is associated with nausea and vomiting, and clonidine with arterial hypotension. Further work is required to determine the lowest effective dose of fentanyl or clonidine in PVA which is not associated with systemic-type side-effects. Levobupivacaine 0.1% alone is ineffective for postoperative paravertebral analgesia after breast surgery."
Butala et al, 2018, India[62]	Randomized, prospective, double-blind, clinical study	60 Volunteer donors planned for retroperitoneal laparoscopic donor nephrectomy (gender and age not specified)	Wound infiltration and periportal infiltration with either: • Bupivacaine and clonidine (30) • Bupivacaine (30)	Pain scores, duration of effective analgesia, percent of donors needing rescue analgesia, total number of rescue analgesic doses	"Clonidine 3 mcg/kg is an effective adjuvant to Bupivacaine for wound infiltration in terms of quality and duration of postoperative analgesia following retroperitoneal laparoscopic donor nephrectomy as compared to Bupivacaine alone."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Buys et al, 2010, US[435]	—	74 Patients undergoing foot or ankle surgery • Sciatic (51%, mean 46.1 y ± 15) • Tibial-peroneal (49%, mean 42.2 y ± 14.6)	Mixture of mepivacaine, clonidine, and sodium bicarbonate administered as a nerve block for: • Sciatic (37) • Tibial-peroneal (37)	Onset of block	"Blocking the tibial and common peroneal nerves in the popliteal fossa separately provides for a faster onset than a prebifurcation sciatic block."
Cabral et al, 2014, Brazil[63]	Prospective, randomized, double-blind study	40 Patients undergoing cataract surgery • Control (35%, mean 68.9 y ± 9.9) • Clonidine (50%, mean 69.5 y ± 8.0)	Sub-Tenon's anesthesia with lidocaine, saline, and hyaluronidase plus either: • Control (20) • Clonidine (20)	Duration of sensory anesthesia, ocular akinesia, akinesia of levator palpebrae superioris and orbicularis oculi muscles, duration of analgesia, overall use of analgesics, adverse effects	"The addition of clonidine 1 mcg/kg to 2% lidocaine in sub-Tenon's anesthesia for cataract surgery increased the duration of sensory anesthesia, ocular akinesia, and the duration of analgesia."
Campanella et al, 2009, Italy[64]	Prospective, observational, randomized, controlled, single-blind study	92 Patients who underwent subarachnoid anesthesia for elective cesarean section (0%, age not specified)	Subarachnoid anesthesia with either: • Levobupivacaine (31) • Levobupivacaine plus sufentanil (31) • Levobupivacaine plus sufentanil and clonidine (31)	Hemodynamic stability, intra- and post-operational pain control, motor recovery, side effects	"Levobupivacaine plus 2 γ sufentanyl and 30 γ clonidine optimized postoperative analgesia by delaying the first endovenously administrated dose of analgesic until the seventh hour following the initiation of surgery. This improves patient comfort and reduces nursing needs, thus improving patient outcomes."
Campbell et al, 2008, UK[436]	Observer-blind, randomized trial	60 Patients scheduled for total knee replacement • Epidural (45.2%, mean 70 y ± 8.4) • Lumbar plexus (48.3%, mean 72 y ± 9.9)	Infusion of levobupivacaine and clonidine via either: • Epidural (31) • Lumbar plexus (29)	Pain, sensory, and motor block, range of movement, mobility, adverse effects	"Lumbar plexus infusion is a reasonable alternative to epidural anaesthesia for total knee arthroplasty."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Campbell et al, 2011, US[502] Campbell et al, 2012, US[6] Campbell, 2014, US[503]	Randomized, double-blind, placebo-controlled, parallel-group, multi-center trial	179 Patients diagnosed with length-dependent painful sensory neuropathy affecting the feet attributable to type 1 or type 2 diabetes mellitus • Placebo (47%, mean 57.6 y ± 9.5) • Clonidine (49%, mean 59.4 y ± 9.9)	• Topical clonidine gel (89) • Placebo gel (90)	Pain score	"Topical clonidine gel significantly reduces the level of foot pain in PDN [painful diabetic neuropathy] subjects with functional (and possibly sensitized) nociceptors in the affected skin as revealed by testing with topical capsaicin. Screening for cutaneous nociceptor function may help distinguish candidates for topical therapy for neuropathic pain."
Campbell et al, 2009, US[65]	Double-blind, placebo-controlled trial	166 Patients with diabetic neuropathy (gender and age not specified)	• Clonidine 1% gel (not reported) • Clonidine 2% gel (not reported) • Placebo gel	Pain score	"These data suggest that topical clonidine gel is a safe and effective treatment for NP [neuropathic pain]. A 12-week study is underway to examine further the efficacy of topical 0.1% clonidine in PDN."
Cannata et al, 2014, Italy[66]	—	90 Patients scheduled for endoscopic urological surgery (gender and age not specified)	IT administration of hyperbaric prilocaine plus either: • Sodium chloride (not reported) • Magnesium (not reported) • Clonidine (not reported)	Time to sensory and motor block, duration of sensory and motor block, side effects, time to first void	"The addition of adjuvants like clonidine and magnesium to prilocaine prolonged sensory and motor block, reducing requirements for postoperative additional analgesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Cao et al, 2011, China[67]	Randomized, double-blind study	57 Patients undergoing orthopedic surgery • Bupivacaine (gender not specified, mean 7.4 y ± 1.2) • Intrathecal clonidine (gender not specified, mean 7.2 y ± 1.3) • Intravenous clonidine (gender not specified, mean 7.3 y ± 1.1)	• IT bupivacaine plus IV saline (19) • IT bupivacaine and clonidine plus IV saline (19) • IT bupivacaine plus IV clonidine (19)	Postoperative analgesia and sedation	"Intrathecal or intravenous clonidine similarly provided better postoperative analgesia and sedation and reduced the requirements of propofol. Only intrathecal clonidine prolonged the duration of sensory and motor blocks."
Capdevila et al, 1999, France[437]	Prospective study	56 Patients scheduled for major knee surgery • Patient-controlled analgesia (PCA; 52.6%, mean 58 y ± 16) • Continuous femoral block (40%, mean 54 y ± 17) • Continuous epidural infusion (58.8%, mean 51 y ± 15)	• PCA with IV morphine (19) Solution of lidocaine, morphine, and clonidine via either: • Continuous femoral block (20) • Continuous epidural infusion (17)	Pain, knee flexion, functional outcome	"Regional analgesic techniques improve early rehabilitation after major knee surgery by effectively controlling pain during continuous passive motion, thereby hastening convalescence."
Carabine et al, 1992, UK[281]	Randomized, double-blind, placebo-controlled study	36 Patients scheduled for laparoscopy • Clonidine (0%, mean 33.8 y ± 4) • Fentanyl (0%, mean 32.8 y ± 6) • Saline (0%, mean 34.8 y ± 6)	IV administration of either: • Clonidine (12) • Fentanyl (12) • Saline (12)	Sedation scores, induction dose of thiopentone, hemodynamic parameters, pain score	"In conclusion, in this study intravenous clonidine did not display significant analgesic properties and offered no additional benefits over fentanyl for improving cardiovascular stability during intermediate gynaecological surgery."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Carroll et al, 1993, UK[504] Carroll et al, 1993, UK[282]	Double-blind, randomized, double-dummy, crossover fashion	10 Patients with chronic back pain who had claimed benefit with a previous extradural dose of clonidine combined with local anesthetic (70%, range 40-77 y)	• IV clonidine (10) • Epidural clonidine (10)	Pain intensity, pain relief, adverse effects, mood, sedation, vital signs	"The results of this study suggest that there is no advantage in giving clonidine alone by the epidural route to patients with chronic back pain since the overall pain relief scores were low. Epidural clonidine had no significant clinical advantage over intravenous clonidine and any analgesic effect of clonidine on its own was achieved with a high incidence of adverse effects. It is likely that using higher doses of clonidine in an attempt to demonstrate analgesic effect would risk even greater adverse effects, thus precluding the use of this drug in this context."
Carvalho et al, 2016, Brazil[283]	Prospective, double-blind, randomized, clinical trial	187 Patients undergoing elective cesarean section • Morphine and clonidine (0%, mean 29.6 y ± 4.9) • Morphine 100 mcg (0%, mean 29.4 y ± 4.8) • Morphine 50 mcg (0%, mean 28.1 y ± 5.2)	IT hyperbaric bupivacaine plus: • Morphine and clonidine (64) • Morphine 100 mcg (63) • Morphine 50 mcg (60)	Pain levels, side effects	"At these doses, there was no benefit of associating clonidine with morphine to improve postcesarean analgesia. Considering that higher doses of morphine were associated with more side effects, 50 mcg of intrathecal morphine alone seems to be a better option for analgesia. The use of clonidine to reduce postoperative shivering must be balanced against the potential risks of hypotension, bradycardia, dizziness, and sedation."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Casati et al, 2001, Italy[68]	Prospective, randomized, double-blind study	30 Patients undergoing upper extremity orthopedic procedures (60%, range 21-70 y)	Axillary brachial plexus block with either: • Ropivacaine (15) • Ropivacaine and clonidine (15)	Time required to achieve surgical block, first analgesic request	"Adding 1 mcg/kg clonidine to 20 ml of ropivacaine 0.75% for axillary brachial plexus anesthesia provided a 3 h delay in first analgesic request postoperatively, without clinically relevant effects on the degree of sedation and cardiovascular homeostasis."
Casati et al, 2000, Italy[69]	Prospective, randomized, double-blind study	30 Patients undergoing hallux valgus repair under combined sciatic-femoral nerve block (16.7%, range 21-74 y)	Sciatic-femoral nerve block with either: • Ropivacaine (15) • Ropivacaine plus clonidine (15)	Hemodynamic variables, oxygen saturation, levels of sedation, time required to achieve surgical block, time to first analgesic request	"We conclude that adding 1 mcg/kg clonidine to 0.75% ropivacaine provided a 3-h delay in first request for pain medication after hallux valgus repair, with no clinically relevant side effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Casati et al, 2005, Italy[366]	Prospective, randomized, double-blind study	60 Patients undergoing total knee arthroplasty (40%, range 18-81 y)	Continuous femoral nerve block: • Induction and maintenance with ropivacaine (20) • Induction with ropivacaine and clonidine, maintenance with ropivacaine (20) • Induction and maintenance with ropivacaine and clonidine (20)	Pain score, total consumption of local anesthetic solution	"Further studies evaluating the possibility of reducing the ropivacaine concentration when adding small concentrations of clonidine for peripheral nerve blocks should be performed to better evaluate the theoretical advantages of the enhancement of nerve block induced by α2-adrenoceptor agonists; however, results of this prospective, randomized, double-blind study suggest that adding clonidine 1 mcg/kg in the initial bolus followed by clonidine 1 mcg/mL in the postoperative infusion solution does not provide clinically relevant advantages in terms of improved postoperative analgesia or reduced volumes of 0.2% ropivacaine required to maintain an adequate analgesia, but it has the potential for delaying the recovery of motor function."
Chakraborty et al, 2010, India[70]	Randomized, double-blind, placebo-controlled trial	63 Patients undergoing upper limb orthopedic procedures • Clonidine (68.8%, mean 41.65 y ± 13.26) • Saline (67.7%, mean 41.70 y ± 9.54)	Supraclavicular approach for brachial plexus block with bupivacaine plus either: • Clonidine (32) • Saline (31)	Onset and duration of sensory and motor blocks, sedation score, duration of analgesia	"Addition of a small dose of clonidine to 0.5% bupivacaine significantly prolonged the duration of analgesia without producing any clinically important adverse reactions other than sedation."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Chaoba Singh et al, 2011, India[71]	—	60 Patients undergoing lower abdominal surgery (gender and age not specified)	IT administration of either: • Hyperbaric bupivacaine (30) • Hyperbaric bupivacaine plus clonidine (30)	Hemodynamic parameters, side effects, duration of analgesia	"It may be concluded that intrathecal clonidine at the dose of 1 mcg/kg significantly prolongs the post-operative pain free period without significant cardiovascular changes and side effects."
Charvin et al, 2020, France[273]	Randomized, double-blind, controlled trial	44 Patients scheduled for bypass surgery • Sham block (85%, mean 63.7 y ± 7.7) • Active block (79.2%, mean 64.8 y ± 8.3)	Combined femoral and sciatic nerve block with either: • Sham block (20) • Active block with levobupivacaine and clonidine (24)	Morphine consumption	"Combining the two regional blocks improves the quality of postoperative care in this frail population, probably by reducing the amount of peri-operative opioid."
Chatrath et al, 2015, India[438]	Prospective, randomized, double-blind study	60 Patients scheduled to undergo forearm or hand surgery • Ropivacaine (80%, mean 35.30 y ± 12.84) • Bupivacaine (73.33%, mean 37.47 y ± 12.78)	Infraclavicular block with clonidine plus either: • Ropivacaine (30) • Bupivacaine (30)	Onset and duration of sensory and motor block, postoperative analgesia, side-effects, complications	"Addition of clonidine to bupivacaine led to early onset and prolonged duration of sensory and motor block with prolonged analgesia as compared to the addition of clonidine to ropivacaine."
Chaudhary et al, 2016, India[284]	Prospective, randomized, double-blind, controlled, clinical trial	90 Patients scheduled to undergo below knee orthopedic surgeries • Control (gender not specified, mean 40.03 y ± 14.74) • Dexmedetomidine (gender not specified, mean 39.10 y ± 15.24) • Clonidine (gender not specified, mean 36.37 y ± 11.61)	Femoro-sciatic nerve block with levobupivacaine plus either: • Control (30) • Dexmedetomidine (30) • Clonidine (30)	Duration of analgesia	"Equal doses of clonidine or dexmedetomidine added to levobupivacaine prolonged the duration of analgesia, decreased requirement of rescue analgesia. Dexmedetomidine delays the requirement of rescue analgesics with better pain scores as compared to clonidine."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Chawda and Sharma, 2010, India[72]	Double-blind, randomized, prospective study	60 Patients undergoing orthopedic upper limb surgical procedures • Epinephrine (53.3%, mean 36.67 y ± 12.81) • Clonidine (43.3%, mean 36.6 y ± 16.54)	Supraclavicular brachial plexus block with lignocaine and bupivacaine plus either: • Epinephrine (30) • Clonidine (30)	Onset of sensory and motor block, duration of postoperative analgesia, hemodynamic changes, sedation scores, adverse effects	"We thereby conclude that clonidine 90 mcg is a better option as an additive than epinephrine 200 mcg for hastening the onset of sensory and motor block with prolonged postoperative analgesia and sedation as the only adverse effect."
Chetty et al, 2018, India[73]	Prospective, randomized, placebo-controlled, double-blind, comparative study	90 Patients scheduled for elective total abdominal hysterectomy • Control (0%, mean 41.4 y ± 5.9) • Nalbuphine (0%, mean 42.9 y ± 5.9) • Clonidine (0%, mean 40.9 y ± 6.8)	IT bupivacaine plus either: • Control (30) • Nalbuphine (30) • Clonidine (30)	Onset and duration of sensory and motor block, duration of analgesia, total postoperative analgesic requirement	"Intrathecal clonidine is associated with prolonged motor and sensory block, better hemodynamic stability, and less postoperative analgesic requirement as compared to nalbuphine."
Chiari et al, 1999, Austria[367]	Prospective, randomized, double-blind study	36 Patients requesting labor analgesia • Clonidine 50 mcg (0%, mean 26 y ± 5.6) • Clonidine 100 mcg (0%, mean 24 y ± 5.2) • Clonidine 200 mcg (0%, mean 28 y ± 7.2)	IT administration of clonidine at dose of either: • 50 mcg (12) • 100 mcg (12) • 200 mcg (12)	Pain score, maternal blood pressure and heart rate, ephedrine requirements, sedation, duration of analgesia	"Duration and quality of analgesia were more pronounced with 100 mcg and 200 mcg than with 50 mcg, but 200 mcg doses were also associated with a high incidence of hypotension. Further studies are warranted to evaluate the safety for the possible clinical use of intrathecal clonidine as the sole analgesic during labor."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Chopra and Talwar, 2014, India[368]	Prospective, randomized, double-blind study	75 Patients scheduled for vaginal hysterectomy with pelvic floor repair or non-descent vaginal hysterectomy • Fentanyl (0%, mean 46.2 y ± 8.6) • Clonidine (0%, mean 51.6 y ± 8.2) • Clonidine and fentanyl (0%, mean 43.5 y ± 7.4)	IT administration of hyperbaric bupivacaine plus either: • Fentanyl (25) • Clonidine (25) • Fentanyl and clonidine (25)	Duration of effective analgesia	"In conclusion, we observed that 30 mcg of clonidine added to bupivacaine and fentanyl increased the duration of effective analgesia as well as the duration of sensory and motor block, as compared to bupivacaine — clonidine and bupivacaine — fentanyl combinations, without causing any significant hemodynamic side effects. The incidence of intraoperative pain and requirement of postoperative analgesics is significantly less with the addition of clonidine to the intrathecal mixture. One of the limitations of our study was the small sample size. Although certain trends could be established in this pilot study, further controlled, large sample-sized studies are required to confirm the results."
Cindea et al, 2012, Romania[74]	Prospective study	93 Patients scheduled for colorectal surgery (gender and age not specified)	IV administration of either: • Clonidine (48) • Saline (45)	Pain intensity, level of sedation, hemodynamic profile, total morphine consumption	"Preoperative intravenous administration of clonidine has been associated with significantly decreased pain level and lower morphine requirement during first 24h after colorectal surgery, without impairment of conscious state or adverse hemodynamic changes."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Collis et al, 2016, US[409]	Prospective, randomized study	105 Patients undergoing primary total knee arthroplasty (TKA) • Liposomal bupivacaine (47%, mean 63.7 y ± 8.8) • Modified Ranawat suspension (27%, mean 63.5 y ± 10.1)	Periarticular injection with either: • Liposomal bupivacaine (54) • Modified Ranawat suspension containing ropivacaine, epinephrine, ketorolac, and clonidine (51)	Postoperative narcotic use, knee range of motion	"Although there were improved walking distances with the liposomal bupivacaine group, this was not found to be statistically significant. Overall, we found there to be no difference in pain scores, narcotic consumption, activity levels, range of motion, and disposition between the liposomal bupivacaine group and the modified Ranawat group after primary TKA."
Connelly et al, 1999, US[285]	Randomized, double-blind study	45 Patients undergoing unilateral inguinal hernia repair • Control (gender not specified, mean 52 y ± 14) • Surgical site (gender not specified, mean 51 y ± 12) • Intramuscular (gender not specified, mean 55 y ± 16)	• Control (15) • Surgical site lidocaine mixed with clonidine plus IM saline (15) • IM clonidine plus surgical site lidocaine mixed with saline (15)	Pain scores, time to first analgesic, total analgesic requirement	"In conclusion, when clonidine is administered to patients undergoing hernia repair, the 2-hour pain scores are lowered. Intramuscular administration of clonidine is no different than administering it directly into the hernia site. Because of the relatively minor benefits from clonidine, we do not recommend it be used in patients undergoing inguinal herniorrhaphy."
Contreras-Domínguez et al, 2007, Chile[75]	Controlled, prospective study	60 Patients undergoing reconstruction of anterior cruciate ligament of the knee • Continuous femoral nerve block (60%, mean 25 y ± 3) • Continuous intravenous analgesia (60%, mean 23 y ± 4)	• Continuous femoral nerve block with bupivacaine and clonidine (30) • Continuous IV analgesia with ketoprofen (30)	Postoperative pain, morphine consumption, satisfaction score, complications	"The three-in-one block with bupivacaine and clonidine in continuous infusion provides more efficient analgesia, patient satisfaction and less consumption of intravenous morphine and PONV than intravenous analgesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Coombs et al, 1986, US[76]	Case report	1 Patient with intractable uterine cervical cancer-related pain (0%, 49 y)	• Implanted IT infusion pump that delivered hydromorphone and clonidine (1)	Pain	"Intrathecal hydromorphone and clonidine successfully controlled this patient's pain without the necessity to resort to destructive neurosurgery."
Corriveau et al, 2016, US[439]	Case report	1 Patient with refractory CRPS (100%, 40 y)	• Bier block with IV lidocaine and clonidine (1)	Resolution of CRPS symptoms	"This patient with symptoms refractory to standard CRPS treatments responded positively to successive Bier block, which then allowed him to return to the operating room for surgical fixation of his left wrist. The performance of a Bier block has been supplanted by other procedures for many of its indications. However, we found sequential Bier block to be effective for treating this patient's CRPS, and with a limited risk profile and possible benefit, Bier block should be considered [in] similar cases of refractory CRPS. This is a novel utilization with no long term outcome data available and further research is warranted."
Couture et al, 2004, US[286]	Prospective, randomized, double-blind investigation	55 Patients undergoing anterior cruciate ligament reconstruction • Control (96.3%, mean 25.2 y ± 4.1) • Clonidine (96.4%, mean 28.5 y ± 6.1)	Combined femoral-sciatic nerve block with bupivacaine and epinephrine plus either: • Control (27) • Clonidine (28)	Pain intensity, duration of sensory analgesia, postoperative analgesic requirements, patient satisfaction	"Based on our results, we do not recommend the addition of clonidine to a femoral-sciatic nerve block when given to facilitate postoperative analgesia in patients undergoing ACL reconstruction."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Crawford et al, 2019, Australia[369]	Randomized, controlled study	80 Patients undergoing laparoscopic gynecological surgery • Control (0%, mean 37.4 y ± 6.5) • Clonidine (0%, mean 37.1 y ± 8.2) • Adrenaline (0%, mean 36.8 y ± 10.5) • Subcutaneous clonidine (0%, mean 36.6 y ± 6.8)	TAP block with ropivacaine plus: • Control (20) • Clonidine (20) • Adrenaline (20) • Subcutaneous clonidine (20)	Total venous plasma ropivacaine concentrations	"These findings indicate that clonidine at a concentration of 1.35 mcg/mL added to ropivacaine for TAP blocks did not produce a reduction in plasma ropivacaine concentrations. This suggests a lack of vasoconstrictor effect during TAP blocks. Further studies should evaluate whether vasoconstriction occurs when clonidine is used at higher concentrations or for other blocks."
Cucchiaro and Ganesh, 2007, US[77]	—	415 Patients undergoing single-shot peripheral nerve block (58.1%, range 2-22 y)	Peripheral nerve block with: • Either bupivacaine or ropivacaine (197) • Either bupivacaine or ropivacaine plus clonidine (118)	Duration of sensory and motor block	"The addition of clonidine to bupivacaine and ropivacaine can extend sensory block by a few hours, and increase the incidence of motor blocks."
Culebras et al, 2001, Switzerland[287]	Prospective, randomized, double-blind study	60 Patients who underwent elective rotator cuff repair using interscalene brachial plexus block • Placebo (75%, mean 52 y ± 10) • Intramuscular clonidine (75%, mean 52 y ± 9) • Perineural clonidine (70%, mean 51 y ± 10)	Interscalene block with bupivacaine and epinephrine plus: • Placebo (20) • IM clonidine (20) • Perineural clonidine (20)	Pain scores, consumption of morphine, hemodynamic changes	"The lack of analgesic benefit along with hemodynamic effects observed precludes us from recommending the use of clonidine in interscalene block when using a long-acting local anesthetic."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Dagher et al, 2003, Lebanon[505] Dagher et al, 2005, Lebanon[288]	Prospective, randomized study	60 Patients scheduled for unilateral inguinal herniorrhaphy (gender and age not specified)	Ilioinguinal nerve block with bupivacaine plus either: • Clonidine (not reported) • Saline (not reported)	Pain scores, sedation, hemodynamic variation, first analgesic request	"Addition of small doses of clonidine to bupivacaine in ilioinguinal and iliohypogastric block does not improve or prolong analgesia following inguinal hernia repair. No specific side effects were found."
Dandriyal et al, 2017, India[78]	Prospective, randomized, controlled, parallel-group study	200 Patients who required extraction of mandibular teeth (gender not specified, mean 31 y)	Inferior alveolar mandibular nerve block with lidocaine plus either: • Adrenaline (100) • Clonidine (100)	Cardiovascular variables, postoperative pain	"We conclude that clonidine could be a useful and safe alternative to adrenaline for intraoral block anaesthesia."
Danelli et al, 2006, Italy[79]	Randomized, double-blind study	40 Patients undergoing elective carotid thrombus endarterectomy (TEA; 72.5%, range 56-82 y)	Superficial cervical plexus block with either: • Ropivacaine (20) • Ropivacaine and clonidine (20)	Nerve block profile, need for intraoperative analgesic supplementation, time to first analgesic request	"Adding 50 mcg clonidine to 150 mg ropivacaine for superficial cervical plexus block shortened the onset time and improved the quality of surgical anesthesia in patients undergoing elective TEA."
Dang et al, 2019, US[410]	Prospective, randomized, double-blind study	56 Patients undergoing foot and ankle surgery (19.6%, age not specified)	Peripheral nerve block with either: • Bupivacaine (30) • Bupivacaine plus buprenorphine, clonidine, and dexamethasone (26)	Pain scores	"Both types of nerve blocks provided equivalent pain control and patient satisfaction in patients undergoing foot and ankle surgery. The 3-additive agent blocks were associated with a longer duration of pain relief and a longer duration of numbness, as well as higher rates of postoperative neurologic symptoms. Longer pain relief may be obtained at the cost of prolonged sensory deficits."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
D'Angelo et al, 2001, US[440]	—	30 Patients receiving labor analgesia • Control (0%, mean 25 y ± 4) • Neostigmine (0%, mean 29 y ± 6)	Spinal bupivacaine, clonidine, and sufentanil plus either: • Control (15) • Neostigmine (15)	Pain, maternal hemodynamics, fetal heart rate, nausea, pruritus, sedation, motor block, sensory levels, maternal oxygen saturation	"In summary, neostigmine 10 mcg failed to enhance spinal labor analgesia when combined with bupivacaine, clonidine, and sufentanil but did significantly increase the incidence of nausea and vomiting. On the basis of these findings, we do not recommend the use of spinal neostigmine in labor patients."
D'Angelo et al, 1999, US[370]	Randomized by double-blind design	30 Patients in early labor • Saline (0%, mean 26 y ± 5) • Clonidine (0%, mean 25 y ± 6)	Spinal injection of sufentanil and bupivacaine plus either: • Saline (15) • Clonidine (15)	Pain scores, side effects	"We conclude that spinal clonidine 50 mcg prolongs analgesia from spinal sufentanil 7.5 mcg plus bupivacaine 2.5 mg without producing serious adverse side effects. Additional studies are required to determine the safety of spinal clonidine and whether spinal clonidine will allow more patients to deliver without requiring epidural analgesia when CSE [combined spinal-epidural] analgesia is used."
Das Adhikari et al, 2018, India[80]	Randomized, controlled study	90 Patients posted for unilateral upper limb surgery • Normal saline (73%, mean 31.7 y ± 12.8) • Clonidine 45 mcg (73%, mean 33.6 y ± 13.4) • Clonidine 90 mcg (80%, mean 38.5 y ± 15.1)	Supraclavicular brachial plexus block with lignocaine, adrenaline, bupivacaine, and either: • Normal saline (30) • Clonidine 45 mcg (30) • Clonidine 90 mcg (30)	Time required for rescue analgesia, pain score, sedation score	"Ninety microgram clonidine is an attractive alternative as an adjuvant in the ultrasound-guided supraclavicular block for upper limb surgical procedures especially in those that need quite long time with minimal side effects and excellent quality of postoperative analgesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Das et al, 2016, India[289]	Prospective, double-blind, randomized, controlled study	90 Patients posted for ambulatory elective hand surgery • Dexmedetomidine (75.55%, mean 34.78 y ± 10.52) • Clonidine (82.22%, mean 37.11 y ± 9.81)	Axillary brachial plexus block with ropivacaine plus either: • Dexmedetomidine (45) • Clonidine (45)	Sensory and motor block onset times and durations, time to first analgesic use, total analgesic need, pain score, hemodynamics, side effects	"We do conclude that during day care hand surgery, addition of 100 mcg dexmedetomidine is more effective than 75 mcg clonidine; regarding early onset of sensory and motor blockade, prolongation of block duration, reducing the requirement of rescue analgesic in postoperative period; when added to ropivacaine 0.50% solution in axillary brachial plexus block without any appreciable side-effect."
Dash et al, 2010, India[81]	—	60 Patients undergoing supratentorial craniotomies (55%, range 18-70 y)	• Scalp block with bupivacaine and normal saline plus IV normal saline (20) • Scalp block with bupivacaine and clonidine plus IV normal saline (20) • Scalp block with bupivacaine and normal saline plus IV clonidine (20)	Hemodynamics, propofol and fentanyl requirements	"The addition of clonidine, either to the scalp block or intravenously, offers better haemodynamic stability intraoperatively, and reduces analgesic and anaesthetic requirements."
Dash et al, 2016, India[82]	Prospective, randomized, parallel-arm study	60 Patients undergoing elective lumbar laminectomy • Clonidine (gender not specified, mean 54.8 y ± 5.7) • Fentanyl (gender not specified, mean 54.7 y ± 5.9)	IT bupivacaine plus either: • Clonidine (30) • Fentanyl (30)	Duration of sensory and motor block, duration of postoperative analgesia, hemodynamic stability	"Both clonidine 75 mcg and fentanyl 25 mcg when used as adjuvants to bupivacaine in the subarachnoid block have comparable beneficial results in terms of duration of analgesia, duration of motor blocks, and hemodynamic stability and also have a comparable incidence of complications."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Datta et al, 2016, India[83]	Prospective, randomized, double-blind study	90 Patients undergoing vaginal hysterectomy • Control (0%, mean 55 y ± 11.2) • Fentanyl (0%, mean 54 y ± 8.5) • Clonidine (0%, mean 56 y ± 9)	IT bupivacaine plus either: • Control (30) • Fentanyl (30) • Clonidine (30)	Onset and regression of sensory and motor blocks, hemodynamic change, side effects, pain intensity, time to first rescue analgesic	"We conclude that low-dose intrathecal clonidine is an effective adjuvant to bupivacaine for spinal anesthesia and provides better postoperative analgesia in comparison with intrathecal fentanyl."
Dauri et al, 2009, Italy[441]	—	52 Patients undergoing anterior cruciate ligament reconstruction (98.1%, range 18-45 y)	Sciatic nerve block with ropivacaine and clonidine plus: • Continuous femoral nerve block with ropivacaine (26) • Single-shot FNB with ropivacaine and clonidine (26)	Hemodynamic, pain scores, adverse effects, need for supplemental analgesia	"Continuous femoral nerve block provides better analgesia than the continuous patellar tendon wound and intra-articular infusions after anterior cruciate ligament reconstruction with patellar tendon."
Dauri et al, 2007, Italy[442]	Prospective, randomized study	70 Patients undergoing ACL reconstruction (87.1%, range 18-45 y)	Femoral nerve block with ropivacaine and clonidine via: • Stimulating catheter (35) • Non-stimulating catheter (35)	Pain scores, adverse effects, need for supplemental analgesia and anesthesia	"Although the use of a stimulating catheter was associated with faster onset time for the femoral nerve block and lower additional analgesics postoperatively, the clinical superiority (analgesia; lateral femoral cutaneous, and obturator nerve block) of stimulating catheters was not evident in this clinical setting."
Davis and Kopacz, 2005, US[84]	Randomized, double-blind, crossover study	8 Healthy volunteers (50%, mean 34 y ± 11)	Spinal anesthesia with either: • 2-Chloroprocaine (8) • 2-Chloroprocaine and clonidine (8)	Pinprick anesthesia, motor strength, tolerance to electrical stimulation and thigh tourniquet, time to ambulation	"We conclude that small-dose clonidine increases the duration and improves the quality of 2-CP [2-chloroprocaine] spinal anesthesia without systemic side effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
De Deyne et al, 2000, Belgium[272]	Placebo-controlled, double-blind, clinical trial	60 Patients scheduled for laparoscopic surgery • Placebo (60%, mean 48 y ± 14) • Clonidine (66.7%, mean 45 y ± 13)	• Placebo (30) • IV clonidine (30)	Sevoflurane requirements, hemodynamic stability, postoperative analgesia requirements	"Mean sevoflurane requirements were not lower with clonidine pretreatment. There was statistically better perioperative hemodynamic stability (i.e., fewer episodes of hypertension and tachycardia) without clinical relevance. A decreased need for postoperative analgesia was observed."
De Kock et al, 1992, Belgium[85]	Prospective study	187 Patients undergoing major abdominal surgery • Clonidine (55.2%, mean 52.7 y ± 15.6) • Control (54.9%, mean 52.3 y ± 15.8)	Balanced anesthesia plus either: • IV clonidine (96) • Control (91)	Analgesic demands, pain scores, sedation scores, side effects	"Considering the absence of side effects with the dosage used, clonidine should be considered as a constituent of the postoperative 'balanced' analgesia."
De Kock et al, 1993, Belgium[506] De Kock et al, 1993, Belgium[290]	Randomized, prospective, double-blind study	40 Patients undergoing intestinal surgery • Epidural clonidine (65%, mean 34.2 y ± 7.6) • Intravenous clonidine (65%, mean 36.8 y ± 10.7)	• Epidural clonidine (20) • IV clonidine (20)	Analgesic requirements, pain scores, sedation, side effects, heart rate, blood pressure	"Epidural clonidine reduces the intra- and early postoperative analgesic requirements when compared with the same dose given by the intravenous route. The side effects were similar with the two routes of administration."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
De Kock et al, 2001, Belgium[86]	Dose-response study	120 Patients scheduled for knee arthroscopy • Ropivacaine (40%, mean 46 y ± 14) • Ropivacaine plus clonidine 15 mcg (56.7%, mean 45 y ± 16) • Ropivacaine plus clonidine 45 mcg (53.3%, mean 45 y ± 18) • Ropivacaine plus clonidine 75 mcg (50%, mean 44 y ± 15)	IT administration of either: • Ropivacaine (30) • Ropivacaine plus clonidine 15 mcg (30) • Ropivacaine plus clonidine 45 mcg (30) • Ropivacaine plus clonidine 75 mcg (30)	Level and duration of sensory block, intensity and duration of motor block, anesthesia quality	"Small-dose intrathecal clonidine (15 mcg) plus 8 mg intrathecal ropivacaine produces adequate and short-lasting anesthesia for knee arthroscopy."
De Kock et al, 1994, Belgium[87]	Double-blind, randomized trial	80 Patients scheduled for colonic resection • Group 1 (100%, mean 44 y ± 15) • Group 2 (100%, mean 49 y ± 14) • Group 3 (100%, mean 47 y ± 15) • Group 4 (100%, mean 47 y ± 13)	• Group 1: Intraoperative fentanyl and postoperative morphine PCA (15) • Group 2: Intraoperative fentanyl and clonidine and postoperative morphine PCA (15) • Group 3: Intraoperative fentanyl and clonidine and postoperative morphine and clonidine PCA (25) • Group 4: Intraoperative fentanyl, clonidine, and lignocaine and postoperative morphine, clonidine, and lignocaine (25)	Analgesic requirements, pain scores, sedation, side effects, heart rate, blood pressure	"Intraoperative clonidine was the major determinant of the reduction in analgesic demands and morphine delivered. Lignocaine, at the dose used, failed to afford any additional benefit."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
De Kock et al, 2005, Belgium[88]	—	60 Patients undergoing right colonic resection • Clonidine (50%, mean 66 y ± 5) • Saline (40%, mean 65 y ± 4) • Bupivacaine (45%, mean 65 y ± 5)	IT administration of either: • Clonidine (20) • Saline (20) • Bupivacaine (20)	Morphine requirements, pain scores	"We conclude that both intraoperative spinal clonidine and bupivacaine improve immediate postoperative analgesia. IT clonidine was, however, more potent than IT bupivacaine to reduce postoperative secondary hyperalgesia."
De Kock et al, 1992, Belgium[443]	—	18 Patients undergoing elective vaginal hysterectomy (0%, range 45-55 y)	• Epidural clonidine and IV saline (6) • Epidural saline and IV clonidine (6) • Epidural and IV saline (6)	Electroencephalogram (EEG) power spectral analysis	"The difference in effect between the IV and epidural clonidine provides evidence for an EEG depressant effect of epidural clonidine. Although our study cannot clarify the mechanism responsible for this observation, we speculate that it may represent a direct spinal action of the α2 agonist, which may lead to a greater depth of anesthesia."
De Negri et al, 1997, Italy[89]	Prospective, randomized study	56 Patients scheduled for minor surgical procedure • Clonidine (100%, mean 24 y ± 4) • Saline (100%, mean 27 y ± 3)	Spinal anesthesia with bupivacaine plus either: • Clonidine (28) • Saline (28)	Mean arterial pressure, heart rate, sensory and motor block, sedation level	"In summary, the addition of clonidine to hyperbaric bupivacaine seems to be particularly useful in unilateral spinal anesthesia, exerting minimal influence on haemodynamic parameters, and guaranteeing a satisfactory postoperative analgesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Delaunay et al, 1991, France[90]	—	20 Patients undergoing thyroid surgery (10%, range 20-52 y)	IV administration of either: • Isotonic saline (10) • Clonidine (10)	Oxygen consumption (VO2), carbon dioxide production (VCO2)	"Clonidine was found to attenuate the increase in VO2 and VCO2 associated with recovery from anaesthesia. The effect of clonidine was associated with a reduction in shivering. Sedative and analgesic properties of clonidine may also contribute to the reduction in metabolic demand during recovery from anaesthesia."
Dereu et al, 2019, Switzerland[291]	Single-center, 1:1-randomized, quadruple-blind, controlled trial	181 Patients undergoing elective cesarean section • TAP block (0%, median 34 y [Interquartile range 30.75-37]) • Intrathecal morphine (ITM; 0%, median 34 y [IQR 31-38])	• Bilateral TAP block with ropivacaine and clonidine (92) • IT morphine (89)	Nausea and vomiting	"A TAP block with clonidine and local anaesthetic does not reduce significantly the incidence of PONV compared with ITM. We confirm the superiority of ITM on acute postcaesarean section analgesia compared with a TAP block, even with clonidine as an adjunct."
Deshmukh et al, 2015, India[91]	Randomized, prospective, double-blind trial	60 Patients admitted undergoing upper limb surgeries (gender not specified, range 20-66 y)	Interscalene brachial plexus block with ropivacaine plus either: • Normal saline (30) • Clonidine (30)	Duration of sensory and motor block, duration of postoperative analgesia, hemodynamics, patient satisfaction	"In conclusion, clonidine added to ropivacaine is an attractive option for improving the quality and duration of interscalene brachial plexus block in upper limb surgeries with stable perioperative hemodynamics."
Dhashmana et al, 2014, India[292]	Prospective, randomized, double-blind study	50 Patients scheduled for elective transurethral resection of prostate (TURP; 100%, age not specified)	IT ropivacaine plus either: • Clonidine (not reported) • Dexmedetomidine (not reported)	Onset, duration and peak sensory level, intensity of motor block, analgesic requirement	"Intrathecal dexmedetomidine with ropivacaine provides faster onset, better operating conditions and patient comfort in patients undergoing TURP. However, it is associated with delayed motor recovery."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Dhashmana and Tiwari, 2017, India[92]	Prospective, randomized, double-blind, comparative study	60 Patients undergoing anorectal surgery (gender and age not specified)	Spinal anesthesia with either: • Hyperbaric ropivacaine (not reported) • Hyperbaric ropivacaine and clonidine (not reported) • Hyperbaric ropivacaine and fentanyl (not reported)	Onset, level, and duration of sensory and motor blockade	"Hypobaric ropivacaine provides adequate surgical conditions for anorectal surgeries. Intrathecal clonidine with 0.1% hypobaric ropivacaine is a better adjuvant than fentanyl as it prolongs the duration and improves the quality of the sensory block and provides long postoperative analgesia."
Di Capua et al, 2015, India[93]	Double-blind, placebo-controlled trial	176 Patients undergoing major shoulder surgery (gender and age not specified)	Single shot interscalene brachial plexus block with levobupivacaine plus either: • Clonidine (88) • Control (88)	Pain score	"In this double-blind placebo-controlled trial, the addition of clonidine significantly prolongs the analgesic effect of levobupivacaine single shot interscalene brachial plexus block."
Di Donato et al, 2006, Italy[444]	—	328 Patients undergoing shoulder arthroscopy • Levobupivacaine (63.4%, mean 58 y) • Ropivacaine (56.1%, mean 55 y)	Interscalene brachial plexus block (IBPB) with tramadol, clonidine, and: • Levobupivacaine (164) • Ropivacaine (164)	Sensory and motor onset times, time required to achieve surgical anesthesia, motor block, analgesia, analgesic requirement	"Our results demonstrate the efficacy of our block technique, showing a high rate of success. Under these conditions, the same volume of 0.5% levobupivacaine has a higher, statistically significant increase in the quality of IBPB compared to 0.75% ropivacaine when used in combination with clonidine and tramadol."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
DiGiusto and Suleman, 2018, US[445]	Case report	1 Patient presenting with an 8-month history of abdominal pain (0%, 18 y)	• Unilateral TAP block and trigger-point injection with ropivacaine and clonidine (1)	Pain relief	"The patient has been followed for over a year and notes that there have been a handful of instances when pain returned, although it has always been short-lived and remitted with rest. She has not required any further interventional procedures and has resumed her life as normal before her abdominal pain."
Dobrydnjov et al, 2005, Sweden[94]	Double-blind, randomized, placebo-controlled study	60 Patients undergoing hip arthroplasty • Group 1 (80%, mean 65 y ± 7) • Group 2 (60%, mean 66 y ± 11) • Group 3 (65%, mean 65 y ± 10)	Spinal anesthesia was provided intraoperatively, and epidural anesthesia was postoperative: • Group 1: Spinal bupivacaine and epidural ropivacaine (20) • Group 2: Spinal bupivacaine and epidural ropivacaine plus clonidine (20) • Group 3: Spinal bupivacaine plus clonidine and epidural ropivacaine plus clonidine (20)	Sensory block, duration of anesthesia, analgesia, and motor block, pain score, morphine consumption, arterial pressure, time to first dose of morphine, heart rate	"Low-dose intrathecal clonidine provided a better quality of anesthesia and longer-lasting analgesia. Epidural clonidine-ropivacaine infusion resulted in improved post-operative analgesia but was associated with a moderate decrease in blood pressure."
Dobrydnjov et al, 2002, Sweden[95]	Double-blind study	45 Patients scheduled for osteosynthesis of a traumatic femur fracture • Saline (20%, mean 55 y ± 6.8) • IT clonidine (13.3%, mean 52 y ± 7.1) • Oral clonidine (20%, mean 56 y ± 6.9)	IT bupivacaine plus either: • Saline (15) • Clonidine (15) • Oral clonidine (15)	First request for analgesics, morphine consumption, mean arterial pressure, heart rate, sedation, side effects	"Intrathecal clonidine is recommended due to the higher quality of postoperative analgesia and the lower degree of hypotension and sedation compared to oral clonidine."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Dobrydnjov et al, 2003, Sweden[96]	Randomized, double-blind study	45 Patients undergoing open inguinal herniorrhaphy as a day-case procedure • Saline (gender not specified, mean 62 y ± 10) • Clonidine 15 mcg (gender not specified, mean 60 y ± 16) • Clonidine 30 mcg (gender not specified, mean 56 y ± 19)	IT hyperbaric bupivacaine plus either: • Saline (15) • Clonidine 15 mcg (15) • Clonidine 30 mcg (15)	Sensory and motor block characteristics, time to first analgesic, postoperative pain, side effects	"We conclude that clonidine 15 mcg with bupivacaine 6 mg produced an effective spinal anesthesia and recommend this dose for inguinal herniorrhaphy, because it did not prolong the motor block."
Dobrydnjov and Samarutel, 1999, Estonia[97]	—	90 Patients scheduled for open prostatectomies, hysterectomies, or osteosynthesis of fractured hip (55.6%, mean 63 y)	• IT lidocaine 100 mg (15) • IT lidocaine 40 mg and clonidine (15) • IT lidocaine 40 mg and oral clonidine (15) • IT lidocaine 80 mg and clonidine (15) • IT lidocaine 80 mg and oral clonidine (15) • IT lidocaine 80 mg and phenylephrine (15)	Onset and duration of sensory and motor block, hemodynamic depression, sedation	"Our results indicate that the addition of clonidine to lidocaine, irrespective of the route of administration, prolongs the duration of spinal block and permits a reduction of the lidocaine dose needed for a given duration of block. Addition of phenylephrine results in a less pronounced statistically significant prolongation of anaesthesia. The regression of sensory block before restoration of motor function seems to be a specific (and unfortunate) effect of both clonidine and phenylephrine."
