

Summary Report

Dextromethorphan hydrobromide

Prepared for:

US Food and Drug Administration

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

Grant number: 5U01FD005946-06

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December 2021

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling \$2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

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Frequently Used Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ALS	Amyotrophic lateral sclerosis
API	Active Pharmaceutical Ingredient
Dextromethorphan HBr	Dextromethorphan Hydrobromide
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
IRB	Institutional Review Board
NMDA	N-methyl-D-aspartate
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 dextromethorphan hydrobromide (dextromethorphan HBr; UNII code: 9D2RTI9KYH), 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 dextromethorphan HBr is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how dextromethorphan HBr 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 dextromethorphan HBr and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Dextromethorphan HBr was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc.

Dextromethorphan HBr was nominated as 5 to 200 mg oral capsules for the treatment of multiple sclerosis, traumatic brain injury, dementia, muscle spasms, and muscular pain.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of dextromethorphan HBr.⁶⁻¹⁰

The reasons provided for nomination to the 503B Bulks List included prescribers wanting higher dosed oral capsules and not oral suspensions, and the excipients in the FDA-approved tablets not being appropriate for use in compounding capsules.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of dextromethorphan HBr 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 usable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for dextromethorphan HBr; name variations of dextromethorphan HBr 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 dextromethorphan HBr. The availability of OTC products (yes/no) in the US and the ROAs of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed two comprehensive search strategies for Ovid MEDLINE and Embase. The first search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: dextromethorphan HBr and therapeutic use for multiple sclerosis, brain injury, dementia, delirium, muscle spasm, muscle pain, fibromyalgia or nonketotic hyperglycinemia. After several studies describing the use of dextromethorphan for neuropathic or surgical pain were discovered in the initial review, a second set of search strategies was developed. The second search strategies used a combination of controlled vocabulary terms and key words to describe two concepts: dextromethorphan HBr and anesthesia, analgesia, or pain (refer to Appendix 1 for full search strategies). Results of both search strategies were limited to human studies in the English language. The first searches were conducted on November 6, 2020; the second searches were conducted on May 18, 2021. In addition, the ECRI Guidelines Trust[®] repository was searched on November 6, 2020, and May 18, 2021, for clinical practice guidelines that recommended the use of dextromethorphan HBr and provided sufficient information on 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 in which dextromethorphan HBr was used as a single-ingredient product in the nominated dosage form and ROA to diagnose, prevent, or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, preclinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if dextromethorphan HBr was used as a dosage form, ROA, or combination that was not nominated; for treatment of cough or cold symptoms; as a probe drug for determining patient's CYP2D6 phenotype; dextromethorphan HBr not used clinically; or dextromethorphan HBr mentioned briefly as a previously failed treatment. Studies in which dextromethorphan HBr was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of dextromethorphan HBr; setting; total number of patients; number of patients who received dextromethorphan HBr; patient population; indication for the use of dextromethorphan HBr; dosage form and strength; dose; ROA; frequency and duration of therapy; use of dextromethorphan HBr in a combination product; use and formulation of dextromethorphan HBr in a compounded product; use of dextromethorphan HBr 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 dextromethorphan HBr was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify medical specialties that would potentially use dextromethorphan HBr. 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 dextromethorphan HBr in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 3 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted to distribute the project Year 3 surveys.

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

- Dextromethorphan HBr is not available as a single-ingredient FDA-approved product in the nominated dosage form and ROA. Dextromethorphan HBr is available as FDA-approved oral products in combination with brompheniramine maleate, guaifenesin, promethazine hydrochloride (HCl), pseudoephedrine HCl, and quinidine sulfate.
- Dextromethorphan HBr is available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for dextromethorphan HBr.
- Dextromethorphan HBr is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, and the UK.

Table 1. Currently approved products – US

No approved products in the US

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 ^c	Approval Date ^b
Dextromethorphan HBr	2.5-30 mg 1-5 mg/mL	Capsule, Liquid, Lozenge, Pastille, Solution, Syrup, Tablet	Oral	Abu Dhabi	Active	–
				Australia	Pharmacy medicine	11/04/1998
				Belgium	Medical prescription or written request	1/17/1994
				Hong Kong	Pharmacy-only	4/27/1979
				Ireland	Pharmacy-only	12/18/1985
				Namibia	–	8/18/2004
				New Zealand	Restricted	10/14/1999
				Saudi Arabia	Prescription	–
				UK	Pharmacy	1/20/1988

Abbreviations: –, not provided.

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

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

^cPharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Results of literature review

Study selection

Database searches yielded 1982 references; 1 additional reference was identified from ClinicalTrials.gov. After duplicates were removed, 1477 titles and abstracts were screened. After screening, the full text of 786 articles was reviewed. One hundred nine studies were included; after multiple reports of the same study were merged, there were 104 included studies. Six hundred seventy-seven studies were excluded for the following reasons: wrong study design (622 studies); non-nominated dosage form or ROA (38); dextromethorphan HBr only mentioned briefly (8); language other than English (3); unable to obtain full text (3); used for treatment of cough or cold symptoms (1); used for management of autism (1); wrong drug (1).

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

Characteristics of included studies

The 104 included studies were published between 1989 and 2021. There were 78 experimental studies, 6 observational studies, 19 descriptive studies, and 1 clinical practice guideline. The 104 studies were conducted in the following countries: Australia, Canada, Denmark, Egypt, Finland, France, Germany, India, Iran, Israel, Italy, Japan, Norway, Poland, Saudi Arabia, Sweden, Switzerland, Taiwan, The Netherlands, the UK, and the US.

A total of 7757 patients participated in the 104 included studies. The number of patients in each study ranged from 1 to 3572.

Outcome measures differed among the included studies and included: allodynia, brain glycine levels, changes in functional status, chorea occurrence, death, encephalopathy resolution, infantile spasms, mental status, neurodevelopmental measures, nystagmus resolution, pain score, pseudobulbar affect symptoms, seizure and myoclonic jerk occurrence, wakefulness, and withdrawal symptoms.

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

Use of dextromethorphan HBr

One patient received dextromethorphan HBr for treatment of signs associated with *ATP1A2* gene mutation, administered orally at a dose of 30 mg twice a day for 4 months.

Sixty patients received dextromethorphan HBr for amyotrophic lateral sclerosis (ALS), administered via an unspecified ROA in doses of 1.5 mg/kg/day or 150-300 mg/day. Duration of treatment ranged from 3 to 12 months.

Twenty-two patients received dextromethorphan HBr for attention-deficit/hyperactivity disorder (ADHD), administered via an unspecified ROA at doses of 30 or 60 mg per day for 8 weeks.

Twenty patients received dextromethorphan HBr for management of hyperglycemia associated with diabetes mellitus, administered orally in doses of 60 or 270 mg for 2 doses.

Forty patients received dextromethorphan HBr for prevention or treatment of emergence agitation, administered orally once at a dose of 1 mg/kg.

Twenty patients received dextromethorphan HBr for endothelial dysfunction associated and inflammation with smoking, administered orally at a dose of 120 mg per day for 6 months.

Eleven patients received dextromethorphan HBr for treatment of signs associated with Huntington's disease, administered via an unspecified ROA at doses ranging from 120 to 960 mg/day. Duration of treatment was 4 to 8 weeks.

Five patients received dextromethorphan HBr for treatment of methotrexate encephalopathy, administered orally at doses of 1 to 2 mg/kg or 90 to 120 mg/day. Duration of treatment ranged from several hours to 10 days.

Six patients undergoing cardiac surgery received dextromethorphan HBr for neuroprotection, administered via nasogastric tube at a dose of 2 to 38 mg/kg/day for 4 days.

Nineteen patients received dextromethorphan HBr for treatment of nonketotic hyperglycinemia, administered via an unspecified ROA in doses of 0.25 to 22.5 mg/kg/day or 105 to 200 mg/day. Duration of treatment ranged from at least 2 weeks to 5 years.

Ninety-one patients received dextromethorphan HBr for management of opioid withdrawal, administered orally in doses of 0 to 60 mg/70 kg or 60 to 480 mg/day. Duration of treatment ranged from 6 days to 8 weeks.

Three thousand three hundred eleven patients received dextromethorphan HBr for the prevention or treatment of pain, administered orally or via an unspecified ROA in doses of 1.5 to 3 mg/kg/day, 0.3 to 1.5 mg/kg, 20 to 960 mg/day, and 10 to 480 mg. Duration of treatment ranged from once to 10 months. Sixteen patients received dextromethorphan HBr for prevention or treatment of pain, administered via nasogastric or orogastric tube at a dose of 0.3 mg/kg every 8 hours. Duration of treatment was 96 hours.

Two patients received dextromethorphan HBr for treatment of pseudobulbar affect, administered via an unspecified ROA in doses of 20-120 mg/day. Duration of treatment ranged from at least 4 weeks to at least 9 months.

Sixty-one patients received dextromethorphan HBr for management of Rett syndrome, administered orally at doses of 0.25-5 mg/kg/day for 3 to 6 months.

Sixty-two patients received dextromethorphan HBr for prevention of tourniquet-associated hypertension, administered orally once at a dose of 30 mg.

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

Dextromethorphan HBr was not used as a compounded product, nor was it used in a combination product.

In 36 studies, the authors' concluding statement recommended the use of dextromethorphan HBr for the management of hyperglycemia in patients with diabetes mellitus, emergency agitation, endothelial dysfunction in patients who smoke, methotrexate neurotoxicity, nonketotic hyperglycinemia, pain, and tourniquet-associated hypertension.¹¹⁻⁴⁷ Clinical practice guidelines from the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine recommended the use of N-methyl-D-aspartate (NMDA) receptor antagonists such as dextromethorphan HBr for the treatment of neuropathic pain.⁴⁸ In 24 studies, the authors concluded that the use of dextromethorphan HBr was not recommended for the treatment of ALS, pain, or tourniquet-associated hypertension.⁴⁹⁻⁷² In 31 studies, the authors concluded that more studies were needed on the use of dextromethorphan HBr in the management of *ATP1A2* gene mutation, ALS, ADHD, Huntington's disease, nonketotic hyperglycinemia, opioid withdrawal, pain, pseudobulbar affect, and Rett syndrome, or as a neuroprotectant.⁷³⁻¹⁰⁴ In 3 studies, the results on the

use of dextromethorphan HBr for pain management were inconclusive.¹⁰⁵⁻¹⁰⁷ In 9 studies, the authors' conclusions did not address the use of dextromethorphan HBr.¹⁰⁸⁻¹¹⁶ One study was a completed clinical trial, the results of which were not published in a journal and therefore had no conclusions from the investigators.¹¹⁷ Refer to Table 5 for 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 dextromethorphan HBr.