Doss and Zaazou, 2003, Egypt[98]	Double-blind study	40 Patients scheduled for shoulder arthroscopy (gender and age not specified)	Interscalene brachial plexus block with either: • Levobupivacaine (20) • Levobupivacaine and clonidine (20)	Block onset time, pulmonary function variables, first requirement of postoperative analgesia, pain scores, hemodynamics, sedation	"The addition of clonidine 0.5 mcg/kg to levobupivacaine 0.5% in interscalene brachial plexus block is well tolerated and gives better and more prolonged analgesia than the use of levobupivacaine 0.5% alone in patients undergoing shoulder arthroscopy."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Duma et al, 2005, Austria[293]	Prospective, randomized, controlled, double-blind, single-center, parallel-group trial	78 Patients undergoing surgery of the forearm or hand • Levobupivacaine and clonidine (55%, mean 45.4 y ± 18.7) • Levobupivacaine (60%, mean 43.5 y ± 19.5) • Bupivacaine and clonidine (60%, mean 43.3 y ± 16.5) • Bupivacaine (61.1%, mean 36.7 y ± 16.1)	Axillary brachial plexus block: • Levobupivacaine and clonidine (20) • Levobupivacaine (20) • Bupivacaine and clonidine (20) • Bupivacaine (18)	Onset of motor and sensory block, duration of sensory block	"Finally, as long as we (i) do not know the relevant factors about the actions and failures of clonidine at peripheral nerves, and (ii) observe inconsistent, unpredictable variations in duration of block without reliable benefit, we cannot recommend the use of clonidine in conjunction with bupivacaine or levobupivacaine for peripheral nerve blocks."
Eisenach et al, 2000, US[411]	—	24 Healthy volunteers requiring treatment of capsaicin-induced hyperalgesia and allodynia (45.8%, mean 33 y ± 7.8)	IT administration of clonidine at a dose of either: • 75 mcg (not reported) • 150 mcg (not reported) • 300 mcg (not reported) Epidural administration of clonidine at a dose of either: • 150 mcg (not reported) • 300 mcg (not reported) • 600 mcg (not reported)	Pain score	"In conclusion, intrathecal clonidine is at least ten times more potent than epidural clonidine to relieve acute noxious heat stimulation, but two, or less, times more potent than epidural clonidine to relieve intradermal capsaicin-induced mechanical hyperalgesia and allodynia in volunteers. These data agree with non-comparative clinical trials and case reports and provide guidance for relative dosing for different pain syndromes and routes of administration. The mechanisms for the apparent increase in potency of epidural clonidine against mechanical hypersensitivity following capsaicin are unknown."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Eisenach et al, 1998, US[99]	Randomized, double-blind manner	16 Healthy volunteers requiring treatment of capsaicin-induced pain, hyperalgesia, and allodynia (31.3%, mean 30 y ± 1.7)	IV administration of clonidine at dose of either: • 50 mcg (4) • 150 mcg (4) IT administration of clonidine at dose of either: • 50 mcg (4) • 150 mcg (4)	Pain score	"To the extent that the experimental pain conditions used in this study reflect those in patients with acute and chronic pain, these data support the spinal rather than IV injection of clonidine for analgesia."
El Saied et al, 2000, UK[100]	Prospective, randomized, double-blind, placebo-controlled study	46 Patients with a history of traumatic injury due to undergo hand or forearm surgery (76.1%, range 17-62 y)	Axillary brachial plexus block with ropivacaine plus either: • Clonidine (23) • Normal saline (23)	Onset and duration of sensory and motor block, duration of analgesia, postoperative pain score, analgesic requirement	"The addition of 150 mcg of clonidine to ropivacaine, for brachial plexus blockade, prolongs motor and sensory block and analgesia, without an increased incidence of side effects."
Eledjam et al, 1991, France[275]	Double-blind study	60 Patients undergoing orthopedic or traumatological surgical procedures of the upper limbs (53.3%, age not specified)	Supraclavicular brachial plexus block with bupivacaine plus either: • Clonidine (30) • Epinephrine (30)	Quality and duration of analgesia, side effects	"We conclude that the injection of clonidine into the brachial plexus sheath is an attractive alternative to epinephrine to prolong the duration of analgesia following upper limb surgery under conduction anaesthesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Elliott et al, 1997, UK[294]	Prospective, randomized, double-blind study	46 Patients presenting for elective unilateral inguinal hernia repair • Group 1 (100%, mean 62.2 y ± 16.6) • Group 2 (93.3%, mean 66.4 y ± 12.7) • Group 3 (100%, mean 59.8 y ± 17.5)	• Group 1: Wound infiltration with bupivacaine and saline with IM saline (16) • Group 2: Wound infiltration with bupivacaine and clonidine with IM saline (15) • Group 3: Wound infiltration with bupivacaine and saline with IM clonidine (15)	Pain scores	"We conclude that for elective inguinal hernia repair, postoperative analgesia obtained by bupivacaine wound infiltration was not improved by the addition of clonidine 150 mcg."
Erlacher et al, 2001, Austria[412]	Controlled, randomized, double-blind design	120 Patients undergoing surgery of the forearm or hand after trauma • Mepivacaine (55%, mean 44 y ± 21) • Mepivacaine and clonidine (50%, mean 46 y ± 19) • Ropivacaine (35%, mean 40 y ± 13) • Ropivacaine and clonidine (45%, mean 46 y ± 20) • Bupivacaine (55%, mean 46 y ± 14) • Bupivacaine and clonidine (45%, mean 48 y ± 20)	Axillary perivascular brachial plexus block with either: • Mepivacaine (20) • Mepivacaine and clonidine (20) • Ropivacaine (20) • Ropivacaine and clonidine (20) • Bupivacaine (20) • Bupivacaine and clonidine (20)	Onset-time and duration of sensory block	"The major finding of the present study is that the addition of clonidine has a different impact on each of the three investigated local anesthetics in terms of onset and block prolonging activity."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Erlacher et al, 2000, Austria[295]	Controlled, randomized, double-blind design	40 Patients undergoing surgery of the forearm or hand after trauma • Control (35%, mean 40 y ± 13) • Clonidine (45%, mean 46 y ± 20)	Perivascular brachial plexus block with ropivacaine plus either: • Control (20) • Clonidine (20)	Onset of sensory and motor block, duration of sensory block	"Since the addition of clonidine does not result in an improved onset, quality or prolongation of block and it is not without risk for patients with cardiovascular disorder, it cannot be recommended as a useful adjuvant for brachial plexus blockade."
Escamilla et al, 2019, Spain[101]	Randomized, double-blind trial	94 Patients scheduled for functional endoscopic sinus surgery (FESS) due to chronic rhinosinusitis (CRS) with or without nasal polyposis (71.3%, mean 47.81 y ± 10.70)	IV administration of either: • Clonidine (47) • Dexmedetomidine (47)	Occurrence of heavy bleeding	"No significant differences were observed between clonidine and dexmedetomidine when used as anesthetic adjuvants in the reduction of surgical bleeding in FESS. A longer experience with clonidine and its lower costs suggest it may be a preferable option as an adjuvant for hypotensive anesthesia."
Helayel et al, 2005, Brazil[296]	—	40 Patients scheduled for orthopedic surgeries on the foot or lateral aspect of the ankle • Control (50%, mean 43.5 y ± 10.3) • IM clonidine (57.1%, mean 43.14 y ± 12) • Perineural clonidine (62.5%, mean 38 y ± 12.9)	Sciatic nerve block with ropivacaine plus either: • Control (10) • IM clonidine (14) • Perineural clonidine (16)	Sensory and motor block characteristics, quality and duration of anesthesia	"Intramuscular or perineural clonidine has not affected anesthetic onset, quality or the duration of postoperative analgesia of 0.5% ropivacaine-induced sciatic nerve block."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Evans and Pittelkow, 2018, US[446]	Case report	1 Patient with a 2-year history of severe anal pain with neuropathic features (0%, 74 y)	• Fluoroscopically-guided ganglion impar block with a solution containing dexamethasone, clonidine, lidocaine, and bupivacaine, with or without pulsed radiofrequency ablation (1)	Pain score, consumption of opioids	"This case demonstrates the successful use of fluoroscopically-guided ganglion impar radiofrequency ablation for intractable anal pain. Ganglion impar radiofrequency ablation should be considered in treatment of anal pain not adequately controlled with more conservative management."
Evans et al, 2020, US[297]	Double-blind, placebo-controlled, randomized trial	56 Patients presenting for cesarean delivery (0%, age not specified)	Bilateral TAP block with ropivacaine, dexamethasone, and epinephrine with either: • Clonidine (29) • Control (27)	Pain score, analgesic requirement	"Our randomized, double-blinded study demonstrated that the addition of clonidine to ropivacaine in a single-shot, ultrasound-guided TAP block cesarean-section under spinal anesthesia does not reduce total MMEs at 24 h."
Fernandes et al, 2018, Brazil[413]	Randomized, placebo-controlled, double-blind trial	64 Patients scheduled for elective cesarean delivery • Control (0%, mean 31.55 y ± 5.87) • IT clonidine (0%, mean 33.05 y ± 6.03) • IV clonidine (0%, mean 30.32 y ± 5.72)	Spinal anesthesia with hyperbaric bupivacaine, morphine, fentanyl, and either: • Control (20) • IT clonidine (22) • IV clonidine (22)	Postoperative pain	"Intrathecal or intravenous clonidine had no effect on postoperative pain after cesarean delivery. Both intrathecal and intravenous clonidine caused more sedation."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Fernandez-Galinski et al, 2004, Spain[414]	Randomized, double-blind, prospective study	45 Patients scheduled for elective surgery under general anesthesia • Alfentanil (46.7%, mean 54.4 y ± 2.7) • Esmolol (50%, mean 52.1 y ± 3.3) • Clonidine (50%, mean 49.3 y ± 2.8)	IV administration of either: • Alfentanil (15) • Esmolol (16) • Clonidine (14)	Mean arterial pressure, heart rate, bispectral index	"None of the study drugs blocked the increase in mean arterial pressure induced by endotracheal intubation, but esmolol provided better overall haemodynamic stability. All groups had an adequate level of hypnosis."
Filos et al, 1993, Greece[507] Filos et al, 1994, Greece[102]	Randomized, prospective, double-blind study	30 Patients scheduled for elective cesarean section • Clonidine 150 mcg (0%, mean 28 y ± 5) • Clonidine 300 mcg (0%, mean 29 y ± 5) • Clonidine 450 mcg (0%, mean 29 y ± 5)	IT administration of clonidine at dose of either: • 150 mcg (10) • 300 mcg (10) • 450 mcg (10)	Pain score, hemodynamic parameters	"These results demonstrate dose-dependent analgesia after intrathecal clonidine at doses as great as 450 mcg. The nearly immediate analgesic effect observed after intrathecal injection of 300 and 450 mcg clonidine strongly argues for a spinal rather than a systemic site of action of this α2-adrenergic agonist. After 300 and 450 mcg intrathecal clonidine a relative hemodynamic stability is observed, suggested a pressor effect at peripheral sites."
Filos et al, 1992, Greece[371]	Double-blind, placebo-controlled clinical trial	20 Patients undergoing elective cesarean section • Normal saline (0%, mean 31.6 y ± 6.1) • Clonidine (0%, mean 28.7 y ± 4.7)	IT administration of either: • Normal saline (10) • Clonidine (10)	Pain scores, first supplemental analgesic request, hemodynamic characteristics	"We believe that before extensive clinical use of intrathecal clonidine is initiated, the following should be determined: 1) the dose range of intrathecal clonidine producing satisfactory postoperative analgesia; 2) the hemodynamic response after different doses; 3) the preferred root of administration; and 4) the preferred infusion technique (bolus vs. continuous)."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Fogarty et al, 1993, UK[298]	—	90 Patients presenting for elective total hip replacement (61.1%, range 44-83 y)	IT administration of either: • Saline (30) • Clonidine (30) • Morphine (30)	Morphine consumption, pain scores	"Intrathecal clonidine prolonged the duration of spinal analgesia but was markedly inferior to the intrathecal morphine in providing subsequent postoperative analgesia."
Fonseca and De Oliveira, 2001, Brazil[103]	Prospective, double-blind study	30 Patients scheduled to undergo surgical inguinal hernia repair • Clonidine 150 mcg (gender not specified, mean 31.6 y ± 12.9) • Clonidine 75 mcg plus bi-distilled water (gender not specified, mean 42.0 y ± 10.6) • Bi-distilled water (gender not specified, mean 40.7 y ± 10.7)	IT administration of either: • Clonidine 150 mcg (10) • Clonidine 75 mcg and bi-distilled water (10) • Bi-distilled water (10)	Sensory and motor block characteristics, sedation scores, postoperative pain, analgesics requirement	"In the conditions of our study, one may conclude that clonidine has not changed cephalad spread and hemodynamic effects of spinal anesthesia with hyperbaric bupivacaine; it was however effective in improving analgesia observed until the fourth hour after the blockade, as well as in prolonging anesthesia duration, being therefore useful as a coadjuvant of spinal blocks with hyperbaric bupivacaine."
Fournier et al, 2012, Switzerland[299]	Prospective, double-blind, randomized trial	60 Patients scheduled for elective foot or ankle surgery • Levobupivacaine (23.3%, mean 52 y ± 15) • Levobupivacaine plus clonidine (43.3%, mean 60 y ± 14)	Sciatic nerve block with either: • Levobupivacaine (30) • Levobupivacaine plus clonidine (30)	Onset and duration of block, hemodynamic changes, need for rescue analgesia, technical or neurologic complications	"Addition of 150 mcg clonidine to 20 mL of levobupivacaine 0.5% in posterior gluteal (Labat) sciatic nerve block did not prolong the duration of analgesia but had a slight effect on systolic arterial pressure."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Fournier et al, 2002, Switzerland[300]	Randomized, double-blind study	45 Patients scheduled for elective total hip replacement (53.3%, range 70-85 y)	IT administration of either: • Sufentanil (15) • Sufentanil and epinephrine (15) • Sufentanil and clonidine (15)	Pain scores, rescue analgesia, adverse effects	"In conclusion, after total hip replacement, IT sufentanil alone or mixed with epinephrine or clonidine provides excellent analgesia (a pain score of 0 was achieved in all patients investigated), with comparable onset and duration of action. Clonidine and epinephrine tend to decrease blood pressure, so we do not recommend adding these agents to sufentanil."
Fox et al, 2016, US[447]	Case report	1 Patient with severe, deep, osseous pelvic pain after removal of infected hardware for acetabular fixation (0%, 42 y)	• TAP block with ropivacaine and clonidine (1)	Pain relief	"Clinically, our results have shown effective pain relief in dermatomes as far caudally as L4-L5. We have primarily used this block post operatively in patients complaining of deep abdominal, pelvic, and/or lateral abdominal wall pain in scenarios when neuraxial technique is not possible or desired by the patient. The uniqueness of this approach and volume placement of local anesthetic offers extended posterior coverage in addition to the abdominal wall and should be considered by the astute regional anesthesiologist."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Frade et al, 2005, Brazil[104]	Placebo-controlled, double-blind design	30 Patients with complex regional pain syndrome type 1 in a dominant upper limb • Control (40%, mean 41 y ± 8) • Intravenous regional anesthesia with parecoxib (50%, mean 41 y ± 8) • Systemic parecoxib group (40%, mean 44 y ± 10)	Loco-regional IV administration of clonidine and lidocaine plus either: • Control (10) • Loco-regional IV parecoxib (10) • Systemic IV parecoxib (10)	Pain score, rescue analgesic consumption	"We conclude the IV 5 mg of parecoxib was an effective anti-inflammatory drug combined with clonidine/lidocaine loco-regional block in CRPS type 1."
Freehill et al, 2019, US[448]	Randomized, prospective, double-blind, controlled trial	40 Patients undergoing arthroscopic shoulder surgery (gender and age not specified)	Administration of bupivacaine, epinephrine, and clonidine via: • Interscalene block (20) • Interscalene block plus PECS II nerve block (20)	Postoperative pain score	"The addition of a PECS II [pectoral nerve] block to an ISB [interscalene block] for patients undergoing arthroscopic shoulder surgery with an open subpectoral biceps tenodesis significantly improved postoperative analgesia and reduced the need for opioids in the PACU [post-anesthesia care unit]."
Freeman et al, 2002, US[301]	—	39 Patients scheduled for elective tonsillectomy and adenoidectomy • Clonidine (gender not specified, mean 76 months ± 26) • Saline (gender not specified, mean 77 months ± 24)	IM administration of either: • Clonidine (19) • Saline (20)	Perioperative analgesic requirements	"We do not recommend adding IM clonidine (2 mcg × kg^{-1}) to the analgesic regimen of children undergoing tonsillectomy and adenoidectomy."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Fukuda et al, 1994, Japan[415]	—	75 Patients that were scheduled for surgical procedures under spinal anesthesia Normotensive patients receiving: • Clonidine (75%, mean 55 y ± 18) • Phenylephrine (68.7%, mean 57 y ± 13) • Control (75%, mean 56 y ± 16) Hypertensive patients receiving: • Clonidine (66.7%, mean 64 y ± 13) • Phenylephrine (66.7%, mean 65 y ± 9) • Control (77.8%, mean 66 y ± 12)	Spinal anesthesia with tetracaine plus either: • Clonidine (25) • Phenylephrine (25) • Control (25) 9 Patients in each group were hypertensive	Analgesic levels, intensity of motor block	"We conclude that the inclusion of clonidine can provide similar effects to that of phenylephrine with respect to prolongation of hyperbaric tetracaine spinal anesthesia, but could cause more hypotension, without bradycardia, in both normotensive and hypertensive patients for a prolonged time (i.e., 420 min)."
Ganesh and Krishnamurthy, 2018, India[105]	Prospective, randomized, double-blind study	150 Patients posted for lower abdominal surgeries (gender and age not specified)	Subarachnoid block with hyperbaric bupivacaine plus either: • Normal saline (50) • Clonidine (50) • Dexmedetomidine (50)	Onset and duration of sensory and motor block, duration of analgesia, vital parameters	"We concluded from our study that dexmedetomidine and clonidine in 3 and 30 mcg, respectively, with bupivacaine hyperbaric when used intrathecally have a faster onset of both motor and sensory block. It also prolongs the duration of analgesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Gaumann et al, 1992, Switzerland[106]	Randomized, double-blind fashion	33 Patients scheduled for elective surgery of the hand or forearm • Clonidine (60%, mean 41 y ± 14) • Epinephrine (88.9%, mean 38 y ± 12)	Axillary block with lidocaine plus: • Clonidine (15) • Epinephrine (18)	Duration of block, postoperative analgesia, lidocaine plasma concentrations	"In contrast to epinephrine, clonidine does not cause local vasoconstriction, which implies a reduced margin of safety with regard to local anesthetic toxicity. Although clonidine does not offer advantages compared with epinephrine, it may be a useful adjunct to local anesthetics in those patients for whom the administration of epinephrine is contraindicated."
Gautier et al, 1998, Belgium[107]	—	97 Patients requesting labor analgesia • Clonidine 15 mcg (0%, mean 27 y ± 2) • Clonidine 30 mcg (0%, mean 29 y ± 3) • Sufentanil 2.5 mcg (0%, mean 30 y ± 6) • Sufentanil 2.5 mcg and clonidine 15 mcg (0%, mean 29 y ± 5) • Sufentanil 2.5 mcg and clonidine 30 mcg (0%, mean 30 y ± 4) • Sufentanil 5 mcg (0%, mean 27 y ± 2) • Sufentanil 5 mcg and clonidine 15 mcg (0%, mean 31 y ± 4) • Sufentanil 5 mcg and clonidine 30 mcg (0%, mean 30 y ± 5)	IT administration of either: • Clonidine 15 mcg (10) • Clonidine 30 mcg (10) • Sufentanil 2.5 mcg (13) • Sufentanil 2.5 mcg and clonidine 15 mcg (13) • Sufentanil 2.5 mcg and clonidine 30 mcg (13) • Sufentanil 5 mcg (12) • Sufentanil 5 mcg and clonidine 15 mcg (13) • Sufentanil 5 mcg and clonidine 30 mcg (13)	Pain score, blood pressure, heart rate, sensory levels, nausea and pruritus, motor blockade, maternal and cord blood concentrations of clonidine	"Thirty micrograms of intrathecal clonidine combined with 2.5 or 5 mcg intrathecal sufentanil significantly increased the duration of analgesia during the first stage of labor without adverse maternal or fetal effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Gecaj-Gashi et al, 2012, Republic of Kosova[108]	Prospective, double-blind study	66 Patients scheduled for transurethral surgical procedures (100%, range 42-70 y)	IT administration of either: • Bupivacaine (33) • Bupivacaine and clonidine (33)	Onset and regression of motor and sensory block, postoperative analgesia, side effects	"The intrathecal application of clonidine in combination with bupivacaine improves the duration and quality of spinal anesthesia; it also provides longer duration of postoperative analgesia, without significant side effects."
Gentili et al, 1999, France[109]	Double-blind, randomized study	40 Patients scheduled for surgery of the hand or forearm • Saline (gender not specified, mean 41 y ± 18) • Clonidine (gender not specified, mean 51 y ± 18)	IV regional anesthesia with lidocaine plus either: • Saline (not reported) • Clonidine (not reported)	Pain score, motor blockade, sedation, arterial pressure, heart rate	"A 150-mcg dose of clonidine added to lidocaine improved tourniquet tolerance during IV regional anesthesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Gentili et al, 2001, France[110]	Double-blind, randomized study	84 Patients scheduled for ambulatory meniscus repair under arthroscopy • Intraarticular clonidine and subcutaneous saline (60%, mean 36 y ± 17) • Intraarticular neostigmine and subcutaneous saline (50%, mean 47 y ± 17) • Intraarticular clonidine and neostigmine and subcutaneous saline (53.8%, mean 40 y ± 15) • Intraarticular clonidine and subcutaneous neostigmine (41.7%, mean 40 y ± 11) • Intraarticular neostigmine and subcutaneous clonidine (60%, mean 45 y ± 20) • Intraarticular saline and subcutaneous saline (46.7%, mean 38 y ± 16)	• Intraarticular clonidine and subcutaneous saline (15) • Intraarticular neostigmine and subcutaneous saline (14) • Intraarticular clonidine and neostigmine and subcutaneous saline (13) • Intraarticular clonidine and subcutaneous neostigmine (12) • Intraarticular neostigmine and subcutaneous clonidine (15) • Intraarticular saline and subcutaneous saline (15)	Pain scores	"Intraarticular administration of 150 mcg of clonidine, 500 mcg of neostigmine, or both produce postoperative analgesia, and the combination is not more effective."
Gentili et al, 1996, France[111]	Double-blind prospective study	40 Patients scheduled for arthroscopic knee surgery • Control (40%, mean 37.8 y ± 18.9) • Intra-articular clonidine (80%, mean 40.8 y ± 15.4) • Subcutaneous clonidine (70%, mean 35.5 y ± 14.1) • Morphine (80%, mean 80%, mean 35.3 y ± 14.6)	• Control (10) • Intra-articular clonidine (10) • Subcutaneous clonidine (10) • Morphine (10)	Pain score	"We conclude that a low dose of intra-articular clonidine, produces analgesia unrelated to vascular uptake of the drug. This study further supports a peripheral analgesic effect of clonidine."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ghai et al, 2010, India[112]	Randomized, double-blind, placebo-controlled trial	120 Patients undergoing elective unilateral cataract surgery (62.5%, range 1-6 y)	IV administration of either: • Clonidine 1 mcg/kg (39) • Clonidine 2 mcg/kg (41) • Normal saline (40)	Postoperative agitation	"Intravenous clonidine 1 mcg/kg is effective for reducing agitation after sevoflurane anaesthesia and midazolam premedication in children undergoing cataract surgery. Intravenous clonidine 2 mcg/kg was also effective and for a longer period but was associated with a longer time to discharge."
Ghodki et al, 2010, India[113]	—	60 Patients undergoing elective laparoscopic surgeries under spinal anesthesia • Bupivacaine (20%, mean 32.4 y ± 12.37) • Bupivacaine plus clonidine (30%, mean 38.43 y ± 15.82)	Spinal anesthesia with either: • Hyperbaric bupivacaine (30) • Hyperbaric bupivacaine plus clonidine (30)	Hemodynamics, duration of spinal anesthesia, quality of postoperative analgesia, intra- and post-operative sedation, incidence of nausea/vomiting and complications	"We therefore recommend the use of low-dose clonidine along with bupivacaine in spinal anaesthesia for short-duration laparoscopic surgeries."
Ghoshmaulik et al, 2012, India[114]	—	65 Patients scheduled to undergo elective below-elbow orthopedic surgeries • Perineural clonidine (57.6%, mean 42 y ± 10) • Subcutaneous clonidine (62.5%, mean 40 y ± 11)	Axillary brachial plexus block with bupivacaine plus either: • Perineural clonidine and subcutaneous normal saline (33) • Perineural normal saline and subcutaneous clonidine (32)	Duration of sensory and motor block, analgesia, hemodynamic changes, adverse effects	"Compared to systemic administration, local clonidine as an adjuvant in axillary block resulted in significant prolongation of duration of sensory and motor blockade, and analgesia without any hemodynamic alteration, probably by locally mediated mechanism of action."
Giannoni et al, 2002, US[449]	Prospective, randomized, double-blind trial	50 Pediatric patients undergoing tonsillectomy (age not specified, 50%)	All patients received tonsillar fossa injections of ropivacaine plus clonidine in addition to either: • IV dexamethasone (25) • IV saline (25)	Pain intensity and quality	"Dexamethasone does not significantly improve the morbidity of pediatric tonsillectomy when preemptive analgesia with ropivacaine and clonidine is used concurrently."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Giannoni et al, 2001, US[115]	Prospective, randomized, triple-blind trial	64 Patients undergoing tonsillectomy • Saline (52.4%, mean 7.4 y ± 3.7) • Ropivacaine (42.9%, mean 7.0 y ± 2.9) • Ropivacaine plus clonidine (59.1%, mean 7.6 y ± 3.5)	Injection of the study drug into the tonsillar fossae: • Saline (21) • Ropivacaine (21) • Ropivacaine and clonidine (22)	Pain score, opioid use, recovery time to normal activity, symptoms such as otalgia	"Preincisional injection of ropivacaine with clonidine prior to tonsillectomy has a preemptive analgesic effect that outlasts the local anesthetic and decreases pain, opioid use, and the time to return to normal activity."
Ginosar et al, 2013, Israel[116]	Randomized, double-blind, crossover study	11 Volunteers (0%, range 21-28 y)	IT administration of either: • Clonidine doses 0-100 mcg (10) • Bupivacaine doses 0-8.8 mg (9) 1 Volunteer did not return for a second study day after receiving bupivacaine on the first study day and was replaced by a different subject. 1 Volunteer assigned to 0.39 mg bupivacaine received a dose of clonidine due to a randomization error, thus receiving 2 doses of clonidine on separate study days; the final analysis did not include the data from the second day	Analgesic effects	"After 50 mcg clonidine or 5 mg bupivacaine, the heat pain tolerance increased by ~1°C, similar to the analgesic effect of 5 mg epidural morphine or 30 mcg epidural fentanyl in previous studies using this experimental heat pain model. Our results provide additional data for rational dose selection of intrathecal clonidine."
Gintautas et al, 1999, US[117]	—	1 Patient with type I complex regional pain syndrome (gender not specified, 40 y)	• IVRA blocks with lidocaine, labetalol, bretylium, and clonidine (1)	Pain relief	"Noninvasive thoracic impedence [sic] is a benign method of obtaining information and is useful to demonstrate the safety of clonidine in an IVRA. Thus, clonidine is safe to use at this dose to treat CPRS type I by IVRA."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Goetz and Anderson, 2017, US[450]	Case report	1 Patient with a left flank incisional hernia following a radical open nephroureterectomy and paraaortic lymphadenectomy presenting for laparoscopic incisional hernia repair (100%, 74 y)	• Ultrasound-guided quadratus lumborum block (QLB) with ropivacaine and clonidine (1)	Pain	"Quadratus lumborum blocks have shown the benefit of greater spread than TAP blocks from T7 to L1 as well as prolonged duration of analgesia. In this case report, we demonstrate the use of QLB as an analgesic adjunct in patients in whom anatomical deficits limit the use of the traditional TAP block."
Goravanchi et al, 2012, US[372]	Case series	5 Patients who underwent surgery for breast cancer (0%, range 46-63 y)	• Multiple-injection, one-time paravertebral block (PVB) with ropivacaine, epinephrine, clonidine, and dexamethasone (5)	Patient satisfaction, analgesic consumption, side effects, complications	"Paravertebral block is an easy and relatively safe procedure for breast surgery. The combination of clonidine, dexamethasone, and epinephrine with ropivacaine in PVB produced analgesia lasting 6 days. This is a preliminary finding and a thorough, prospective, randomized trial is warranted to study the most effective combination of these additives for use in PVB."
Gorgias et al, 2001, Greece[118]	Prospective, randomized, double-blind study	45 Patients undergoing hand or forearm surgery (gender not specified, mean 47.2 y ± 15.3)	IVRA with lidocaine plus either: • Saline (15) • Clonidine (15) • Ketamine (15)	Tourniquet pain	"In conclusion, the addition of clonidine 1 mcg/kg or ketamine 0.1 mg/kg to lidocaine 0.5% for IVRA delays the onset of tourniquet pain and decreases analgesic consumption for tourniquet pain relief during the time period the cuff remains inflated. Both drugs could be useful when tourniquet use is prolonged, although ketamine has a more potent effect."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Górniak et al, 2014, the Netherlands[302]	Prospective, randomized, controlled, double-blind trial	101 Patients with a rhegmatogenous retinal detachment scheduled to undergo external buckling surgery and cryocoagulation • Control (57.7%, mean 55.5 y ± 11.2) • Clonidine (61.2%, mean 55.5 y ± 11.1)	Retrobulbar block with levobupivacaine plus either: • Control (52) • Clonidine (49)	Postoperative pain, use of analgesics, blood pressure, plasma clonidine concentration	"In conclusion, the use of clonidine as an adjuvant to conventional, local anesthesia in ophthalmic surgery appears to be safe. Nevertheless, benefits are limited, in terms of reduced postoperative pain or less frequent use of analgesic medication. Therefore, in our setting, the use of clonidine in conventional scleral buckle surgery, with or without cryocoagulation, does not seem warranted."
Grace et al, 1995, UK[303]	—	90 Patients undergoing total hip replacement • Sodium chloride (46.7%, mean 67 y ± 8) • Morphine (46.7%, mean 65 y ± 9) • Morphine and clonidine (46.7%, mean 69 y ± 7)	Spinal anesthesia with bupivacaine followed by: • Sodium chloride (30) • Morphine (30) • Morphine and clonidine (30)	Patient-controlled morphine requirements	"In summary, co-administration of clonidine 75 mcg and morphine 0.5 mg provided profound analgesia after total hip replacement under IT anaesthesia, but this combination conferred no additional analgesic benefit over IT morphine 0.5 mg alone, and furthermore, it was associated with marked reductions in MAP [mean arterial blood pressure] between 2 and 5 h after IT administration."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Grace et al, 1994, UK[416]	—	90 Patients undergoing hip replacement (46.7%, range 43-80 y)	IT administration of either: • Bupivacaine (30) • Bupivacaine and morphine (30) • Pethidine and clonidine (30)	Duration of sensory and motor block, postoperative morphine consumption, pain scores	"In summary, we found that the combination of pethidine and clonidine administered intrathecally produced acceptable anaesthesia of adequate duration for total hip replacement. Anaesthesia was comparable in quality with that obtained with a conventional isobaric bupivacaine technique. The technique was associated with greater hypotension than that produced by standard anaesthetic techniques. Postoperative analgesia was similar to that obtained with 0.5% bupivacaine alone but inferior to that obtained with a 0.5% bupivacaine-morphine technique. The incidence of side effects (nausea, vomiting, pruritus) did not differ between the groups. The greater incidence of hypotension and the lack of additional analgesia compared with a conventional isobaric bupivacaine technique suggest that the technique is not indicated for routine use. It may, however, prove a useful technique on the rare occasion when a patient with a history of allergy to local anaesthetic agents presents for surgery."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Graf Zupcic et al, 2018, Croatia[119]	Randomized, prospective, single-center, double-blind trial	60 Patients scheduled for inguinal hernia repair surgery • Levobupivacaine (86.7%, mean 43.5 y ± 9.2) • Levobupivacaine plus clonidine (86.7%, mean 46.7 y ± 10.3)	IT administration of either: • Levobupivacaine (30) • Levobupivacaine plus clonidine (30)	Cutaneous silent period, motor and sensory block	"Intrathecal addition of clonidine to levobupivacaine for SAB [subarachnoid block] in comparison with levobupivacaine alone results in a diminished inhibitory tonus and shortened CSP [cutaneous silent period]."
Grandhe et al, 2008, India[120]	Prospective, randomized, double-blind study	45 Patients undergoing unilateral lower limb surgery • Normal saline (73.3%, mean 34.5 y ± 0.4) • Clonidine 1 mcg/kg (73.3%, mean 31.3 y ± 8.3) • Clonidine 1.5 mcg/kg (66.7%, mean 36.5 y ± 9.7)	IT administration of hyperbaric bupivacaine plus either: • Normal saline (15) • Clonidine 1 mcg/kg (15) • Clonidine 1.5 mcg/kg (15)	Hemodynamics, level of sensory block, grade of motor block, level of sedation, pain score	"Addition of clonidine to bupivacaine for unilateral spinal block prolongs the duration of anaesthesia and postoperative analgesia with minimal adverse effects."
Gupta, 2015, India[304]	Double-blind, randomized study	90 Patients scheduled to undergo infra-umbilical surgery (gender not specified, range 18-65 y)	IT administration of isobaric ropivacaine plus either: • Saline (30) • Clonidine (30) • Dexmedetomidine (30)	Time to onset of sensory block, maximum level of sensory block and time to achieve it, time of sensory block regression, duration of sensory block, time to onset of complete motor block, total duration of motor block, hemodynamics	"Our study concluded that dexmedetomidine is superior to clonidine, as intrathecal adjuvant to plain isobaric ropivacaine. Dexmedetomidine significantly prolonged the sensory and motor block, even greater than clonidine, when added as adjuvant to plain ropivacaine intrathecally. The onset of action of motor and sensory block is faster with clonidine, compared to dexmedetomidine."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Gupta et al, 2014, India[121]	Prospective, double-blind, randomized clinical study	64 Patients scheduled for upper extremity surgeries • Normal saline (65.6%, mean 36.4 y ± 12.4) • Clonidine (71.9%, mean 37.3 y ± 9.3)	Supraclavicular block with ropivacaine plus either: • Saline (32) • Clonidine (32)	Onset and duration of sensory and motor blockade, hemodynamics, sedation, respiratory adequacy, adverse effects	"Clonidine as an adjuvant to ropivacaine for ultrasound guided supraclavicular brachial plexus enhanced duration of post-operative analgesia. There was no incidence of vessel puncture or pneumothorax."
Gupta et al, 2018, India[122]	Prospective, randomized study	90 Patients scheduled for lower abdominal and lower limb surgeries • Bupivacaine (36.67%, mean 46.10 y ± 13.03) • Bupivacaine and clonidine 50 mcg (30%, mean 46.13 y ± 11.19) • Bupivacaine and clonidine 75 mcg (33.33%, mean 48.60 y ± 13.25)	IT anesthesia with either: • Bupivacaine (30) • Bupivacaine plus clonidine 50 mcg (30) • Bupivacaine plus clonidine 75 mcg (30)	Quality of analgesia, sedation, amnesia, side effects	"In conclusion it can be said that the addition of clonidine 75 mcg to 3 mL of 0.5% bupivacaine (heavy) provides significantly better pain relief in lower limb and lower abdominal surgeries leading to reduction in pain (VAS) scores, less consumption of additional analgesics, minimal sedation and amnesia without any major side effects."
Gupta and Gupta, 2013, India[305]	Prospective, randomized, double-blind study	90 Patients scheduled for gynecological surgeries (0%, age not specified)	Spinal anesthesia with heavy bupivacaine plus either: • Normal saline (not reported) • Dexmedetomidine (not reported) • Clonidine (not reported)	Onset time to reach peak sensory and motor level, regression time for sensory and motor block, hemodynamic changes, side effects	"Low dose DXM (3 mcg) seems to be a good alternative to clonidine as an adjuvant to intrathecal bupivacaine, with [an] acceptable side effect profile. Its routine use may be recommended for long duration surgeries."
Gupta et al, 2019, India[123]	Double-blind, randomized, controlled trial	80 Patients scheduled for elective laparoscopic cholecystectomy (gender and age not specified)	• IV clonidine (not reported) • IV fentanyl (not reported)	Heart rate, mean blood pressure	"I.V. fentanyl can be used to attenuate the hemodynamic response in normotensive patients whereas clonidine will be a better choice in hypertensive patients."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Hadbi, 2019, Algeria[124]	Comparative, prospective, open study	224 Patients undergoing cesarean delivery (0%, age not specified)	Spinal anesthesia with bupivacaine plus either: • Fentanyl and clonidine (112) • Fentanyl (112)	Quality and duration of sensory and motor blockade, duration of postoperative analgesia, hemodynamic parameters	"Low-dose bupivacaine reduces the hemodynamic impact of spinal anesthesia, while the combination of clonidine improves the duration of effective anesthesia."
Hamdi et al, 2016, Tunisia[306]	Prospective, double-blind study	60 Patients admitted for hip surgery (gender and age not specified)	IT administration of hyperbaric bupivacaine plus either: • Clonidine (not reported) • Dexmedetomidine (not reported)	Time to sensory and motor blockade, heart rate, blood pressure	"Adding dexmedetomidine to bupivacaine reduces the delay and lengthen the duration of sensory block during spinal anesthesia."
Hansen et al, 2004, Denmark[373]	Randomized, double-blind, controlled pediatric study	44 Patients undergoing hypospadias repair (100%, range 53-68 months)	Caudal bupivacaine plus either: • IV clonidine (23) • Caudal clonidine (21)	Need for additional analgesia	"In conclusion, within the context of the present study, using IV or caudal clonidine (2 mcg kg^{-1}) as an additive to caudal block with bupivacaine 0.25%, 0.5 mL kg^{-1} in children undergoing hypospadias repair results in comparable analgesia. Further studies are required to elucidate the exact mechanisms of analgesia from clonidine when administered together with local anaesthetic agent."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Haque and Lu, 2016, US[451]	Case report	1 Patient with proximal shoulder pain exhibiting signs of complex regional pain syndrome (0%, 55 y)	• Stellate ganglion block with bupivacaine with or without clonidine (1)	Pain relief	"Though the mechanism is not fully understood, sympathetically maintained pain is thought to be a result of a positive feedback loop due to changes in both the peripheral and central somatosensory processes. It is encouraging that some patients that may not represent a classic indication for sympathetic nerve block may still attain significant relief secondary to blockage of the sympathetically maintained component of patient's pain."
Harsten et al, 2013, Sweden[307]	Consecutive, randomized study	60 Patients with osteoarthritis scheduled for total knee arthroplasty • General anesthesia (53.3%, mean 67 y ± 9) • Intrathecal anesthesia (53.3%, mean 69 y ± 7)	• General anesthesia (30) • IT bupivacaine, morphine, and clonidine and local infiltration analgesia (30)	Need for additional analgesia	"General anaesthesia combined with intraoperative glucocorticoids and accelerated postoperative care, compared with, intrathecal blockade and traditional postoperative care, seems to generate the same overall pain ratings and a decrease in length-of-hospital stay, in patients undergoing elective total knee arthroplasty."
Hassenbusch et al, 2002, US[125]	Prospective, phase I/II study	31 Patients previously implanted with programmable intrathecal pumps and unable to obtain adequate pain relief with opioids and adjuvant oral medications (35.5%, range 23-77 y)	• IT clonidine (31)	Pain scores, side effects	"This study demonstrates the tolerability and effectiveness of intrathecal clonidine in the treatment of chronic pain. The physician using clonidine for long-term intrathecal infusion should be cognizant of the risk that severe rebound systemic hypertension can occur with abrupt cessation of the intrathecal infusion of clonidine."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Hassenbusch et al, 1995, US[126]	—	42 Patients with chronic lower body pain, predominately neuropathic in character (26.2%, range 25-73)	• Spinal cord stimulation (26) • Spinal infusions with either morphine or sufentanil (16) 3 Patients who failed to obtain long-term pain relief with either morphine or sufentanil received IT clonidine	Pain relief	"The review indicates that spinal infusions may be best for bilateral or axial pain that has not responded to spinal stimulation. Clonidine appears to be an alternative in high-dose morphine patients."
Hauck et al, 2006, Germany[404]	—	7 Healthy volunteers being investigated for pain-evoked activity (100%, mean 26 y ± 3)	Order of IV doses was randomized and double-blinded: • Clonidine 1.5 mcg/kg (7) • Clonidine 3 mcg/kg (7)	Pain score	"Given the close association of pain perception and vigilance, the observed attenuation of pain evoked responses, represented at the level of the SII cortex, can be explained by a reduction of vigilance and arousal, effects of clonidine that have been reported earlier and something for which clonidine is well known. Further studies using physiological indicators of sedation in combination with those of pain can better discriminate the relative contribution of unspecific sedative and specific analgesic clonidine actions."
Henshaw et al, 2016, US[452]	Prospective, patient- and observer-blinded, randomized trial	147 Patients undergoing medial unicondylar knee arthroplasty (UKA) • Adductor canal block (ACB; 55%, mean 63 y ± 10.2) • Psoas compartment block (PCB; 47%, mean 63 y ± 10.5)	All patients received bupivacaine, epinephrine, and clonidine as: • ACB (74) • PCB (73)	Pain scores	"An ACB provides equivalent analgesia after medial UKA when compared with a PCB. In addition, the ACB caused significantly less motor weakness. An ACB should be considered for postoperative analgesia after medial UKA."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Henshaw et al, 2016, US[453] Yelle et al, 2016, US[508]	Case report	1 Patient with a history of type II CRPS of the right arm and hand after an injury to the superficial radial nerve during venous cannulation (0%, 46 y)	• Peripheral nerve catheter in close proximity to the superficial radial nerve with continuous infusion of ropivacaine with clonidine and a continuous IV infusion of ketamine (1)	Pain scores	"Although the use of regional anesthesia and perineural infusions of local anesthetic have previously been described as viable treatment options for CRPS, this case report represents the first known use of a superficial radial nerve catheter for treating CRPS as well as the first description of a technique for placing a superficial radial nerve (SRN) catheter using ultrasound guidance."
Hinarejos et al, 2016, Spain[308]	Prospective, randomized, double-blind study	100 Patients who underwent total knee arthroplasty (25%, mean 72.1 y ± 6.9)	• Local infiltration analgesia with ropivacaine, epinephrine, ketorolac, and clonidine (50) • Placebo (50)	Pain score, analgesic consumption	"Adding local infiltration of analgesics to peripheral nerve blocks after TKA surgery only provides minimal benefit for pain control. This benefit may be considered as non-clinically relevant. Moreover, the need for additional analgesics was the same in both groups. Therefore, the use of local infiltration of analgesics treatment in TKA surgery cannot be recommended if peripheral nerve blocks are used."
Ho and Sadiq, 2012, US[127]	Retrospective chart analysis	21 Patients with multiple sclerosis and various spinal cord disorders (33.3%, range 22-60 y)	• IT clonidine (13) • IT baclofen and clonidine (8)	Relief of pain and spasticity	"This study, despite having the drawbacks of being unblinded, uncontrolled and retrospective, provides a clinical basis for the use of ITC [intrathecal clonidine] as a therapeutic option in selected patients with spasticity or pain."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Hoffmann et al, 1997, Belgium[128]	Randomized, double-blind fashion	75 Patients undergoing minor orthopedic surgery of the arm • Saline (66.7%, mean 47.5 y) • Bupivacaine (53.3%, mean 52.9 y) • Clonidine (53.3%, mean 37.3 y) • Sufentanil (53.3%, mean 39.3 y) • Tenoxicam (33.3%, mean 53.3 y)	IV regional anesthesia with prilocaine plus either: • Saline (15) • Bupivacaine (15) • Clonidine (15) • Sufentanil (15) • Tenoxicam (15)	Time to complete sensory block, return of sensory function, pain scores	"Both clonidine and, to a lesser degree, tenoxicam proved useful additives to postpone the development of postoperative pain."