Dextromethorphan was first approved by the FDA in 1958 for use as a cough suppressant and is one of the most common drugs found in OTC cough and cold medications.¹¹⁸⁻¹²⁰ Dextromethorphan acts on several receptors including serotonin transporters, noradrenaline transporters, sigma-1 receptors, alpha-3-beta-4 nicotinic acetylcholine receptors; it also acts as an uncompetitive, low-affinity NMDA receptor antagonist.^{119,120} While dextromethorphan is derived from levorphanol, a mu-opioid agonist, and is an enantiomer of methorphan, a morphine derivative, "it has no direct agonist activity at the classic opioid receptors" and therefore is not associated with the same CNS or opioid effects that are characteristic of other opioids when taken at normal doses (60 to 120 mg/day in divided doses).^{120,121} However, when taken at doses 5 to 10 times higher than the approved maximum doses, dissociative and psychotropic effects similar to what is seen with ketamine occur.^{120,121}

Dextromethorphan is rapidly metabolized by the liver enzyme cytochrome P450 CYP2D6, with a half-life of around 2 hours, and is often used as a probe drug to determine CYP2D6 metabolizer status.¹¹⁹⁻¹²¹ In order to decrease the rate of metabolism and increase the half-life, dextromethorphan was formulated with quinidine, a potent CYP2D6 inhibitor, and was approved by FDA in 2010 under the brand name Nuedexta[®] for the treatment of pseudobulbar affect.^{119,120} This combination has also been studied to treat agitation and aggression in patients with probable Alzheimer's disease and patients with multiple sclerosis complicated by pseudobulbar affect and comorbid migraine.¹²²⁻¹²⁶ Dextromethorphan has also been formulated with bupropion, a norepinephrine and dopamine reuptake inhibitor that also acts to increase dextromethorphan plasma concentrations, and is currently being studied for use in major depressive disorder and agitation associated with Alzheimer's disease.¹²⁷⁻¹³⁰ This formulation is not FDA-approved but has received a Breakthrough Therapy designation from the FDA for both major depressive disorder and Alzheimer's disease agitation.¹³¹

NMDA receptors "play a critical role in excitatory neurotransmission, brain development, synaptic plasticity associated with memory formation, central sensitization during persistent pain, excitotoxicity and neurodegenerative diseases in the CNS [central nervous system]."¹³² As a result, there has been interest in the role of NMDA receptor antagonists in the management of neurodegenerative diseases.¹³² Due to dextromethorphan's NMDA receptor antagonist activities, and because as a low-affinity blocker it is better tolerated than high affinity blockers, dextromethorphan has been studied for use in the treatment of pain, depression, methotrexate toxicity, Parkinson's disease, autism, epilepsy, seizures, as a neuroprotectant for acute brain injury or stroke, and for neurodegenerative disorders.^{119,120,132-137}

NMDA antagonists, including dextromethorphan, have been studied for use as a perioperative analgesic adjunct.¹³⁸ A recent systematic review and meta-analysis evaluated the effect of dextromethorphan administered preoperatively on opioid consumption and postoperative pain scores.¹³⁸ The review included 21 randomized, double-blinded, placebo-controlled studies in which dextromethorphan was used either orally, intramuscularly, or intravenously prior to surgery.¹³⁸ The authors concluded that perioperative dextromethorphan reduces postoperative opioid use and pain

scores.¹³⁸ (Several of the studies included were also included in this literature review; refer to the *Results of literature* review section.) However, due to the variability in dosing used and surgeries performed in the included studies, no recommendations were provided and the authors stated that additional studies are needed to determine the benefit.¹³⁸

Dextromethorphan has also been studied for use in neuropathic pain. A 2008 literature review summarized the results of randomized, placebo-controlled clinical trials evaluating the treatment options for postherpetic neuralgia and painful diabetic neuropathy.¹³⁹ The review included 2 studies and in both studies dextromethorphan was effective for the treatment of painful diabetic neuropathy but not postherpetic neuralgia.^{32,139,140} Similarly, a review conducted in 2010 also stated that there are “no clinically important results from RCTs [randomized controlled trials] about the effects of dextromethorphan for pain relief in established postherpetic neuralgia” and a review in 2011 stated that dextromethorphan could be used to treat complex regional pain syndrome but not postherpetic neuralgia.^{141,142} Sang reviewed studies that used dextromethorphan for experimental and neuropathic pain and found that lower doses of dextromethorphan did not relieve pain while higher doses were effective at providing pain relief. However, with the higher doses, all patients developed adverse effects limiting the effectiveness.¹⁴³ Refer to the *Results of literature review* section for more information.

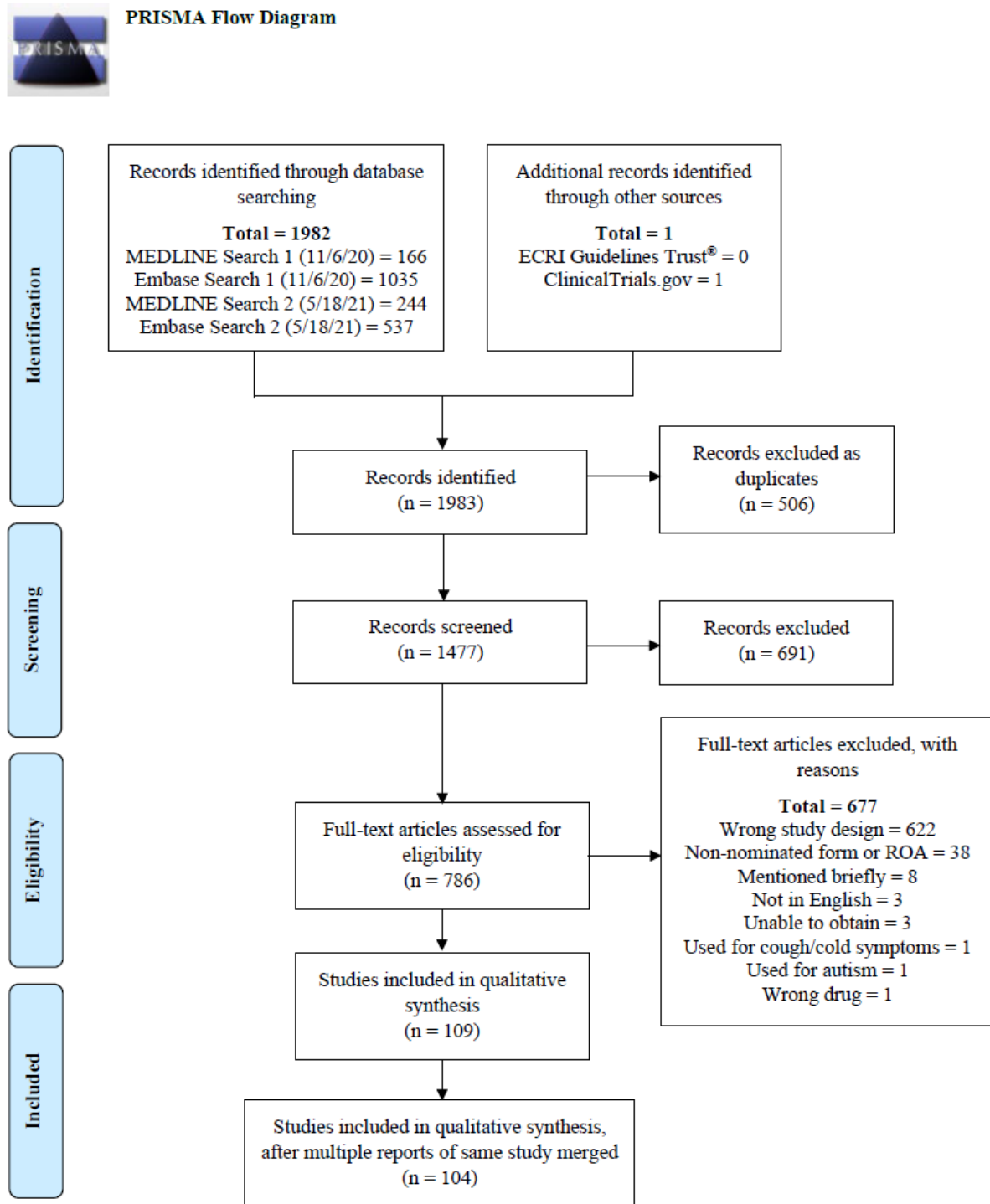
Mueller et al studied the use of dextromethorphan for the treatment of pain due to fibromyalgia. The mechanism by which fibromyalgia causes pain is unknown, but “research has pointed to abnormal nociceptive/pain processing in the central nervous system.”⁶⁸ One hypothesis is that patients with fibromyalgia have increased microglia activation in the brain, which leads to the production of proinflammatory cytokines resulting in the characteristic features of fibromyalgia.⁶⁸ Dextromethorphan has been shown to reduce the microglial production of proinflammatory cytokines, suggesting a potential use in fibromyalgia; lower doses could be used, as the target is to reduce inflammation and not act as an NMDA antagonist.⁶⁸ Mueller et al conducted a pilot study of 14 women with fibromyalgia who received a placebo for 5 weeks followed by 10 mg of dextromethorphan twice a day for 10 weeks.⁶⁸ At the end of the study there was no difference in self-reported daily pain or physical activity between the placebo and dextromethorphan; the authors concluded, “[W]e did not find strong evidence to support DXM [dextromethorphan] as an important treatment for FM [fibromyalgia].”⁶⁸

Nonketotic hyperglycinemia is a rare genetic metabolic disorder in which there is an inborn error of glycine metabolism due to deficient activity of the glycine cleavage system; this results in large quantities of glycine accumulating in all body tissues, particularly in the central nervous system.¹⁴⁴ Severe classic nonketotic hyperglycinemia often presents in the first few weeks of life with lethargy, vomiting, or convulsions, and progresses to hypotonia, loss of reflexes, myoclonic seizures, apnea typically requiring ventilation, coma, and potentially death.^{144,145} Patients who survive have severe developmental delays, neurological disabilities, and intractable seizures.¹⁴⁴ Attenuated classic nonketotic hyperglycinemia can present either in the neonatal period, with symptoms similar to that of the severe classic form but with less severe seizures and improved psychomotor development, or in infancy after normal development for the first few months of life, with mild to moderate psychomotor delays.¹⁴⁴ Treatment is focused on reducing glycine levels with sodium benzoate at doses ranging from 250 to 750 mg/kg/day and blocking the effects of glycine on NMDA receptors with dextromethorphan in doses from 5 to 22 mg/kg/day.¹⁴⁶ Several studies were included in which dextromethorphan was used to treat nonketotic hyperglycinemia; refer to the *Results of literature review* section.

Rett syndrome is a neurodevelopmental disorder caused by mutations in the MECP2 gene on the X chromosome. It predominately affects girls and is characterized by “normal development for the first 6-18 months of age, followed by a phase of developmental stagnation (stage I), which progresses to a period of regression (stage II).”¹⁴⁷ Stages III-IV are late stages and typically include severe growth retardation, seizures, aggravated motor problems, and scoliosis.¹⁴⁷ Treatment is focused on managing symptoms and can vary depending on the clinical presentation of a patient.¹⁴⁷ Due to dextromethorphan’s mechanism as an NMDA receptor antagonist, dextromethorphan has been studied to improve cognition and reduce seizures in patients with Rett syndrome; refer to the *Results of literature review* section.^{84,102,117,147,148}

The background research and literature review revealed several formulations for compounded dextromethorphan products. In 2009 a formulation for a combination capsule containing oxycodone 10 mg and dextromethorphan 20 mg was published, as well as a combination capsule containing propoxyphene 100 mg and dextromethorphan 30 mg.^{149,150} In 2011 a formulation for a dextromethorphan 15 mg oral film strip was published.¹⁵¹ Mishkan highlighted the need for compounding dextromethorphan capsules for the treatment of pain, since they are not commercially available.¹⁵² Compounding pharmacies compound capsules as 15 mg, 27 mg, 30 mg, and 60 mg with lactose as a filler, with dosing regimens ranging from 15 to 30 mg every 6 hours or 10 to 30 mg 6 times daily; the maximum dose is 240 mg/day.¹⁵² References to topical formulations are also included with recommendations for application to the site of pain every 1 to 2 hours as needed.¹⁵² The topical formulations are typically formulated in either a Pluronic lecithin organogel or vanishing-penetrating base in concentrations ranging from 5% to 10%.¹⁵² Kane and Glasnapp also emphasized the importance of compounding dextromethorphan for the treatment of chronic pain referencing dosing regimens of 15 mg every 6 hours, 30 mg 3 times daily, and 27 mg 3 times daily.¹⁵³

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



Adapted from:

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

<http://www.prisma-statement.org/>

Table 3. Types of studies

Types of Studies	Number of Studies
Descriptive ^{14,16,20,22,33,38,46,73,85,86,93,94,103,106,108,110,113-115,154}	19
Observational ^{15,21,36,74,82,104,109}	6
Experimental ^{11-13,17-19,23-32,34,35,37,39-45,47,49-72,75-81,83,84,87-92,95-102,105,107,111,112,116,117,155}	78
Clinical practice guideline ⁴⁸	1

Table 4. Number of studies by country

Country	Number of Studies
Australia ^{56,72}	2
Canada ^{51,53}	2
Denmark ^{57,61,87,88}	4
Egypt ¹¹	1
Finland ^{58,62,90}	3
France ^{28,29,50}	3
Germany ³⁴	1
India ⁸⁹	1
Iran ^{18,19,37,49,59,63,64,75,76,99,100}	10
Israel ^{40-45,78,79}	8
Italy ^{30,31,67}	2
Japan ^{13,25,47}	3
Norway ⁸⁰	1
Poland ³⁵	1
Saudi Arabia ^{12,69}	2
Sweden ^{77,97,155}	3
Switzerland ¹⁰¹	1
Taiwan ^{26,27,81,92}	4

Thailand ^{71,105}	2
The Netherlands ⁹¹	1
UK ^{24,60,65,66,107}	5
US ^{14,16,17,20-23,32,33,38,39,46,48,52,54,55,68,70,73,74,82-86,93-96,98,102-104,106,108-117,154}	43
Multiple Countries <ul style="list-style-type: none"> • Australia and US^{15,36} 	1
Total US ^a : 44 Total Non-US Countries ^a : 61	

^aStudy 15 and 36 (multiple reports of 1 study) counted in both US and non-US total.