Holthusen et al, 2002, Germany[454]	Double-blind, randomized, prospective study	30 Patients undergoing transperitoneal tumor nephrectomy via median laparotomy (63.3%, range 42-79 y)	All patients received morphine, ketamine, and clonidine via an IV motor-driven pump either: • Before surgery (16) • After surgery (14)	Analgesic requirement, pain scores	"In contrast to encouraging observations on the combination of antinociceptive drugs, the multireceptor approach tested here failed to exert a clinically relevant effect."
Horn et al, 1997, Germany[129]	—	60 Patients undergoing elective ear or nose surgery Isoflurane plus either: • Saline (33.3%, mean 34 y ± 14) • Clonidine (60%, mean 48 y ± 16) Propofol plus either: • Saline (66.7%, mean 41 y ± 15) • Clonidine (53.3%, mean 42 y ± 17)	Isoflurane plus IV administration of either: • Saline (15) • Clonidine (15) Propofol plus IV administration of either: • Saline (15) • Clonidine (15)	Shivering, pain score	"Clonidine administration significantly reduced postoperative pain. The incidence of postanesthetic shivering was significantly less after propofol anesthesia than after isoflurane/nitrous oxide anesthesia. However, a late intraoperative bolus administration of 3 mcg/kg clonidine prevents postoperative shivering in patients given either type of anesthesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Hrishi et al, 2019, India[130]	Prospective, randomized, double-blind study	50 Patients undergoing elective upper limb surgery under supraclavicular brachial plexus block • Bupivacaine and lignocaine (80%, mean 37.28 y ± 9.45) • Bupivacaine, lignocaine, and clonidine (68%, mean 41.20 y ± 8.81)	Supraclavicular brachial plexus block with either: • Bupivacaine and lignocaine (25) • Bupivacaine, lignocaine, and clonidine (25)	Onset and duration of sensory and motor block, duration of analgesia, sedation, hemodynamic parameters	"The inclusion of 100 mcg of clonidine with bupivacaine in ultrasound-guided supraclavicular brachial plexus blocks prolongs both sensory and motor blockade. It also provides significant postoperative analgesia and mild sedation which is beneficial in the immediate stressful postoperative period."
Hünseler et al, 2014, Germany[131]	Prospective, double-blind, randomized, controlled, multi-center trial	201 Patients requiring ventilation (60%, mean 86 days ± 146)	Continuous IV infusion of either: • Clonidine (95) • Placebo (106)	Consumption of fentanyl and midazolam	"In ventilated newborn infants, but not in older infants, a continuous infusion of clonidine 1 mcg/kg/hr reduced the consumption of fentanyl and midazolam, provided better analgesia and sedation, and reduced physical withdrawal symptoms. Continuous infusion of clonidine had no apparent short-term risks. Hence, a comedication with clonidine might be beneficial to reduce the negative consequences associated with prolonged use of opioids and benzodiazepines in this setting."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Hutchins et al, 2015, US[455]	Retrospective age- and case-matched study	30 Patients undergoing shoulder surgery (gender and age not specified)	Interscalene block with either: • Ropivacaine, clonidine, and epinephrine (15) • Bupivacaine and liposomal bupivacaine (15)	Total opioid use	"Although retrospective in nature, this study shows the benefits of decreased opioids and increased duration of analgesia with liposomal bupivacaine compared to ropivacaine in an interscalene block for postoperative analgesia after shoulder surgery. This remains an off label use of liposomal bupivacaine and as such future prospective blinded randomized trials are needed to confirm these results."
Hutschala et al, 2004, Austria[132]	Randomized, double-blind, crossover fashion	7 Healthy volunteers undergoing three brachial block procedures (57.1%, mean 26.6 y ± 1.3)	Brachial plexus block with bupivacaine and epinephrine plus: • Perineural and IM saline (7) • Perineural saline and IM clonidine (7) • Perineural clonidine admixture and IM saline (7)	Onset and duration of complete blockade, sedation, hemodynamics, plasma clonidine concentrations	"To conclude, our study suggests that small doses of clonidine added to bupivacaine 0.25% 1 mg kg^{-1}) + epinephrine 1:200,000 leads to prolonged and enhanced brachial plexus blockade in healthy volunteers. No relevant side-effects due to clonidine admixture were observed. This clonidine effect is likely mediated locally."
Ikeda et al, 2010, Brazil[417]	Prospective, randomized, double-blind study	30 Patients who underwent bone surgery of the upper limb • Plexus clonidine (26.7%, mean 38.2 y ± 12.4) • Subcutaneous clonidine (13.3%, mean 31.6 y ± 9.7)	Brachial plexus injection of either: • Bupivacaine and clonidine with subcutaneous saline (15) • Bupivacaine and saline with subcutaneous clonidine (15)	Onset of analgesia, time to surgical anesthesia, duration of analgesia, pain intensity	"There was no difference in the analgesic efficacy of clonidine (150 mcg) injected into the brachial plexus or subcutaneously."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ilfeld et al, 2003, US[309]	Randomized, double-blind, controlled study	34 Patients undergoing moderately painful upper extremity orthopedic surgery • Ropivacaine (23.5%, mean 49 y ± 14) • Ropivacaine and clonidine (23.5%, mean 51 y ± 15)	Postoperative infraclavicular block catheter infusion with either: • Ropivacaine (17) • Ropivacaine and clonidine (17)	Pain scores, patient-controlled bolus doses, oral analgesic use, sleep quality, complications	"In conclusion, this study did not find evidence of clinically relevant benefits to adding clonidine 1 mcg/mL to a ropivacaine infraclavicular perineural infusion after moderately painful upper extremity surgery."
Ilfeld et al, 2005, US[310]	Randomized, double-blind, controlled study	20 Patients undergoing moderately painful orthopedic surgery of the shoulder • Clonidine and ropivacaine (40%, mean 50 y ± 15) • Ropivacaine (60%, mean 47 y ± 17)	Continuous interscalene perineural infusion with either: • Clonidine and ropivacaine (10) • Ropivacaine (10)	Most intense pain during the day after surgery	"We conclude that adding clonidine 2 mcg/mL to a ropivacaine interscalene perineural infusion does not decrease breakthrough pain intensity the day after surgery. For the additional end-points, our negative findings are only suggestive of a lack of effect and require further study for verification."
Imani et al, 2011, Iran[133]	Randomized, prospective, single-blind, clinical trial	90 Patients with histories of substance abuse selected for orthopedic surgery • Group 1 (100%, mean 36 y ± 10) • Group 2 (100%, mean 38 y ± 11) • Group 3 (100%, mean 39 y ± 10)	Patient-controlled IV analgesia with either: • Group 1: Morphine, chlorpromazine, promethazine, and midazolam (30) • Group 2: Morphine, chlorpromazine, promethazine, midazolam, and clonidine (30) • Group 3: Morphine (30)	Pain score, extra opioid usage, nausea and vomiting, sedation	"This study showed that, compared to simply increasing the dose of morphine, adding chloropromazine [sic], promethazine, midazolam, and clinidine [sic] to morphine significantly controlled pain scores and increased treatment satisfaction in addicted patients without notable side effects."
Iohom et al, 2005, France[134]	Prospective, randomized, double-blind, controlled, clinical trial	41 Patients undergoing incision and drainage of paronychia under axillary brachial plexus block (58.5%, range 18-76 y)	Axillary brachial plexus block with mepivacaine plus either: • Clonidine (21) • Saline (20)	Onset of sensory block, duration of anesthesia, time to first analgesic requirement, pain scores	"Thus clonidine added to axillary brachial plexus block with mepivacaine may be useful in the presence of a distal upper limb infection."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Iskandar et al, 2003, France[311]	Double-blind study	40 Patients scheduled for shoulder arthroscopy • Group 1 (60%, mean 47 y ± 13) • Group 2 (60%, mean 53 y ± 11) Study did not specify which demographics related to which study group	• Interscalene block with clonidine and subcutaneous saline (20) • Interscalene saline and subcutaneous clonidine (20)	Pain scores, analgesic duration, nalbuphine consumption, side effects	"In conclusion, clonidine administered to the interscalene plexus enhanced analgesia compared with systemic administration. There was an increased time to first analgesic request and a decreased need for postoperative analgesics. Nevertheless, the adverse effect of clonidine and its insufficiency in producing alone a profound depth of analgesia limits its use as routine management for postoperative analgesia."
Iskandar et al, 2001, France[135]	Prospective, randomized, double-blind study	55 Patients scheduled for elective hand surgery • Control (63%, mean 44 y ± 10) • Clonidine (67.9%, mean 43 y ± 9)	Midhumeral block with mepivacaine plus either: • Control (27) • Clonidine (28)	Onset of surgical anesthesia, duration of sensory and motor block, plasma mepivacaine concentrations, onset for complete sensory block	"In conclusion, by selectively applying clonidine with local anesthetics in the midhumeral block technique, it is possible to prolong the duration of sensory block in one or several trunks of the brachial plexus. Additionally, our data support a specific effect of clonidine on peripheral nerves. This could have some interesting clinical implications, particularly in ambulatory surgery or in the planned repair of tendons in which motor function is best maintained."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ivani et al, 2002, Italy[374]	Prospective, randomized, observer-blinded study design	40 Pediatric patients aged 1-7 years (gender and age not specified)	Ropivacaine and clonidine via: • Caudal block (20) • Ilioinguinal-iliohypogastric nerve block (20)	Pain score, requirement for supplemental analgesia, sedation	"This pilot study demonstrates a trend for better postoperative analgesia following peripheral administration of clonidine compared with central application. However, the main mechanism for the adjunct analgesic effect of clonidine when administered together with local anaesthetics requires further study."
Ivie et al, 2011, US[312]	Double-blind, randomized, placebo-controlled study	52 Patients scheduled for elective endoscopic carpal tunnel release • 0 mcg/kg (gender not specified, mean 49.8 y ± 10.9) • 0.25 mcg/kg (gender not specified, 49.22 y ± 13.8) • 0.5 mcg/kg (gender not specified, mean 48.6 y ± 13.9) • 1 mcg/kg (gender not specified, 45.7 y ± 16.4) • 1.5 mcg/kg (gender not specified, mean 55.3 y ± 9.7)	IVRA with lidocaine plus clonidine at doses of: • 0 mcg/kg (11) • 0.25 mcg/kg (9) • 0.5 mcg/kg (10) • 1 mcg/kg (10) • 1.5 mcg/kg (12)	Intraoperative fentanyl, pain scores, time to first postsurgical analgesic, total amount of acetaminophen/codeine tablets consumed, sedation, hypotension, bradycardia	"There was no benefit from any dose of clonidine compared to placebo. There were no clonidine-related side effects seen within the dose range studied. In short duration minor hand surgery, the addition of clonidine to lidocaine-based intravenous regional anesthesia provides no measurable benefit."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Jaffe et al, 2017, US[402]	Retrospective chart review	40 Patients who underwent left colorectal surgery (gender and age not specified)	Posterior TAP block with either: • Liposomal bupivacaine (not reported) • Non-liposomal bupivacaine with epinephrine and clonidine (not reported)	Cumulative opioid consumption, pain scores	"In patients undergoing left LPA [laparoscopic] colorectal surgery, our analysis revealed no statistically significant difference in post-operative opioid consumption or pain scores between the groups. While our investigation did not uncover a difference between the groups in this patient population, it remains to be determined using larger prospective randomized trials whether a statistically significant difference would be found."
Jaiswal et al, 2013, India[313]	Prospective, randomized, controlled, double-blind study	60 Patients undergoing hand or forearm surgery under axillary plexus blockade using nerve stimulator • Normal saline (80%, age not specified) • Clonidine (83.3%, age not specified)	Axillary plexus blockade with ropivacaine plus either: • Normal saline (30) • Clonidine (30)	Sensory and motor block, sedation	"Addition of clonidine (150 mcg) is of no benefit in the onset and duration of axillary plexus block."
Javahertalab et al, 2020, Iran[351]	Double-blind, randomized, clinical trial	120 Patients undergoing spinal anesthesia in lower limb orthopedic surgery • Dexmedetomidine (50%, mean 35.2 y ± 4.55) • Clonidine (50%, mean 34.85 y ± 5.62) • Placebo (50%, mean 34.75 y ± 5.14)	IV administration of either: • Dexmedetomidine (40) • Clonidine (40) • Placebo (40)	Pain score, time to achieve and onset of sensory and motor block, hemodynamic changes	"Though, DEX [dexmedetomidine] prolongs the duration of sensory and motor block and relieves postoperative pain, it besides reduces BP [blood pressure], thus it is advisable to use caution in special patients such as the elderly. CLO [clonidine] and DEX have effective pain control and prolonged duration of sensory and motor block, as compared with the PBO [placebo]. DEX has greater efficacy in contrast to CLO."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Jindal et al, 2011, India[136]	Prospective, randomized, double-blind study	50 Patients undergoing cleft lip surgery • Clonidine and bupivacaine (68%, mean 8.48 months ± 7.11) • Bupivacaine (76%, mean 7.92 months ± 6.48)	Bilateral infraorbital nerve block with either: • Clonidine and bupivacaine (25) • Bupivacaine (25)	Hemodynamic parameters, intraoperative requirement of volatile anesthetic agent, muscle relaxant, and analgesic, pain	"Addition of clonidine as an adjunct to local anesthetic significantly decreased the requirement of other anesthetic drugs and significantly prolonged the duration of postoperative analgesia without any adverse effects."
Jiwanmall et al, 2017, India[137]	Randomized, double-blind, placebo-controlled study	60 Patients undergoing functional endoscopic sinus surgery (FESS; gender and age not specified)	IV administration of either: • Placebo (30) • Clonidine (30)	Mean arterial blood pressure	"Clonidine is effective in achieving controlled hypotension in patients undergoing FESS. It reduces intra-operative blood loss, requirement of additional hypotensive drugs, improves the surgical field and offers good analgesia without significant side effects."
John et al, 2018, India[138]	Prospective, randomized, double-blind study	60 Patients undergoing laparoscopic cholecystectomy (gender and age not specified)	• Control (not reported) • Multimodal analgesia (MMA) with IV acetaminophen and clonidine (not reported)	Depth of balanced anesthesia, consumption of isoflurane, duration of anesthesia	"MMA with EtCA [end-tidal control anesthesia] significantly reduces isoflurane consumption due to inhibition of nociception at all levels of pain processing along with its synergistic effect with isoflurane."
Joshi et al, 2012, India[314]	Randomized, participant- and observer-blind, prospective, parallel group, clinical trial	50 Patients posted for lower abdominal surgery • Midazolam (76%, mean 40.40 y ± 15.45) • Clonidine (84%, mean 44.92 y ± 11.61)	IT bupivacaine plus either: • Midazolam (25) • Clonidine (25)	Postoperative analgesia, analgesic requirement in 24 hours, onset and duration of block, hemodynamic stability, adverse effects	"Postoperative analgesia with clonidine is short lived with some bradycardia. Intrathecal midazolam provides superior analgesia without clinically relevant adverse effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Julião and Lauretti, 2000, Brazil[139]	Randomized, double-blind study	72 Patients undergoing gynecological abdominal surgery with spinal anesthesia • Control group (0%, mean 45 y ± 7) • Sufentanil (0%, mean 43 y ± 10) • Clonidine (0%, mean 41 y ± 7) • Sufentanil and clonidine (0%, mean 41 y ± 8)	IT bupivacaine plus either: • Control (17) • Sufentanil (18) • Clonidine (17) • Sufentanil and clonidine (20)	Level of sensory block, anesthetic time, time to first rescue analgesic, number of rescue analgesic doses, adverse effects	"Intrathecal 15- and 30-mcg clonidine doses expanded the anesthesia sensory block and duration of motor block, and provided analgesia."
Kaabachi et al, 2007, Tunisia[140]	Placebo-controlled, randomized study	83 Patients scheduled for orthopedic surgery • Control (58.5%, mean 13.0 y ± 2.3) • Clonidine (64.3%, mean 13.7 y ± 2.0)	Spinal anesthesia with isobaric bupivacaine plus either: • Control (41) • Clonidine (42)	Duration of sensory block	"In adolescents, clonidine 1 mcg/kg prolonged the duration of sensory block achieved with bupivacaine by 30 min and postoperative analgesia by 120 min without severe adverse events."
Kaabachi et al, 2005, Tunisia[315]	—	98 Patients scheduled for elective outpatient herniorrhaphy or orchidopexy • Clonidine (gender not specified, mean 5.4 y ± 5.4) • Placebo (gender not specified, mean 5.0 y ± 3.5)	Ilioinguinal-iliohypogastric nerve block with bupivacaine plus either: • Clonidine (49) • Placebo (49)	Postoperative analgesic requirement, time to first analgesic supplementation, sedation score	"Our study failed to demonstrate any advantage in addition of 1 mcg × kg^{-1} clonidine to 0.25% bupivacaine for ilioinguinal-iliohypogastric nerve block compared with bupivacaine 0.25% alone."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kakunje et al, 2016, India[141]	Randomized, double-blind, placebo-controlled study	90 Patients scheduled for lower limb or lower abdominal surgeries • Saline (50%, mean 38.97 y ± 11.92) • Clonidine 15 mcg (43.3%, mean 43.20 y ± 10.03) • Clonidine 30 mcg (43.3%, mean 39.67 y ± 10.18)	Spinal anesthesia with hyperbaric ropivacaine plus either: • Saline (30) • Clonidine 15 mcg (30) • Clonidine 30 mcg (30)	Block characteristics, hemodynamic parameters, side effects	"Addition of low-dose clonidine to intrathecal hyperbaric ropivacaine causes a significant prolongation of the duration of sensory and motor blockade as well as postoperative analgesia compared with saline placebo. However, it increases the incidence of hypotension and bradycardia which can be managed with routine clinical measures."
Kallapur et al, 2017, India[142]	Double-blind, randomized, controlled, clinical study	105 Patients undergoing elective cesarean section (0%, mean 26.18 y ± 2.38)	IT administration of: • Bupivacaine 2 mL plus saline (35) • Bupivacaine 1.5 mL plus clonidine (35) • Bupivacaine 2 mL plus clonidine (35)	Onset and duration of sensory and motor block, postoperative analgesia	"The dose of intrathecal bupivacaine 0.5% was effectively reduced to 7.5 mg by adding 1 mcg/kg of clonidine as adjuvant in patients undergoing elective cesarean section."
Kamble and Deshpande, 2016, India[143]	Prospective, randomized, observer-blind study	90 Patients undergoing percutaneous nephrolithotomy (PCNL) • Bupivacaine (66.7%, mean 44.07 y ± 9.85) • Bupivacaine plus clonidine (56.7%, mean 40.17 y ± 11.93) • Control (60%, mean 38.70 y ± 11.89)	Paravertebral block with either: • Bupivacaine (30) • Bupivacaine and clonidine (30) • Control (30)	Propofol requirement, hemodynamic parameters, need for rescue analgesia, adverse effects	"In conclusion, 0.5% Bupivacaine ± 1 mcg/kg clonidine in a single level paravertebral block is useful, effective and safe for providing intra as well as postoperative analgesia during PCNL surgeries."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kamel et al, 2005, Egypt[144]	Double-blind, randomized study	80 Patients undergoing vitrectomy and retinal detachment repair (gender and age not specified)	Peribulbar anesthesia with either: • Ropivacaine (not reported) • Ropivacaine plus clonidine (not reported)	Onset and duration of anesthesia, akinesia, and analgesia	"Clonidine 1 mcg/kg, when used as an adjuvant to ropivacaine 0.75%, prolongs the duration of anaesthesia and analgesia which suits the lengthy ophthalmic surgery with minimal adverse effects."
Kanazi et al, 2006, Lebanon[145]	Prospective, double-blind study	51 Patients undergoing transurethral resection of prostate or bladder tumor under spinal anesthesia • Bupivacaine (100%, mean 70 y ± 10) • Bupivacaine plus clonidine (100%, mean 70 y ± 6) • Bupivacaine plus dexmedetomidine (100%, mean 69 y ± 9)	Spinal block with either: • Bupivacaine (19) • Bupivacaine plus clonidine (16) • Bupivacaine plus dexmedetomidine (16)	Onset times to reach peak sensory and motor regression times, hemodynamic changes, level of sedation	"In conclusion, our report shows that the supplementation of bupivacaine spinal block with a low dose of intrathecal dexmedetomidine or clonidine produces a significantly shorter onset of motor block and a significantly longer sensory and motor block than bupivacaine alone. Dexmedetomidine 3 mcg and clonidine 30 mcg have an equipotent effect on the characteristics of the block without any significant hemodynamic instability or sedation."
Karthikeyan et al, 2013, India[146]	Double-blind, randomized, placebo-controlled trial	60 Patients undergoing elective thyroidectomy • Bupivacaine (10%, mean 37.50 y ± 9.92) • Bupivacaine and clonidine (10%, mean 41.05 y ± 10.14) • Normal saline (15%, mean 34.40 y ± 9.88)	Bilateral superficial cervical plexus block (BSCPB) with either: • Bupivacaine (20) • Bupivacaine plus clonidine (20) • Normal saline (20)	Postoperative pain scores, nausea, vomiting, sedation	"BSCPB with 0.25% bupivacaine with or without clonidine is effective in reducing both intraoperative and postoperative pain and analgesic requirements in thyroidectomy, and adding clonidine to bupivacaine reduces postoperative vomiting."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kaur et al, 2017, India[316]	Prospective, double-blind, randomized, controlled study	40 Patients undergoing elective or emergency upper limb surgery • Magnesium sulfate (55%, mean 48.8 y ± 17.9) • Clonidine (45%, mean 49.7 y ± 15.8)	IVRA with lignocaine plus either: • Magnesium sulfate (20) • Clonidine (20)	Pain score, time to first rescue analgesic, total number of rescue analgesics required, side effects	"MgSO4 provides better postoperative analgesia as compared to clonidine when used as an adjunct to lignocaine in IVRA with fewer side effects."
Kaur et al, 2016, India[317]	Prospective, randomized, double-blind study	120 Patients scheduled for elective lower abdominal surgery • Dexmedetomidine (36.7%, mean 41.04 y ± 14.03) • Clonidine (41.7%, mean 42.88 y ± 12.47)	IV administration of either: • Dexmedetomidine (60) • Clonidine (60)	Sedation, bispectral index (BIS)	"Intravenous dexmedetomidine infusion has shorter arousal time from sedation than clonidine during spinal anesthesia. A strong correlation exists between BIS and RSS [Ramsay sedation score] during recovery from sedation."
Kelika and Arun, 2017, India[147]	Double-blind, randomized study	90 Patients scheduled for upper limb orthopedic surgery • Tramadol (60%, mean 36.0 y ± 9.5) • Clonidine 1 mcg/kg (53.3%, mean 39.9 y ± 9.7) • Clonidine 1.5 mcg/kg (50%, mean 39.2 y ± 9.2)	Supraclavicular block with lignocaine, adrenaline, sodium bicarbonate, and bupivacaine plus an adjuvant of either: • Tramadol (30) • Clonidine 1 mcg/kg (30) • Clonidine 1.5 mcg/kg (30)	Onset and duration of sensory and motor block, duration of postoperative analgesia	"Clonidine in a dose of 1.5 mcg/kg body weight provided the fastest onset of sensory as well as motor block and the longest duration of postoperative analgesia and thus is a good additive to local anesthetic solutions for brachial plexus blocks."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Khafagy et al, 2011, Egypt[509] Khafagy et al, 2012, Egypt[375]	Prospective, randomized, double-blind, controlled study	120 Patients scheduled for open cholecystectomy • Control (26.7%, mean 40.7 y ± 3.0) • Clonidine (20%, mean 39.0 y ± 3.9) • Magnesium sulfate (16.7%, mean 40.5 y ± 2.7) • Ketamine (13.3%, mean 39.6 y ± 4.5)	Total IV anesthesia (TIVA) with: • Clonidine (30) • Magnesium sulfate (30): Ketamine (30): Isotonic saline (30)	Intraoperative hemodynamics, induction time, anesthetic consumption, recovery indices, PACU discharge	"Clonidine, magnesium, and ketamine can be useful adjuvant agents to BIS-guided TIVA. Pharmacokinetic studies of such drug combinations were recommended to investigate their interaction."
Khandelwal et al, 2012, India[456]	Prospective, randomized, placebo-controlled, double-blind study	120 Patients scheduled for elective total abdominal hysterectomy (0%, age not specified)	IT bupivacaine plus either: • IT saline and placebo patch (30) • IT saline and transdermal nitroglycerin patch (30) • IT clonidine and placebo patch (30) • IT clonidine and transdermal nitroglycerin patch (30)	Level of sensory and motor blockade, duration of analgesia, duration of motor block, need for rescue analgesia	"In this study, tNTG [transdermal nitroglycerin] has enhanced the post-operative analgesic effect of IT clonidine without any significant alteration of haemodynamics and increase in incidence of nausea and vomiting. The effect was synergistic and possibly mediated through NO [nitric oxide]."
Khandelwal et al, 2017, India[148]	Prospective, randomized, double-blind, placebo-controlled study	90 Patients scheduled for lower abdominal surgery • Normal saline (13.3%, mean 42.87 y ± 8.58) • Clonidine (10%, mean 39.9 y ± 8.83) • Magnesium sulfate (10%, mean 43.73 y ± 8.86)	Spinal anesthesia with hyperbaric bupivacaine plus either: • Normal saline (30) • Clonidine (30) • Magnesium sulfate (30)	Duration of analgesia	"Intrathecal clonidine added to bupivacaine prolongs the duration of post-operative analgesia, and hastens the onset and prolongs the duration of sensory and motor block compared to magnesium or controls."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Khezri et al, 2014, Iran[376]	Prospective, randomized, double-blind study	90 Patients scheduled for cesarean section • Clonidine (0%, mean 30.43 y ± 3.70) • Fentanyl (0%, mean 30.20 y ± 5.41) • Placebo (0%, mean 29.16 y ± 5.11)	Spinal anesthesia with bupivacaine plus either: • Clonidine (30) • Fentanyl (30) • Placebo (30)	Time to first analgesic request, analgesic requirement, sensory and motor blockade onset time, duration of sensory and motor blockade, hypotension, ephedrine requirements, bradycardia, hypoxemia	"We concluded that intrathecal clonidine 75 mcg with bupivacaine prolonged intraoperative anesthesia and the time to first analgesic request compared to fentanyl, however, the total analgesic consumption in the first 24 h postoperative was similar in fentanyl and clonidine groups following elective cesarean delivery. Further studies are needed to evaluate the analgesic efficacy of clonidine with other neuraxial drug combinations such as epinephrine, ketamine, and magnesium to provide better analgesia and reduce the incidence and severity of side effects."
Kiani et al, 2015, Iran[377]	Randomized, double-blind, parallel-group trial	139 Patients with type 2 diabetes who had diabetic peripheral neuropathy (DPN) • Capsaicin (29%, mean 56.49 y ± 10.25) • Clonidine (25.7%, mean 56.88 y ± 9.54)	• Clonidine gel (70) • Capsaicin cream (69)	Reduction in pain scores	"In general, in our study clonidine was well tolerated and safe during this 12-week study. There were more discontinuations due to adverse events in the capsaicin treatment group than in the clonidine treatment group. This study compared the efficacy of clonidine gel with capsaicin cream, a[n] FDA approved drug, but prolonged therapy and evaluation for a longer duration than the 12 weeks can better evaluate the benefits of this drug. More studies are required to better evaluate the efficacy and safety of this topical compound for relieving pain in DPN."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kim et al, 2011, US[457]	Chart review	35 Patients with intrathecal pumps implanted for lumbar postlaminectomy syndrome (70%, mean 60 y)	Some patients were able to stay on their trial IT medication (morphine - 32, hydromorphone - 3), but after a year, a variety of different therapies were used due to unsatisfactory pain relief: • Morphine (13) • Hydromorphone (8) • Hydromorphone and bupivacaine (5) • Morphine and bupivacaine (2) • Fentanyl, bupivacaine, and clonidine (2) • Ziconotide (2) • Fentanyl (1) • Morphine and clonidine (1) • Hydromorphone and clonidine (1)	Change in pain score, change in intrathecal dose, medication change	"Trial dose, age, and partially pain location are good predictors of pain relief."
King et al, 2013, US[403]	—	70 Patients who underwent unilateral total knee arthroplasty (gender and age not specified)	• Control (34) • Preoperative celecoxib, oxycodone, and acetaminophen, femoral nerve block with ropivacaine and epinephrine, and periarticular injection of ketorolac, epinephrine, clonidine, and ropivacaine (36)	Length of stay	"In this retrospective study, spinal anesthesia plus combination femoral nerve block and multimodal analgesic therapy significantly reduced hospital length of stay. Prospective data and larger sample sizes are needed to confirm these findings."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kjølhede et al, 2017, Sweden[510] Kjølhede et al, 2019, Sweden[352]	Open-label, randomized trial	80 Patients undergoing abdominal surgery for gynecologic malignancy • Epidural analgesia (EDA; 0%, median 59.0 y [IQR 51.5-66.0]) • Intrathecal morphine (0%, median 58.5 y [IQR 54.0-62.5])	• IT morphine, clonidine, and bupivacaine (40) • Epidural bupivacaine, adrenaline, and fentanyl (40)	Length of stay	"Compared with EDA ITM is simpler to administer and manage, is associated with shorter hospital stay and reduces opioid consumption postoperatively with an equally good QoL [quality of life]. ITM is effective as postoperative analgesia in gynaecological cancer surgery."
Kleinschmidt et al, 1997, Germany[378]	Randomized, double-blind fashion	56 Patients scheduled for elective minor surgical procedures on the hand or forearm • Group 1 (gender not specified, mean 35.0 y ± 13.4) • Group 2 (gender not specified, mean 31.5 y ± 11.9) • Group 3 (gender not specified, mean 28.8 y ± 9.1)	• Group 1: IVRA prilocaine and saline with an IV saline supplement (19) • Group 2: IVRA prilocaine and clonidine with an IV saline supplement (20) • Group 3: IVRA prilocaine and saline with an IV clonidine supplement (17)	Characteristics of sensory and motor block, quality of analgesia, postoperative pain sensation, hemodynamic variables	"In conclusion, the addition of clonidine to prilocaine for IVRA tended to a prolong the time to recovery from motor block and to the appearance of the first pain sensations after tourniquet release, probably as a result of a 'prolonged local co-anaesthetic effect.' Although the results described in the present study did not reach statistical significance, further investigation concerning clonidine dose regimens and/or local anaesthetics may prove useful. If a longer 'pain free' period after tourniquet release can be achieved by the addition of clonidine (e.g., higher doses than 2 mcg $kg^{-1)}$ to local anaesthetics without hazardous side effects such as hypotension, bradycardia or sedation, this might be of clinical relevance in situations where the tourniquet has to be deflated before wound closure to optimize haemostasis at the surgeon's request."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Klimscha et al, 1995, Austria[149]	Prospective, randomized, double-blind study	40 Patients scheduled for lower extremity orthopedic surgery • Continuous spinal anesthesia (40%, mean 74 y [SEM 3.2]) • Continuous spinal anesthesia plus clonidine (10%, mean 75 y [SEM 5.1]) • Continuous epidural anesthesia (40%, mean 72 y [SEM 2.7]) • Continuous epidural anesthesia plus clonidine (40%, mean 71 y [SEM 2.9])	• Continuous spinal anesthesia with bupivacaine (10) • Continuous spinal anesthesia with bupivacaine and clonidine (10) • Continuous epidural anesthesia with bupivacaine (10) • Continuous epidural anesthesia with bupivacaine and clonidine (10)	Mean arterial pressure, heart rate, duration of anesthesia	"In conclusion, addition of intrathecal, but not epidural clonidine, 150 mcg, decreased MAP significantly compared with plain bupivacaine. The addition of clonidine does not cause cumulative hemodynamic depression after repetitive administration. The addition of clonidine to bupivacaine yields long-lasting, profound pain relief, although hemodynamic effects require careful monitoring."
Kloster and Domangue, 2018, US[458]	Retrospective analysis	24 Patients with chronic intractable pain who had failed conservative pain management treatments (gender not specified, mean 53 y ± 9.6)	All patients originally had an implanted peristaltic IT drug delivery system (IDDS) and later switched to valve-gated IDDS implant 8 different drug substances were recorded, but bupivacaine, clonidine, and hydromorphone were reported to be the most common. Other substances were not identified and number of patients per substance was not reported.	Number and dosage of medications in pump, change in pain score	"Retrospective review of real-world cases demonstrated a reduction in medication dosages, dose escalation rates, and pain scores (VAS) up to 24 months following titration period of medications compared to peristaltic-based IDDS. A prospective clinical trial with appropriately powered sample size may further confirm the findings that intrathecal pharmacotherapy with a valve-gated IDDS has clinical benefits compared to peristaltic systems."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kohli et al, 2013, India[150]	Prospective, double-blind, randomized study	60 Patients undergoing upper limb surgeries • Clonidine 1 mcg/kg (76.7%, mean 32.5 y ± 11.5) • Clonidine 2 mcg/kg (66.7%, mean 34.5 y ± 11.0)	Brachial plexus block (BPB) with bupivacaine plus either: • Clonidine 1 mcg/kg (30) • Clonidine 2 mcg/kg (30)	Onset and duration of sensorimotor blockade, hemodynamic variables, duration of analgesia, level of sedation, adverse effects	"Higher dose of clonidine in BPB hastens the onset, prolongs the duration of sensorimotor blockade and postoperative analgesia without significant hemodynamic alterations. It also causes more sedation, which although ensures patient comfort in most cases, but might be undesirable in certain situations."
Koppert et al, 2003, Germany[418]	Randomized, crossover, double-blind, placebo-controlled study	13 Healthy volunteers experiencing pain and secondary mechanical hyperalgesia induced by transcutaneous electrical stimulation at high current density (100%, mean 31.2 y ± 5.3)	All patients received each IV treatment trial at least 1 week apart: • Remifentanil (13) • S-ketamine (13) • Clonidine (13) • Saline (13) • Remifentanil and S-ketamine (13) • Remifentanil and clonidine (13)	Postinfusion pain, hyperalgesia	"Opioid-induced postinfusion hyperalgesia could be abolished by S-ketamine, suggesting an N-methyl-D-aspartate-receptor mechanism. In contrast, elevated pain ratings after infusion were not reduced by ketamine but were alleviated by the α2-receptor agonist clonidine. The results of this study suggest different mechanisms of opioid-induced postinfusion antianalgesia and secondary hyperalgesia."
Kothari et al, 2011, India[151]	Randomized, single-blind trial	210 Patients undergoing emergency cesarean section • Hyperbaric bupivacaine 12.5 mg (0%, mean 26 y ± 2) • Hyperbaric bupivacaine 8 mg plus clonidine (0%, mean 26 y ± 3) • Hyperbaric bupivacaine 10 mg plus clonidine (0%, mean 27 y ± 3)	IT administration of either: • Hyperbaric bupivacaine 12.5 mg (70) • Hyperbaric bupivacaine 8 mg plus clonidine (70) • Hyperbaric bupivacaine 10 mg plus clonidine (70)	Regression of spinal blockade, duration of pain relief	"Addition of intrathecal clonidine provides adequate analgesia and motor paralysis at significantly lower dose of bupivacaine. It causes some sedation in the postoperative period but patients were responsive to simple verbal commands, thus intrathecal use of clonidine is recommended to reduce dose of bupivacaine for better hemodynamic stability and prolonged postoperative analgesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Krishnappa et al, 2015, India[318]	Prospective, randomized, double-blind study	50 Patients undergoing lower abdominal surgeries • Clonidine (16%, mean 41.04 y ± 14.13) • Dexmedetomidine (28%, mean 39.72 y ± 13.76)	IT hyperbaric ropivacaine plus: • Clonidine (25) • Dexmedetomidine (25)	Spinal block characteristics, duration of surgery, duration of postoperative analgesia, first 24-hour analgesic consumption, hemodynamic parameters, adverse effects	"Dexmedetomidine as an adjuvant to ropivacaine spinal anesthesia, provided excellent quality of postoperative analgesia with minimal side effects in prolonged surgeries compared to clonidine."
Kulka et al, 1995, Germany[152]	Randomized, double-blind study	48 Patients undergoing coronary artery bypass grafting (CABG) • Placebo (83.3%, mean 64 y ± 6) • Clonidine 2 mcg/kg (83.3%, mean 62 y ± 6) • Clonidine 4 mcg/kg (66.7%, mean 62 y ± 7) • Clonidine 6 mcg/kg (91.7%, mean 60 y ± 8)	IV administration of either: • Placebo (12) • Clonidine 2 mcg/kg (12) • Clonidine 4 mcg/kg (12) • Clonidine 6 mcg/kg (12)	Sedation, cardiovascular variables, catecholamine plasma levels, anesthetic requirements	"In summary, we have shown that the IV administration of clonidine up to a dose of 6 mcg/kg proved to be safe even in CABG patients. The effects on hemodynamic variables, sedation, catecholamine plasma levels, and anesthetic requirements were dose-related up to a dose of 4 mcg/kg. Increasing the dose did not further enhance efficacy."
Kulkarni et al, 2012, India[153]	Prospective, randomized, controlled trial	60 Patients scheduled for upper extremity orthopedic procedures • Clonidine (60%, mean 43.56 y ± 5.34) • Normal saline (66.7%, mean 43.02 y ± 6.75)	Brachial plexus block through supraclavicular approach with bupivacaine plus either: • Clonidine (30) • Normal saline (30)	Onset and duration of sensory block, postoperative analgesic requirements	"It was found that addition of clonidine to bupivacaine in brachial plexus block had faster onset of sensory block and also prolonged the duration of analgesia, without any major side effects other than sedation, which is beneficial in clinical practice."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kumara, 2016, India[459]	Prospective, randomized study	60 Patients scheduled to undergo elective arthroscopic shoulder surgery (gender and age not specified)	Bupivacaine and clonidine given via either: • Interscalene brachial plexus block (30) • Suprascapular nerve block (SSB) (30)	Pain scores, time to first rescue analgesia	"Both interscalene and SSB can be used to provide intra-operative and post-operative analgesia in patients undergoing shoulder arthroscopy."
Kumari et al, 2015, India[154]	Prospective, randomized, double-blind, placebo-controlled study	90 Patients scheduled for elective ear, nose, and throat (ENT) surgeries • Group 1 (36.7%, mean 34.03 y ± 13.61) • Group 2 (53.3%, mean 30.03 y ± 10.20) • Group 3 (53.3%, mean 31.33 y ± 11.02)	• Group 1: IV clonidine bolus followed by clonidine infusion (30) • Group 2: IV clonidine bolus followed by placebo infusion (30) • Group 3: IV placebo bolus followed by placebo infusion (30)	Sedation, bleeding score, patient and surgeon satisfaction, postoperative Aldrete score, pain score, rescue sedative and analgesic consumption, complications	"Being a safe, well tolerated, cheap and effective regime, our study favors the use of clonidine 3 mcg/kg IV bolus followed by infusion of 0.3 mcg/kg/hr as an adjunct to conventional MAC [monitored anesthesia care] regime of midazolam and fentanyl in ENT surgeries as it provides effective sedation and bloodless surgical field."
Kumari et al, 2012, India[155]	Prospective, double-blind, randomized, clinical study	60 Patients undergoing ENT surgery under monitored anesthesia care (MAC) • Clonidine (50%, mean 40.37 y ± 14.07) • Midazolam (46.66%, mean 33.83 y ± 13.55)	IV administration of either: • Clonidine (30) • Midazolam (30)	Sedation, requirement of rescue sedation and analgesia, pain score, adverse effects, recovery profile, patient satisfaction	"We conclude that clonidine along with rescue sedation using propofol infusion can be a better alternative to midazolam in MAC since it provides a calm patient with better intraoperative & postoperative analgesia, and a bloodless surgical field leading to increased satisfaction of both patient and surgeon."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Lauretti et al, 2009, Brazil[511] Lauretti et al, 2012, Brazil[156]	—	54 Patients with chronic ocular pain secondary to glaucoma (gender and age not specified)	• Retrobulbar block (RB) with clonidine and lidocaine plus stellate ganglion block (SGB) with saline (18) • Retrobulbar block with saline plus stellate ganglion block with clonidine, dexamethasone, and lidocaine (18) • Retrobulbar block with clonidine and lidocaine plus stellate ganglion block with clonidine, dexamethasone, and lidocaine (18)	Pain, visual field, ocular pressure	"The combination of SGB and RB with clonidine, lidocaine and dexamethasone resulted in at least 16 weeks of analgesia without compromising the controlled ocular pressure. The absence of any improvement in the visual field could be secondary to advanced disease and already compromised visual field in the population selected."
Lauretti et al, 2009, Brazil[460]	—	75 Patients undergoing orthopedic surgery (gender and age not specified)	IT bupivacaine plus either: • Spinal and epidural saline (not reported) • Spinal clonidine and epidural saline (not reported) • Spinal clonidine and neostigmine and epidural saline (not reported) • Spinal clonidine and epidural depot dexamethasone (not reported) • Spinal clonidine and neostigmine and epidural depot dexamethasone (not reported)	Analgesia, adverse effects	"Spinal 1 mg neostigmine further enhanced analgesia from spinal bupivacaine/clonidine combined with epidural dexamethasone, without increasing the incidence of adverse effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Lavand'homme et al, 2008, Belgium[157]	—	96 Patients undergoing elective cesarean section • Sufentanil (0%, mean 33 y ± 5) • Sufentanil and clonidine (0%, mean 35 y ± 5) • Clonidine (0%, mean 33 y ± 6)	IT bupivacaine plus either: • Sufentanil (32) • Sufentanil and clonidine (32) • Clonidine (32)	Extent and incidence of peri-incisional punctate mechanical hyperalgesia	"Intrathecal clonidine 150 mcg combined with bupivacaine had a postoperative antihyperalgesic effect expressed as a significant reduction in the extent and incidence of periincisional punctate mechanical hyperalgesia at 48 h after elective cesarean delivery compared with intrathecal bupivacaine-sufentanil and intrathecal clonidine 75 mcg-bupivacaine-sufentanil."
Lavand'homme et al, 2005, Belgium[461]	Randomized, double-blind trial	80 Patients scheduled to undergo neoplastic colonic resection • Group 1 (60%, mean 53 y ± 8) • Group 2 (65%, mean 54 y ± 8) • Group 3 (60%, mean 55 y ± 8) • Group 4 (60%, mean 53 y ± 10)	Intraoperative IV lidocaine, sufentanil, and clonidine followed by PCA with either: • IV lidocaine, morphine, and clonidine (20) • Epidural bupivacaine, sufentanil, and clonidine (20) Intraoperative epidural bupivacaine, sufentanil, and clonidine followed by patient-controlled analgesia with either: • IV lidocaine, morphine, and clonidine (20) • Epidural bupivacaine, sufentanil, and clonidine (20)	Pain scores, analgesic consumption, wound area of punctuate hyperalgesia, residual pain, analgesics needed	"Combined with an antihyperalgesic dose of ketamine, intraoperative epidural analgesia provides effective preventive analgesia after major digestive surgery."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Lemes et al, 2008, Brazil[158]	Randomized, double-blind, placebo-controlled study	68 Patients undergoing cataract surgery under peribulbar block • Clonidine (39.4%, mean 63.42 y ± 15.34) • Placebo (37.1%, mean 69.11 y ± 10)	IV administration of either: • Placebo (35) • Clonidine (33)	Intraocular pressure (IOP), mean arterial pressure, heart rate, pulse oximetry, sedation	"In conclusion, the use of intravenous clonidine as a pre-anesthetic medication, administered 30 minutes before ophthalmologic procedures, demonstrated to be effective in reducing IOP and maintaining hemodynamic stability besides protecting against the development of hypertension. Sedation levels varied from light to moderate without influencing the length of stay in the recovery room."
Lena et al, 2005, France[159]	Prospective, blinded, randomized study	40 Patients selected for coronary artery bypass graft surgery • Fast-track group (85%, mean 66.4 y ± 8.3) • Control group (75%, mean 66.2 y ± 8.3)	• Fast-track group with remifentanil plus spinal morphine and clonidine (20) • Control group with sufentanil (20)	Pain score, intravenous morphine consumption	"The combination of anesthesia with remifentanil and spinal analgesia with morphine and clonidine produces effective analgesia after coronary artery surgery and a rapid extubation time."
Lena et al, 2003, France[160]	Double-blind, randomized study	45 Patients having coronary artery bypass graft surgery (82.2%, range 33-80 y)	IV patient-controlled analgesia with morphine plus either: • Control (15) • IT morphine (15) • IT morphine and clonidine (15)	Pain score, intravenous morphine consumption	"Intrathecal morphine and clonidine provide effective analgesia after coronary artery bypass graft surgery and allow earlier extubation."