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
<i>ATPIA2</i> gene mutation ¹⁰³	30 mg twice a day	–	–	Oral	4 months
Huntington’s disease ¹⁰⁴	120-960 mg/day	–	–	–	4-8 weeks
Methotrexate encephalopathy ^{16,33,46,115}	1-2 mg/kg	–	–	Oral	“Several hours” – 12 hours
	90-120 mg/day				3 days
	–			–	10 days
Nonketotic hyperglycinemia ^{14,15,22,36,38,73,85,86,113,114}	5-20 mg/kg/day	–	Syrup	–	More than 1 month – 95 days
	0.25-22.5 mg/kg/day		–		At least 2 weeks – 5 years
	105-200 mg/day		–		38 days – 11 months
Opioid withdrawal ^{96,112}	0-60 mg/70 kg	30 mg	Capsule	Oral	–
	120-480 mg/day	–	–	–	12 days
Pain ^{17,20,21,23,32,39,48,52,54,55,68,70,74,82,83,95,98,106,108-111,116,154}	20-960 mg/day	10 mg, 120 mg	Capsule	Oral	Once – 10 months
		–			
	0.5-1 mg/kg	30 mg	Tablet		
		7.5 mg/5 mL	Syrup		
	15-480 mg	–	Elixir		
			–		
		Solution			

	1.5-3 mg/kg/day		–		
Pseudobulbar affect ^{93,94}	20-120 mg/day	–	Syrup	–	At least 4 weeks – 9 months
Rett Syndrome ^{84,102,117}	0.25-5 mg/kg/day	–	–	Oral	3-6 months

Abbreviations: –, not provided.

Table 7. Dosage by indication – non-US countries

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Amyotrophic lateral sclerosis ^{50,57,77}	150-300 mg/day	3 mg/mL	“Mixture”	–	3-12 months
		30 mg	Tablet		
	1.5 mg/kg/day	–	Capsule		
Attention-deficit/hyperactivity disorder ⁸¹	30-60 mg/day	–	Tablet	–	8 weeks
Diabetes mellitus ³⁴	60 or 270 mg	–	–	Oral	Twice
Emergence agitation ¹¹	1 mg/kg	–	–	Oral	Once
Endothelial dysfunction ²⁷	120 mg/day	60 mg	Tablet	Oral	6 months
Neuroprotection ¹⁰¹	2-38 mg/kg/day	–	Solution	Nasogastric tube	4 days
Opioid withdrawal ^{92,100}	60-240 mg/day	–	Capsule	–	6 days – 8 weeks
			–	Oral	

Pain ^{12,13,18,19,24-26,28-31,35,37,40-45,49,51,53,56,58,60-67,69,71,72,75,76,78-80,87-91,97,99,105,107,155}	27-200 mg	27 mg	Capsule	Oral	Once – 3 months
		–			
	30-240 mg	30, 60, 120 mg	Tablet		
		–			
		30 mg	–		
	13.5-45 mg	3 mg/mL	Syrup		
		–			
	1 mg/kg	–			
	10-270 mg	–	–		
		2 mg/mL	–		
90-480 mg/day	–	–			
0.3-1.5 mg/kg	–	Solution			
	–	–	Orogastric or nasogastric tube		
Tourniquet-associated hypertension ^{47,59}	30 mg	–	–	Oral	96 hours
					Once

Abbreviations: –, not provided.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from included studies

Table 10. Compounded products – non-US countries

No compounded products from included studies

Results of interviews

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Seven SMEs discussed dextromethorphan HBr. Among these 7 SMEs, there were 5 medical doctors, 1 nurse practitioner, and 1 PhD. The SMEs specialized and/or were board-certified in anesthesiology, neurology, oncology, pain medicine, psychology, and psychiatry, working in academic medical institutions, clinical research, and retired. The SMEs had been in practice for 12 to 37 years.

One SME discussed the use of topical pain products, stating that they do use them, but these topical formulations are never first-line options. They are only used if the patient asks for a product they do not have to take by mouth or if the patient has tried topical lidocaine or Voltaren® (diclofenac) gel with no relief. When determining the appropriate formulation, the differing pathologies of pain a patient presents with will guide the selection of ingredients. Typically, each formulation has three or four APIs allowing them to use multiple mechanisms of action to treat the patient's pain or to treat pain of multiple etiologies (for example, neuropathic and inflammatory). 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 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. The SME has seen other NMDA antagonists included in these formulations; they have not seen dextromethorphan as an option. Another SME was not familiar with the use of topical dextromethorphan and commented that this would not make sense when treating patients with fibromyalgia. The pain associated with fibromyalgia is deep muscular pain and so there would be challenges with formulation to achieve the desired level of penetration. Additionally, a topical formulation would not cross the blood-brain barrier and so would not lead to a central effect.

One SME discussed the use of dextromethorphan preoperatively to decrease acute pain. The SME was interested in identifying alternative medications to opioids to decrease pain postoperatively and found literature for the use of NMDA antagonists, including amantadine, memantine, and dextromethorphan. The SME had not used dextromethorphan for this purpose but had used amantadine. The decision to use amantadine over dextromethorphan was due to availability from the hospital pharmacy. Dextromethorphan was only available as a cough syrup in combination with guaifenesin, while amantadine came as an oral tablet. The SME commented, "it's curious to me that there's reasonable evidence for things like dextromethorphan, but they're just not used in practice." The SME speculated that dextromethorphan may not be used as frequently because ketamine, another NMDA antagonist, is commonly used intraoperatively and postoperatively for acute pain, and "people are educated on its perioperative use." However, ketamine is primarily administered as an IV product; dextromethorphan would have the added benefit of being given orally.

One SME discussed the use of dextromethorphan for the treatment of pain due to fibromyalgia. Dextromethorphan is an NMDA antagonist that can lead to a reduction in pain, but the doses needed to obtain this effect (around 200 mg per dose) are associated with several adverse effects. Previous studies have shown that patients with fibromyalgia have an increase in microglia activation that is associated with an increase in inflammation in the brain. Dextromethorphan and its active metabolite 3-hydroxymorphinan may play a role in reducing inflammation due to its acting as a toll-like receptor 4 antagonist, resulting in pain relief. The dose needed to obtain this effect is around the cough-suppressant dose, which is much lower than the dose needed to block NMDA, so there are fewer concerns about adverse effects. The SME referenced a pilot study that was conducted to evaluate the use of dextromethorphan for fibromyalgia but found that most of the patients did not experience significant pain reduction. However, the SME stated that dextromethorphan could potentially be considered as a treatment option if a patient has failed all other treatments. The SME commented that while the half-life of dextromethorphan is relatively short, a commercially available product contains quinidine, which may extend the effects of dextromethorphan.

Another SME discussed the use of dextromethorphan in Rett syndrome. In patients with Rett syndrome, there is a certain phase in brain development in which the NMDA receptors increase enormously; then after the age of 8 the receptors “go down to below normal.” During this period of brain development, the “disease progression rages with [an] increase in irritability, and then it slowly subsides, and they have leftover results like seizures.” The seizures begin around the same time that there is an increase in NMDA receptors; therefore, administering an NMDA antagonist like dextromethorphan could improve quality of life and lead to an “amelioration of the condition.” The SME referenced a preliminary study in which commercially available Delsym® (dextromethorphan polistirex) was administered in doses of 0.5 mg/kg, 2.5 mg/kg, and 5 mg/kg. The study found that patients’ receptive language improved and their irritability subsided. While dextromethorphan “would be a very useful tool, especially for irritability,” the SME mentioned that prescribers “moved on to some other things.” The SME also mentioned that dextromethorphan has been used for nonketotic hyperglycinemia in newborns and children under the age of 1, leading to improvement of seizures.

Two SMEs mentioned that they have used the commercially available dextromethorphan product that contains quinidine for emotional incontinence and emotional stability in patients with multiple sclerosis and for patients with pseudobulbar palsy (quinidine is used to inhibit the metabolism of dextromethorphan). One SME commented that “treating any sort of agitated behavior in people with brain diseases is hard to do,” continuing that there are black box warnings related to the use of antipsychotics in patients with dementing illnesses. The SME also stated that this product is “terribly expensive.” Another SME stated that they do not see a lot of patients with emotional incontinence, so they do not use that product very frequently, but commented that it does work well when needed.

One SME was not familiar with the use of oral dextromethorphan for pain, while another SME has used it for muscular pain but stated that 200 mg is “awfully high,” commenting that, “I have never used doses that high.”

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

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtained varied from less than 1% to the majority of compounded products used at one participant’s facility. A participant stated, “we have this method that we use where if we can

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

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

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

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover, leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency with which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant stated that, while they do not obtain a lot of products from outsourcing facilities,

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

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

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

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products used. However, the products used in a facility are often developed in-house over decades based on physician and nurse requests, and, more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, “these practices had evolved somewhat disparately. Even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines.” This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, “I think we made 9 different epidural concentrations, all driven by anesthesia, and they want what they want, and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn’t going to go through the expense of adding that to their product list.” The participant also said that

“similar with the ADCs [automated dispensing cabinets], we’ve run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses 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 continued that “it would be great if the FDA could look at the size of the container that they’re approving and whether that’s a realistic dose: is it a unit dose, or isn’t it?”

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

A few participants commented on the use of API by outsourcing facilities. One commented that as long as they are conducting end-product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. As long as buyers are familiar with regulations and know what to look for, another participant commented, there should not be any issues with purchasing products compounded starting from API. Another participant stated that as more outsourcing facilities began using API, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using API if there is a shortage, stating, “I think the FDA has really looked closely at API, and they’re slowly pushing the 503B outsourcers to a sterile-to-sterile.” Only 1 participant commented that they prefer sterile-to-sterile. Another participant stated that the companies they use are all sterile-to-sterile.

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. So, there is a need for this product to be compounded from API as a preservative-free product. One participant stated that “if there’s not a preservative-free containing option, it really should be something that should be able to be compounded from bulk . . . especially for the pediatric patient population.” However, another participant from a children’s hospital said that they have never needed to use an outsourcing facility for preservative-free products. Preservative-free is also an issue for ophthalmic products; however, one participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing

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

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

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

times than not, they go unused and expire.” Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for which they need to use alum. The participant had it stat shipped when needed. Another participant stated that “we had a meeting with the head of urology who was baffled, why they’re even ordering it. He was like, ‘this is . . . old, really old. I don’t even know why we’re using it’ and basically approved for us to not even make it anymore for now.”

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

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

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

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

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because “it just hasn’t been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to. . . . It just isn’t worth the dating that they gave us or can give us.” Another commented that they obtain very little product from outsourcing facilities due to “the amount of work for vetting and continually validating quality of these 503B outsourcing facilities.” The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that “[t]raditionally, we’ve found 503Bs

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

Results of survey

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

A prequestionnaire was distributed to participants in the roundtable discussion (refer to Appendix 3.2 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 15 for respondent characteristics. Among respondents, 35 (81% of 43 total respondents) 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) obtained drug products from outsourcing facilities due to a need for ready-to-use products and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 16).

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

Dextromethorphan was not included on the prequestionnaire (refer to Table 18).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which dextromethorphan HBr prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded dextromethorphan HBr

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded dextromethorphan HBr

No respondents to survey distributed via professional medical associations

Table 15. Demographics of prequestionnaire respondents' facilities

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

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

^aRespondents were allowed to select more than one type of facility.

^bSpecialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, oncology.

Table 16. Reasons for obtaining products from outsourcing facilities

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

^aRespondents were allowed to select multiple categories.

^bRespondents reported staffing shortages, need for extended dating, volume of product used, standardization projects as additional reasons for utilizing outsourcing facilities.

Table 17. Categories of products obtained from outsourcing facilities

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

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

^aRespondents were allowed to select multiple categories.

^bRespondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost anti-seizure medications, antiviral medications, topical pain, and oral tablets/capsules.

Table 18. Products obtained from an outsourcing facility

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

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

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

^aRespondents were allowed to select multiple products.

CONCLUSION

Dextromethorphan HBr was nominated for inclusion on the 503B Bulks List as oral capsules for the treatment of multiple sclerosis, traumatic brain injury, dementia, and muscle spasms or muscular pain. Dextromethorphan HBr is not available as a single-ingredient FDA-approved product in the nominated form and ROA. Dextromethorphan HBr is available in FDA-approved oral products in combination with brompheniramine maleate, guaifenesin, promethazine hydrochloride (HCl), pseudoephedrine HCl, and quinidine sulfate. Dextromethorphan HBr is available as an OTC product in the US. Dextromethorphan HBr is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, and the UK.

From the literature review, oral dextromethorphan HBr was used in the management of a variety of conditions, including *ATP1A2* gene mutation; ADHD; ALS; diabetes mellitus; emergence agitation; endothelial dysfunction in persons who smoke; Huntington's disease; methotrexate encephalopathy; for neuroprotection; nonketotic hyperglycinemia; opioid withdrawal; pain; pseudobulbar affect; Rett syndrome; and tourniquet-associated hypertension. The authors' conclusions on the effectiveness of dextromethorphan HBr for these conditions were mixed, with some conclusions recommending the use of dextromethorphan HBr (36 studies), some not recommending its use (24 studies), and others either recommending further investigation (31 studies) or inconclusive (3 studies). The conclusions of 9 studies did not address the use of dextromethorphan HBr. One clinical practice guideline from the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine recommended the use of NMDA receptor antagonists such as dextromethorphan HBr for the treatment of neuropathic pain. One clinical trial had no published conclusions.

From the interviews, there were mixed opinions on the use of dextromethorphan for pain. One SME does use topical pain products but was not familiar with the use of topical dextromethorphan, and another SME stated that a topical formulation would not make sense to treat patients with fibromyalgia. Regarding oral dextromethorphan, a few SMEs had used the commercially available dextromethorphan with quinidine product for patients with multiple sclerosis and emotional incontinence and patients with pseudobulbar palsy. However, one SME commented that this product is relatively expensive. One SME stated that there is literature that supports the use of dextromethorphan preoperatively to reduce acute pain but mentioned that this is not commonly done in practice, potentially due to the availability of and higher awareness about the use of ketamine for this indication. Another SME had used oral dextromethorphan to treat muscular pain but never in doses as high as 200 mg. Another SME commented that there is the potential for use of lower doses in fibromyalgia, but a recent study did not find that patients experienced a significant reduction in pain.

No responses were received to the survey distributed via professional medical associations and available on the project website.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy 1

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to November 5, 2020
- Date last searched: November 6, 2020
- Limits: Humans (search hedge); English language
- Number of results: 166

1	dextromethorphan/	1848
2	d dethorphan\$.tw.	0
3	delta met?orphan\$.tw.	0
4	dextro met?orphan\$.tw.	2
5	dextromet?orphan\$.tw.	2660
6	dextro met?orfan\$.tw.	0
7	dextromet?orfan\$.tw.	2
8	or/1-7	2932
9	exp multiple sclerosis/	59,493
10	amyotrophic lateral sclerosis/	19,185
11	((multiple or disseminated or insular or lateral or multiplex) adj3 scleros\$).tw.	99,418
12	((charcot\$ or gehrig\$) adj3 diseas\$).tw.	3480
13	exp brain injuries/	70,112
14	pseudobulbar palsy/	148
15	((brain\$ or capitis or cerebr\$ or crani\$ or forebrain\$ or head\$ or hemispher\$ or intracrani\$ or intercrani\$ or skull\$) adj3 (bruise\$ or concuss\$ or contusion\$ or damag\$ or encephalopath\$ or fracture\$ or injur\$ or trauma\$ or wound\$)).tw.	158,346
16	commotio cerebri.tw.	64
17	contusio cerebri.tw.	19
18	postconcuss\$.tw.	1358
19	post concuss\$.tw.	1766

20	exp dementia/	168,493
21	exp delirium/	9722
22	hydrocephalus, normal pressure/	2292
23	dement\$.tw.	115,391
24	alzheimer\$.tw.	148,016
25	(lewy adj2 body\$.tw.	3835
26	organic brain diseas\$.tw.	301
27	organic brain syndrom\$.tw.	766
28	benign senescent forget\$.tw.	18
29	((cerebr\$ or cogniti\$ or corticostrat\$ or frontal lobe or frontotempor\$ or memory or neurofibrilla\$) adj3 (declin\$ or degenerat\$ or deteriorat\$ or disorder\$ or disturb\$ or insufficien\$ or loss or tangle\$)).tw.	78,818
30	((hereditary or juvenile or major or progress\$) adj3 chorea).tw.	304
31	huntington\$.tw.	17,938
32	kosaka shibayama.tw.	5
33	korsako.tw.	0
34	klu?ver bucy.tw.	244
35	(pick adj2 diseas\$.tw.	2182
36	biswanger.tw.	2
37	(creutzfeldt adj2 (jacob or jakob)).tw.	6467
38	delirium.tw.	15,475
39	acute brain dysfunction\$.tw.	106
40	acute brain fail\$.tw.	26
41	acute brain syndrom\$.tw.	49
42	acute confusion\$.tw.	936
43	acute psychoorganic syndrom\$.tw.	0
44	acute psycho organic syndrom\$.tw.	6
45	(cloud\$ adj2 conscious\$.tw.	243

46	pseudobulbar.tw.	767
47	((normal pressure or normotens\$) adj3 hydrocephal\$).tw.	2702
48	exp spasm/	9798
49	muscle spasticity/	9241
50	muscle cramp/	2208
51	tetany/	2498
52	exp musculoskeletal pain/	5276
53	exp back pain/	39,429
54	neck pain/	7144
55	fibromyalgia/	8529
56	((back or muscl\$ or myofascia\$ or neck) adj3 (cramp\$ or pain\$ or sore\$ or spas\$ or tender\$)).tw.	77,988
57	myospas\$.tw.	35
58	myoton\$.tw.	8319
59	paramyoton\$.tw.	362
60	trismus\$.tw.	2310
61	tetan\$.tw.	32,828
62	spasmophil\$.tw.	256
63	dorsalg\$.tw.	110
64	notalg\$.tw.	120
65	myalg\$.tw.	10,092
66	polymyalg\$.tw.	2805
67	fibromyalg\$.tw.	10,492
68	fibrosit\$.tw.	536
69	myodyn\$.tw.	92
70	hyperglycinemia, nonketotic/	224
71	hyperglycin?em\$.tw.	637

72	glycin?em\$.tw.	20
73	(glycine adj2 encephalopath\$).tw.	84
74	or/9-73	778,373
75	and/8,74	221
76	exp animals/ not humans/	4,753,439
77	75 not 76	174
78	limit 77 to english language	166

MEDLINE search strategy 2

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to May 17, 2021
- Date last searched: May 18, 2021
- Limits: Humans (search hedge); English language
- Number of results: 244

1	dextromethorphan/	1874
2	d dethorphan\$.tw.	0
3	delta met?orphan\$.tw.	0
4	dextro met?orphan\$.tw.	2
5	dextromet?orphan\$.tw.	2707
6	dextro met?orfan\$.tw.	0
7	dextromet?orfan\$.tw.	2
8	or/1-7	2981
9	exp "anesthesia and analgesia"/	237,977
10	exp pain/	410,373
11	exp pain management/	36,424
12	an?esth\$.tw.	387,928
13	analges\$.tw.	128,677
14	pain\$.tw.	733,480
15	or/9-14	1,330,108
16	and/8,15	372
17	exp animals/ not humans/	4,829,671
18	16 not 17	260
19	limit 18 to english language	244

Embase search strategy 1

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: November 6, 2020
- Limits: Humans (search hedge); English language
- Number of results: 1035

1	'dextromethorphan'/de	7486
2	'd dethorphan*':ti,ab,tn	0
3	'delta met\$orphan*':ti,ab,tn	0
4	'dextro met\$orphan*':ti,ab,tn	13
5	'dextromet\$orphan*':ti,ab,tn	3668
6	'dextro met\$orfan*':ti,ab,tn	0
7	'dextromet\$orfan*':ti,ab,tn	4
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	7948
9	'multiple sclerosis'/de	137,907
10	'amyotrophic lateral sclerosis'/de	40,096
11	((multiple OR disseminated OR insular OR lateral OR multiplex) NEAR/3 scleros*):ti,ab	154,806
12	((charcot* OR gehrig*) NEAR/3 diseas*):ti,ab	5130
13	'brain injury'/exp	196,819
14	'pseudobulbar palsy'/de	760
15	'pseudobulbar affect'/de	75
16	((brain* OR capitis OR cerebr* OR crani* OR forebrain* OR head* OR hemispher* OR intracrani* OR intercrani* OR skull*) NEAR/3 (bruise* OR concuss* OR contusion* OR damage* OR encephalopath* OR fracture* OR injur* OR trauma* OR wound*)):ti,ab	224,438
17	'commotio cerebri':ti,ab	183
18	'contusio cerebri':ti,ab	53
19	'postconcuss*':ti,ab	4149
20	'post concuss*':ti,ab	2990
21	'dementia'/exp	374,950

22	'delirium'/exp	33,937
23	'normotensive hydrocephalus'/de	4028
24	'dement*':ti,ab	171,314
25	'alzheimer*':ti,ab	204,428
26	(lewy NEAR/2 bod*):ti,ab	14,666
27	'organic brain diseas*':ti,ab	559
28	'organic brain syndrom*':ti,ab	1131
29	'benign senescent forget*':ti,ab	27
30	((cerebr* OR cogniti* OR corticostriat* OR 'frontal lobe' OR frontotempor* OR memory OR neurofibrilla*) NEAR/3 (declin* OR degenerat* OR deteriorat* OR disorder* OR disturb* OR insufficien* OR loss OR tangle*)):ti,ab	120,528
31	((hereditary OR juvenile OR major OR progress*) NEAR/3 chorea):ti,ab	506
32	'huntington*':ti,ab	24,655
33	'kosaka shibayama':ti,ab	6
34	'korsako':ti,ab	3
35	'klu\$ver bucy':ti,ab	327
36	(pick NEAR/2 diseas*):ti,ab	4656
37	'binswanger':ti,ab	820
38	(creutzfeldt NEAR/2 (jacob OR jakob)):ti,ab	8483
39	'delirium':ti,ab	25,367
40	'acute brain dysfunction*':ti,ab	174
41	'acute brain fail*':ti,ab	39
42	'acute brain syndrom*':ti,ab	116
43	'acute confusion':ti,ab	583
44	'acute organic brain syndrom*':ti,ab	62
45	'acute confusion* state':ti,ab	640
46	'acute psychoorganic syndrom*':ti,ab	2
47	'acute psycho organic syndrom*':ti,ab	6

48	(cloud* NEAR/2 conscious*):ti,ab	548
49	'pseudobulbar':ti,ab	1433
50	((('normal pressure' OR normotens*) NEAR/3 hydrocephal*):ti,ab	3899
51	'muscle spasm'/exp	91,979
52	'spasticity'/de	28,200
53	'musculoskeletal pain'/exp	157,349
54	'myalgia'/exp	110,209
55	((back OR muscul* OR myofascia* OR neck) NEAR/3 (cramp* OR pain* OR sore* OR spas* OR tender*)):ti,ab	114,594
56	'myospas*':ti,ab	65
57	'myoton*':ti,ab	11,922
58	'paramyoton*':ti,ab	509
59	'trismus*':ti,ab	3186
60	'tetan*':ti,ab	43,120
61	'spasmophil*':ti,ab	532
62	'dorsalg*':ti,ab	197
63	'notalg*':ti,ab	167
64	'myalg*':ti,ab	16,660
65	'polymyalg*':ti,ab	4453
66	'fibromyalg*':ti,ab	16,978
67	'fibrosit*':ti,ab	795
68	'myodyn*':ti,ab	157
69	'hyperglycinemia'/de	879
70	'hyperglycinsem*':ti,ab	901
71	'glycinsem*':ti,ab	268
72	(glycine NEAR/2 encephalopath*):ti,ab	117
73	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	1,412,734

	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 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72	
74	#8 AND #73	1179
75	[animals]/lim NOT [humans]/lim	6,116,306
76	#74 NOT #75	1096
77	#74 NOT #75 AND [english]/lim	1035

Embase search strategy 2

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: May 18, 2021
- Limits: Humans (search hedge); English language
- Number of results: 537