Lena et al, 2008, France[161]	Prospective, randomized, controlled study	83 Patients who underwent cardiac surgery with cardiopulmonary bypass • Fast-track (83.3%, mean 66 y ± 9) • Control (75.6%, mean 66 y ± 10)	• Fast-track group with remifentanil plus spinal morphine and clonidine (42) • Control with sufentanil (41)	Pain score, intravenous morphine consumption	"Fast-track anesthesia combined with morphine-clonidine spinal analgesia controlled postoperative pain better and obtained a better QoR [quality of recovery score] than conventional analgesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Leslie et al, 1992, Australia[162]	Randomized, double-blind, controlled trial	60 Patients who presented for elective surgery • Control (55%, mean 27.1 y ± 7.7) • Clonidine 2.5 mcg/kg (50%, mean 28.4 y ± 6.4) • Clonidine 5 mcg/kg (45%, mean 31.0 y ± 8.5)	IV administration of either: • Control (20) • Clonidine 2.5 mcg/kg (20) • Clonidine 5 mcg/kg (20)	Thiopental dose requirement	"Our results suggest that limited advantage may be gained by increasing the dose of clonidine to 5.0 mcg/kg. Intravenous clonidine may be safely administered before induction of anesthesia, allowing further evaluation of the many useful effects during general anesthesia."
Li et al, 2015, China[163]	Double-blind, controlled study	84 Patients undergoing elective cesarean section • Control (0%, mean 30.30 y ± 3.81) • Fentanyl (0%, mean 30.94 y ± 4.01) • Clonidine (0%, mean 29.57 y ± 3.35) • Dexmedetomidine (0%, mean 29.09 y ± 4.23)	Spinal hyperbaric bupivacaine plus either: • Control (21) • Fentanyl (21) • Clonidine (21) • Dexmedetomidine (21)	Onset of blockade, duration of analgesia, degree and recovery time of motor block, sedation, maternal-fetal repercussions	"Addition of dexmedetomidine and clonidine as adjuvants to hyperbaric bupivacaine provided adequate anesthesia and postoperative analgesia compared to fentanyl adjuvant without causing any significant side effects."
Lurie et al, 2000, US[164]	Crossover design	15 Healthy volunteers receiving upper extremity IVRA with a double-cuffed tourniquet (13.3%, age not specified)	IVRA with either: • Lidocaine (15) • Lidocaine and clonidine (15)	Pain scores	"This study shows that the addition of 1 mcg/kg of clonidine to 40 mL of 0.5% IVRA-L delays the onset time of tourniquet pain in healthy, unsedated volunteers."
Macres and Richeimer, 2000, US[165]	Case report	1 Patient with hypertension, peripheral vascular disease, and painful erythromelalgia refractory to multiple treatment modalities (0%, 82 y)	• IT pump with hydromorphone and clonidine (1)	Pain scores	"Administration of intrathecal opioid and an alpha2-agonist can be effective in the treatment of the pain of erythromelalgia and offers an alternative pain treatment modality for patients with unremitting pain refractory to more conservative therapy."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Madabhushi et al, 2007, US[379]	Case report	1 Patient who presented for elective left above-knee amputation (AKA) due to ischemic necrosis secondary to peripheral vascular disease (100%, 68 y)	• Sciatic nerve infiltration with bupivacaine and clonidine, followed by epidural injection and infusion of bupivacaine and clonidine (1)	Pain score, side effects	"In conclusion, we describe a 4-day postoperative perineural infusion of bupivacaine and clonidine after AKA in a patient with a previous history of phantom limb and stump pain of the operative extremity. This technique provided excellent postoperative analgesia while eliminating both stump and phantom limb pain postoperatively. We are currently enrolling patients in a prospective, randomized, double-blind study to evaluate the efficacy of this technique for lower extremity amputation."
Madan et al, 2001, India[166]	Dose-response study	60 Patients undergoing cataract surgery • Control (53.3%, mean 50 y ± 15) • Clonidine 0.5 mcg/kg (73.3%, mean 57 y ± 13) • Clonidine 1 mcg/kg (40%, mean 60 y ± 11) • Clonidine 1.5 mcg/kg (66.7%, mean 58 y ± 10)	Peribulbar block with lidocaine, hyaluronidase, and either: • Control (15) • Clonidine 0.5 mcg/kg (15) • Clonidine 1 mcg/kg (15) • Clonidine 1.5 mcg/kg (15)	Onset and duration of lid and globe akinesia, globe anesthesia and analgesia, postoperative analgesic requirement, adverse effects	"We conclude that 1.0 mcg/kg clonidine with a mixture of lidocaine (2%) significantly prolonged the duration of anesthesia and analgesia after peribulbar block with limited side effects."
Madhava Reddy et al, 2019, India[167]	—	60 Patients undergoing single level spine surgery under spinal anesthesia • Fentanyl (70%, mean 42.7 y ± 11.4) • Clonidine (66.7%, mean 41.4 y ± 8.4)	Spinal anesthesia with bupivacaine plus either: • Fentanyl (30) • Clonidine (30)	Duration of analgesia, sedation, patient comfort	"Intrathecal fentanyl and clonidine are safe and effective adjuvants to bupivacaine in prone position whereas clonidine is better in providing intraoperative patient's comfort and postoperative analgesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Mahendru et al, 2013, India[319]	Double-blind, controlled study	120 Patients undergoing lower limb surgery under spinal anesthesia • Saline (93.3%, mean 33.5 y ± 14.8) • Fentanyl (83.3%, mean 38.1 y ± 13.5) • Clonidine (96.7%, mean 37.0 y ± 12.0) • Dexmedetomidine (86.7%, mean 37.8 y ± 15.6)	Spinal anesthesia with hyperbaric bupivacaine plus either: • Saline (30) • Fentanyl (30) • Clonidine (30) • Dexmedetomidine (30)	Onset to peak sensory and motor level, regression time of sensory and motor block, hemodynamic changes, side effects	"Intrathecal dexmedetomidine is associated with prolonged motor and sensory block, hemodynamic stability, and reduced demand of rescue analgesics in 24 h as compared to clonidine, fentanyl, or lone bupivacaine."
Malchow et al, 2018, US[419]	Comprehensive review of a prospectively collected 6-year database	10,338 Patients undergoing 13,888 regional anesthesia procedures (53.4%, mean 43.1 y ± 17.4)	13,888 Regional anesthesia procedures with the following local anesthetics: • Ropivacaine (9872) • Mepivacaine (2359) • Bupivacaine (592) • Lidocaine (330) • Chloroprocaine (186) • Mepivacaine/Ropivacaine (481) • Mepivacaine/Bupivacaine (60) The following adjuncts were used for the procedures: • None (8856) • Clonidine and dexamethasone (1857) • Clonidine (1733) • Dexamethasone (1451)	Block success, patient satisfaction, postoperative nausea and vomiting, postoperative neurologic symptoms (PONS)	"A regional anesthesia-based practice in ambulatory surgery is an effective means of providing excellent postoperative analgesia and is associated with a low rate of PONV and unexpected admissions. Dexamethasone, clonidine, and their combination when combined with 0.5% ropivacaine may have mixed effects on PONS risk that warrant dose/concentration alterations of these three drugs in the context of off-label perineural adjunct use."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Malinovsky et al, 1993, France[320]	—	12 Patients undergoing transurethral resection of prostate (100%, mean 70 y ± 8)	IT administration of either: • Clonidine 75-150 mcg (6) • Clonidine 300-450 mcg (6)	Pain relief, heart rate, arterial blood pressure	"Thus, we conclude that IT clonidine alone is not suitable for intraoperative regional anesthesia because of inadequate anesthesia and marked sedation."
Malinovsky et al, 2003, France[462]	—	18 Patients with spinal cord injury and 18 uninjured patients about to have lower urinary tract surgery under spinal anesthesia (gender not specified, range 21-73 y)	IT bupivacaine plus either: • IT clonidine 50 mcg (12) • IT clonidine 150 mcg (12) • IM clonidine (12)	Sedation, bispectral index	"We conclude that sedation after spinal clonidine is mainly a systemic effect. Delayed onset of sedation in patients with traumatic spinal cord injury could be related to several mechanisms including altered resorption from spinal cord sites, altered susceptibility to sedative agents especially in patients receiving treatment for spasticity, rather than a delayed cephalad spread of clonidine in the CSF."
Malviya et al, 2006, US[380]	Randomized, double-blind study	120 Patients undergoing brief, minimally painful procedures • Clonidine (70%, mean 3.6 y ± 2.3) • Placebo (75%, mean 3.7 y ± 2.3)	IV administration of either: • Clonidine (59) • Placebo (61)	Degree of emergence agitation (EA), side effects	"This study demonstrated that IV clonidine administered after induction of anesthesia significantly reduced the incidence of EA in young children, but was associated with sleepiness postoperatively. This study has addressed the prophylactic use of clonidine to minimize the occurrence of EA. The potential use of α2-agonists in treating EA as recently suggested, requires further investigation."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Mammen et al, 2017, India[321]	Randomized, prospective, comparative study	90 Patients scheduled for surgery below the umbilicus • IT neostigmine (66.7%, mean 35.9 y ± 9.22) • IT neostigmine and clonidine (73.3%, mean 37.6 y ± 9.1) • IT neostigmine and transdermal nitroglycerin patch (tNTG; 70%, mean 36.1 y ± 10.4)	IT hyperbaric bupivacaine plus: • IT neostigmine (30) • IT neostigmine and clonidine (30) • IT neostigmine and tNTG patch (30)	Heart rate, mean arterial pressure, analgesic properties, complications	"Both IT clonidine and tNTG patch with bupivacaine + neostigmine spinal anesthesia were found effective in pain control. Results were found better with tNTG patch."
Mannion et al, 2005, Ireland[168]	Randomized, prospective, double-blind trial	36 Patients requiring hip fracture surgery • IV saline (25%, mean 80 y ± 7) • IV clonidine (41.7%, mean 78 y ± 10) • IV saline and perineural clonidine (25%, mean 81 y ± 10)	Psoas compartment block (PCB) with levobupivacaine plus either: • IV saline (12) • IV clonidine (12) • IV saline and perineural clonidine (12)	Time to first supplementary analgesic administration, cumulative morphine and acetaminophen consumption, adverse effects	"We conclude that IV but not perineural clonidine (1 mcg/kg) prolongs analgesia after PCB without increasing the incidence of adverse effects."
Manpreet et al, 2016, India[322]	Prospective, randomized study	120 Patients scheduled for elective infraumbilical surgery under spinal anesthesia • Dexmedetomidine (82.5%, mean 39.83 y ± 14.225) • Clonidine (72.5%, mean 37.85 y ± 10.935) • Normal saline (77.5%, mean 37.38 y ± 12.646)	IV loading and maintenance dose of either: • Dexmedetomidine (40) • Clonidine (40) • Normal saline (40)	Time to achieve target sedation, prolongation of analgesia and motor blockade, hemodynamic parameters, side effects	"Intravenous dexmedetomidine infusion is better than intravenous clonidine as it provides earlier onset of adequate sedation along with prolongation of analgesia and motor blockade during bupivacaine spinal anesthesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Maranto et al, 2018, US[169]	Case report	1 Patient presenting to clinic with severe right-sided axillary and anterolateral chest wall pain (0%, 42 y)	• Combined superficial and deep serratus plane block with bupivacaine, dexamethasone, and clonidine (1)	Pain relief	"In conclusion, we feel that a combined superficial and deep serratus anterior block could serve as a low-risk treatment option for patients with PMPS [postmastectomy pain syndrome]. It is easy to perform in an outpatient chronic pain setting. We also feel that with the addition of clonidine and dexamethasone, as presented in this case, this block could have improved therapeutic benefit for these patients in whom other commonly used treatment options have failed."
Marinangeli et al, 2002, Italy[170]	Double-blind, randomized study	80 Patients undergoing lumbar hemilaminectomy for herniated disk (gender and age not specified)	IV loading dose of study drug followed by continuous infusion of same drug: • Clonidine 5 mcg/kg (20) • Clonidine 3 mcg/kg (20) • Clonidine 2 mcg/kg (20) • Sodium chloride (20)	Total morphine requirement, blood pressure, heart rate, sedation	"In conclusion, this study demonstrates that, when sedation and analgesic effect of clonidine is required, 3 mcg/kg bolus dose followed by a continuous infusion of 0.3 mcg/kg per hour has to be considered the optimal intravenous dose. The higher dose of intravenous clonidine (5 mcg/kg) produced better analgesia but the degree of hypotension and sedation was more severe and longer lasting; it required ephedrine administration and careful monitoring of the patient. On the other hand, the bolus of intravenous clonidine 2 mcg/kg (group C) was less effective in terms of pain relief but with similar side-effects to the 3 mcg/kg dosage (group B)."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Marinangeli et al, 2000, Italy[171]	Double-blind fashion	100 Patients undergoing elective surgery under general anesthesia • Clonidine and thiopental (56%, mean 60 y ± 8) • Clonidine and propofol (52%, mean 57 y ± 13) • Placebo and thiopental (52%, mean 56 y ± 9) • Placebo and propofol (60%, mean 62 y ± 6)	IV clonidine plus either: • Thiopental (23) • Propofol (24) • IV placebo plus either: • Thiopental (25) • Propofol (24) 4 Patients were excluded from the study because laryngoscopy lasted longer than 30 seconds	Mean arterial pressure, hemodynamic stability	"Certainly, the clonidine-propofol association is not a problem in healthy patients, in whom clonidine premedication could only be advantageous, as it reduces intraoperative anaesthetic requirements, neuroendocrine response to stressful stimuli in the perioperative period, and the variability of intraoperative blood pressure. However, clonidine-propofol should be used cautiously in patients affected by cardiovascular disease or with previous cerebrovascular history. When using propofol in these patients, haemodynamic stability may be obtained without clonidine simply by giving propofol at a low infusion rate (300 mL kg^{-1} h^{-1}). The result is reduction of the incidence of unwanted effects and reduction of the total dose required."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Mark et al, 2013, US[381]	Retrospective study	64 Patients who underwent total knee arthroplasty by a single orthopedic surgeon (gender and age not specified)	• Preoperative multimodal oral analgesics with celecoxib, oxycodone, and acetaminophen, femoral nerve block with ropivacaine and epinephrine, and intraoperative multimodal peri-articular injection containing ketorolac, epinephrine, clonidine, and ropivacaine (33) • Control (31)	Pain scores, requirement for rescue analgesia	"In this retrospective study, femoral nerve block plus multimodal analgesia significantly reduced early postoperative pain scores at rest and during physical therapy with ambulation. Stronger significance was noted for early ambulation. Our data suggests that this combination mode of therapy may also reduce pain scores immediately postoperatively (POD 0), enabling very early mobilization of patients undergoing total knee arthroplasty. This may have significant clinical benefit as it may lower the incidence of deep venous thrombosis. Further studies with larger sample sizes are needed to confirm these observations."
Martinez et al, 2017, US[463]	Case series	6 Patients with refractory epigastric pain from chronic pancreatitis (50%, mean 45.3 y ± 10)	IT pump therapy (ITPT) with either: • Hydromorphone with bupivacaine (4) • Hydromorphone (1) • Hydromorphone, bupivacaine, and clonidine (1)	Pain scores, morphine equivalents, hospitalizations	"Our study yields promising results as an alternative treatment. However, larger scale studies are needed to further assess both efficacy and potential risks of ITPT for chronic pancreatitis."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
McClain et al, 2001, US[172]	Case report	1 Patient experiencing opioid-induced myoclonus (100%, 96 days)	• IV clonidine (1)	Opioid-induced myoclonus, opioid taper	"The continuous intravenous administration of clonidine allowed titration of sedation and facilitated execution of the methadone taper. In conclusion, we have demonstrated that clonidine is an effective treatment for recalcitrant agitation and myoclonus."
McRoberts et al, 2016, US[173]	Case report	1 Patient with failed back surgery syndrome (FBSS) who previously failed conservative therapies (0%, 53 y)	• IT clonidine (1)	Pain relief	"For patients with FBSS who are unable to tolerate intrathecal opiates, clonidine delivered via patient-administered boluses may provide an alternative therapy for recalcitrant pain."
Melton, 2012, US[174]	—	2171 Single shot peripheral nerve blocks over 3 years (gender and age not specified)	All peripheral nerve blocks included clonidine with either: • Bupivacaine 0.25% (not reported) • Bupivacaine 0.5% (not reported)	Analgesic duration, incidence of local anesthetic systemic toxicity	"We have demonstrated that a reduced bupivacaine concentration, with low dose clonidine, preserves desirable analgetic duration, without affecting safety."
Memis et al, 2005, Turkey[175]	Randomized, double-blind	60 Patients scheduled for total abdominal hysterectomy • Bupivacaine (0%, mean 53.6 y ± 12.7) • Bupivacaine plus tramadol (0%, mean 51.8 y ± 12.6) • Bupivacaine plus clonidine (0%, mean 52.7 y ± 9.3)	Administration of the study drug into the peritoneal cavity: • Bupivacaine (20) • Bupivacaine plus tramadol (20) • Bupivacaine plus clonidine (20)	Postoperative pain, analgesic consumption, vital signs	"We concluded that the combinations of bupivacaine plus tramadol and bupivacaine plus clonidine administered intraperitoneally in total abdominal hysterectomy operations provide more effective analgesia than bupivacaine alone during the early postoperative period."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Mercier et al, 1998, France[176]	Prospective, randomized, double-blind study	50 Patients in painful labor requiring analgesia • Sufentanil and clonidine (0%, mean 28 y ± 4) • Sufentanil (0%, mean 28 y ± 3)	All patients received IT administration of the study drug followed by epidural bupivacaine • Sufentanil and clonidine (24) • Sufentanil (26)	Time until first request for additional analgesia	"The addition of 30 mcg clonidine to 5 mcg intrathecal sufentanil extended the duration of labor analgesia without producing motor blockade. However, as previously reported with 100-200 mcg clonidine, the incidence of hypotension and the ephedrine requirements were also increased, even when 30 mcg clonidine only was added."
Merivirta et al, 2009, Finland[177]	—	60 Patients undergoing outpatient knee arthroscopy • Bupivacaine (40%, mean 48.3 y ± 14.3) • Bupivacaine plus clonidine (46.7%, mean 46.6 y ± 12.3)	IT administration of either: • Hyperbaric bupivacaine (30) • Hyperbaric bupivacaine plus clonidine (30)	Sensory and motor block characteristics	"Using 5 mg hyperbaric bupivacaine with 15 mcg of clonidine, the unilaterality can be achieved and spinal anaesthesia intensified without affecting home-readiness. More vasopressors are needed in the beginning, but after the surgery patients experienced less pain."
Minzer et al, 2017, US[464]	Single-center, IRB-approved, prospective, randomized, non-inferiority designed trial	103 Patients scheduled for unilateral primary total knee arthroplasty (gender and age not specified)	All patients received oral premedication, spinal bupivacaine anesthesia, intraoperative periarticular infiltration of ketorolac, clonidine, ropivacaine, and epinephrine, a postoperative analgesic order set, and either: • Femoral nerve block (not reported) • No FNB (not reported)	Time to hospital discharge	"Future research should evaluate the impact of FNB on patient-reported outcomes."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Missant et al, 2004, Belgium[323]	Double-blind, randomized trial	38 Patients in active labor and requesting analgesia • Ropivacaine and sufentanil (0%, mean 30.1 y ± 4.5) • Ropivacaine, sufentanil, and clonidine (0%, mean 29.9 y ± 4.9)	Combined spinal epidural analgesia with IT administration of either: • Ropivacaine and sufentanil (20) • Ropivacaine, sufentanil, and clonidine (18)	Duration of initial spinal analgesia	"Intrathecal clonidine prolongs spinal analgesia with ropivacaine and sufentanil at the expense of maternal hypotension, worse fetal well being and worse neonatal umbilical artery pH. We do not recommend routine administration of spinal clonidine 30 mcg to sufentanil and ropivacaine for labour pain relief."
Mjahed et al, 1996, Morocco[178]	Prospective, double-blind	60 Patients undergoing elective cataract surgery • Saline (37%, mean 62 y ± 10) • Clonidine (43%, mean 64 y ± 9)	Retrobulbar block with lidocaine plus either: • Saline (30) • Clonidine (30)	Intraocular pressure, sedation, duration of analgesia and akinesia	"Addition of clonidine to lidocaine for retrobulbar block causes a decrease in intraocular pressure, a sedative effect, and an increased duration of analgesia and akinesia, with relatively stable hemodynamic parameters."
Mohamed and Abdel-Ghaffar, 2013, Egypt[179]	Randomized, prospective, double-blind study	140 Patients scheduled for modified radical mastectomy with axillary dissection for breast carcinoma • Saline (0%, mean 38.92 y ± 6.005) • Bupivacaine (0%, mean 40.05 y ± 4.36) • Clonidine 150 mcg (0%, mean 40.28 y ± 5.51) • Clonidine 250 mcg (0%, mean 39.48 y ± 5.91)	Irrigation of the study drug into the surgical field before skin closure: • Saline (35) • Bupivacaine (35) • Bupivacaine and clonidine 150 mcg (35) • Bupivacaine and clonidine 250 mcg (35)	Total dose of analgesic consumed postoperatively	"The addition of clonidine to topical bupivacaine accentuated its early postoperative analgesic efficacy."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Molnar et al, 1997, Australia[180]	Double-blind, randomized, prospective trial	40 Patients scheduled to undergo carotid endarterectomy under cervical plexus block • Epinephrine (55%, mean 66.9 y ± 2.2) • Clonidine (70%, mean 69.6 y ± 1.7)	Cervical plexus block with lidocaine plus either: • Clonidine (20) • Epinephrine (20)	Block onset and duration	"Clonidine 5 mcg/mL is a useful additive to lidocaine 1.5% for cervical plexus block to reduce the incidence of tachycardia; however, omission of epinephrine results in higher serum lidocaine levels."
Moss et al, 2011, US[324]	Prospective, randomized, double-blind, placebo-controlled trial	120 Patients scheduled for outpatient tonsillectomy • Saline (40%, median 6.0 y [IQR 5.0-9.0]) • Lidocaine and bupivacaine (50%, median 7.0 y [IQR 5.0-11.0]) • Lidocaine, bupivacaine, and clonidine (42%, median 8.0 y [IQR 5.0-10.2])	Injection of the study drug into the peritonsillar mucosa: • Saline (40) • Lidocaine and bupivacaine (40) • Lidocaine, bupivacaine, and clonidine (40)	Total number of analgesic doses consumed	"Pretonsillectomy injection of lidocaine, 1%, and bupivacaine, 0.5%, with or without clonidine (25 mcg) is not recommended for the reduction of posttonsillectomy pain."
Moustaka et al, 2012, Greece[465]	—	50 Patients undergoing shoulder surgery (gender and age not specified)	• General anesthesia (25) • Interscalene brachial plexus block with ropivacaine and clonidine (25)	Onset of ready to surgery time, postoperative complications, postoperative need of analgesics	"Nevertheless, interscaline [sic] brachial plexus block has many advantages compared to general anesthesia for magor [sic] surgery at the area of shoulder and it should be preferred in most cases."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Nader et al, 2009, US[382]	—	85 Patients undergoing coronary artery bypass graft • Morphine and clonidine (97.8%, mean 65.2 y ± 12.1) • Morphine (100%, mean 64.7 y ± 12.6)	IT administration of either: • Morphine and clonidine (45) • Morphine (40)	Postoperative pain, opioid use within first 24 hours, time to extubation	"Addition of clonidine to neuraxial opioids improves the quality of analgesia postoperatively and expedites the process of weaning from mechanical ventilation. There were no serious adverse events in the cohort of the patients studied. However, the safety profile of this medication remains to be examined with a larger group of patients."
Nagappa et al, 2018, India[181]	Prospective, double-blind, randomized trial	64 Patients undergoing elective craniotomy • Group 1 (gender not specified, mean 42.28 y ± 11.07) • Group 2 (gender not specified, mean 39.59 y ± 10.17) • Scalp block (56%, age not specified) • Clonidine (50%, age not specified) While the mean age was provided for both groups, the table did not specify which group was reflected	• Scalp block with ropivacaine (32) • IV clonidine (32)	Heart rate, blood pressure, need for fentanyl and propofol	"IV clonidine maximally attenuated the hemodynamic response to application of head pins in a dose of 2 mcg/kg compared to ropivacaine scalp block, thus maintaining intracranial pressure for neurosurgical anesthesia."
Naja et al, 2004, Lebanon[182]	Prospective, randomized, clinical trial	60 Patients scheduled for laparoscopic cholecystectomy • Control (17%, mean 46.2 y ± 13.8) • Paravertebral block (30%, mean 48.4 y ± 15.1)	General anesthesia plus: • Control (30) • Paravertebral block with lidocaine, epinephrine, bupivacaine, fentanyl, and clonidine (30)	Postoperative pain, opioid consumption	"When used as a complement to general anaesthesia, bilateral nerve-stimulator guided paravertebral blockade with lidocaine, bupivacaine, fentanyl and clonidine may improve postoperative pain relief."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Naja et al, 2005, Lebanon[466]	Prospective, randomized, double-blind, clinical trial	100 Patients undergoing elective circumcision • Ring block (RB; 100%, mean 1.41 y ± 1.32) • Dorsal penile nerve block (100%, mean 1.65 y ± 1.53) • Ring block plus dorsal penile nerve block (100%, mean 1.53 y ± 1.69)	All patients received the same local anesthetic mixture of lidocaine, bupivacaine, fentanyl, and clonidine via either: • Ring block (33) • Dorsal penile block (32) • Ring block plus dorsal penile block (35) 91 Patients completed the clinical trial due to 3 failed blocks and 6 follow-up losses	Postoperative pain	"Dorsal penile block plus RB technique is superior to dorsal penile block alone and RB alone in reducing postcircumcision pain in children."
Naja et al, 2006, Lebanon[467]	Randomized, double-blind, placebo-controlled trial	50 Patients diagnosed with cervicogenic headache • Block (24%, mean 46.44 y ± 9.63) • Placebo (28%, mean 47.36 y ± 10.25)	Patients received greater and lesser occipital blocks, with some patients receiving facial nerve blockade, depending on the extension of the headache. The injected mixture contained either: • Lidocaine, epinephrine, bupivacaine, fentanyl, and clonidine (25) • Placebo (25)	Reduction in analgesic consumption	"The nerve stimulator-guided occipital nerve blockade significantly relieved cervicogenic headache and associated symptoms at two weeks following injection."
Naja et al, 2014, Lebanon[183]	Prospective, randomized, double-blind study	60 Patients scheduled to undergo laparoscopic gastric sleeve • Clonidine (23.3%, mean 32.13 y ± 9.6) • Dexmedetomidine (43.3%, mean 31.21 y ± 6.9)	IV administration of either: • Clonidine (30) • Dexmedetomidine (30)	Pain, analgesic consumption	"This study concluded that clonidine and dexmedetomidine yielded similar outcomes with a difference in pain and analgesic consumption at 12 h postoperatively."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Naja et al, 2013, Lebanon[184]	Prospective, double-blind, randomized surgery	60 Patients scheduled for breast cancer surgery • Clonidine (0%, mean 56.7 y ± 7.8) • Saline (0%, mean 54.3 y ± 8.6)	Paravertebral block (PVB) with lidocaine, epinephrine, bupivacaine, and either: • Clonidine (30) • Saline (30)	Analgesic consumption, pain score	"The addition of clonidine enhanced the analgesic efficacy of PVB up to 3 days postoperatively for patients undergoing breast surgery."
Naja et al, 2013, Lebanon[468]	Prospective, double-blind study	80 Patients scheduled to undergo hypospadias repair • Pudendal nerve block (PNB; 100%, mean 3.1 y ± 1.1) • Caudal block (CB; 100%, mean 3.2 y ± 1.1)	Bupivacaine and clonidine via: • PNB (40) • Caudal block (40)	Analgesic consumption, pain score	"Patients who received PNB had reduced analgesic consumption and pain within the first 24 hours postoperatively compared with CB."
Nascimento et al, 2010, Brazil[469]	—	43 Patients with complex regional pain syndrome type I (6.98%, range 25-54 y)	• Stellate ganglion block with lidocaine (14) • Stellate ganglion block with lidocaine and clonidine (15) • IV regional block with lidocaine and clonidine (14)	Pain intensity and duration	"The three methods were similar regarding changes in pain intensity and duration of analgesia. However, IVRB seems to be preferable to SBG [sympathetic ganglion block] due to its easier execution and lower risk of undesirable effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Nasir et al, 2017, US[274]	Randomized, observed-blinded, prospective study	83 Patients scheduled to undergo upper extremity surgery • Ropivacaine (60%, mean 49 y ± 16) • Ropivacaine plus clonidine (50%, mean 48 y ± 11) • Ropivacaine plus dexamethasone (40.9%, mean 43 y ± 14) • Ropivacaine plus dexamethasone and clonidine (50%, mean 50 y ± 11)	Ultrasound-guided supraclavicular brachial plexus block with either: • Ropivacaine (25) • Ropivacaine plus clonidine (16) • Ropivacaine plus dexamethasone (22) • Ropivacaine plus dexamethasone and clonidine (20)	Pain scores, sensory and motor function	"The results demonstrated that clonidine significantly prolongs the duration of ropivacaine effects for the postoperative analgesia in patient underwent upper arm surgeries."
Nazareth et al, 2013, India[470]	Prospective, double-blind, randomized, controlled study	100 Patients undergoing orthopedic lower limb surgeries • Clonidine (60%, mean 31.50 y ± 5.46) • Clonidine and fentanyl (56%, mean 30.12 y ± 4.14)	All patients received subarachnoid block with hyperbaric bupivacaine plus either: • Clonidine (50) • Clonidine and fentanyl (50)	Duration of analgesia, hemodynamic changes	"In conclusion, this study has demonstrated that addition of 20 mcg fentanyl to intrathecal 30 mcg clonidine and 12 mg bupivacaine enhanced the duration of post-operative analgesia with moderately increased sedation and was not associated with hemodynamic instability or other complications."
Nazir et al, 2019, India[325]	Prospective, randomized study	75 Patients scheduled for upper limb surgeries • Saline (76%, mean 44.72 y ± 9.19) • Clonidine (72%, mean 45.64 y ± 8.91) • Dexmedetomidine (72%, mean 46.44 y ± 9.29)	Supraclavicular brachial plexus block with ropivacaine plus either: • Saline (25) • Clonidine (25) • Dexmedetomidine (25)	Onset and duration of sensory and motor blockade, duration of analgesia, hemodynamic side effects	"Therefore, in present study it was found that addition of clonidine and dexmedetomidine to 0.5% ropivacaine are effective in supraclavicular brachial plexus block. However, dexmedetomidine is a better alternative to clonidine as adjuvant for 0.5% ropivacaine in to obtain early onset and prolong the duration of sensory and motor block and postoperative analgesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Niemi, 1994, Finland[185]	—	40 Patients undergoing knee arthroscopy under spinal anesthesia (37.5%, range 15-53 y)	Spinal anesthesia with bupivacaine plus either: • Clonidine (20) • Control (20)	Sensory analgesia, blood pressure, heart rate, sedation	"Addition of clonidine prolonged the bupivacaine spinal block. However, marked haemodynamic changes and sedation may limit the usefulness of intrathecal clonidine."
Nováček and Sanders, 2014, Czech Republic and UK[420]	Randomized, double-blind, placebo-controlled study	50 Patients undergoing elective total hip or total knee replacement • Clonidine (48%, mean 60.3 y ± 10.6) • Placebo (44%, mean 65.6 y ± 7.0)	IV administration of either: • Clonidine (25) • Placebo (25)	Desflurane consumption	"Intravenous clonidine decreases the consumption of desflurane during general anaesthesia. This sparing effect is not associated with increased time to ROC [return of consciousness]."
Novak-Jankovič et al, 1997, Slovenia[421]	—	14 Patients undergoing lung surgery (gender and age not specified)	Epidural morphine plus either: • Epidural clonidine (7) • IV clonidine (7)	Plasma concentrations of stress hormones	"Our study showed no significant difference in endocrine stress response between epidural or IV clonidine with epidural morphine."
Oddby-Muhrbeck et al, 2002, Sweden[471]	—	60 Patients undergoing breast cancer surgery (0%, range 33-83 y)	IV administration of either: • Clonidine (30) • Placebo (30)	Nausea and vomiting, patient satisfaction	"Coinduction with clonidine significantly increased the number of PONV-free patients after breast cancer surgery with general anesthesia."
O'Donnell et al, 2009, Ireland[472]	Randomized, controlled trial	30 Patients scheduled for upper limb trauma surgery • General anesthesia (26.7%, mean 37.7 y ± 11.6) • Ultrasound-guided axillary block (60%, mean 40.6 y ± 18.7)	• General anesthesia (15) • Ultrasound-guided axillary block with lidocaine, epinephrine, bupivacaine, and clonidine (15)	Pain scores	"Ultrasound-guided axillary brachial plexus block with 20 mL local anesthetic mixture provided satisfactory anesthesia and superior analgesia after upper limb trauma surgery when compared with general anesthesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Olsen and Jacob, 2016, US[422]	Retrospective analysis	1621 Interscalene blocks were performed during the study period (gender and age not specified) Number of patients was not specified	Interscalene blocks performed: • With clonidine (289) • Without clonidine (1332)	Pain scores	"This review, while significantly larger in size than any prior study, suffers from the limitations of a retrospective study including the inability to control for all possible confounding factors or to record all measurements of interest including characterization of block quality. In summary, this study suggests only slight gains with the addition of clonidine; albeit without significant side effects."
Oriola et al, 2007, France[186]	Prospective, randomized, double-blind study	70 Patients undergoing surgery for hysterectomy or prolapse repair • Ilioinguinal block (0%, mean 48 y ± 9) • Placebo (0%, mean 46 y ± 6)	Ilioinguinal block with either: • Ropivacaine and clonidine (35) • Placebo (35)	Total morphine consumption, pain score	"The use of bilateral ilioinguinal nerve block for postoperative analgesia after hysterectomy decreased morphine consumption by one-half during the first two postoperative days without differences in side effects from morphine between groups."
Owen et al, 2000, Turkey[383]	—	45 Patients in active labor • Fentanyl (0%, mean 26 y ± 4) • Fentanyl and clonidine (0%, mean 27 y ± 4) • Fentanyl, clonidine, and neostigmine (0%, mean 26 y ± 5)	Patients received combined-spinal epidural with IT administration of bupivacaine plus either: • Fentanyl (15) • Fentanyl and clonidine (15) • Fentanyl, clonidine, and neostigmine (15)	Pain, sensory levels, motor block, side effects, maternal vital signs, fetal heart rate	"The addition of clonidine and neostigmine significantly increased the duration of analgesia from IT bupivacaine-fentanyl during labor, but neostigmine caused more nausea. Although serious side effects were not observed in this study, safety must be further addressed before the routine use of multiple IT drugs is advocated."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Paech et al, 2004, Australia[187]	Randomized, double-blind trial	232 Patients scheduled for elective cesarean delivery • Morphine (0%, mean 31.3 y ± 6.0) • Clonidine (0%, mean 31.4 y ± 6.1) • Morphine plus clonidine 30 mcg (0%, mean 31.6 y ± 5.0) • Morphine plus clonidine 60, 90, or 150 mcg (0%, mean 30.8 y ± 4.6)	Spinal analgesia with either: • Morphine (39) • Clonidine (39) • Morphine plus clonidine 30 mcg (41) • Morphine plus clonidine 60, 90, or 150 mcg (113)	Time to patient-controlled morphine use and cumulative morphine consumption	"Because there was no difference in primary or secondary outcomes among groups receiving morphine with clonidine 60–150 mcg, we conclude that the minimal effective dose range of subarachnoid clonidine, when combined with bupivacaine, fentanyl 15 mcg, and morphine 100 mcg, is 30–60 mcg."
Pal et al, 2009, India[188]	Randomized, prospective study	35 Patients undergoing thyroid surgery • IV normal saline (18.2%, mean 34.6 y ± 10.8) • Perineural clonidine and IV normal saline (16.7%, mean 35.5 y ± 12.1) • IV clonidine (25%, mean 33.2 y ± 11.6)	Cervical plexus block with bupivacaine and: • IV normal saline (11) • Perineural clonidine and IV normal saline (12) • IV clonidine (12)	Pain intensity	"Addition of clonidine to bupivacaine significantly increases the duration and quality of cervical plexus block."
Pan et al, 1998, US[384]	Double-blind, randomized design	80 Patients scheduled for cesarean delivery • No added drug (0%, mean 30 y ± 6) • Neostigmine (0%, mean 29 y ± 7) • Clonidine (0%, mean 30 y ± 4) • Neostigmine plus clonidine (0%, mean 29 y ± 5)	Spinal bupivacaine plus: • No added drug (20) • Neostigmine (19) • Clonidine (20) • Neostigmine and clonidine (21)	Maximum spread of anesthesia, duration of analgesia and motor block, vital signs, adverse effects	"Our study showed that the combination of 150 mcg IT clonidine and 50 mcg neostigmine provided longer postsurgical analgesia than with either drug used alone. However, this combination also produced significantly more adverse effects of prolonged motor block and nausea and vomiting. A further study combining the two study drugs but using a lower dose of IT neostigmine (e.g., 25 mcg) is recommended."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Pan and Qian, 2016, China[189]	Double-blind, prospective, randomized, controlled trial	150 Patients scheduled to undergo lower segment cesarean section • Clonidine 15 mcg (0%, mean 23.8 y ± 2.56) • Clonidine 30 mcg (0%, mean 25.2 y ± 3.14) • Clonidine 60 mcg (0%, mean 22.9 y ± 2.9)	Spinal anesthesia with bupivacaine and: • Clonidine 15 mcg (35) • Clonidine 30 mcg (35) • Clonidine 60 mcg (35)	Hemodynamic parameters, onset, peak, and duration of sensory and motor block, sedation scores, Apgar scores, side effects, duration of postoperative analgesia	"Intrathecal addition of 15 and 30 mcg clonidine are better options when sedation is not desirable; on the contrary, addition of 60 mcg provides excellent quality of spinal analgesia when some amount of sedation is acceptable or required without any deleterious effects on the mother and baby."
Pandazi et al, 2013, Greece[190]	—	62 Patients with non-inflammatory osteoarthritis undergoing elective total hip arthroplasty (THA; gender and age not specified)	• Periarticular infiltration with ropivacaine, clonidine, morphine, epinephrine, and corticosteroids (20) • Continuous epidural ropivacaine (21) • PCA morphine (21)	Morphine consumption, pain scores, blood loss, mean arterial pressure, adverse effects	"In our study periarticular infiltration was clearly superior to PCA with morphine after THA, providing better pain relief and lower opioid consumption postoperatively. Infiltration seems to be equally effective to epidural analgesia without having the potential side effects of the latter."
Parag et al, 2019, India[423]	Prospective, randomized, controlled trial	80 Patients undergoing hernia repair or genital surgery • Clonidine (gender not specified, mean 5.40 y ± 2.46) • Fentanyl (gender not specified, mean 5.80 y ± 2.63)	Spinal anesthesia with heavy bupivacaine plus: • Clonidine (40) • Fentanyl (40)	Propofol consumption, hemodynamic profile, adverse events, intraoperative complications	"We conclude that intrathecal adjuvant fentanyl maintains a better hemodynamic profile in terms of adverse events such as bradycardia, systolic hypotension, and diastolic hypotension. Intrathecal clonidine maintains a better sedation level requiring less propofol for sedation. Complications such as apnea and respiratory obstruction can be attributed more to the deep sedation caused by bolus of propofol rather than the inherent properties of intrathecal adjuvant clonidine or fentanyl."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Parameswara et al, 2012, India[473]	—	60 Patients receiving supratentorial tumor excision (gender and age not specified)	• IV clonidine (30) • IV dexmedetomidine (30)	Hemodynamics, brain relaxation and recovery	"Both clonidine and dexmeditomidine [sic] show similar changes on hemodynamics, brain relaxation and recovery. However, being shorter acting dexmeditomidine [sic] needs to be given as continuous infusion, as compared to clonidine."
Patil and Singh, 2015, India[191]	Double-blind, prospective, randomized study	60 Patients undergoing elective upper limb orthopedic surgeries • Control (63.3%, mean 38.10 y ± 12.25) • Clonidine (60%, mean 43.33 y ± 12.39)	Supraclavicular brachial plexus block with ropivacaine and: • Control (30) • Clonidine (30)	Onset and duration of sensory and motor block, duration of analgesia, incidence of hypotension and bradycardia	"Ropivacaine 0.75% is well-tolerated and provides effective surgical anesthesia as well as relief of postoperative pain. Clonidine as an adjuvant to ropivacaine significantly enhances the quality of supraclavicular brachial plexus block by faster onset, prolonged duration of sensory and motor block and improved postoperative analgesia, without associated adverse effects at the dose used."
Patnaik et al, 2018, India[474]	Randomized, controlled, observer-blind study	72 Patients undergoing elective unilateral breast surgery • Anatomical landmark technique (ALT; 0%, mean 42.75 y ± 8.85) • Ultrasound-guided (USG; 0%, mean 49.25 y ± 9.37)	All patients received paravertebral block (PVB) with a local anesthetic mixture containing ropivacaine, adrenaline, and clonidine administered via either: • ALT (36) • USG (36)	Success rate of anesthesia	"Ultrasound-guided PVB provided better anesthesia and perioperative analgesia than the landmark technique for breast surgery."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Pedoto et al, 2020, US[385]	Case report	1 Patient with breast cancer metastatic to the lungs and pleura presented for medical thoracoscopy, lysis of adhesions, and talc poudrage for the management of a recurrent, loculated, malignant right-sided pleural effusion (0%, 55 y)	• Midpoint transverse process to pleura (MTP) block with normal saline, bupivacaine HCl, lidocaine, dexamethasone, and clonidine (1)	Need for additional analgesia	"US [Ultrasound]-guided high volume–low concentration MTP block appears to be a safe and effective intra- and postoperative analgesic option for patients undergoing medical thoracoscopy and talc pleurodesis performed under monitored anesthetic care. This block can potentially become part of an enhanced recovery after surgery protocol, in the attempt to decrease the use of opioids by favoring multimodal analgesia. Further studies are required to define appropriate patient selection, elucidate optimal medication dosing and volumes, and compare with other regional anesthesia modalities."
Peniche et al, 2017, US[512] Peniche et al, 2017, US[513] Peniche et al, 2018, US[475]	Case	1 Patient with a history of chronic obstructive pulmonary disease (COPD), scoliosis post-multiple spine surgeries, implantation of spinal cord stimulator and intrathecal pump (0%, 70 y)	• IT PCA pump with a mixture of hydromorphone, ketamine, bupivacaine, and clonidine (1)	Pain control	"Despite the increasing prevalence of outpatient IT-PCA use, many hospitals ban inpatient use due to safety concerns. This frequently leads to escalation of IV opioid administration, which may result in more complications and increased length of hospital stay. This case highlights the importance of close communication among all providers and understanding the difference in IT versus systemic opioid kinetics in the management of postoperative pain management. We are currently developing hospital policy for safe and appropriate care of inpatients with IT-PCA."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Petroheilou et al, 2012, Greece[386]	Randomized, prospective, controlled study	66 Patients scheduled for elective mild to moderate painful foot and ankle surgery • Placebo (35%, mean 9 y ± 2) • Clonidine (56.5%, mean 10 y ± 2) • Clonidine and ropivacaine (45.5%, mean 10 y ± 2)	Sciatic lateral popliteal block (SLPB) plus femoral block with: • Placebo (20) • Clonidine (23) • Clonidine and ropivacaine (22)	Time to first rescue analgesia	"In conclusion, clonidine appears promising more as an adjuvant in 0.2% ropivacaine and less than alone in the SLPB plus femoral block with regard to mild, moderate intraoperative and postoperative pain management, along with the absence of incidence of PONV, and the high parental satisfaction, in children undergoing foot surgery. Considering the lack of similar studies in children using this technique in this single shot scheme, further investigation is needed to elucidate the definite role of clonidine, and the utility of SLPB for effective analgesia and patient outcome after foot, ankle and knee surgery."
Pinto Neto et al, 2009, Brazil[326]	Randomized, double-blind study	30 Patients undergoing carotid endarterectomy • Clonidine (66.7%, mean 64.7 y ± 8.5) • Bupivacaine (40%, mean 66.2 y ± 9.9)	Deep and superficial cervical plexus blocks with bupivacaine and: • Clonidine (15) • Without clonidine (15)	Heart rate and blood pressure, need for anesthetic supplementation, time until first analgesic supplementation, amount of analgesic used, pain severity	"The association of 150 mcg of clonidine and bupivacaine in cervical plexus block for carotid endarterectomy did not promote a significant improvement of analgesia, evaluated by pain severity, the first analgesic supplementation, and the amount of analgesic supplementation."
Pinto et al, 2000, Italy[192]	—	40 Patients receiving combined spinal-epidural analgesia for labor (0%, age not specified)	• Subarachnoid fentanyl and clonidine (not reported) • Epidural fentanyl and clonidine (not reported)	Quality of analgesia	"We conclude that fentanyl 15 mcg - clonidine 15 mcg intrathecally provides rapid and effective analgesia of 1-2 hours duration during labor. "