1	dextromethorphan'/mj	2124
2	d dethorphan*':ti,ab,tn	0
3	delta met\$orphan*':ti,ab,tn	0
4	dextro met\$orphan*':ti,ab,tn	12
5	dextromet\$orphan*':ti,ab,tn	3733
6	dextro met\$orfam*':ti,ab,tn	0
7	dextromet\$orfam*':ti,ab,tn	4
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	4180
9	'anesthesiological procedure'/exp	893,624
10	'pain'/exp	1,474,382
11	'an\$esth*':ti,ab	561,795
12	'analges*':ti,ab	189,609
13	'pain*':ti,ab	1,127,100
14	#9 OR #10 OR #11 OR #12 OR #13	2,774,961
15	#8 AND #14	733
16	[animals]/lim NOT [humans]/lim	6,208,685
17	#15 NOT #16	572
18	#15 NOT #16 AND [english]/lim	537

Appendix 2. Table 5. Summary of included studies

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: <i>ATP1A2</i> gene mutation					
Ueda et al, 2018, US ¹⁰³	Case report	12-Year-old male patient with <i>ATP1A2</i> gene mutation	Dextromethorphan (1)	Pain relief	“Behavioral cognitive and cerebellar symptoms associated with <i>ATP1A2</i> gene mutation in a single patient improved with NMDA [N-methyl-D-aspartate] receptor antagonists. Our patient had worsening headaches while receiving memantine and dextromethorphan. However his recent episodes of headaches may have been related more closely to concussion rather than to a symptom of his underlying alternating hemiplegia. Further study is needed to better understand the role of NMDA receptor antagonists in the treatment of patients with <i>ATP1A2</i> mutations.”
Indication 2: Amyotrophic lateral sclerosis (ALS)					
Askmark et al, 1993, Sweden ⁷⁷	Double-blind crossover trial Open trial	14 Patients with ALS (35.7%, range 47-80 y)	Crossover trial: <ul style="list-style-type: none"> • Dextromethorphan (13) • Placebo (14) Open label: <ul style="list-style-type: none"> • Dextromethorphan (10) 	Clinical and neurophysiological parameters	“The lack of any obvious effect from dextromethorphan in our study does not necessarily imply that the underlying hypothesis is wrong. The process of degeneration may have proceeded too far and the NMDA receptor antagonistic activity of dextromethorphan in the tested doses may have been too weak. In a pilot study of this type there is also a risk of type II error. However, as there were no positive effects in any of the parameters, we find it unlikely that the drug in the doses given has any beneficial value of clinical importance in the treatment of ALS.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Blin et al, 1996, France ⁵⁰	Parallel group double-blind placebo-controlled study	49 Patients with ALS (mean 64 y ± 10) <ul style="list-style-type: none"> Dextromethorphan (58.3%) Placebo (60.8%) 	<ul style="list-style-type: none"> Dextromethorphan (24) Placebo (25) 	Change in functional status, survival	“We failed to demonstrate a significant effect of dextromethorphan on rates of survival and functional deterioration in this randomized, double-blinded, placebo-controlled study of 49 patients with ALS.”
Gredal et al, 1997, Denmark ⁵⁷	Randomized, double-blind, placebo-controlled study	45 Patients with ALS <ul style="list-style-type: none"> Placebo (48%, mean 58 y ± 9.8) Dextromethorphan (50%, mean 60 y ± 9.5) 	<ul style="list-style-type: none"> Dextromethorphan (22) Placebo (23) 	Death from all causes within 12 months	“Treatment with a relatively low dose of dextromethorphan did not result in an improvement in 12-month survival in ALS.”
Indication 3: Attention-deficit/hyperactivity disorder (ADHD)					
Chuang et al, 2019, Taiwan ⁸¹	Randomized double-blind clinical trial	44 Patients with a diagnosis of ADHD <ul style="list-style-type: none"> Methylphenidate (100% mean 9.16 y ± 1.71) Methylphenidate and dextromethorphan (100% mean 9.27 y ± 1.73) 	<ul style="list-style-type: none"> Methylphenidate (22) Methylphenidate and dextromethorphan (22) 	ADHD symptoms	“Although our results had suggested that DM [dextromethorphan] may potentially have negative effects when combined with MPH [methylphenidate] on the treatment of children with ADHD it had improved symptoms including withdrawn/depression and thought problems of children. Further studies on the long-term effects and efficacy of the DM added on therapy with MPH incorporating serum cytokines changes should be investigated in larger groups of children with ADHD.”
Indication 4: Diabetes mellitus					
Stirban et al, 2014, Germany ³⁴	Randomized double blind crossover study	20 Patients with type 2 diabetes (100% mean 59 y range 46-66)	<ul style="list-style-type: none"> Amantadine (20) Dextromethorphan (20) 	Glycemic excursions	“DXM [dextromethorphan] in contrast to AMT [amantadine] significantly stimulated insulin secretion and at a higher dose also reduced postprandial glycemic excursions.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 5: Emergence agitation					
Abdelmawgoud and Mohy, 2012, Egypt ¹¹	Randomized double-blind study	120 Patients undergoing adenotonsillectomy <ul style="list-style-type: none"> Dextromethorphan (60.5% mean 6.5 y ± 1.7) Ketamine (53.8% mean 6.6 y ± 1.5) Placebo (61.5% mean 6.4 y ± 1.5) 	<ul style="list-style-type: none"> Dextromethorphan (40) Ketamine (40) Placebo (40) 	Child separation and cooperation at induction; state of emergence on admission to post anesthesia care unit using emergence agitation scale; number of patients who required postoperative fentanyl to control agitation	“We concluded that oral premedication with either dextromethorphan 1 mg/kg or ketamine 5 mg/kg were comparable in reducing significantly the incidence of postoperative sevoflurane related emergence agitation in comparison to placebo treated group without reported side effects in children under-going adenotonsillectomy and ketamine premedication improved child separation from parents and face mask application at induction with slight prolongation of extubation emergence and anesthesia durations when compared to both dextromethorphan and placebo treated groups.”
Indication 6: Endothelial dysfunction					
Liu et al, 2008, Taiwan ²⁷	Randomized double-blind clinical trial	40 Healthy habitual smoking volunteers <ul style="list-style-type: none"> Dextromethorphan (100%, mean 31.6 y ± 0.2) Placebo (100%, mean 31.5 y ± 1.4) 	<ul style="list-style-type: none"> Dextromethorphan (20) Placebo (20) 	Flow-mediated dilation; inflammatory and oxidative markers	“Our study suggests that a 6-month treatment with DM [dextromethorphan] can improve endothelial function and attenuate vascular oxidative stress and inflammation markers in habitual smokers.”
Indication 7: Huntington's disease					
Walker and Hunt, 1989, US ¹⁰⁴	Open label trial	11 Patients with Huntington's disease (36.6%, range 19-67 y)	<ul style="list-style-type: none"> Escalating doses of dextromethorphan polisitirex (11) 	Shoulson Score; quantitative neurologic examination; videotaping; neurophysical tests and timed tests	“Although not beneficial symptomatically further trials of dextromethorphan as protective therapy in HD [Huntington's disease] may be warranted.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 8: Methotrexate encephalopathy					
Coker et al, 2017, US ¹⁶	Case report	24-Year-old male and 65-year-old female with methotrexate encephalopathy due to treatment of hematological malignancies	<ul style="list-style-type: none"> • Oral dextromethorphan (2) 	Resolution of encephalopathy	“These two cases suggest that N-methyl d-aspartate receptor activation by homocysteine may play an important role in the pathogenesis of methotrexate neurotoxicity.”
Rogers et al, 2017, US ¹⁵	Case report	18-Year-old female patient with previously diagnosed acute lymphoblastic leukemia	<ul style="list-style-type: none"> • Dextromethorphan (1) 	Symptom report	“It is important to diagnosis identify and facilitate the administration of the correct antidote in a timely fashion because it provides symptomatic relief in this population.”
Sessions and Streitz, 2015, US ³³	Case report	19-Year-old female patient with T-cell acute lymphoblastic leukemia	<ul style="list-style-type: none"> • Leucovorin, oral dextromethorphan (1) 	Symptom resolution	“MTX [methotrexate] is a mainstay of the treatment of ALL [acute lymphoblastic leukemia]; however severe neurotoxicity can occur even in the absence of overdose. Dextromethorphan should be considered in patients presenting with MTX neurotoxicity. Agonism of NMDA receptors by dextromethorphan may prevent homocysteine induced neuronal apoptosis.”
Yadav et al, 2018, US ⁴⁶	–	26-Year-old female with methotrexate-induced leukoencephalopathy	<ul style="list-style-type: none"> • Dextromethorphan and folinic acid (1) 	Resolution of symptoms	“Restricted diffusion in the centrum semiovale is one of the commonest findings in MTX [methotrexate] induced leukoencephalopathy and is often reversible. Pathogenesis is thought to be related to altered folate homeostasis. An elevated level of homocysteine has been seen in plasma and cerebrospinal fluid with intrathecal MTX. Homocysteine is an N-methyl-d-aspartate (NMDA) receptor agonist. Dextromethorphan, a NMDA antagonist has shown improvement.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 9: Neuroprotection					
Schmitt et al, 1997, Switzerland ¹⁰¹	Pilot study	13 Patients undergoing cardiac surgery with cardiopulmonary bypass requiring protection against perioperative brain injury (61.5%, range 3-35 months)	Nasogastric tube administration of either: <ul style="list-style-type: none"> • Dextromethorphan (6) • Placebo (7) 	Occurrence of brain injury	“Good resorption and the excellent tolerance of orally administered dextromethorphan during cardiac surgery with CPB [cardiopulmonary bypass] encourage further studies.”
Indication 10: Nonketotic hyperglycinemia (NKH)					
Alemzadeh et al, 1996, US ⁷³	Case report	10-Month-old male with NKH	<ul style="list-style-type: none"> • Dextromethorphan (1) 	Seizure occurrence, resolution of horizontal nystagmus, improvement of eye contact and interactive behavior	“This case suggests that low-dose DM [dextromethorphan] treatment should be studied further in patients with NKH, perhaps with measurement of the DM metabolic product.”
Arnold et al, 1997, US ¹⁴	Case reports	29-Day-old female and 9-year-old female with NKH	<ul style="list-style-type: none"> • Dextromethorphan (2) 	Seizures	“Our experience with DM [dextromethorphan] in NKH supports the findings of recent investigators and thus suggests a role for this compound as a potential anticonvulsant agent in patients with this disease. Clinicians should consider the plasma concentrations of both DM and DX [dextrophan] since their accumulation to levels far in excess of those associated with the antitussive action of DM could potentially produce adverse effects.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bjoraker et al, 2016, Australia and US ¹⁵ Swanson et al, 2013, Australia and US ³⁶	–	8 Patients with attenuated NKH (62.5%, range 1 year and 2 months – 9 years)	Sodium benzoate and dextromethorphan either: <ul style="list-style-type: none"> • Treated late for the first child diagnosed (4) • Treated early for the second child diagnosed (4) 	Neurodevelopmental measures	“Early treatment with dextromethorphan and sodium benzoate sufficient to normalize plasma glycine levels is effective at improving outcome if used in children with attenuated disease with mutations providing residual activity and when started from the neonatal period.”
Gabis et al, 2001, US ¹¹³	Case report	2-Month-old male with NKH	<ul style="list-style-type: none"> • Sodium benzoate and dextromethorphan (1) 	Brain glycine levels, occurrence of seizures, myoclonic jerks, opisthotonos	“CSF [cerebrospinal fluid] measurement of amino acids remains the gold standard for the diagnosis of NKH. MRS [magnetic resonance spectroscopy] can provide additional information of biochemical changes in the brain tissue, which may not be represented in the body fluids.”
Hall and Ringel, 2004, US ²²	Case report	42-Year-old female with NKH crisis presenting as severe chorea and encephalopathy	<ul style="list-style-type: none"> • Dextromethorphan and sodium benzoate (1) 	Mental status, chorea occurrence	“Once benzoate and dextromethorphan were initiated, the patient's mental status and chorea improved, suggesting that reversing the metabolic derangement is vital to management in these patients. She was discharged shortly thereafter to assisted living and her mental status and dyskinesias had improved to baseline at her 1-month follow-up appointment. This case illustrates the importance of recognizing this syndrome and promptly initiating appropriate therapy.”
Hamosh et al, 1998, US ⁸⁵ Hamosh et al, 1992, US ⁸⁶	Case report	4 Patients with NKH (75%, range 2 days – 6 years)	<ul style="list-style-type: none"> • Benzoate and dextromethorphan (4) 	Child development, seizure occurrence	“Additional studies of these agents on more patients and perhaps a blinded placebo-controlled trial will be necessary to ascertain what proportion of patients respond to benzoate and DM [dextromethorphan] and to what extent.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Lin et al, 2006, US ¹¹⁴	Case report	8-Year-old male with NKH	<ul style="list-style-type: none"> Combinations including dextromethorphan, sodium benzoate, folic acid, phenobarbital, clonazepam, diphenhydramine, and a low-protein diet (1) 	Reduction in seizures	“Although we know of no link between glycine and serotonin metabolism, and our patient had low, rather than high, central and peripheral serotonin, this case might represent a novel infantile disorder that affects both the glycine and serotonin neurotransmitter systems.”
Tsao et al, 2005, US ³⁸	Clinical report	25.5-Month-old female with Cri du chat syndrome associated with infantile spasms, hypsarrhythmia, NKH, and heterotopia	<ul style="list-style-type: none"> Sodium Benzoate and dextromethorphan (1) 	Wakefulness and infantile spasms	“Since treatment with sodium benzoate and dextromethorphan at age 25½ months, her wakefulness and infantile spasms have improved dramatically with more than 90% reduction of infantile spasms.”
Indication 11: Opioid withdrawal					
Cornish et al, 2002, US ¹¹²	Randomized double-blind placebo-controlled safety study	15 Methadone-maintained inpatients <ul style="list-style-type: none"> Dextromethorphan hydrobromide (100% mean 45.1 y ± 6.1) Placebo (100% mean 42.8 y ± 2.7) 	<ul style="list-style-type: none"> Dextromethorphan hydrobromide (10) Placebo (5) 	Adverse events	“In sum the present study demonstrates that DM [dextromethorphan HBr] is generally well-tolerated by methadone-maintained opiate-dependent individuals. Although not requiring clinical intervention the levels of BP [blood pressure] and HR [heart rate] reached by peak responders suggest that future studies closely monitor cardiovascular changes when high-dose DM is administered. DM did produce far more self-reports of adverse events than did placebo. However the nature of these events (sedation, euphoria, gastric upset) was consistent with the idea that DM may serve to reduce tolerance development during methadone treatment. Further exploration of this possibility appears warranted.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Lin et al, 2014, Taiwan ⁹²	Double-blind, randomized, placebo-controlled clinical trial	65 Patients going through heroin withdrawal requiring detoxification (96.9%, mean 35.7 y ± 8.8)	Clonidine plus either: <ul style="list-style-type: none"> • Dextromethorphan (33) • Placebo (32) 	Symptoms of withdrawal	“We suggest that dextromethorphan has some beneficial effect in attenuating the severity of opioid withdrawal symptoms and can be used as an adjunction medication in the treatment of opioid withdrawal, whereas the exact efficacy needs further investigation.”
Oliveto et al, 2004, US ⁹⁶	—	17 Opioid-dependent volunteers maintained on methadone (59%, range 24-51 y)	<ul style="list-style-type: none"> • Subjects were trained to discriminate naloxone injected intramuscularly into the upper arm from placebo (vehicle) under an instructed novel-response discrimination procedure (17) • Subjects were exposed to naloxone and placebo twice each in a randomized order and had to meet an accuracy criterion of ≥ 80% correct responding on four consecutive sessions in order to enter the testing phase of the study (17) • Dose-effect curves for isradipine and dextromethorphan, each alone and in combination with the training dose of naloxone, were determined (12)* <p>*5 patients discontinued from the study due to noncompliance with study protocols or elevated liver function tests</p>	Correct responding as a result of learned discrimination between naloxone and placebo	“In summary the calcium channel blocker isradipine but not the NMDA receptor antagonist dextromethorphan blocked the discriminative stimulus and self-reported effects of naloxone in methadone-maintained humans trained to discriminate naloxone from placebo under a novel-response discrimination procedure.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Salehi et al, 2011, Iran ¹⁰⁰	Double-blind randomized clinical trial	72 Patients with a history of opiate abuse undergoing methadone maintenance therapy <ul style="list-style-type: none"> • Dextromethorphan (100%, mean 31.6 y ± 6.9) • Placebo (100%, mean 30.9 y ± 7.2) 	<ul style="list-style-type: none"> • Dextromethorphan (36) • Placebo (36) 	Methadone consumption dosage, quality of life, and withdrawal symptoms	“Although DM [dextromethorphan] might be useful for opioid dependence treatment results of the current study did not reveal any statistically significant differences. Therefore, further studies exploring this possibility are needed.”
Indication 12: Pain					
Abu-Samra and Ismaeil, 2009, Saudi Arabia ¹²	Prospective double blind randomized controlled study	80 Patients undergoing nasal surgery <ul style="list-style-type: none"> • Dextromethorphan (65.8%, mean 28 y ± 11) • Placebo (71.1%, mean 26 y ± 10) 	<ul style="list-style-type: none"> • Dextromethorphan (40) • Placebo (40) 	Post-operative pain, pain during pack removal, post-operative morphine requirement	“In conclusion premedication with DM [dextromethorphan] has a beneficial effect on postoperative pain following nasal surgery leading to reduction of opioid requirements in the first postoperative hour and has a marked pain reduction effect during removal of nasal packing. Further studies are needed to clarify the optimum dosage timing and frequency of DM administration preoperatively and if possible to continue its use postoperatively to maintain constant drug blood levels and consequently more beneficial effects.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Alghamdi et al, 2020, US ⁷⁴	Prospective pilot study	10 Patients undergoing adenoidectomy (50%, mean 5 y, range 3-8 y)	<ul style="list-style-type: none"> • Dextromethorphan and acetaminophen plus single intraoperative boluses of dexmedetomidine and ketamine (10) 	Post-operative pain and other analgesic requirements	<p>“Based on the findings of this pilot study future studies should focus on continued adaptations and modifications to various non opioid pain techniques with regard to differing dosing timing and medication combinations. More importantly further studies with larger pediatric cohorts are needed to evaluate what types of more painful procedures such as adeno-tonsillectomy and at-risk patients such as those with obesity and obstructive sleep apnea would benefit from an opioid-sparing analgesic approach without compromising pain management while minimizing opioid-related side effects.”</p>
Ali et al, 2008, Iran ⁴⁹	Randomized study	90 Patients undergoing adenotonsillectomy <ul style="list-style-type: none"> • Placebo (50%, mean 7.61 y ± 1.93) • Dextromethorphan (53.3%, mean 7.46 y ± 1.85) • Tramadol (50%, mean 7.53 y ± 1.88) 	<ul style="list-style-type: none"> • Dextromethorphan (30) • Tramadol (30) • Placebo (30) 	Post-operative pain and other analgesic requirements	<p>“The increasing number of day case procedures and a tendency toward early discharge could see an increasing use of tramadol as an intraoperative analgesic and subsequent pain relief in tablet after discharge from hospital but dextromethorphan alone is not sufficient so need combination with another analgesic. However future studies in pediatric anesthesia assessing these potentials are required before these drugs can be recommended for their use. In conclusion we found that tramadol is more suitable than dextromethorphan in reducing postop pain in children undergoing adenotonsillectomy.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
American Society of Anesthesiologists Task Force on Chronic Pain Management, 2010, US ⁴⁸	Practice guideline	Patients with diabetic neuropathy, postherpetic neuralgia, or other neuropathic pain conditions such as phantom limb pain, peripheral nerve injury, or complex regional pain syndrome (CRPS)	<ul style="list-style-type: none"> • NMDA receptor antagonists such as dextromethorphan and memantine 	–	“Randomized, placebo-controlled controlled trials of NMDA receptor antagonists (e.g., dextromethorphan and memantine) are equivocal regarding pain relief for patients with diabetic neuropathy, postherpetic neuralgia, or other neuropathic pain conditions (e.g., phantom limb pain, peripheral nerve injury, and CRPS) (Category C2 evidence). Observational data from these studies indicate that NMDA receptor antagonists provide pain relief for neuropathic pain for assessment periods ranging from 2 to 16 weeks (Category B2 evidence). Consultants, ASA members, and ASRA members agree that NMDA receptor antagonists should be used for neuropathic pain.”
Amiri et al, 2016, Iran ⁷⁵	Randomized double-blind clinical trial	80 Patients undergoing radical neck dissection surgery <ul style="list-style-type: none"> • Combination of pregabalin, acetaminophen, naproxen, and dextromethorphan (55%, mean 49.58 y ± 13.96) • Placebo (47.5%, mean 49.86 y ± 14.59) 	<ul style="list-style-type: none"> • Combination of pregabalin, acetaminophen, naproxen, and dextromethorphan (40) • Placebo (40) 	Postoperative pain and other analgesic requirements	“Using a combination of acetaminophen dextromethorphan naproxen and pregabalin as preemptive analgesia can decrease the need for opioid analgesics and improve pain control for radical neck dissection surgery patients. Further studies are required to establish more definitive guidelines on recommended dosages and choices of agents for preemptive analgesia.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Amiri et al, 2020, Iran ⁷⁶	Double-blind study	60 Patients undergoing a major surgery <ul style="list-style-type: none"> • Second dose (83.3%, mean 55.50 y ± 13.73) • Placebo (73.3%, mean 58.20 y ± 12.67) 	<ul style="list-style-type: none"> • Second dose of pregabalin, acetaminophen, naproxen, and dextromethorphan (30) • Placebo (30) 	Post-operative pain and other analgesic requirements	<p>“To conclude in the current study the PAND [pregabalin acetaminophen naproxen and dextromethorphan] combination was used to pain management. Our results show that preemptive analgesia with a second dose of PAND is an effective method for reducing pain and morphine consumption after surgery. The prerequisite for making preemptive analgesia guidelines is more research in various surgeries.”</p>
Aoki et al, 2006, Japan ¹³	Randomized prospective double-blinded	111 Patients undergoing mandibular third molar extraction <ul style="list-style-type: none"> • Dextromethorphan (48.6%, mean 27.9 y ± 1.3) • Diclofenac (32.3%, mean 28.7 y ± 1.1) • Placebo (32.4%, mean 27.8 y ± 1.5) 	<ul style="list-style-type: none"> • Dextromethorphan (37) • Diclofenac (38) • Placebo (36) 	Postoperative pain relief	<p>“In conclusion compared with the control group patients premedicated with dextromethorphan 30 mg required significantly fewer analgesics for postoperative pain relief without any incidences of adverse effects after unilateral mandibular third molar extraction under local anesthesia.”</p>
Ben Abraham et al, 2002, Israel ⁷⁸	Double-blind crossover trial	3 Postamputation patients with cancer and phantom pain (66.7%, range 35-55 y)	<ul style="list-style-type: none"> • Dextromethorphan (3) • Placebo (3) 	Pain scores	<p>“We thus have demonstrated presumably for the first time the efficacy of oral dextromethorphan at a dosage of 120 to 180 mg daily for the control of phantom pain in 3 patients with cancer. Further clinical trials may determine the optimal clinical dosage and means of identifying the patients most likely to benefit from this therapeutic approach.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ben Abraham et al, 2003, Israel ⁷⁹	Double-blind crossover placebo-controlled trial	10 Postamputation patients with phantom pain (50%, mean 50 y ± 14)	<ul style="list-style-type: none"> • Dextromethorphan (10) • Placebo (10) 	Pain scores	“In conclusion oral DM [dextromethorphan] 120 to 270 mg/day was effective in reducing phantom pain by 50% and did so with no side effects. Further clinical trials are still necessary to refine our understanding of the mechanisms involved and to delineate the best therapeutic regimen of DM that would provide consistent and predictable phantom pain attenuation.”
Bennitz and Bautista, 2016, US ¹⁰⁸	Case report	46-Year-old male with opioid-induced hyperalgesia and allodynia in chronic pancreatitis	<ul style="list-style-type: none"> • Morphine sustained-release, dextromethorphan, and clonidine (1) 	Resolution of allodynia	“Treatment modalities include opioid rotation, buprenorphine, NMDA receptor antagonists (e.g., ketamine, dextromethorphan), methadone, COX-2 inhibitors, and α2 receptor agonists. The treatment of OIH [opioid-induced hyperalgesia] can be time consuming and frustrating. Many patients in pain are reluctant to decrease their narcotic dose, and results may not be seen immediately.”
Carlsson et al, 2004, Norway ⁸⁰	Placebo-controlled double-blind randomized crossover study	15 Patients with post-traumatic neuropathic pain (46.7%, mean 41.1 y ± 12.7)	<ul style="list-style-type: none"> • Dextromethorphan (15) • Placebo (15) 	Pain scores	“In conclusion this study evaluated the analgesic and adverse effects of a single high dose of dextromethorphan. The results suggest that the main metabolite dextrophan is important for the analgesic effect. The adverse effects seem to be dose related and this may limit further use of dextromethorphan. However dextromethorphan may be beneficial for some carefully selected patients. For these individuals an optimum dose to maximize the analgesic effect and minimize the adverse effects would have to be determined.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Chau-In et al, 2007, Thailand ¹⁰⁵	Double-blinded randomized placebo-controlled study	100 Patients undergoing transabdominal hysterectomy <ul style="list-style-type: none"> • Dextromethorphan (0%, mean 44.62 y ± 6.23) • Placebo (0%, mean 45.48 y ± 8.28) 	<ul style="list-style-type: none"> • Dextromethorphan (50) • Placebo (50) 	Post-operative pain and other analgesic requirements	“Several studies suggest that DEX [dextromethorphan] has an analgesic effect for neuropathic pain; notwithstanding acute postoperative pain might differ from inflammatory or neuropathic pain. Our placebo-controlled study showed a statistically significant improvement in analgesic effect only during the intraoperative period and in the PACU [post-anesthesia care unit] when using low doses of the NMDA receptor antagonist DEX before and after surgery in patients undergoing abdominal hysterectomy.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Choi et al, 2003, Canada ⁵¹	Prospective randomized double-blind study	<p>123 Patients undergoing Caesarian section under spinal anesthesia</p> <ul style="list-style-type: none"> • Morphine 0.05 mg and placebo (0%, mean 36 y, range 23-43 y) • Morphine 0.05 mg and dextromethorphan (0%, mean 34 y, range 26-42 y) • Morphine 0.1 mg and placebo (0%, mean 35 y, range 27-44 y) • Morphine 0.1 mg and dextromethorphan (0%, mean 32 y, range 28-40 y) • Morphine 0.2 mg and placebo (0%, mean 34 y, range 25-41 y) • Morphine 0.2 mg and dextromethorphan (0%, mean 35 y, range 24-42 y) 	<ul style="list-style-type: none"> • Morphine 0.05 mg and placebo (20) • Morphine 0.05 mg and dextromethorphan (20) • Morphine 0.1 mg and placebo (20) • Morphine 0.1 mg and dextromethorphan (20) • Morphine 0.2 mg and placebo (20) • Morphine 0.2 mg and dextromethorphan (20) 	Pain on movement at 48 hours and the incidence of nausea, vomiting and pruritus at 24 hours	“Postoperative pain after Caesarean section under spinal anaesthesia was not reduced by the addition of oral dextromethorphan to a multimodal approach including intrathecal morphine.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Cohen and Abdi, 2002, US ¹⁵⁴	Case report	53-year-old female patient with central pain	<ul style="list-style-type: none"> Dextromethorphan (1) 	Pain scores	“In conclusion this case study describes a woman with symptoms strongly suggestive of CP [central pain] who was noted to have multiple giant cerebral venous malformations contralateral to her pain complaints. It is the first reported association between venous malformations and CP. In view of our patient’s response to dextromethorphan this case underscores the need for further evaluation of NMDA antagonists in this disorder.”
Cohen et al, 2004, US ¹⁰⁹	–	25 Patients with neuropathic pain (40%, mean 46.0 y ± 15.9)	<ul style="list-style-type: none"> Ketamine and dextromethorphan (25) 	Pain scores	“Based on these results we conclude that an IV [intravenous] ketamine test may be useful in predicting response to oral DX [dextromethorphan]. More research is needed to determine the ideal candidates for such a test and the optimal dose and cutoff value for the response to ketamine.”
Cohen et al, 2006, US ⁸²	–	34 Patients with fibromyalgia (11.8%, mean 44.2 y ± 9.9)	<ul style="list-style-type: none"> Intravenous ketamine test before oral dextromethorphan (34) 	Pain score	“Thus, although the data from this pilot study provide preliminary evidence supporting the use of an IV [intravenous] ketamine test in FM [fibromyalgia], prospective, double-blind outcome trials are needed to confirm the validity of the test and assess the long-term response to oral DX [dextromethorphan] in this syndrome.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Cohen et al, 2007, US ¹¹⁰	Case report	34-Year-old male and 57-year-old male with postamputation pain	<ul style="list-style-type: none"> • Epidural steroid injection with triamcinolone and ropivacaine (1) • Dextromethorphan, calcitonin nasal spray, right translaminar C5-C6 epidural steroid injection and right C5 selective nerve block (1) 	Pain score	<p>“These two cases share several common characteristics. First, both patients experienced pain in dermatomes that were no longer innervated after the amputation, a feature consistent with phantom limb pain. Second, in each case postamputation pain was superimposed on an underlying pathologic condition. Third, both cases responded well to treatment intended for the pre-existing medical condition, which in this case included ESI. For both acute radiculopathy and postherpetic neuralgia, neuraxial steroids have been shown to be an effective treatment in selected patients.”</p>