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Porkkala et al, 1998, Finland[193]	Double-blind, randomized study	20 Patients undergoing orthopedic or abdominal surgery • Clonidine (50%, mean 33.5 y ± 9.0) • Placebo (60%, mean 37.6 y ± 7.1)	• IV clonidine (10) • Placebo (10)	Somatosensory evoked potentials (SEPs)	"The effect of clonidine in reducing the requirements of anesthetics during general anesthesia is not seen in the cortical SEPs. The isoflurane-induced burst-suppression in the EEG was not affected by clonidine, suggesting that the EEG effects of clonidine and isoflurane were not additive. If SEPs are monitored intraoperatively, clonidine can be used as an adjuvant during isoflurane anesthesia without harmful effects on SEP monitoring."
Potter, 2015, US[194]	Case report	1 Patient with bilateral shoulder pain and bilateral nondisplaced humerus fractures scheduled for surgical repair (0%, 71 y)	• Bilateral ultrasound-guided single shot suprascapular and axillary nerve blocks with ropivacaine, dexamethasone, and clonidine (1)	Ability to tolerate procedure	"In summary, we used the combination of bilateral suprascapular and axillary nerve blocks to achieve adequate postoperative analgesia in an elderly medically complex patient with a recent history of altered mental status and a relative contraindication to interscalene brachial plexus block. We hope that it will provide others an example of the application of regional anesthesia to better achieve perioperative anesthetic goals."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Potti et al, 2017, India[271]	Prospective, randomized, double-blind, controlled study	75 Patients who underwent elective surgery for infraumbilical procedures • IV saline (gender not specified, mean 4.32 y ± 2) • Caudal clonidine and IV saline (gender not specified, mean 4.7 y ± 2) • IV clonidine (gender not specified, mean 4.6 y ± 1)	Caudal bupivacaine and: • IV saline (25) • Caudal clonidine and IV saline (25) • IV clonidine (25)	Postoperative pain, sedation, motor blockade	"Caudal clonidine results in increased duration of analgesia when supplemented to levobupivacaine with no increased frequency of side effects. In addition, when compared with IV clonidine, caudal clonidine had a prolonged duration of analgesia, probably due to its direct effect on the spinal cord. This finding needs further studies to support this mechanism of action."
Pratap et al, 2007, UK[387]	—	20 Healthy volunteers (gender and age not specified)	All volunteers received both subcutaneous infiltration interventions, one in each arm: • Lidocaine with normal saline (20) • Lidocaine with clonidine (20)	Time to return of normal sensation	"The results however suggest that use of this additive may be beneficial for postoperative analgesia in the context of plastic or other superficial surgical procedures, in addition to reducing local blood flow, which may aid surgery. Additional, more clinically focused trials may clarify the benefits of adding clonidine to local anesthetic for infiltration, particularly in relation to other local anesthetic additives such as epinephrine and bicarbonate. Further studies are required to elucidate the mechanism underlying the peripheral effect of clonidine."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Priyadarshi et al, 2018, India[195]	Randomized, doubled-blind, controlled study	60 Patients admitted for elective upper limb surgery (gender and age not specified)	Brachial plexus block via supraclavicular approach with ropivacaine and: • Normal saline (30) • Clonidine (30)	Sensory function, first analgesic request	"Clonidine produces faster onset and longer duration of sensory, motor blockage, analgesia without any significant side effect and complication when used as an adjuvant to ropivacaine for supraclavicular brachial plexus block."
Purohit, 2016, India[196]	Prospective, randomized, controlled, double-blind study	60 Patients undergoing supratentorial craniotomies (gender and age not specified)	Scalp block with ropivacaine and either: • Normal saline (30) • Clonidine (30)	Hemodynamic parameters, cumulative propofol and fentanyl doses required	"Ropivacaine infiltration with clonidine for scalp block attenuates hemodynamic responses to skin incision and decreases anesthetic and analgesic necessity."
Quintin et al, 1996, France[197]	Double-blind, controlled, randomized study	21 Patients with hypertension reporting for aortic surgery • Placebo (80%, mean 68.7 y ± 5.4) • Clonidine (81.8%, mean 63.8 y ± 8.2)	All patients received oral administration of the study drug before induction and then the same drug as an IV infusion: • Placebo (10) • Clonidine (11)	Anesthetic requirements, circulatory variables, interventions, isoproterenol dose-response curves	"Clonidine was effective in reducing anesthetic requirements and in improving circulatory stability in hypertensive patients presenting for major vascular procedures."
Racle et al, 1987, France[198]	—	60 Patients scheduled for orthopedic hip surgery • Normal saline (35%, mean 82.7 y ± 1.3) • Epinephrine (40%, mean 80.8 y ± 1) • Clonidine (45%, mean 79.1 y ± 1.1)	Spinal anesthesia with bupivacaine plus: • Normal saline (20) • Epinephrine (20) • Clonidine (20)	Characteristics of sensory and motor block	"In conclusion, clonidine (0.15 mg) added to plain bupivacaine 0.5% spinal anesthesia is more effective than epinephrine (0.2 mg) in prolonging sensory and motor blockade."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions

Ragavendran et al, 2016, Canada[388]	Double-blind, randomized, controlled study	69 Healthy participants (52%, mean 23.2 y ± 6.27)	Each group received 2 topical interventions in a crossover design
			• Group 1:
			  ○ Low-dose clonidine and pentoxifylline (23)
			  ○ Placebo vehicle (23)
			• Group 2:
			  ○ High-dose clonidine and pentoxifylline (23)
			  ○ Placebo vehicle (23)
			• Group 3:
			  ○ Clonidine (23)
			  ○ Pentoxifylline (23)
				Pain score in response to capsaicin	"Results also revealed significant inhibition of postcapsaicin dynamic mechanical allodynia and PMA [punctate mechanical allodynia] for the high-dose combination compared with placebo, and of PMA for CLON [clonidine] compared with the low-dose combination. Hence, the present data are supportive of further clinical investigation of the high-dose topical combination of CLON + PTX [pentoxifylline] in complex regional pain syndrome and neuropathic pain patients, for which our preclinical data predict efficacy."

Ramsodit and Timmerman, 2016, the Netherlands[327]	Randomized, double-blind study	61 Patients scheduled for orthopedic foot surgery (16%, mean 51.8 y)	Popliteal nerve block with levobupivacaine and: • Control (not reported) • Clonidine (not reported)	First analgesic request	"The use of clonidine as an additive to levobupivacaine for popliteal nerve block did not result in a significant difference in the duration of postoperative analgesia in orthopaedic foot surgery."
Rao et al, 2017, India[199]	Prospective, randomized, double-blind trial	100 Patients undergoing total abdominal hysterectomy • Clonidine (0%, mean 42.26 y ± 11.91) • Normal saline (0%, mean 48.52 y ± 12.18)	IT hyperbaric bupivacaine plus: • Clonidine (50) • Normal saline (50)	Duration of sensory and motor block, duration of postoperative analgesia	"Addition of intrathecal clonidine 50 mcg to bupivacaine (15 mg, 0.5%) prolongs the duration of sensory and motor block and duration of analgesia, thus produces an effective spinal anesthesia and good postoperative analgesia for longer duration and reduced postoperative analgesic requirement."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Rauck et al, 2015, US[200]	Double-blind, crossover study	22 Patients with complex regional pain syndrome (40.9%, mean 44 y ± 10)	• IT clonidine (22) • IT adenosine (22)	Pain reduction	"Both intrathecal clonidine and adenosine acutely inhibit experimentally induced and clinical hypersensitivity in patients with chronic regional pain syndrome. Although these drugs do not differ in analgesia by the primary outcome measure, their difference in effect on pain scores over time and lack of correlation between effect on pain and hypersensitivity suggest that analgesia does not parallel antihyperalgesia with these treatments."
Rauf et al, 2013, Ireland[328]	—	30 Patients scheduled for semi elective bimalleolar surgery of the ankle (gender and age not specified)	Combined sciatic-saphenous nerve block with either: • Lignocaine and clonidine (not reported) • Bupivacaine (not reported)	Time to first rescue analgesia, sedation post block performance, hemodynamic instability	"We conclude that the lidocaine plus clonidine combination induced sensory and motor blockade of lesser duration than that achieved with an equal volume of bupivacaine 0.5%."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ray et al, 2010, India[201]	Randomized, placebo-controlled, double-blind study	75 Patients undergoing elective upper limb orthopedic surgery • Clonidine (80%, mean 37.96 y ± 9.61) • Magnesium sulfate (76%, mean 43.52 y ± 8.52) • Normal saline (56%, mean 35.8 y ± 9.51)	IV administration of either: • Clonidine (25) • Magnesium sulfate (25) • Normal saline (25)	Induction time, recovery time, consumption of propofol and fentanyl	"To conclude, perioperative use of both clonidine and magnesium sulphate significantly reduced the requirement of propofol and fentanyl citrate. They were able to attenuate the haemodynamic response to tracheal intubation. Both clonidine and magnesium sulphate caused bradycardia and hypotension. Besides, magnesium sulphate caused a delay in recovery. Therefore, both clonidine and magnesium sulphate need careful management, to be used as adjuvant agents to general anaesthetics."
Reddy et al, 2013, India[329]	Prospective, randomized, double-blind, placebo-controlled study	75 Patients scheduled for orthopedic lower limb surgery under spinal anesthesia • Placebo (36%, mean 48.81 y ± 7.16) • Clonidine (32%, mean 47.23 y ± 6.84) • Dexmedetomidine (36%, mean 47.7 y ± 6.93)	IV administration of study agent before subarachnoid anesthesia: • Placebo (25) • Clonidine (25) • Dexmedetomidine (25)	Onset and regression time of sensory and motor blockade, maximum upper level of sensory blockade, duration of postoperative analgesia, sedation scores, side effects	"Premedication with intravenous dexmedetomidine is better than intravenous clonidine to provide intraoperative sedation and postoperative analgesia during bupivacaine spinal anesthesia."
Reena and Kumar, 2018, India[330]	Prospective, randomized, double-blind study	60 Patients scheduled for urogenital surgery • Clonidine (76.7%, mean 7.0 y ± 3.0) • Dexmedetomidine (70%, mean 7.5 y ± 2.0)	IV administration of either: • Clonidine (30) • Dexmedetomidine (30)	Sedation score, parental separation anxiety level, degree of mask acceptance, highest level of sensory blockade, time of two segment regression, time of first request of analgesic	"Dexmedetomidine is superior to clonidine as a premedication drug in pediatric patients undergoing spinal anesthesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Reena and Vikram, 2017, India[202]	Prospective, randomized, placebo-controlled, double-blind study	90 Patients undergoing spinal surgery • Clonidine (70%, mean 32.43 y ± 10.09) • Magnesium sulfate (70%, mean 33.67 y ± 10.24) • Normal saline (63.3%, mean 33.87 y ± 9.25)	IV anesthesia with either: • Clonidine (28) • Magnesium sulfate (29) • Normal saline (30) 3 Patients dropped due to symptomatic bradycardia or hypotension	Intraoperative hemodynamics, recovery times, anesthetic consumption	"Clonidine and magnesium sulfate both are effective in maintaining hemodynamic stability in patients undergoing lumbar spine surgeries. Both reduce intraoperative anesthetics consumption significantly. Magnesium delays the postoperative recovery in comparison to clonidine and control group."
Reinhart et al, 1996, US[203]	Prospective, double-blind, randomized	82 Patients scheduled for unilateral bunionectomy or hammer toe repair • Sterile water (16.7%, mean 45 y ± SE 5) • Clonidine 10 mcg/mL (29.6%, mean 41 y ± SE 4) • Clonidine 20 mcg/mL (28%, mean 44 y ± SE 5)	Ankle or metatarsal block with lidocaine plus either: • Sterile water (30) • Clonidine 10 mcg/mL (27) • Clonidine 20 mcg (25)	Time to loss and return of sensation, onset of postsurgical pain, time to first oral pain medication intake	"Compared to 1.73% lidocaine, combining clonidine (10 mcg/mL) with lidocaine for local anesthetic block for foot surgery significantly increases the duration and quality of postoperative analgesia."
Ren et al, 2020, China[494]	Randomized, controlled trial protocol	Patients undergoing elective total knee arthroplasty (gender and age not specified)	All patients would receive periarticular infiltration (PAI) mixture intraoperatively with scheduled and patient-requested oral and IV analgesics for postoperative breakthrough pain: • With adductor canal block with ropivacaine and clonidine (not reported) • Without ACB (not reported)	Morphine consumption in first 24 hours	Study protocol; authors hypothesize "that patients receiving adductor canal block + PAI would have significantly lower morphine consumption and pain scores after surgery."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Reuben[b] and Connelly, 1999, US[204]	—	50 Patients scheduled to undergo elective arthroscopic meniscal surgery • Intraarticular (IA) bupivacaine (40%, mean 41 y ± 8) • Intraarticular bupivacaine and clonidine (30%, mean 44 y ± 10) • Intraarticular bupivacaine and subcutaneous clonidine (60%, mean 47 y ± 12) • Intraarticular bupivacaine and epinephrine (50%, mean 45 y ± 10) • Intraarticular clonidine (40%, mean 42 y ± 10)	• Intraarticular bupivacaine (10) • Intraarticular bupivacaine and clonidine (10) • Intraarticular bupivacaine and subcutaneous clonidine (10) • Intraarticular bupivacaine and epinephrine (10) • Intraarticular clonidine (10)	Need for oral postoperative analgesics, duration of analgesia	"In conclusion, we have shown that clonidine, when administered along with bupivacaine via the IA route, results in a significant improvement in analgesia. There was an increased time to first analgesic request and a decreased need for postoperative analgesics."
Reuben[b] et al, 2006, US[389]	Randomized, double-blind study	80 Patients scheduled to undergo elective lower extremity amputation because of ischemic necrosis secondary to peripheral vascular disease • Clonidine infiltration (57.5%, mean 68 y ± 12) • Control (62.5%, mean 65 y ± 17)	• Perineural bupivacaine and clonidine (40) • Control (40)	Pain scores, opioid use, phantom limb and stump pain	"In conclusion, a single perineural injection of clonidine at the time of nerve transection provides for a reduction in acute postoperative pain but offers no prolonged benefit in reducing phantom or stump pain following lower extremity amputation. We are currently enrolling patients in a prospective, randomized, double-blind study to evaluate the efficacy of long-term perineural infusions of clonidine for lower extremity amputation surgeries."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Reuben[b] and Sklar, 2002, US[205]	Case reports	7 Patients with a diagnosis of complex regional pain syndrome of the knee (28.6%, range 23-58 y)	• IVRA clonidine (IVRA-C) with lidocaine (7)	Pain score, duration of pain relief	"IVRA-C is a useful treatment modality in the management of CRPS of the knee. Clonidine doses of 1 g/kg appear to be well tolerated without significant side effects."
Reuben[b] et al, 1999, US[206]	—	45 Patients undergoing ambulatory hand surgery • Control (gender not specified, mean 55 y ± 13) • IV clonidine (gender not specified, mean 46 y ± 11) • IVRA-C (gender not specified, mean 50 y ± 17)	• Control plus IVRA lidocaine (15) • IV clonidine plus IVRA lidocaine (15) • IVRA-C with lidocaine (15)	Pain and sedation scores, analgesic use	"The addition of 1 mcg/kg clonidine to lidocaine, 0.5%, for IVRA in patients undergoing ambulatory hand surgery improves postoperative analgesia without causing significant side effects during the first postoperative day."
Reuben[b] et al, 1998, US[207]	Case reports	10 Patients with symptoms of sympathetically maintained pain (40%, range 34-48 y)	• IV regional clonidine (IVRC) with either normal saline or lidocaine as the diluent (10)	Pain score	"We report the successful use of IVRC in 10 patients with sympathetically maintained pain of < 3 months duration. Clonidine doses of 1 mcg/kg appear to be well tolerated without significant side effects."
Reynolds et al, 2017, US[390]	Retrospective review	40 Patients who underwent right colon surgery or total colectomy with a supraumbilical hand port incision and received bilateral posterior approach and subcostal TAP blocks (gender and age not specified)	Bilateral posterior and subcostal TAP blocks with either: • Liposomal bupivacaine (not reported) • Non-liposomal bupivacaine with epinephrine and clonidine (not reported)	Pain scores, cumulative opioid consumption	"In patients undergoing right colon surgery or total colectomy, our analysis revealed no statistically significant difference in post-operative opioid consumption or pain scores between the groups. While our investigation did not uncover a difference between the groups in this patient population, it remains to be determined using larger prospective randomized trials whether a statistically significant difference would be found."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Reynolds et al, 2019, US[476]	Prospective, randomized, observer- and patient-blinded, single-institution trial	40 Patients scheduled for elective shoulder arthroscopy with a planned open, subpectoral biceps tenodesis • Interscalene block (ISB; 72%, mean 52.9 y ± 11) • ISB plus pectoral nerve block II (Pecs II; 53%, mean 53.8 y ± 10.4)	• Single-injection ISB with bupivacaine, epinephrine, and clonidine (20) • ISB plus Pecs II block with bupivacaine, epinephrine, and clonidine (20)	Postoperative pain scores	"The addition of a Pecs II block to an ISB for patients undergoing arthroscopic shoulder surgery with an open subpectoral biceps tenodesis significantly improved postoperative analgesia and reduced the need for opioids in the PACU."
Rhee et al, 2003, South Korea[208]	Double-blind, placebo-controlled, prospective study	78 Patients scheduled for orthopedic surgery • Control (76.9%, mean 39 y ± 14) • Clonidine 10 minutes (73.1%, mean 43 y ± 15) • Clonidine 60 minutes (65.4%, mean 42 y ± 14)	Spinal bupivacaine followed by IV administration of either: • Control (26) • Clonidine for 10 minutes, 10 minutes after spinal block (26) • Clonidine for 10 minutes, 50 minutes after spinal block (26)	Duration of sensory and motor block	"Therefore, intravenous clonidine could be a clinically useful method for prolonging spinal anesthesia after the block when the operation lasts longer than presumed."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Rochette et al, 2004, France[391]	Controlled, prospective, dose-ranging study	75 Patients scheduled for elective inguinal hernia repair • Control (gender not specified, median 40 weeks) • Clonidine 0.25 (gender not specified, median 41.5 weeks) • Clonidine 0.5 (gender not specified, median 41.5 weeks) • Clonidine 1 (gender not specified, median 42 weeks) • Clonidine 2 (gender not specified, median 42.5 weeks)	Spinal anesthesia with isobaric bupivacaine plus either: • Control (15) • Clonidine 0.25 mcg/kg (16) • Clonidine 0.5 mcg/kg (15) • Clonidine 1 mcg/kg (15) • Clonidine 2 mcg/kg (14)	Mean arterial blood pressure, heart rate, oxygen saturation, sensory block extension and duration	"Our study demonstrates that clonidine 1 mcg/kg doubles neonatal spinal anesthesia duration without providing undesirable hemodynamic effects in the immediate postoperative period. Investigations on a larger number of patients for a longer period should be conducted to address long-term effects of spinal clonidine in newborns."
Rohan et al, 2014, India[209]	Prospective, randomized, double-blind, controlled trial	75 Patients scheduled to undergo elective surgery on the upper extremity • Saline (80%, mean 38.20 y ± 15.74) • Lignocaine (72%, mean 42.64 y ± 16.39) • Clonidine (76%, mean 39.04 y ± 16.47)	Supraclavicular block with ropivacaine plus either: • Saline (25) • Lignocaine (25) • Clonidine (25)	Characteristics of anesthesia and analgesia	"When compared to the use of ropivacaine alone, the addition of 150 mcg clonidine to ropivacaine for brachial plexus block achieved earlier analgesic onset and improved duration of analgesia, without unwanted side effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Rohrbach et al, 1999, Germany[392]	Double-blind, placebo-controlled study	40 Patients undergoing an abdominal hysterectomy (0%, range 26-69 y)	IV administration of either: • Clonidine (20) • Placebo (20)	Pain intensity, piritramide consumption, hemodynamic parameters, shivering, nausea, vomiting, sedation	"In conclusion, the intraoperative infusion of clonidine 5 mcg kg^{-1} reduces the postoperative sympathetic stress response and its effects on the cardiovascular system, after abdominal hysterectomy with remifentanil anaesthesia. We were not able to demonstrate a direct analgesic effect due to clonidine. However, further studies are warranted to establish more detailed dose-response curves for clonidine when used in combination with different intraoperative opioids."
Routray et al, 2017, India[210]	Randomized, controlled study	80 Patients scheduled for lower limb orthopedic surgery • Clonidine (75%, mean 27.63 y ± 3.98) • Fentanyl (70%, mean 27.12 y ± 4.13)	IT hyperbaric bupivacaine plus: • Clonidine (40) • Fentanyl (40)	Duration of postoperative analgesia, sensory and motor block characteristics, hemodynamic parameters, side effects	"Intrathecal clonidine (50 μg) when added to bupivacaine in spinal anesthesia provides prolonged duration of postoperative analgesia than 25 μg of fentanyl but with higher degree of sedation. Fentanyl (25 μg) may be recommended as a better option when sedation is not desirable."
Ruan et al, 2010, US[211]	Case report	1 Patient with recurrent cellulitis and persistent leg edema associated with intrathecal morphine and hydromorphone infusion therapy (0%, 61 y)	• IT baclofen and clonidine (1)	Pain control, resolution of persistent edema	"Intrathecal baclofen and clonidine may be used as alternatives to provide spinally mediated antinociception when intraspinal opioid fails due to pharmacological side effects such as persistent edema."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Runge et al, 2016, Denmark[477]	Double-blind, randomized, controlled trial	75 Patients who underwent total knee arthroplasty • Combined obturator nerve block (ONB) and femoral triangle block (FTB; 57.7%, mean 71 y ± 8.0) • Single FTB (56.5%, mean 73 y ± 7.1) • Local infiltration analgesia (LIA; 42.3%, mean 70 y ± 8.4)	• ONB and FTB with bupivacaine, epinephrine, clonidine, and dexamethasone (26) • FTB with bupivacaine, epinephrine, clonidine, and dexamethasone (23) • LIA with ropivacaine, epinephrine, and ketorolac (26)	Morphine consumption	"Addition of ONB to FTB significantly reduced opioid consumption and pain after TKA compared with a single FTB or LIA, without impaired ambulation."
Sachan et al, 2014, India[478]	Single-blind, prospective, randomized, controlled study	60 Patients scheduled for elective cesarean section • Mixture of clonidine and hyperbaric bupivacaine (0%, mean 26.43 y ± 4.52) • Clonidine followed by hyperbaric bupivacaine (0%, mean 25.13 y ± 4.10)	IT administration of either: • Mixture of clonidine and hyperbaric bupivacaine (30) • Clonidine followed by hyperbaric bupivacaine through separate syringes (30)	Duration of analgesia, time to achieve highest sensory block and complete motor block, hemodynamic instability, neonatal outcome	"When clonidine and hyperbaric bupivacaine were administered in a sequential manner, block characteristics improved significantly compared to the administration of the mixture of the two drugs."
Sachan et al, 2014, India[479]	Prospective, randomized, single-blind study	90 Patients scheduled for elective cesarean section • Mixture of clonidine and hyperbaric bupivacaine (HB; 0%, mean 26.43 y ± 4.52) • Hyperbaric bupivacaine followed by clonidine (0%, mean 25.53 y ± 3.86) • Clonidine followed by hyperbaric bupivacaine (0%, mean 25.13 y ± 4.10)	IT administration of either: • Mixture of clonidine and hyperbaric bupivacaine (30) • Hyperbaric bupivacaine followed by clonidine through separate syringes (30) • Clonidine followed by hyperbaric bupivacaine through separate syringes (30)	Time to complete sensory and motor block, duration of analgesia, hemodynamic parameters, sedation	"Sequential technique reduces time to achieve complete sensory and motor block, delays block regression, and significantly prolongs the duration of analgesia. However, it did not matter much whether clonidine was administered before or after HB."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sadigursky et al, 2017, Brazil[480]	Prospective and comparative study	59 Patients with a diagnosis of primary osteoarthritis of the knee who underwent elective surgeries for total knee arthroplasty (39%, mean 68 y)	• Spinal anesthesia with bupivacaine and morphine and periarticular infiltration of bupivacaine, epinephrine, triamcinolone, clonidine, and saline (29) • Conventional IV analgesia with tramadol, dipyrone, and morphine (30)	Postoperative complications, pain, functional capacity, range of motion, transfusion, rescue opioids	"The analysis of data obtained demonstrated that the periarticular infiltration of analgesic agents is significantly effective for pain control and functional recovery."
Sahi et al, 2016, India[331]	Randomized, double-blind study	120 Patients scheduled for elective laparoscopic cholecystectomy under general anesthesia (gender and age not specified)	IV administration of either: • Clonidine (30) • Tramadol (30) • Dexmedetomidine (30) • Normal saline (30)	Shivering episodes, sedation, pain, respiratory depression, nausea and vomiting	"Clonidine caused significant postoperative sedation while patients who received tramadol and dexmedetomidine were not sedated compared to clonidine. All the three drugs provided postoperative analgesia with tramadol exhibiting maximum analgesic efficacy. There was no difference in analgesic efficacies of clonidine and dexmedetomidine. Thus, tramadol was found to be the most suitable agent in preventing postanesthesia shivering with the additional benefit of longer analgesic effect and least side effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sahni et al, 2015, India[212]	Prospective, randomized, double-blind study	80 Patients undergoing arthroscopic anterior cruciate ligament repair • Control (85%, mean 27.15 y ± 5.67) • Intrathecal (80%, mean 29.60 y ± 9.64) • Intraarticular (80%, mean 29.35 y ± 8.28) • Femoro-sciatic nerve block (FSNB; 90%, mean 30.30 y ± 9.61)	All groups received IT hyperbaric bupivacaine plus either: • Control (20) • IT clonidine (20) • Intraarticular clonidine and bupivacaine (20) • FSNB with bupivacaine and clonidine (20)	Postoperative pain-free interval, block characteristics	"Clonidine in a dose of 1 mcg/kg with bupivacaine is effective in prolonging postoperative analgesia after arthroscopic ACL repair when administered through various routes. Clonidine was most effective when administered through FSNB and provided longest pain-free period, decreased pain score and least rescue analgesic requirement making it ideal for post knee surgery pain."
Saied et al, 2017, US[213]	Observational study	3706 Patients who received regional anesthesia in an outpatient surgery center (58.4%, mean 44 y ± 17.3)	Brachial plexus single injection blocks with ropivacaine plus either: • No adjuvants (1535) • Epinephrine (293) • Clonidine (527) • Clonidine and epinephrine (16) • Dexamethasone (204) • Dexamethasone and epinephrine (303) • Dexamethasone and clonidine (795) • Epinephrine, clonidine, and dexamethasone (33)	Block duration	"For brachial plexus blocks, epinephrine did not affect the duration of analgesia when added to ropivacaine. Epinephrine did not enhance the observed increase of block duration induced by clonidine or the combination of clonidine and dexamethasone. The most block duration enhancement was observed when combination of clonidine and dexamethasone were added to ropivacaine."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Salengros et al, 2011, Belgium[332]	Double-blind, randomized study	68 Patients scheduled for elective surgery • Placebo (35.3%, mean 45.4 y ± 13.2) • Clonidine and ketamine (47.1%, mean 46.4 y ± 15.4)	All patients received an initial IV piritramide injection. If pain score was still elevated afterwards, the patients were randomized to IV administration of either: • Placebo (34) • Ketamine plus clonidine (34)	Reduction of time necessary to achieve a numerical rating score (NRS) < 4	"It was concluded that in the immediate postoperative period, the acute administration of small combined doses of intravenous ketamine (0.125 mg/kg) and clonidine (0.5 mcg/kg) does not reduce the onset of an opioid-based analgesia in patients with an initial poor response to intravenous opioids."
Samantaray et al, 2012, India[214]	Prospective, randomized, double-blind, placebo-controlled trial	58 Patients undergoing thoracic surgery • Clonidine (53.3%, mean 48.4 y ± 9.2) • Placebo (50%, mean 45.6 y ± 6.3)	• IV clonidine (30) • Placebo (28)	Severity of post-operative pain during cough, time to first analgesic request in the PACU, 24-hour postoperative fentanyl requirement	"A single intravenous dose of clonidine (3 mcg/kg) given before induction of anaesthesia significantly reduced the post-operative VAS [visual analogue scale] score in the initial period and fentanyl consumption during 24 h after thoracic surgery."
Samantaray et al, 2016, India[333]	Randomized, double-blind, clinical efficacy study	60 Patients scheduled for general endotracheal anesthesia (gender and age not specified)	IV administration of either: • Clonidine (not reported) • Dexmedetomidine (not reported)	Sedation level, blood pressure, heart rate	"Dexmedetomidine and clonidine attenuated the heart rate response but the return to base line value was quicker in dexmedetomidine. Both drugs resulted in a significant fall in blood pressure. Dexmedetomidine appears to be superior to clonidine because it resulted in lesser magnitude of hypotensive episodes."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Samsó et al, 1996, Spain[334]	Randomized, double-blind, placebo-controlled protocol	60 Patients undergoing abdominal hysterectomy • Epidural (0%, mean 44.0 y ± 1.3) • Intramuscular (0%, mean 45.7 y ± 2.0) • Saline (0%, mean 44.9 y ± 2.3)	• Epidural clonidine and IM saline (20) • Epidural saline and IM clonidine (20) • Epidural and IM saline (20)	Isoflurane requirements, hemodynamic evaluation, evaluation of stress response, postoperative evaluation	"Epidural and intramuscular clonidine decreased isoflurane requirements similarly, but only the epidural route provided postoperative analgesia, suggesting a spinal site for the analgesic action."
Santiago et al, 2014, Brazil[215]	Double-blind, randomized trial	40 Patients undergoing cataract surgery • Clonidine (35%, mean 64.3 y ± 8.2) • Placebo (45%, mean 65.5 y ± 10.7)	IV administration of either: • Clonidine (20) • Saline (20)	Intraoperative analgesia, intraocular pressure, blood pressure, heart rate, occurrence of arrhythmias, and myocardial ischemia	"The results of the present study suggest that clonidine at a dose of 4 mc/kg via an intravenous route promotes an analgesic effect and sedation appropriate for cataract extraction by means of phacoemulsification under topical anesthesia without altering the heart rate or the systemic arterial pressure. The results of the recent study further suggest that the use of clonidine reduces the incidence of arrhythmia."
Santiveri et al, 2002, Spain[216]	Controlled, prospective, double-blind study	37 Patients scheduled for elective transurethral resection of bladder tumors under spinal anesthesia with prilocaine • Clonidine (gender not specified, mean 68.05 y ± 7.6) • Control (gender not specified, mean 70.44 y ± 7.4)	Spinal anesthesia with prilocaine plus either: • Clonidine (19) • Control (18)	Hemodynamic changes, pulse oximetry, upper level of block, onset and duration of sensory and motor block, postoperative analgesia, adverse effects	"The addition of clonidine 75 mcg to prilocaine 75 mg for subarachnoid anaesthesia increased the duration of sensory and motor block and reduced the need for additional postoperative analgesics by providing excellent analgesia for about 8 h during recovery from transurethral resection of bladder tumours."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sapate et al, 2014, India[20]	—	60 Patients undergoing below-knee orthopedic surgery (gender and age not specified)	IT administration of hyperbaric bupivacaine plus either: • Normal saline (30) • Clonidine (30)	Onset and peak of sensory and motor blocks, analgesia duration, sensory block regression	"Intrathecal clonidine potentiates bupivacaine induced spinal sensory block and motor block and reduces the analgesic requirement in the early post-operative period in unilateral spinal anesthesia for lower limb below knee surgery."
Sardar et al, 2017, India[393]	Hospital-based, prospective, randomized, double-blind, prospective trial	60 Patients scheduled for elective hernia surgery • Group I (95%, mean 3.97 y ± 2.02) • Group II (90%, mean 4.76 y ± 2.69) • Group III (85%, mean 3.37 y ± 1.90)	• Group I: Oral midazolam and regional bupivacaine (20) • Group II: Oral midazolam and clonidine and regional bupivacaine (20) • Group III: Oral midazolam and regional clonidine and bupivacaine (20) Regional administration was provided as an ilioinguinal/iliohypogastric block	Preoperative sedation and separation score, postoperative duration and quality of analgesia, analgesic need, sedation score, side effects	"Clonidine enhanced the duration and quality of analgesia in ilioinguinal/iliohypogastric nerve block when used in both oral and regional route. However, oral clonidine was found to have slightly better analgesic efficacy than regional clonidine in terms of duration of analgesia. Addition of clonidine did not increase the risk of side effects in any of the groups. Both the clonidine groups were observed to produce significant sedation in initial 2 h of postoperative period which may be an advantage in pediatric patients though oral clonidine produces better parental separation compared to others. Further large-scale multicentric studies are needed to establish superiority between oral and regional clonidine."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sardesai et al, 2015, India[335]	Prospective, randomized, double-blind study	60 Patients undergoing elective upper limb orthopedic surgeries • Clonidine (60%, mean 42.63 y ± 11.51) • Dexmedetomidine (63.3%, mean 37.47 y ± 11.41)	IV regional anesthesia (IVRA) with lignocaine plus either: • Clonidine (30) • Dexmedetomidine (30)	Sensorimotor block onset, pain score, fentanyl consumption, sedation, duration of analgesia	"Dexmedetomidine significantly facilitates onset, prolongs recovery of sensory as well as motor block and also prolongs duration of analgesia as compared to clonidine. Both decrease tourniquet pain satisfactorily and have comparable intra-operative fentanyl requirement. Patient satisfaction is better with dexmedetomidine."
Sarma et al, 2015, India[217]	Randomized	150 Patients scheduled to undergo lower limb surgeries • Normal saline (gender not specified, mean 33.68 y ± 8.786) • Clonidine (gender not specified, mean 31.04 y ± 7.926) • Dexmedetomidine (gender not specified, mean 33.20 y ± 6.827)	Spinal bupivacaine plus either: • Normal saline (50) • Clonidine (50) • Dexmedetomidine (50)	Onset and duration of sensory and motor block, highest level of sensory blockade, duration of analgesia, side effects	"Supplementation of bupivacaine spinal block with a low dose of intrathecal dexmedetomidine (5 mcg) or clonidine (50 mcg) produces a significantly shorter onset of motor and sensory block and a significantly longer sensory and motor block than bupivacaine alone."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Schechtmann et al, 2010, Sweden[218]	Randomized, double-blind, placebo-controlled, clinical trial	10 Patients with a confirmed diagnosis of chronic neuropathic pain experiencing insufficient pain relief with spinal cord stimulation (SCS) alone (50%, range 39-68 y)	All patients received IT administration of 3 different doses of clonidine, 3 different doses of baclofen, and 2 placebos once daily over a 2-week period in combination with SCS for bolus trials: • Clonidine 25, 50, and 75 mcg (10) • Clonidine 100 mcg (2) • Baclofen 25, 50, and 75 mcg (10) • Placebo (10) 4 Patients underwent pump implantation for long-term administration of IT: • Clonidine (2) • Baclofen (2)	Pain scores	"A trial with clonidine and baclofen combined with SCS may be warranted in patients who do not obtain satisfactory pain relief with SCS alone or experienced a decreasing therapeutic effect."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Schulz et al, 2015, US[336]	Retrospective chart review	56 Patients who underwent total knee arthroplasty and received a preoperative adductor canal nerve block with combined spinal epidural as primary anesthetic technique (gender and age not specified)	• ACB with bupivacaine, buprenorphine, and clonidine (28) • ACB with bupivacaine (28)	Pain scores, opioid use, ambulation distance, PACU/hospital times	"In this retrospective study, it appears there is no advantage to buprenorphine and clonidine adjuvant use in ACB for TKA. A larger patient sample size may have demonstrated significance in other categories but few were trending toward significance. Standardized institutional factors may have contributed to our outcomes - including scheduled pain regimens, PACU wait time for beds and physical therapy routines. In addition, an increased number of patients discharged home on POD 2 in the additives group may have impacted the ambulation data in favor of the non-additives group. Further ACB studies are warranted to evaluate additional additives (i.e., dexamethasone), volume of injection and LA [local anesthetic] concentration."
Seering et al, 2019, US[394]	Prospective, randomized, triple-blind, clinical trial	158 Patients undergoing elective shoulder surgery • Control (64.1%, mean 45 y ± 14) • Clonidine (82.5%, mean 43 y ± 15) • Dexamethasone (77.5%, mean 42 y +/ -14) • Buprenorphine (76.9%, mean 45 y ± 14)	Interscalene block with ropivacaine and either: • Control (39) • Clonidine (40) • Dexamethasone (40) • Buprenorphine (39)	Duration of analgesia	"There was no significant improvement in the duration of analgesia with addition of any of the three adjuncts to interscalene blocks. However, there was a larger than expected variability in patient response, hence the study may have been underpowered for the primary outcome."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Selvaraj, 2016, India[219]	Prospective, randomized, double-blind study	100 Patients posted for abdominal hysterectomy • Bupivacaine and clonidine (0%, mean 41.34 y ± 6.15) • Bupivacaine (0%, mean 43.18 y ± 7.05)	Wound infiltration with either: • Bupivacaine and clonidine (50) • Bupivacaine (50)	Duration of effective analgesia, pain score, percent of patients requiring rescue medication, number of tramadol and fentanyl doses	"To conclude, clonidine is an effective adjuvant to bupivacaine for local infiltrative analgesia in improving the quality and duration of postoperative analgesia in patients who have undergone total abdominal hysterectomy."
Sen and Sen, 2015, India[220]	Prospective study	20 Patients undergoing sub-umbilical surgeries • Clonidine (gender not specified, mean 74.6 ± 3.71) • Saline (gender not specified, mean 74.8 y ± 3.73)	Spinal anesthesia with heavy bupivacaine plus: • Clonidine (10) • Saline (10)	Level of subarachnoid block, duration of motor block, request for first dose of analgesia, arterial pressure, heart rate, side effects	"We conclude that addition of clonidine in the dose of 7.5 mcg to bupivacaine significantly increases the duration of spinal analgesia with clinically insignificant influence on hemodynamic parameters."
Senapathi et al, 2019, Indonesia[221]	Double-blind, randomized study	46 Patients who underwent craniotomy surgery due to brain tumor • Levobupivacaine and clonidine (43.5%, mean 36.74 y ± 14.004) • Levobupivacaine (52.2%, mean 40.04 y ± 13.258)	Scalp block with: • Levobupivacaine and clonidine (23) • Levobupivacaine (23)	Intraoperative fentanyl requirement, period to postoperative first PCA dose, total need of postoperative morphine by PCA	"The addition of clonidine to levobupivacaine 0.25% on scalp block is effective in reducing the need for intraoperative and postoperative opioids, reducing postoperative pain, extending the duration of scalp nerve block, and delaying the first PCA dose."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Seyedhejazi et al, 2014, Iran[222]	Double-blind, randomized trial	67 Patients scheduled for elective inguinal hernia repair • Caudal (79.4%, mean 4.80 y ± 1.83) • Ilioinguinal/iliohypogastric nerve block (84.8%, mean 3.86 y ± 1.87)	Bupivacaine and clonidine via: • Caudal block (34) • Ilioinguinal/iliohypogastric nerve block (33) 1 Patient was excluded from the study after caudal block was performed because the surgeon decided they did not need surgery	Postoperative analgesia, analgesic use, side effects	"In this study, ilioinguinal/iliohypogastric nerve block was as effective as caudal regarding the quality and duration of post-operative analgesia. This result is also supported by previous reports that compared the effectiveness of these blocks in providing post-operative analgesia in patients undergoing inguinal surgery and concluded that both ilioinguinal/iliohypogastric and caudal blocks provide useful post-operative analgesia for children following inguinal surgeries."
Shadmehr et al, 2017, Iran[223]	Prospective, randomized, double-blind study	98 Patients with irreversible pulpitis in mandibular molar teeth undergoing root canal • Epinephrine (53.1%, mean 31 y ± 7) • Clonidine (55.1%, mean 28 y ± 10)	Inferior alveolar nerve block (IANB) with lidocaine and either: • Epinephrine (49) • Clonidine (49)	Success rate of IANB	"For mandibular molars with irreversible pulpitis, addition of clonidine to lidocaine improved the success rate of IANB compared to a standard lidocaine/epinephrine solution."
Shah et al, 2011, India[276]	Randomized, double-blind, controlled study	40 Patients scheduled for lower abdominal and lower extremity surgeries Clonidine (50%, mean 38.15 y ± 12.89) Control (35%, mean 38.2 y ± 11.00)	IT hyperbaric bupivacaine plus: • Clonidine (20) • Control (20)	Analgesic efficacy, quality of block, duration of analgesia, adverse effects	"Adding clonidine 1 mcg/kg to intrathecal bupivacaine prolongs the duration of spinal anaesthesia and analgesia. It is safe and is likely to be as effective as higher doses of bupivacaine without severe adverse effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Shah et al, 2011, India[514] Shah et al, 2015, India[224] Arora and Shah, 2010, India[515]	Prospective, randomized, placebo-controlled trial	53 Patients undergoing upper limb surgery Normal saline (81.8%, mean 29.36 y ± 7.22) Dexamethasone (66.7%, mean 31.42 y ± 8.37) Clonidine (72.2%, mean 35.61 y ± 13.89)	Infraclavicular brachial plexus block with lignocaine, adrenaline, and either: • Normal saline (11) • Dexamethasone (12) • Clonidine (18)	Time to onset and peak effect, duration of sensory and motor block, postoperative analgesia requirement	"We conclude that clonidine is more efficacious than dexamethasone as an adjuvant to 1.5% lignocaine in brachial plexus blocks."
Shah et al, 2012, India[225]	Prospective, randomized, double-blind study	60 Patients undergoing genitourinary surgeries Clonidine (83.3%, mean 46.90 y ± 11.73) Saline (96.7%, mean 45.93 y ± 13.80)	Spinal anesthesia with heavy bupivacaine and either: • Clonidine (30) • Saline (30)	Efficacy of analgesia, side effects	"Addition of low dose clonidine (1 mcg/kg) to bupivacaine increases the duration of spinal analgesia as compared to bupivacaine alone with clinically insignificant influence on haemodynamic parameters and level of sedation."
Shalini et al, 2019, India[226]	Prospective, double-blind, randomized, clinical study	60 Patients scheduled for elective infra umbilical surgeries Nalbuphine (76.7%, mean 41.9 y ± 12.80) Clonidine (73.3%, mean 40.5 y ± 11.11)	Spinal anesthesia with levobupivacaine and either: • Nalbuphine (30) • Clonidine (30)	Sensory analgesia and motor block, hemodynamic parameters, adverse effects	"On the basis of the results of our study, we conclude that addition of 30 mcg of clonidine to intrathecal 0.5 % isobaric levobupivacaine as adjuvant is preferable to 1 mg of nalbuphine, as it provides comparatively more prolonged sensory and motor blockade with better perioperative analgesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sharan et al, 2016, India[227]	Randomized, double-blind, controlled study	100 Patients undergoing lower abdominal surgeries Clonidine (82%, mean 41.08 y ± 10.17) Fentanyl (80%, mean 42.24 y ± 10.26)	Spinal anesthesia with ropivacaine and either: • Clonidine (50) • Fentanyl (50)	Onset and duration of sensory and motor block, hemodynamic parameters, quality of surgical analgesia, total analgesia time, sedation score, side effects	"Ropivacaine when combined with either clonidine or fentanyl provided an adequate subarachnoid block for lower abdominal surgeries. As an adjuvant, clonidine has advantage over fentanyl as it increased the duration of the subarachnoid block and the postoperative analgesia."
Shidhaye et al, 2014, India[228]	Prospective, randomized study	40 Patients undergoing cesarean section Fentanyl (0%, mean 23.1 y ± 2.55) Clonidine (0%, mean 24.7 y ± 3.15)	IT hyperbaric bupivacaine with: • Fentanyl (20) • Clonidine (20)	Duration of effective analgesia	"Intrathecal addition of 25 mcg fentanyl to bupivacaine provides good analgesia with less sedation and is a better option when sedation is not desirable. However intrathecal addition of 60 mcg clonidine to bupivacaine provides longer duration of postoperative analgesia than 25 mcg of fentanyl and is a preferred option when sedation is acceptable or required."
Shin and Ko, 2012, Republic of Korea[395]	—	Patients undergoing spinal surgery (gender and age not specified)	• IV fentanyl, continuous intraoperative morphine through PCA infusion, and bolus dose of clonidine (not reported) • Bolus IV morphine immediately before skin closure (not reported)	Pain scores, analgesic requirements, side effects	"The intravenous fentanyl administration during the induction, intraoperative continuous intravenous morphine infusion and single dose of intravenous clonidine were effective in reducing postoperative pain immediately after surgery. However, further investigations with regard to optimization of the agents used, their combination and timing of administration will be necessary."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Shivakumar et al, 2014, India[229]	—	100 Patients undergoing gynecological surgeries (0%, age not specified)	IT administration of either: • Hyperbaric bupivacaine (50) • Hyperbaric bupivacaine plus clonidine (50)	Onset of sensory and motor block, time to two segment regression of sensory block, intraoperative hemodynamic stability, total duration of analgesia	"The results suggest that the use of 75 mcg clonidine provides relative intraoperative hemodynamic stability and prolonged postoperative analgesia with minimal side effects."
Sia, 2000, Singapore[230]	Randomized, double-blind, controlled study	45 Patients requiring labor analgesia (0%, age not specified)	IT administration of sufentanil and bupivacaine plus either: • Clonidine 0 mcg (15) • Clonidine 15 mcg (15) • Clonidine 30 mcg (15)	Duration of analgesia	"The optimal dose of intrathecal clonidine to enhance labour analgesia with the current sufentanil-bupivacaine regimen is 15 mcg. In view of the side effect profile, doses greater than 30 mcg clonidine are unlikely to be useful."
Sia and Lepri, 1999, Italy[337]	Double-blind study	45 Patients scheduled for elective surgery of the arm and forearm Saline (60%, mean 39 y ± 13) Clonidine (46.7%, mean 41 y ± 13) Bupivacaine (53.3%, mean 38 y ± 13)	Axillary brachial plexus block with either: • Saline (15) • Clonidine (15) • Bupivacaine (15)	Time to onset of pain and to first analgesic request, total pain medication consumption, pain score	"In this study, the administration of clonidine 150 mcg alone into the brachial plexus sheath did not produce postoperative analgesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Siddall et al, 2000, Australia[231]	Double-blind, randomized, controlled trial	15 Patients who had neuropathic pain after spinal cord injury and were unresponsive to other treatment (gender not specified, mean 50 y)	All patients received all IT options in varying doses: • Saline (15) • Morphine (15) • Clonidine (15) • Morphine and clonidine (15)	Pain relief	"We conclude that intrathecal administration of a mixture of clonidine and morphine is more effective than either drug administered alone and is related to the CSF-borne drug concentration above the level of spinal cord injury. If there is pathology that may restrict CSF flow, consideration should be given to intrathecal administration above the level of spinal cord damage to provide an adequate drug concentration in this region."
Simoni et al, 2009, Brazil[338]	Randomized, double-blind, placebo-controlled study	126 Patients scheduled for laparoscopic surgeries Methadone (38.1%, mean 45 y ± 12) Clonidine (30.9%, mean 42 y ± 15) Placebo (26.2%, mean 40 y ± 10)	IV administration of either: • Methadone (42) • Clonidine (25) • Placebo (25)	Postoperative pain	"Methadone was more effective than clonidine in the control of postoperative pain in videolaparoscopic surgeries under total intravenous anesthesia with remifentanil; and using clonidine was not better than not using it."