Cohen et al, 2009, US ¹¹¹	–	56 Patients with recurrent pain (48.2%, mean 47.6 y ± 15.3)	<ul style="list-style-type: none"> • Ketamine and dextromethorphan (56) 	Pain scores	<p>“Based on these results we conclude that an i.v. [intravenous] ketamine test may be a valuable tool in predicting subsequent response to DX treatment in opioid-exposed patients with persistent pain.”</p>
Compton et al, 2008, US ⁵²	Placebo-controlled randomized clinical trial	<p>40 Patients with hyperalgesia</p> <ul style="list-style-type: none"> • Dextromethorphan (50%, mean 50.54 y ± 7.23) • Placebo (55%, mean 45.94 y ± 6.15) 	<ul style="list-style-type: none"> • Dextromethorphan (18) • Placebo (22) 	Pain response	<p>“In conclusion these data do not support that ongoing NMDA [N-methyl-D-aspartate]-receptor antagonist therapy as provided by DEX [dextromethorphan] and under the dosing conditions evaluated reduces or mitigates [opioid-induced hyperalgesia] in MM [methadone-maintenance] patients and may in fact worsen pain responses in female patients. As noted these negative findings are not inconsistent with an increasing literature on the lack of clinical efficacy of the NMDA antagonist [dextromethorphan] to prevent or reduce [opioid-induced hyperalgesia] which may in part be attributed to its weak antagonist activity at the NMDA receptor.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Dawson et al, 2001, US ¹⁷	Prospective randomized double-blinded placebo-controlled study	40 Patients scheduled for adenotonsillectomy <ul style="list-style-type: none"> • Dextromethorphan and midazolam (38.1%, mean 7.02 y ± 1.98) • Placebo and midazolam (47.3%, mean 7.75 y ± 2.7) 	<ul style="list-style-type: none"> • Dextromethorphan and midazolam (21) • Placebo and midazolam (19) 	Total dose requirement of intravenous morphine within a 6-hour postoperative observation period	<p>“We found dextromethorphan a safe inexpensive non-narcotic agent to be an effective preoperative adjunct in reducing postoperative narcotic analgesia in pediatric adenotonsillectomy. Its benefit within the first 6 hours after surgery is clear and its use for this indication at our hospital has been adopted. The use of this premedication for other pediatric surgical procedures is promising and warrants further investigation.”</p>
Dudgeon et al, 2007, Canada ⁵³	Phase III randomized double-blind placebo-controlled study	65 Cancer patients with pain <ul style="list-style-type: none"> • Slow-release morphine and dextromethorphan (48%, median 59.2 y) • Slow-release morphine and placebo (34%, median 62.1 y) 	<ul style="list-style-type: none"> • Slow-release morphine and dextromethorphan (25) • Slow-release morphine and placebo (27) 	Pain scores	<p>“In summary this trial showed little enhancement of analgesia or modulation of opioid tolerance in cancer patients with pain when DM [dextromethorphan] was added to morphine. This lack of effect was also evident in patients with neuropathic pain and those taking higher doses of morphine. Participants receiving the DM also had more toxicity particularly dizziness. This toxicity and the limited evidence of effect do not support the use of DM to enhance opioid analgesia or to modulate opioid tolerance in cancer patients.”</p>
Entezary et al, 2014, Iran ¹⁸	Double-blind randomized clinical trial	112 Patients who are candidates for arthroscopic surgery <ul style="list-style-type: none"> • Dextromethorphan (66.7%, mean 28.1 y ± 8.6) • Placebo (63.8%, mean 30.2 y ± 7.5) 	<ul style="list-style-type: none"> • Dextromethorphan (54) • Placebo (58) 	Pain scores, use of opioids, first request for analgesics	<p>“The present study results revealed that administration of dextromethorphan can reduce consumption of opioid analgesics compared to the placebo after arthroscopic knee surgery. However this study failed to significantly reduce the incidence of opioid side effects by preoperative consumption of Dextromethorphan in comparison to the placebo.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Faiz et al, 2018, Iran ¹⁹	Double-blind placebo-controlled randomized clinical trial	60 Patients undergoing vitrectomy <ul style="list-style-type: none"> • Placebo (53%, mean 56.6 y ± 3.9) • Dextromethorphan (50%, mean 57.5 y ± 4.7) 	<ul style="list-style-type: none"> • Dextromethorphan (30) • Placebo (30) 	Post-operative pain, sedation	“Prescribing 30 mg dextromethorphan before surgery can reduce postoperative pain in patients with vitrectomy; it also has postoperative sedation effects.”
Fillingim et al, 1998, US ²⁰	Case report	24-Year-old female with generalized allodynia due to repetitive innocuous vibrotactile stimulation in attempt to treat temporomandibular disorder	<ul style="list-style-type: none"> • Dextromethorphan or placebo 1 hour prior to vibratory stimulation session (1) 	Pain	“Administration of the N-methyl-d-aspartate (NMDA) receptor antagonist dextromethorphan (DM), but not vehicle, attenuated the vibration-induced pain at both sites.”
Frymoyer et al, 2007, US ⁵⁴	Double-blind placebo-controlled crossover study	22 Healthy volunteers (36.4%, median 27 y, range 22-52 y)	<ul style="list-style-type: none"> • Dextromethorphan and morphine (11) • Placebo and morphine (11) • Morphine and dextromethorphan (22) • Morphine (22) 	Areas of secondary hyperalgesia to brush and von Frey hair stimulation in both sensitization models and the painfulness of acute thermal noxious stimulation on the upper arm	“Adding dextromethorphan to morphine (1:1 ratio) did not enhance analgesia on measures of experimental cutaneous sensitization and acute noxious thermal stimulation in healthy volunteers. The results differ from preclinical studies but agree with clinical trials. Human experimental models of pain and neuronal sensitization which are responsive to oral opioids allow efficient study of opioid combination analgesics and simplify the process for determining the optimal dose and/or dose ratio.”
Gilron et al, 2000, US ⁸³	Randomized double-blind crossover trial	16 Patients with facial neuralgias (23%, mean 53 y)	<ul style="list-style-type: none"> • Dextromethorphan (19) • Lorazepam (19) 	Pain	“Dextromethorphan shows little or no analgesic efficacy in pain due to possible trigeminal neuropathy and anesthesia dolorosa. Additional trials are necessary to conclusively evaluate the efficacy of NMDA-receptor antagonists in trigeminal neuralgia.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Gordon et al, 1999, US ⁵⁵	Parallel-group double-blind study	75 Patients undergoing surgical removal of impacted third molars <ul style="list-style-type: none"> Dextromethorphan (67%, mean 21.5 y ± 0.6) Placebo (64%, mean 22.0 y ± 0.8) 	<ul style="list-style-type: none"> Dextromethorphan (36) Placebo (39) 	Pain	“The results suggest that DM [dextromethorphan] at maximally tolerated doses does not produce an analgesic effect in the immediate postoperative period but reduces pain at 48 hours. This may be related to antagonism of NMDA receptors necessary for the expression of hyperalgesia associated with noxious afferent input postoperatively.”
Grace et al, 1998, Australia ⁵⁶	Randomized double-blind	40 Patients undergoing laparotomy <ul style="list-style-type: none"> Dextromethorphan hydrobromide (66.7%, mean 51 y, range 25-75) Placebo (63.2%, mean 49 y, range 25-71) 	<ul style="list-style-type: none"> Dextromethorphan hydrobromide (18) Placebo (19) 	Pain scores	“We conclude that the preemptive use of 60 mg of oral dextromethorphan given the night before and again an hour before surgery reduces intraoperative but not postoperative morphine requirements. Any demonstrable effect of dextromethorphan on post-laparotomy analgesia and morphine requirements would probably require at a minimum continuation of drug administration into the postoperative period.”
Gwacham et al, 2020, US ²¹	Retrospective review	3572 Patients undergoing a Cesarean section (0%, age not provided)	<ul style="list-style-type: none"> Multimodal analgesia with a combination of ibuprofen acetaminophen and dextromethorphan (1463) Historical cohort (2109) 	Number of opioid units used, mean morphine equivalent	“Post-operative pain control can be achieved in a majority of patients undergoing CS [cesarean section] without routine use of opioids in a standardized ERAS [enhanced recovery after surgery] pathway.”
Hasan et al, 2004, US ²³	Prospective randomized double-blinded and placebo-controlled study	38 Patients undergoing tympanomastoid surgery <ul style="list-style-type: none"> Dextromethorphan (sex not provided, mean 12.2 y ± 3.4) Placebo (sex not provided, mean 11.5 y ± 3.7) 	<ul style="list-style-type: none"> Dextromethorphan (19) Placebo (19) 	Total amount of intravenous morphine administered in the postoperative period	“Premedication with DM reduces the need for opioid administration in the perioperative period in children undergoing tympanomastoid surgery.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Heiskanen et al, 2002, Finland ⁵⁸	Randomized crossover double-blind placebo-controlled study	20 Patients with chronic pain (75%, mean 51.5 y \pm 2.3)	<ul style="list-style-type: none"> Dextromethorphan (20) Placebo (20) 	Pain scores	“In the present study dextromethorphan pretreatment did not significantly improve short-term morphine analgesia in chronic pain patients as compared with placebo pretreatment. Higher dextromethorphan doses and a different time schedule could possibly have produced more favourable results.”
Henderson et al, 1999, Scotland ²⁴	Double-blinded study	50 Patients undergoing elective total abdominal hysterectomy <ul style="list-style-type: none"> Dextromethorphan (0%, mean 44 y \pm 8) Placebo (0%, mean 42 y \pm 10) 	<ul style="list-style-type: none"> Dextromethorphan (24) Placebo (23) 	Pain scores, analgesic consumption	“Patients given dextromethorphan before and after surgery had a significant reduction in some pain scores at rest but not on movement. There was a trend to lower morphine requirements in the first 24 h. Over the next 48 h oral analgesic usage was significantly reduced.”
Hughes et al, 2002, UK ⁶⁰	Randomized double-blind placebo-controlled three period crossover double dummy design	12 Healthy volunteers (100%, range 21-50 y)	<ul style="list-style-type: none"> Dextromethorphan and ketamine (12) Placebo and ketamine (12) Placebo (12) 	Acute nociceptive thresholds and wind-up of second pain	“There was no effect with either ketamine or dextromethorphan on the acute nociceptive threshold indicating that the acute nociceptive mechanisms were not influenced by the NMDA-modulators ketamine and dextromethorphan.”
Ilkjaer et al, 2000, Denmark ⁸⁷	Double-blind randomized and placebo-controlled study	50 Patients scheduled for non-malignant elective abdominal hysterectomy <ul style="list-style-type: none"> Dextromethorphan (0%, mean 47 y, range 45-49 y) Placebo (0%, mean 46 y, range 44-49 y) 	<ul style="list-style-type: none"> Dextromethorphan (25) Placebo (25) 	Pain scores and hyperalgesia	“In conclusion preoperative oral dextromethorphan 150 mg reduced PCA [patient-controlled analgesia] morphine consumption immediately (0 \pm 4 h) after hysterectomy without prolonged effects on pain or wound hyperalgesia. No side effects were observed compared with placebo. These promising results should be confirmed in studies with continued administration of dextromethorphan into the postoperative period.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ilkjaer et al, 1997, Denmark ⁸⁸	Randomized double-blind placebo-controlled crossover study	24 Healthy volunteers (100%, range 21-28 y)	<ul style="list-style-type: none"> • Dextromethorphan 60 mg (24) • Dextromethorphan 120 mg (24) • Placebo (24) 	Hyperalgesia	“In this study we found dextromethorphan to have a slight but statistically significant inhibitory effect on mechanical allodynia for pinprick in the area of secondary hyperalgesia after a burn injury in humans. There was no effect on heat pain detection thresholds in normal or injured skin on mechanical allodynia for stroke in the area of secondary hyperalgesia or on pain evoked by prolonged heat stimuli.”
Ilkjaer et al, 2000, Denmark ⁶¹	Double-blind placebo-controlled study	<p>100 Patients scheduled for elective termination of pregnancy</p> <ul style="list-style-type: none"> • Placebo (0%, mean 23 y, range 22-31) • Ibuprofen (0%, mean 25 y, range 22-32) • Dextromethorphan (0%, mean 26 y, range 23-31) • Ibuprofen and dextromethorphan (0%, mean 27 y, range 23-32) 	<ul style="list-style-type: none"> • Placebo (25) • Ibuprofen (25) • Dextromethorphan (25) • Ibuprofen and dextromethorphan (25) 	Pain and analgesic requirements	“In conclusion we observed no analgesic effects of oral dextromethorphan 120 mg on pain after surgical termination of labour and no additive analgesic effects when combined with ibuprofen 400 mg. Ibuprofen reduced both VAS pain scores and analgesic consumption compared with placebo.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kale et al, 2020, India ⁸⁹	–	36 Patients undergoing surgical removal of the mandibular third molars <ul style="list-style-type: none"> • Dextromethorphan (58.3%, mean 32.75 y ± 13.83) • Ibuprofen (33.3%, mean 30.92 y ± 6.90) • Placebo (58.3%, mean 32.25 y ± 6.92) 	<ul style="list-style-type: none"> • Dextromethorphan (12) • Ibuprofen (12) • Placebo (12) 	Pain score, number of postoperative analgesics consumed	“The concept of preemptive analgesia is encouraging and should be routinely incorporated into clinical practice wherever possible to better control the postoperative pain. DM [dextromethorphan] is a safe preemptive analgesic agent capable of minimizing the postoperative pain and also the count of postoperative analgesics needed. Further studies on a large scale are however needed to definitively establish the preemptive analgesic effects of this drug in a dental setting.”
Kaupilla et al, 1995, Finland ⁹⁰	Double-blind placebo-controlled crossover study	8 Healthy volunteers (62.5%, range 22-54 y)	<ul style="list-style-type: none"> • Dextromethorphan (8) • Placebo (8) 	Pain scores and thresholds	“Our results indicate that systemically administered dextromethorphan does not attenuate pain at doses that are clinically applicable. It is likely that at higher doses or with more subjects tested at a dose of 200 mg significant pain-attenuating effects by dextromethorphan would be obtained but with unbearable side effects.”
Kawamata et al, 1998, Japan ²⁵	Double-blinded randomized study	36 Patients scheduled for elective bilateral tonsillectomy <ul style="list-style-type: none"> • Controls (58.3%, 31.0 y ± 4.0) • Dextromethorphan 30 mg (58.3%, 36.9 y ± 3.6) • Dextromethorphan 45 mg (58.3%, 32.0 y ± 3.0) 	<ul style="list-style-type: none"> • Controls (12) • Dextromethorphan 30 mg (12) • Dextromethorphan 45 mg (12) 	Postoperative pain relief	“In summary premeditation with oral dextromethorphan 45 mg but not 30 mg reduced postoperative pain not only at rest but also on swallowing after bilateral tonsillectomy. To determine the extent of dextromethorphan's effectiveness for postoperative pain management it is necessary to examine whether post-operative administration is effective and whether larger doses are more effective.”