Singelyn et al, 1992, Belgium[232]	Randomized, double-blind fashion	30 Patients scheduled for elective hand surgery • Control (40%, mean 39 y ± 5) • Subcutaneous clonidine (30%, mean 43 y ± 4) • Perineural clonidine (60%, mean 51 y ± 3)	Axillary perivascular brachial plexus block with mepivacaine plus epinephrine and subcutaneous infiltration of lidocaine: • Control (10) • Subcutaneous clonidine (10) • Perineural clonidine (10)	Onset time, duration of anesthesia, duration of analgesia, postoperative pain score, intake of analgesics, adverse effects	"One hundred fifty micrograms clonidine added to mepivacaine for brachial plexus block prolongs the duration of anesthesia and analgesia. Our results suggest that this effect of clonidine is local rather than systemic."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Singelyn and Gouverneur, 2000, Belgium[481]	Prospective, randomized, double-blind study	45 Patients scheduled for elective unilateral total knee arthroplasty • Continuous infusion (26.7%, mean 70 y ± 2) • Continuous infusion plus PCA bolus (33.3%, mean 67 y ± 4) • PCA bolus (33.3%, mean 63 y ± 3)	All patients received bupivacaine with clonidine via a femoral nerve sheath catheter via either: • Continuous infusion (15) • Continuous infusion plus PCA boluses (15) • PCA boluses only (15)	Pain scores, sensory block, supplemental analgesia, bupivacaine consumption, side effects, satisfaction scores	"We conclude that extended '3-in-1' block provides efficient pain relief after total knee arthroplasty and that, compared with a continuous infusion, PCA techniques reduce the local anesthetic consumption without compromise in patient satisfaction or visual analog scale scores. Of the two PCA techniques tested, PCA boluses (10-mL lockout; time, 60 min) of 0.125% bupivacaine with 1 mg/mL clonidine was associated with the smallest local anesthetic consumption, and is, therefore, the recommended extended '3-in-1' block technique."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Singelyn et al, 1996, Belgium[233]	Double-blind, randomized study	80 Patients undergoing elective hand surgery under axillary brachial plexus anesthesia • Clonidine 0 mcg/kg (40%, mean 39 y ± 18) • Clonidine 0.1 mcg/kg (60%, mean 42 y ± 15) • Clonidine 0.2 mcg/kg (60%, mean 46 y ± 22) • Clonidine 0.3 mcg/kg (20%, mean 36 y ± 19) • Clonidine 0.4 mcg/kg (50%, mean 39 y ± 17) • Clonidine 0.5 mcg/kg (50%, mean 43 y ± 19) • Clonidine 1 mcg/kg (20%, mean 43 y ± 17) • Clonidine 1.5 mcg (70%, mean 42 y ± 14)	Axillary brachial plexus block with mepivacaine plus either: • Clonidine 0 mcg/kg (10) • Clonidine 0.1 mcg/kg (10) • Clonidine 0.2 mcg/kg (10) • Clonidine 0.3 mcg/kg (10) • Clonidine 0.4 mcg/kg (10) • Clonidine 0.5 mcg/kg (10) • Clonidine 1 mcg/kg (10) • Clonidine 1.5 mcg/kg (10)	Onset time, duration of anesthesia and analgesia, postoperative pain score, intake of analgesics, adverse effects	"We conclude that the dose of clonidine required to prolong significantly the duration of both anesthesia and analgesia after axillary brachial plexus blockade is 0.5 mcg/kg and that, at this dose, clonidine may be used without important reported side effects even in outpatients."
Singelyn et al, 1999, Belgium[482]	Prospective, randomized, double-blind study	60 Patients scheduled for elective open shoulder surgery • Continuous infusion (40%, mean 52 y ± 16) • Continuous infusion plus PCA bolus (45%, mean 56 y ± 15) • PCA bolus (45%, mean 54 y ± 18)	All patients had an interscalene catheter with bupivacaine, sufentanil, and clonidine via either: • Continuous infusion (20) • Continuous infusion plus PCA bolus (20) • PCA bolus (20)	Pain scores, sensory block, supplemental analgesia, bupivacaine consumption, side effects, satisfaction scores	"In this study, we demonstrated that continuous interscalene analgesia requires a background infusion to provide efficient pain relief after open shoulder surgery. A basal infusion of 5 mL/h combined with patient-controlled analgesia boluses (2.5 mL/30 min) seems to be the most appropriate technique."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Singelyn et al, 2001, Belgium[483]	Prospective, randomized, double-blind study	45 Patients receiving extended femoral nerve sheath block after total hip arthroplasty • Continuous infusion (26.7%, mean 61 y ± 17) • PCA bolus 10 mL with 60-minute lockout (26.7%, mean 66 y ± 9) • PCA bolus 5 mL with 30-minute lockout (40%, mean 65 y ± 3)	All patients received a solution containing bupivacaine, clonidine, and sufentanil through a femoral nerve sheath catheter via either: • Continuous infusion (15) • PCA bolus 10 mL with 60-minute lockout (15) • PCA bolus 5 mL with 30-minute lockout (15)	Pain scores, sensory block, supplemental analgesia, bupivacaine consumption, side effects, satisfaction scores	"We conclude that, to maintain extended femoral nerve sheath block after total hip arthroplasty, PCA techniques reduce the local anesthetic consumption without compromise in the patient satisfaction or visual analog scale scores."
Singh and Singam, 2020, India[339]	Randomized, controlled trial	100 Patients scheduled for elective surgery under spinal anesthesia • Dexmedetomidine (gender not specified, mean 45.6 y ± 6.9) • Clonidine (gender not specified, mean 45.7 y ± 7.3)	IV administration of either: • Dexmedetomidine (50) • Clonidine (50)	Onset and duration of sensory and motor block following intrathecal bupivacaine	"Premedication with intravenous dexmedetomidine is better than intravenous clonidine to provide early onset of sensory analgesia, prolonged post-operative analgesia and adequate sedation."
Singh et al, 2016, India[234]	—	90 Patients undergoing transurethral resection of the prostate (TURP) surgeries under spinal anesthesia (100%, age not specified)	Subarachnoid block with hyperbaric bupivacaine plus either: • Normal saline (30) • Fentanyl (30) • Clonidine (30)	Level of sensory block, duration of motor block, duration of sensory blockade, quality of postoperative analgesia, side effects	"Intrathecal clonidine in a combination of bupivacaine for TURP provides more satisfactory anesthesia and analgesia and has less side effects."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Singh et al, 2014, India[235]	Double-blind, randomized trial	100 Patients scheduled for lower abdominal surgery • Clonidine (gender not specified, mean 42.26 y ± 11.91) • Placebo (gender not specified, mean 38.52 y ± 12.18)	IT administration of bupivacaine admixed with either: • Clonidine (50) • Placebo (50)	Duration of sensory and motor block, duration of postoperative analgesia, pain score, hemodynamic stability	"The findings in this study suggested that use of clonidine 50 mcg added to bupivacaine for spinal anesthesia effectively increased the duration of sensory block, duration of motor block, and duration of analgesia."
Singh et al, 2013, India[236]	Randomized, controlled trial	102 Patients to undergo elective lower segment cesarean section (LSCS) under spinal anesthesia • Fentanyl (0%, mean 24.85 y ± 2.58) • Clonidine 50 mcg (0%, mean 25.23 y ± 3.62) • Clonidine 75 mcg (0%, mean 25.71 y ± 4.21)	IT hyperbaric bupivacaine plus either: • Fentanyl (33) • Clonidine 50 mcg (35) • Clonidine 75 mcg (34)	Duration of postoperative analgesia	"Addition of 75 mcg clonidine to hyperbaric bupivacaine in spinal anesthesia for LSCS significantly prolongs the duration of postoperative analgesia without any increase in maternal side effects. There was no difference in neonatal outcome."
Singh et al, 2016, India[237]	Randomized, double-blind, controlled trial	100 Patients undergoing LSCS under spinal anesthesia (0%, age not specified)	TAP block bilaterally with either: • Bupivacaine (50) • Bupivacaine and clonidine (50)	Total duration of analgesia, patient satisfaction score, total requirement of analgesics, side effects	"Addition of clonidine 1 mcg/kg to 20 mL bupivacaine 0.25% in TAP block bilaterally for cesarean section significantly increases the duration of postoperative analgesia, decreases postoperative analgesic requirement, and increases maternal comfort compared to 20 mL of bupivacaine 0.25% alone."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Singh et al, 2015, India[238]	—	100 Patients scheduled for lower limb surgery under spinal anesthesia • Normal saline (92%, mean 34.16 y ± 16.26) • Fentanyl (72%, mean 31.84 y ± 14.11) • Clonidine (92%, mean 37.48 y ± 14.90) • Fentanyl and clonidine (88%, mean 42.12 y ± 17.98)	Spinal anesthesia with hyperbaric bupivacaine plus: • Normal saline (25) • Fentanyl (25) • Clonidine (25) • Fentanyl and clonidine (25)	Onset and duration of sensory and motor block, highest level of sensory blockade, time to complete motor block recovery, duration of spinal anesthesia, hemodynamics, side effects	"We conclude that the addition of clonidine in doses of 75 mcg and 37.5 mcg to low-dose bupivacaine and bupivacaine-fentanyl prolongs the sensory and motor block while increasing the duration of postoperative analgesia without significant side-effects."
Singh and Singam, 2019, India[340]	—	90 Patients scheduled for various upper limb surgeries under supraclavicular brachial plexus block • Normal saline (60%, mean 42.10 y ± 15.12) • Clonidine (56.7%, mean 43.86 y ± 14.20) • Dexmedetomidine (56.7%, mean 42.40 y ± 13.14)	Supraclavicular brachial plexus block with ropivacaine and either: • Normal saline (30) • Clonidine (30) • Dexmedetomidine (30)	Duration of analgesia	"Dexmedetomedine [sic] and clonidine when added to ropivacaine for supraclavicular brachial plexus block prolong the duration of analgesia. But dexmedetomedine [sic] is a better adjuvant as compared to clonidine."
Singh and Aggarwal, 2010, India[239]	Prospective, randomized, double-blind, controlled trial	50 Patients undergoing surgery of the upper limb under supraclavicular brachial plexus block • Clonidine (28%, mean 36.04 y ± 10.43) • Normal saline (16%, mean 33.68 y ± 7.83)	Supraclavicular block with bupivacaine plus either: • Clonidine (25) • Normal saline (25)	Onset of sensory block, duration of analgesia and motor block, duration of recovery of sensation, hemodynamic changes, sedation, adverse effects	"These findings suggest that clonidine added to bupivacaine is an attractive option for improving the quality and duration of supraclavicular brachial plexus block in upper limb surgeries."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sites et al, 2003, US[240]	Double-blind, placebo-controlled protocol	81 Patients undergoing either a single or bilateral total knee arthroplasty • Placebo (42.8%, mean 65 y ± 12) • Morphine (50%, mean 68 y ± 11) • Morphine plus 25 mcg clonidine (45%, mean 66 y ± 6) • Morphine plus 75 mcg clonidine (40%, mean 64 y ± 11)	Spinal anesthesia with hyperbaric bupivacaine plus either: • Placebo (21) • Morphine (20) • Morphine plus 25 mcg clonidine (20) • Morphine plus 75 mcg clonidine (20)	Pain score, cumulative intravenous morphine consumption, hemodynamics, nausea, ancillary drugs, side effects	"We conclude that the coadministration of intrathecal clonidine and morphine decreases the 24-h IV morphine consumption and improves the 24-h VAS score when compared with intrathecal morphine alone."
Sites et al, 2004, US[241]	Single-blind, controlled trial	40 Patients undergoing unilateral TKA • Intrathecal morphine (45%, mean 65 y ± 9) • Femoral nerve block (50%, mean 63 y ± 10)	IT hyperbaric bupivacaine plus: • IT morphine (20) • FNB with ropivacaine, epinephrine, and clonidine (20)	Amount of intravenous morphine used in the first 24 hours	"We conclude that, in comparison with IT morphine, a single injection femoral nerve block provides equivalent analgesia but with a significant reduction in side effects for patients having TKA under bupivacaine intrathecal anesthesia."
Skhiri et al, 2009, Tunisia[242]	Prospective, randomized, double-blind trial	36 Pediatric patients scheduled for hypospadias surgery or ureteral fistula repair (100%, age not specified)	Penile block using bupivacaine and: • Clonidine (19) • Normal saline (17)	Postoperative analgesia, analgesic use, side effects	"The addition of clonidine to bupivacaine in the penile block improves postoperative analgesia in foreskin's average length surgery in children."
Smaoui et al, 2011, Tunisia[243]	Prospective, randomized, double-blind study	40 Patients undergoing laparoscopic cholecystectomy (gender and age not specified)	• General anesthesia with bilateral TAP block containing bupivacaine and clonidine (20) • General anesthesia with saline TAP block (20)	Pain scores, postoperative complications	"The TAP block can be utilized as a useful analgesic method during and after the operation after laparoscopic cholecystectomy. Also, it reduces the use of curare."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Solanki and Singh, 2018, India[244]	—	75 Patients undergoing upper limb surgeries • Normal saline (80%, mean 39.08 y ± 9.32) • Magnesium sulphate (84%, mean 39.56 y ± 9.64) • Clonidine (76%, mean 39.28 y ± 8.52)	IV regional anesthesia with lignocaine plus either: • Normal saline (25) • Magnesium sulphate (25) • Clonidine (25)	Onset and recovery time for sensory and motor block, intraoperative tourniquet pain, time to first tramadol requirement, mean tramadol dosage, quality of operative conditions, hemodynamic parameters, postoperative pain scores	"Block quality, total tramadol requirement (as an additional analgesic) and duration of postoperative analgesia was better in clonidine group as compared to magnesium when added to lignocaine."
Solanki et al, 2013, India[341]	Randomized, double-blind study	90 Patients scheduled for lower limb surgery under subarachnoid block • Normal saline (66.7%, mean 33.6 y ± 12.0) • Clonidine (70%, mean 32.4 y ± 10.1) • Dexmedetomidine (76.7%, mean 33.8 y ± 9.8)	IT hyperbaric bupivacaine plus: • Normal saline (30) • Clonidine (30) • Dexmedetomidine (30)	Postoperative analgesic efficacy	"In conclusion, dexmedetomidine 5 mcg added to intrathecal bupivacaine 15 mg produces longer postoperative analgesia than clonidine 50 mcg among trauma patients undergoing lower limb surgery."
Sprung et al, 2006, US[484]	Randomized, controlled trial	89 Patients receiving subarachnoid block for vaginal hysterectomy • Spinal anesthesia (0%, mean 52.2 y ± 11.9) • General anesthesia (0%, mean 51.8 y ± 12.8)	• Spinal anesthesia with bupivacaine, clonidine, and morphine (45) • General anesthesia (44)	Evaluation of pain and functional status	"For patients desiring excellent analgesia in the immediate postoperative period, SAB can be recommended, but for this surgical procedure the choice of primary anesthetic has little influence on longer-term outcomes."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sree kumar et al, 2013, India[342]	—	60 Pediatric patients undergoing elective inguinal hernia repair (gender and age not specified)	Ilioinguinal nerve block (IINB) with: • Bupivacaine (not reported) • Bupivacaine with 1 mcg/kg clonidine (not reported) • Bupivacaine with 4 mcg/kg clonidine (not reported)	Postoperative pain	"Addition of clonidine in doses of 1 mcg/kg or 4 mcg/kg to bupivacaine in IINB in children does not improve the duration or quality of analgesia. The 4 mcg/kg dose causes sedation and delay in day care discharge time."
Srinivas and Lakshminarasimhaiah, 2019, India[245]	Randomized, double-blind, controlled trial	90 Patients scheduled to undergo elective infra-umbilical surgeries under subarachnoid block • Placebo (53.3%, mean 39.97 y ± 11.89) • Dexmedetomidine (53.3%, mean 42.10 y ± 11.98) • Clonidine (60%, mean 39.10 y ± 12.40)	Subcutaneous administration of: • Normal saline (30) • Dexmedetomidine (30) • Clonidine (30)	Duration of postoperative analgesia	"Both subcutaneous clonidine and dexmedetomidine prolonged the duration of postoperative analgesia and reduced analgesic requirements when used as adjuvants to SAB with stable hemodynamics, hence both of these drugs can be used effectively as adjuvants to SAB."
Sripriya et al, 2018, India[246]	Randomized, prospective, observer-blind study	75 Patients admitted for laparoscopic surgeries • Intravenous clonidine (32%, mean 36 y ± 12) • Intrathecal clonidine (44%, mean 32 y ± 10) • Control (44%, mean 36 y ± 10)	• IV clonidine (25) • IT clonidine (25) • Control (25)	Need for nitroglycerin to maintain mean arterial pressure, postoperative pain, sedation	"Both IT and IV clonidine provide early post-operative analgesia without causing much sedation."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Srivastava et al, 2016, India[247]	Randomized, double-blind study	60 Patients scheduled for elective lower limb orthopedic surgery • Control (60%, mean 36.26 y ± 8.721) • Clonidine (56.7%, mean 34.73 y ± 9.317)	Spinal anesthesia with ropivacaine and either: • Control (30) • Clonidine (30)	Block characteristics, hemodynamic changes, postoperative analgesia, adverse effects	"We concluded that addition of clonidine 30 mcg to ropivacaine 18 mg produced an early and prolonged spinal anesthesia and decrease the dose of postoperative analgesic requirement."
Srivastava et al, 2014, India[396]	Prospective, randomized, controlled, open-label study	70 Patients on mechanical ventilation with concomitant sedation • Clonidine (51.4%, median 46 y [IQR 43-59]) • Dexmedetomidine (57.1%, median 49 y [IQR 45-63])	IV administration of either: • Clonidine (35) • Dexmedetomidine (35)	Quality of sedation, hemodynamic changes, adverse effects	"Both dexmedetomidine and clonidine can be used as sedative agents for short term ICU sedation of postsurgical patients. On the basis of our study data, we derived that dexmedetomidine has a better cardiovascular safety profile. Further trials with both drugs may define their exact role for sedation of ICU patients."
Sruthi et al, 2019, India[248]	Double-blind, randomized trial	80 Patients undergoing elective laparoscopic-assisted vaginal hysterectomy • Clonidine 75 mcg (0%, mean 53.4 y ± 8.6) • Clonidine 150 mcg (0%, mean 53.7 y ± 9.1)	TAP block with levobupivacaine plus either: • Clonidine 75 mcg (40) • Clonidine 150 mcg (40)	Duration of analgesia	"The 150 mcg dose of clonidine in TAP block prolongs the duration of analgesia but with higher incidence of sedation."
Staudt et al, 2020, US[485]	Retrospective chart review	11 Patients with chronic pain treated with both spinal cord stimulation and intrathecal pump therapy (63.6%, range 30-84 y)	IT administration of either: • Ziconotide (8) • Baclofen (1) • Hydromorphone (1) • Morphine and clonidine (1)	Pain severity	"Dual modality therapy is a potential treatment option in patients who have lost efficacy with a single neuromodulation modality. Further study is required to identify potential responders and nonresponders."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Stevens et al, 2007, Australia[486]	Randomized, double-blind study	44 Patients receiving a modified fascia iliaca block for unilateral total hip arthroplasty • Control (50%, mean 66.8 y ± 9.1) • Trial (68%, mean 68.7 y ± 9.7)	Modified fascia iliaca block with: • Control (22) • Trial with bupivacaine, adrenaline, and clonidine (22)	Patient-controlled morphine analgesia	"We conclude that a modified fascia iliaca compartment block has a significant morphine-sparing effect in unilateral total hip arthroplasty."
Stocche et al, 2004, Brazil[343]	Double-blind, randomized, placebo-controlled study	45 Patients undergoing middle ear procedures • Sodium chloride (60%, mean 28.13 y ± 10.39) • Clonidine 3 mcg/kg (53.3%, mean 24.47 y ± 6.03) • Clonidine 5 mcg/kg (46.7%, mean 30.87 y ± 12.51)	IV administration of either: • Sodium chloride (15) • Clonidine 3 mcg/kg (15) • Clonidine 5 mcg/kg (15)	Incidence of complications, halogenate consumption, anesthesia duration, recovery time	"Intravenous clonidine (3 mcg kg^{-1}) decreases sevoflurane consumption without prolonging phase I recovery. Although decreasing sevoflurane consumption, 5 mcg kg^{-1} clonidine prolongs phase II recovery, thus being inadequate for outpatient procedures."
Strebel et al, 2004, Switzerland[249]	Dose-response study	75 Patients scheduled for elective hip or knee arthroplasties • Saline (55%, mean 62 y ± 9) • Clonidine 37.5 mcg (41.2%, mean 62 y ± 15) • Clonidine 75 mcg (50%, mean 57 y ± 16) • Clonidine 150 mcg (45%, mean 66 y ± 10)	IT isobaric bupivacaine plus either: • Saline (20) • Clonidine 37.5 mcg (17) • Clonidine 75 mcg (18) • Clonidine 150 mcg (20)	Time to spinal blockade regression, duration of pain relief	"We conclude that small doses of intrathecal clonidine (≤ 150 mcg) significantly prolong the anesthetic and analgesic effects of bupivacaine in a dose-dependent manner and that 150 mcg of clonidine seems to be the preferred dose, in terms of effect versus unwarranted side effects, when prolongation of spinal anesthesia is desired."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Striebel et al, 1993, Germany[344]	Prospective, randomized, double-blind, placebo-controlled study	60 Patients who had undergone a cholecystectomy • Clonidine (0%, mean 49.0 y ± 2.0) • Control (0%, mean 49.4 y ± 2.4)	IV administration of either: • Clonidine (30) • Control (30)	Pain intensity, blood pressure, heart rate, respiratory rate, arterial hemoglobin saturation, side effects	"During the first 2 postoperative hours following cholecystectomy, postoperative meperidine intake could not be reduced by IV administration of clonidine 300 mcg."
Sukhthanker et al, 2020, India[250]	Randomized, double-blind, controlled study	100 Patients undergoing lower limb orthopedic procedures • Clonidine (58%, mean 31.58 y ± 5.49) • Morphine (56%, mean 30.2 y ± 4.10)	Spinal anesthesia with hyperbaric bupivacaine and either: • Clonidine (50) • Morphine (50)	Quality and duration of anesthesia	"Clonidine improves the quality of spinal anaesthesia in terms of faster onset of sensory block and longer duration of sensory as well as motor block compared to morphine, when added as an adjunct. However, the duration of postoperative analgesia was prolonged more with the addition of morphine compared to clonidine."
Surve et al, 2018, India[251]	Prospective, double-blind, randomized, controlled study	60 Patients scheduled to undergo elective infraumbilical surgeries • Clonidine (63.3%, mean 39.33 y ± 9.40) • Normal saline (80%, mean 37.73 y ± 9.75)	IT heavy bupivacaine plus either: • Clonidine (30) • Normal saline (30)	Duration of analgesia	"Intrathecal clonidine in a dose of 0.5 mcg/kg shortens the onset of sensory blockade, increases the duration of sensory blockade and complete motor recovery. Duration of postoperative analgesia is significantly prolonged and the time for requirement of rescue analgesia is prolonged without causing significant side effects if clonidine is used in low doses."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Suthar et al, 2015, India[345]	Randomized, double-blind, placebo-controlled trial	75 Patients undergoing surgery • Normal saline (60%, mean 33 y ± 8.8) • Clonidine (68%, mean 31 y ± 8.8) • Dexmedetomidine (64%, mean 33 y ± 6.8)	IT hyperbaric bupivacaine plus: • Normal saline (25) • Clonidine (25) • Dexmedetomidine (25)	Duration of analgesia, adverse effects, hemodynamic changes	"The addition of dexmedetomidine to intrathecal bupivacaine prolongs the motor and sensory block and postoperative analgesia when compared to bupivacaine with or without clonidine, with preserved hemodynamic stability in lower limb surgeries."
Swami et al, 2012, India[346]	Randomized, double-blind, prospective study	60 Patients scheduled for elective upper limb surgeries under supraclavicular brachial plexus block • Clonidine (73.3%, mean 33.73 y ± 12.09) • Dexmedetomidine (63.3%, mean 33.83 y ± 16.78)	Supraclavicular brachial plexus block with bupivacaine plus either: • Clonidine (30) • Dexmedetomidine (30)	Duration and quality of sensory and motor block, duration of analgesia	"Dexmedetomidine when added to local anesthetic in supraclavicular brachial plexus block enhanced the duration of sensory and motor block and also the duration of analgesia. The time for rescue analgesia was prolonged in patients receiving dexmedetomidine. It also enhanced the quality of block as compared with clonidine."
Thakur et al, 2013, India[252]	Randomized, double-blind study	75 Patients undergoing inguinal herniorrhaphy surgery under spinal anesthesia • Normal saline (gender not specified, mean 32.12 y ± 15.29) • Clonidine 15 mcg (gender not specified, mean 30.84 y ± 8.87) • Clonidine 30 mcg (gender not specified, mean 33.16 y ± 10.60)	IT administration of hyperbaric bupivacaine plus either: • Normal saline (25) • Clonidine 15 mcg (25) • Clonidine 30 mcg (25)	Duration of sensory and motor block, adequacy of analgesia, side effects	"30 mcg of clonidine was associated with more incidence and duration of hypotension than 15 mcg of clonidine. 15 mcg clonidine added to 11 mg bupivacaine provides better sensory and motor blockade for inguinal herniorrhaphy."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Thurm et al, 2017, Sweden[253]	Randomized, controlled study	135 Patients with renal cell carcinoma (RCC) allocated to open kidney surgery (62.2%, range 35-85 y)	• Spinal injection of a mixture of hyperbaric bupivacaine, morphine, and clonidine (69) • Epidural bupivacaine, fentanyl, and adrenaline (66)	Postoperative analgesia, time to mobilization, length of hospital stay	"In this randomized controlled study, spinal analgesia with clonidine was superior to continuous epidural analgesia in patients operated on with open nephrectomy, based on shorter LOS [length of stay]. A shorter LOS in the study group indicates faster mobilization and improved analgesia. Spinal analgesia did not carry more complications than epidural analgesia."
Tran et al, 2005, US[254]	Randomized, prospective study	34 Patients undergoing anterior cruciate ligament reconstruction • Femoral-sciatic nerve block (FSNB; 18.75%, mean 15 y ± 2) • Intraarticular injection (50%, mean 15 y ± 2)	• FSNB with bupivacaine, epinephrine, and clonidine (16) • Intraarticular (IA) injection of bupivacaine, clonidine, and morphine (18)	Morphine consumption	"After ACL reconstruction in children, FSNB with bupivacaine-clonidine provides better analgesia with fewer side effects than IA with bupivacaine-clonidine-morphine."
Trifa et al, 2012, Tunisia[347]	Prospective, double-blind, controlled trial	60 Patients scheduled to undergo forearm or hand surgery • Clonidine (50%, mean 3.5 y ± 2) • Saline (60%, mean 3.5 y ± 2)	Axillary brachial plexus block (ABPB) with ropivacaine plus either: • Clonidine (30) • Saline (30)	Pain score, postoperative analgesia requirements	"Ropivacaine (0.2% 0.4 $mL*kg^{-1}$) for ABPB provides sufficient postoperative analgesia in children scheduled for forearm or hand surgery. The addition of clonidine to ABPB does not improve overall postoperative analgesia but may increase the time to first analgesia request."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Trifa et al, 2016, Tunisia[397]	Prospective, randomized, double-blind study	28 Pediatric patients undergoing unilateral foot surgery under combined saphenous/sciatic nerve blocks (gender and age not specified)	Combined saphenous/vastus medialis and sciatic nerve block with bupivacaine plus either: • Clonidine (14) • Normal saline (14)	Pain score, time to first analgesia request, total dose of analgesic given, duration of motor block, sedation	"In conclusion, this small study indicates that the addition of clonidine to 0.25% bupivacaine may not improve the quality of analgesia or increase the duration of analgesia in saphenous/sciatic nerve blocks for foot surgery in children. Study population size considerations of future prospective clinical studies of clonidine in peripheral nerve blocks are essential and could be based on this and previously published studies."
Tripathi et al, 2016, India[348]	Prospective, randomized, double-blind study	60 Patients scheduled for moderate orthopedic surgeries on the upper limb under supraclavicular brachial plexus block • Clonidine (73.3%, mean 37.83 y ± 11.28) • Dexmedetomidine (66.7%, mean 38.03 y ± 11.25)	Supraclavicular brachial plexus block with bupivacaine plus either: • Clonidine (30) • Dexmedetomidine (30)	Onset and duration of sensory and motor block, duration of analgesia, quality of anesthesia	"The addition of dexmedetomidine prolongs the durations of sensory and motor block and duration of analgesia and improves the quality of anesthesia as compared with clonidine when injected with bupivacaine in supraclavicular brachial plexus block."
Trivedi and Patel, 2010, India[255]	Randomized, controlled, clinical trial	60 Patients presenting for elective upper limb orthopedic surgery • Clonidine (76.7%, mean 32.8 y ± 11.63) • Midazolam (76.7%, mean 32.63 y ± 13.24)	Supraclavicular brachial plexus block with bupivacaine, lignocaine, and either: • Clonidine (30) • Midazolam (30)	Onset and duration of sensory and motor blockade, sedation score, postoperative analgesia	"So injection clonidine provides better postoperative analgesia and more sedation than midazolam."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Tschernko et al, 1998, Austria[256]	—	36 Patients undergoing thoracotomy • Control (53.8%, mean 62 y ± 2.1) • Intramuscular (66.7%, mean 60 y ± 1.5) • Block (53.8%, mean 63 y ± 2.3) Despite the authors saying there were 3 groups of 12 patients each, the gender-specific information for the Control and Block groups were each for 13 patients.	Intercostal nerve block with bupivacaine and epinephrine plus either: • Saline (12) • IM clonidine (12) • Clonidine as an adjunct in the block (12)	Blood gases, pain scores, analgesic demand	"Clonidine administered directly on the nerves enhanced analgesia and improved oxygenation for a short time compared with systemic administration or control."
Tumber and Fitzgibbon, 1998, US[257]	Case report	1 Patient referred for management of severe sacral and bilateral lower extremity pain secondary to an inoperable sacral chordoma (100%, 48 y)	• IT administration of bupivacaine and clonidine with or without morphine (1)	Control of cancer pain	"We describe a case of severe cancer pain where these medications were used successfully by continuous intrathecal infusion and patient controlled intrathecal analgesia."
Turner et al, 2018, US[487]	Double-blind, randomized, controlled, equivalency trial	60 Patients undergoing total knee arthroplasty • Single-injection adductor canal block (SACB; 43%, mean 70.9 y ± 7.9) • Continuous adductor canal block (CACB; 70%, mean 68.8 y ± 10) • 59 Patients were included in the intention-to-treat analysis due to 1 patient's surgery being cancelled	• SACB with bupivacaine, clonidine, buprenorphine, dexamethasone, and epinephrine (30) • CACB with bupivacaine and epinephrine (29)	Pain scores	"An SACB provides equivalent analgesia for up to 36 hours after block placement when compared with a CACB for patients undergoing total knee arthroplasty, though a CACB was favored at 42 hours and beyond."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Tyagi et al, 2016, India[258]	Prospective, double-blind, randomized study	60 Patients undergoing surgery (gender and age not specified)	IT hyperbaric bupivacaine plus: • Normal saline (30) • Clonidine (30)	Onset and level of sensory and motor block, intensity of motor blockade, time of analgesia required postoperatively	"Thus, [the] overall combined effect of intrathecal clonidine-bupivacaine is far superior over bupivacaine alone."
Tzortzopoulou et al, 2009, Greece[259]	Randomized, double-blind study	50 Patients undergoing surgery for femur fracture (gender not specified, range 60-85 y)	Subcutaneous wound infusion with: • Ropivacaine (25) • Ropivacaine and clonidine (25)	Postoperative pain at rest and movement, pethidine requirements, adverse events	"The coadministration of clonidine in ropivacaine infusion provides superior postoperative pain control and reduces postoperative opioid consumption."
van Tuijl et al, 2008, the Netherlands[260]	Randomized, controlled trial	75 Patients undergoing outpatient knee arthroscopy • Clonidine 0 mcg (65%, mean 38 y ± 15) • Clonidine 15 mcg (92%, mean 39 y ± 13) • Clonidine 30 mcg (84%, mean 35 y ± 12)	Spinal bupivacaine plus either: • Clonidine 0 mcg (26) • Clonidine 15 mcg (24) • Clonidine 30 mcg (25)	Time between injection and complete regression of the motor block	"The addition of 15 mcg clonidine to 5 mg of intrathecal hyperbaric bupivacaine prolongs the duration of motor block and improves the quality of the block."
van Tuijl et al, 2006, the Netherlands[261]	Randomized, controlled, double-blind trial	106 Patients presenting for elective cesarean section • Normal saline (0%, mean 35 y) • Clonidine (0%, mean 34 y)	IT bupivacaine plus either: • Normal saline (53) • Clonidine (53)	Total morphine consumption	"The addition of clonidine (75 mcg) to hyperbaric bupivacaine prolongs spinal anaesthesia after Caesarean section and improves early analgesia, but does not reduce the postoperative morphine consumption during the first 24 h. No clinically relevant maternal or neonatal side-effects were detected."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Velazquez-Delgado et al, 2017, Mexico[349]	Comparative, longitudinal, controlled, randomized study	105 Patients scheduled for elective arthroscopic shoulder surgery • Control (36%, mean 49.9 y) • Clonidine (43%, mean 47.2 y) • Dexmedetomidine (38%, mean 44.9 y)	Single-shot, ultrasound-guided interscalene block with ropivacaine plus either: • Control (35) • Clonidine (35) • Dexmedetomidine (35)	Sensory and motor blockade, pain intensity, sedation level, heart rate, respiratory rate, blood pressure	"The prolonged interscalene block produced by dexmedetomidine provided better postoperative pain control during the first 24 h."
Vermeylen et al, 2016, Belgium[262]	Double-blind, randomized, placebo-controlled study	57 Patients undergoing hallux vagal surgery (0%, mean 48 y ± 15)	Ultrasound-guided single-shot popliteal fossa block with ropivacaine supplemented with: • Saline (18) • Dexamethasone (19) • Clonidine (21)	Time to first pain sensation	"Addition of DXM [dexamethasone] and clonidine to ropivacaine significantly prolonged the duration of postoperative sensory and motor block."
Vieira et al, 2010, US[488]	Prospective, randomized, double-blind investigation	88 Patients scheduled for outpatient shoulder arthroscopy • Control (75%, mean 48 y ± 12) • Dexamethasone (59.1%, mean 51 y ± 10)	Interscalene brachial plexus block with bupivacaine, epinephrine, and clonidine plus adjuvant of either: • Control (44) • Dexamethasone (44)	Pain score, analgesic consumption, duration of analgesia	"The addition of dexamethasone to a bupivacaine-epinephrine-clonidine interscalene block prolongs sensory block and reduces opioid use."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Viel et al, 1991, France[263]	Randomized, double-blind trial	60 Patients undergoing orthopedic or traumatologic surgery of the upper limbs • Epinephrine (56.7%, age not specified) • Clonidine (50%, age not specified)	Brachial plexus block with bupivacaine and either: • Epinephrine (30) • Clonidine (30)	Time to onset of sensory and motor blockade, total duration of analgesia, blood pressure, heart rate	"The major findings of this study are: 1) addition of CLO [clonidine] to B [bupivacaine] for brachial plexus block resulted in an increase of the duration of analgesia. 2) Analgesia lasted significantly longer with CLO than with E [epinephrine]. 3) The onsets of motor and sensory blockades were not different with CLO vs E. 4) There were no significant differences in the variation of hemodynamic parameters between CLO and E. 5) There were no side effects either with CLO or E; especially no sedation as found with CLO. It is unlikely that CLO was responsible of a local vasoconstriction, reducing the vascular absorption of B, as often proposed as a mechanism of action of E to prolong the duration of local anesthetic action. The present findings give further support to the theory that alpha adrenergic agonists could act directly on the alpha-type receptors of the central nervous system which are involved in the neurotransmission of pain."
Vinayak et al, 2020, India[264]	—	40 Patients undergoing elective spine surgeries • Clonidine and fentanyl (55%, mean 41.1 y ± 12.66) • Fentanyl (65%, mean 43.55 y ± 15.07)	• IV clonidine and fentanyl (20) • IV fentanyl (20)	Postoperative pain (POP)	"Intravenous clonidine 1.5 mcg/kg as an add onto premedication with intravenous fentanyl 1 mcg/kg decreased POP thus reducing requirement of rescue analgesia in patients undergoing spine surgeries."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Viviano et al, 2010, Germany[516] Viviano et al, 2012, Germany[350]	Double-blind, prospective, randomized, controlled trial	60 Patients undergoing lung resection • Remifentanil (65%, median 66.5 y) • Remifentanil and clonidine (55%, median 66.5 y) • Ropivacaine (80%, median 65.5 y)	• IV remifentanil (20) • IV remifentanil and clonidine (20) • Epidural ropivacaine (20)	Pain scores, cytometric bead array	"Intraoperative TEB [thoracic epidural block] decreases the Th1/Th2 [T helper cell] ratio and provides better pain therapy immediately after surgery."
Wahi et al, 2016, India[398]	Randomized, double-blind study	90 Patients undergoing surgery below the level of umbilicus • Clonidine 150 mcg (53.3%, mean 34.87 y ± 9.7) • Clonidine 75 mcg (60%, mean 35.53 y ± 11.26) • Normal saline (53.3%, mean 32.2 y ± 9.83)	Spinal anesthesia with bupivacaine plus either: • Clonidine 150 mcg (30) • Clonidine 75 mcg (30) • Normal saline (30)	Onset and duration of sensory block, highest dermatomal level of sensory block, motor block, time to complete motor block recovery, duration of spinal anesthesia	"This study concludes that intrathecal clonidine as an adjuvant to bupivacaine is an effective and convenient method to prolong spinal anaesthesia in a dose dependent manner for prolonged surgeries below the level of umbilicus with a limitation of close monitoring of NIBP [noninvasive blood pressure] and need of further studies with different doses to find the ideal dose of clonidine."
Weller and Henshaw, 2017, US[489]	Prospective, double-blind, randomized, placebo-controlled trial	29 Patients undergoing major ankle surgery (gender and age not specified)	All patients received an ultrasound-guided saphenous catheter with bupivacaine, epinephrine, and clonidine and a subgluteal sciatic catheter with the same solution. All patients received a sciatic ropivacaine infusion before being randomized to a saphenous infusion of either: • Ropivacaine (15) • Saline (14)	Pain scores, quadriceps strength, time to first analgesic, opioid use, nausea and vomiting, sleep interruptions	"Quadriceps motor function was well preserved with continuous saphenous block. While this has now been shown by a number of investigators, it had not been proven when this study was initiated."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Whiting et al, 2009, US[399]	Case report	2 Patients who underwent posterolateral corner reconstruction of the knee with postoperative sciatic perineural analgesia (100%, range 17-45 y)	• Sciatic perineural analgesia with clonidine and buprenorphine (2)	Pain scores, gross motor function	"Our initial experience with combined perineural buprenorphine and clonidine is encouraging and warrants further bench and clinical research."
Wiesmann et al, 2014, Germany[490]	—	80 Patients scheduled for elective non-cemented total hip arthroplasty • Femoral nerve block (37.5%, mean 67 y ± 11) • Standard treatment (55%, mean 66 y ± 13)	• Single shot FNB with bupivacaine and clonidine (40) • Standard treatment without nerve block (40)	PACU discharge, lung function, pain control	"Supplemental single shot femoral nerve block for total hip arthroplasty resulted in earlier PACU discharge capability, improved lung function during the first six hours and better pain control within the first 24 postoperative hours."
Wolf et al, 2014, UK[400]	Prospective, multicenter, randomized, double-blind, equivalence study	129 Patients expected to require ventilation in the pediatric intensive care unit for > 12 hours and requiring sedation (62.8%, range 0.08-13.85 y)	IV administration of either: • Clonidine (65) • Midazolam (64)	Adequate sedation	"Neither drug in combination with morphine provided ideal sedation, suggesting that in unparalysed patients a third background agent is necessary. The disappointing recruitment rates reflect a reluctance of parents to provide consent when established on a sedation regimen, and reluctance of clinicians to allow sedation to be studied in unstable critically ill children. Future studies will require less exacting protocols allowing enhanced recruitment."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
YaDeau et al, 2019, US[401]	Prospective, observational, cohort study	102 Patients scheduled for an elective total shoulder arthroplasty (TSA) or reverse TSA for degenerative conditions (52.9%, mean 66 y ± 9)	• Single-injection bupivacaine interscalene block with adjuvant clonidine, dexamethasone, and buprenorphine (102)	Pain score	"Future research could investigate what the individual components of this protocol contribute. Larger cohort studies or registries would document the incidence of rare complications. Randomized controlled trials could directly compare analgesic effectiveness and cost-benefits for this protocol versus alternative strategies, such as perineural catheters or liposomal bupivacaine. Perhaps most importantly, future studies could seek ways to further reduce peak pain and opioid usage on POD 2 and POD 3."
YaDeau et al, 2016, US[491]	Prospective, double-blind, randomized, controlled trial	80 Patients with osteoarthritis scheduled for a primary TSA • Control (50%, mean 68 y ± 7) • High dose (35%, mean 66 y ± 8) • Medium dose (55%, mean 64 y ± 9) • Low dose (25%, mean 69 y ± 7) 2 Patients, 1 from the Control group and 1 from the Medium dose group, were excluded from analysis due to patients declining assessment	• Control: Interscalene block with ropivacaine and IV administration of buprenorphine, clonidine, and dexamethasone (19) Interscalene block with buprenorphine, clonidine, and dexamethasone plus either: • High dose: Ropivacaine 0.375% (20) • Medium dose: Ropivacaine 0.2% (19) • Low dose: Ropivacaine 0.1% (20)	Pain score	"For maximum pain reduction, combining perineural additives with ropivacaine 0.375% or 0.2% is suggested. To minimize motor blockade, perineural additives can be combined with ropivacaine, 0.1%."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
YaDeau et al, 2008, US[265]	Randomized, double-blind, placebo-controlled study	98 Patients scheduled for hospital admission after foot or ankle surgery • Block clonidine (48.5%, mean 49 y ± 15) • Intramuscular clonidine (45.5%, mean 55 y ± 14) • Control (43.7%, mean 53 y ± 14)	Popliteal nerve block with bupivacaine and epinephrine plus: • Block clonidine (33) • IM clonidine (33) • Control (32)	Duration of analgesia	"Clonidine significantly prolongs the analgesic duration after popliteal fossa nerve blockade with bupivacaine."
Yadeau et al, 2012, US[492]	Randomized, double-blind, placebo-controlled trial	56 Patients scheduled for hospital admission after foot or ankle surgery • Placebo (36%, mean 61 y ± 12) • Pregabalin (39%, mean 60 y ± 9)	All patients received popliteal fossa sciatic nerve block with bupivacaine, clonidine, and epinephrine plus either: • Placebo (28) • Pregabalin (28)	Number of hours that patients reported moderate to severe pain	"No clinical benefit was obtained from perioperative administration of pregabalin (100 mg preoperative, then 50 mg every 12 hrs) as part of a multimodal postoperative analgesic regimen following foot and ankle surgery."
Yallapragada et al, 2016, India[266]	Prospective, randomized, double-blind study	50 Patients scheduled for spinal anesthesia • Clonidine (84%, mean 41.56 y ± 14.23) • Normal saline (80%, mean 44.2 y ± 13.33)	Spinal anesthesia with bupivacaine plus either: • Clonidine (25) • Normal saline (25)	Hemodynamic stability, duration of anesthesia	"Addition of low-dose clonidine to intrathecal bupivacaine not only prolonged the duration of spinal anesthesia but also provided a stable intraoperative hemodynamic profile."
Yazbeck-Karam et al, 2011, Lebanon[267]	Prospective, randomized, controlled trial	80 Patients undergoing vitreoretinal surgery with or without scleral buckling • Control (82.5%, mean 60.3 y ± 9.4) • Clonidine (77.5%, mean 64.9 y ± 9.9)	Retrobulbar block with lidocaine, bupivacaine, and either: • Control (40) • Clonidine (40)	Time to first analgesic request, frequency of postoperative pain, number of postoperative pain requests	"The addition of clonidine 0.5 mcg/kg to the local anesthetics of a retrobulbar block for vitreoretinal surgery decreases the frequency of postoperative pain and prolongs the time of analgesia."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ydemann et al, 2016, Denmark[517] Ydemann et al, 2018, Denmark[268]	Randomized, placebo-controlled, double-blind trial	379 Patients who were scheduled for anesthesia with sevoflurane and fentanyl (80.2%, range 1-5 y)	IV administration of either: • Clonidine (191) • Placebo (188)	Occurrences of postoperative agitation	"On the basis of our results, clonidine might be used to safely prevent postoperative agitation in boys anesthetised with sevoflurane."
Yoganarasimha et al, 2012, India[269]	Prospective, randomized, double-blind study	50 Patients posted for lower abdominal surgeries • Normal saline (40%, mean 38.2 y) • Clonidine (44%, mean 37.6 y)	Spinal anesthesia with hyperbaric bupivacaine plus either: • Normal saline (25) • Clonidine (25)	Sensory and motor characteristics, side effects	"With this study we conclude intrathecal clonidine in the dose of 75 mcg along with 2.5 ml of 0.5% hyperbaric bupivacaine provides an attractive alternative combination to anesthesiologist armamentarium for prolonging spinal analgesia."
Yoganarasimha et al, 2014, India[424]	Prospective, randomized, double-blind study	50 Patients posted for lower abdominal surgery • Neostigmine (72%, mean 28.72 y ± 9.35) • Clonidine (44%, mean 37.6 y ± 4.13)	Spinal anesthesia with hyperbaric bupivacaine plus either: • Neostigmine (25) • Clonidine (25)	Sensory and motor block characteristics, hemodynamic parameters	"The use of intrathecal neostigmine 50 mcg added to 12.5 mg hyperbaric bupivacaine significantly hastens the onset of sensory and motor block without prolonging the duration of analgesia compared to clonidine 75 mcg. But clonidine is associated with increased incidence of hypotension."
Yogarajan and Nelson, 2015, India[270]	Randomized, double-blind study	40 Patients undergoing upper limb surgeries (gender not specified, range 20-72 y)	Supraclavicular block with bupivacaine plus either: • Clonidine (20) • Fentanyl (20)	Quality and onset of block, time to complete block, duration of block, sedation, requirement of rescue analgesia, incidence of complications	"The addition of clonidine to local anesthetic solution in supraclavicular approach to brachial plexus block prolongs the duration of postoperative analgesia and motor blockade, when compared to fentanyl."

Author(s), Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Zuniga et al, 2002, US[493]	Case reports	2 Patients who developed CRPS type I, following multiple lower extremity surgeries (0%, range 43-60 y)	IT (intrathecal) pump with either: • Combination of baclofen and clonidine (1) • Baclofen (1)	Pain score	"IT baclofen appears to be an option for patients with intractable CRPS who have failed other modalities, including IT morphine."

Abbreviations: —, not provided; ACB, adductor canal block; ACL, anterior cruciate ligament; CRPS, complex regional pain syndrome; CSF, cerebrospinal fluid; FNB, femoral nerve block; IM, intramuscular; IQR, interquartile range; IT, intrathecal; ITM, intrathecal morphine; IV, intravenous; IVRA, intravenous regional anesthesia; MAP, mean arterial pressure; PACU, post-anesthesia care unit; PCA, patient-controlled analgesia; POD, postoperative day; PONV, postoperative nausea and vomiting; TAP, transversus abdominis plane; SAB, subarachnoid block; TKA, total knee arthroplasty.

[a]As defined by authors.

[b]While these studies have not been retracted, several other studies by Reuben SS have been retracted due to the use of fabricated data.

Appendix 3.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

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

2. Do you prescribe or administer clonidine hydrochloride to your patients?
    - Yes
    - No
3. Do you prescribe or administer clonidine hydrochloride by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Infiltration
    - Intraarticular/Periarticular injection
    - Intramuscular injection
    - Intrathecal injection
    - Intravenous injection
    - Irrigation
    - Ophthalmic/Intraocular injection
    - Perineural injection
    - Subcutaneous injection
    - Topical products including but not limited to cream, emulsion, gel, ointment, solution, suspension
    - None of the above
4. I prescribe or administer clonidine hydrochloride for the following conditions or diseases: (check all that apply)
    - Pain
    - Anesthesia
    - Other (please explain) _____
5. I prescribe or administer clonidine hydrochloride in combination with other active pharmaceutical ingredients as a multi-ingredient product.
    - Yes
    - No
6. I prescribe or administer clonidine hydrochloride with my patients as the following: (check all that apply)
    - FDA-approved drug products
    - Compounded drug products

- Other (please explain) _____

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

Appendix 3.2. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

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

2. Which of the following drugs do you prescribe or administer to your patients? (please check all that apply)
    - ○ Acetylcysteine
    - ○ Bupivacaine hydrochloride
    - ○ Clonidine hydrochloride
    - ○ Tetracaine hydrochloride
    - ○ Triamcinolone acetonide
    - ○ Tropicamide
    - ○ None of the above
3. I prescribe or administer compounded [substance from question 2] in combination with other active pharmaceutical ingredients as a multi-ingredient product.
    - ○ Yes, please explain _____
    - ○ No
4. Do you prescribe or administer [substance from question 2] by any of the following dosage forms and/or routes of administration? (please check all that apply)
    a. Local/perineural injection
    b. Intracameral injection
    c. Intraocular injection
    d. Ophthalmic solution, suspension, or gel
    e. Other (please describe) _____
    f. None of the above
5. I prescribe or administer [substance from question 2] for the following conditions or diseases:
    a. Anesthesia for ophthalmic procedures
    b. Dilation for mydriasis induction
    c. Dry eye caused by meibomian gland dysfunction
    d. Peribulbar or retrobulbar block
    e. Other, please explain _____
    f. None of the above
6. I prescribe or administer [substance from question 2] with my patients as the following:
    a. FDA-approved drug product
    b. Compounded drug product

c. Over-the-counter drug product
d. Other (please explain) _____

7. I used compounded [substance from question 2] because: (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
    - Patient allergies prevent me from using commercially available products (please explain) _____
    - Patient conditions prevent me from using commercially available products (please explain) _____
    - I am not aware of any commercially available products containing [substance from question 2]
    - Other (please explain) _____
8. Do you stock non–patient-specific compounded [substance from question 2] at your practice?
    - Yes
    - No
    - I'm not sure
9. I obtain compounded [substance from question 2] from the following: (please check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
10. What is your practice setting? (please check all that apply)
    - Physician office/private practice
    - Outpatient clinic
    - Hospital/health system
    - Academic medical center
    - Emergency room
    - Operating room
    - Other (please describe) _____
11. What degree do you hold? (please check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

Appendix 3.3. Survey instrument for pharmacy roundtable prequestionnaire

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

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

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

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

Appendix 4. Survey distribution to professional associations

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

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