Author, Year, Country	Study Type^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kemppainen et al, 1997, Finland ⁶²	Double-blind placebo-controlled crossover study	4 Healthy volunteers (100%, range 25-45 y)	<ul style="list-style-type: none"> • Dextromethorphan (4) • Placebo (4) 	Pain scores	“In the present study systemically administered dextromethorphan (100 mg) had no marked effect on tooth-pulp-evoked sensory or reflex responses nor did it attenuate capsaicin-induced pain.”
Kinnman et al, 1997, Sweden ¹⁵⁵	Double-blind study	10 Healthy volunteers (20%, mean 50 y, range 36-62 y)	<ul style="list-style-type: none"> • Placebo (10) • Dextromethorphan (10) 	Pain scale	“The present study calls for further research concerning development of drugs that act on the NMDA receptor. Preferably such drugs should act on the proposed nociceptive neuron-specific subtypes of the NMDA receptors. Clinical use of drugs that are NMDA-receptor subtype specific will probably be less limited by pronounced side effects compared to those induced by currently clinically available NMDA-receptor antagonists.”
Kuiken et al, 2002, The Netherlands ⁹¹	Placebo-controlled randomized crossover study	9 Healthy volunteers (44.4%, median 22 y, range 19-36 y)	<ul style="list-style-type: none"> • Placebo (9) • Dextromethorphan 10 mg (9) • Dextromethorphan 30 mg (9) 	Pain score, nausea, satiation, proximal gastric tone, and gastric compliance	“Dextromethorphan increases the perception of non-painful sensations during gastric distension without altering the perception of pain. Therefore application of dextromethorphan as a visceral analgesic is questionable. Future studies with more specific NMDA receptor antagonist are warranted.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Lin et al, 2004, Taiwan ²⁶	Double-blind study	75 Patients schedule for hemorrhoidectomy <ul style="list-style-type: none"> • Placebo (52%, mean 44.2 y ± 2.7) • Regrow 120 mg (56%, mean 44.9 y ± 3.0) • Regrow 240 mg (48%, mean 43.9 y ± 2.1) 	<ul style="list-style-type: none"> • Placebo (25) • Dextromethorphan 120 mg (25) • Dextromethorphan 240 mg (25) 	Reduction in seizures	<p>“In conclusion the long-acting slow-released DM [dextromethorphan] at the dose of 240 mg provides a preemptive analgesic effect which improves postoperative pain management by decreasing narcotic dose and related side effects with good patient compliance. The DM-related side effects are not observed at this high dose of 240 mg four times a dose suggested by the pharmaceutical company. It is safe to use slow release DM as premedication particularly for day surgery; it diminishes the postoperative pain management. The present results offer an alternative way for the management of postoperative pain in minor and day surgeries.”</p>
Mahmoodzadeh et al, 2009, Iran ⁶³ Mahmmodzadeh et al, 2010, Iran ⁶⁴	Randomized double-blinded and placebo-controlled study	72 Patients scheduled for elective cholecystectomy <ul style="list-style-type: none"> • Dextromethorphan 45 mg (43.5%, mean 48.2 y ± 14.3) • Dextromethorphan 90 mg (41.7%, mean 46.2 y ± 23.2) • Placebo (40.9%, mean 48.3 y ± 14.5) 	<ul style="list-style-type: none"> • Dextromethorphan 45 mg (23) • Dextromethorphan 90 mg (24) • Placebo (22) 	Pain score, morphine consumption, time for first morphine injection	<p>“Dextromethorphan 45 mg and 90 mg administrated orally two hours before surgery had no effect on postoperative morphine requirement or pain intensity.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Martin et al, 2019, France ²⁸	Randomized double-blind placebo-controlled crossover study	23 Healthy volunteers (100%, age not provided)	<ul style="list-style-type: none"> • Dextromethorphan (20) • Placebo (20) 	Antihyperalgesia, calculated with the area under the curve of the percentage change in mechanical pain threshold	“This study shows that low-dose (30-mg) dextromethorphan is antihyperalgesic in humans on the areas of primary and secondary hyperalgesia and reverses peripheral and central neuronal sensitization. Because dextromethorphan had no intrinsic antinociceptive effect in acute pain on healthy skin N-methyl-D-aspartate receptor may need to be sensitized by pain for dextromethorphan to be effective.”
Martin et al, 2019, France ²⁹	Randomized control trial	60 Patients that had received a ketamine infusion for refractory neuropathic pain <ul style="list-style-type: none"> • Dextromethorphan (20%, mean 50.6 y, range 34-72 y) • Memantine (55%, mean 51.7 y, range 37-77 y) • Placebo (40%, mean 52.6 y, range 32-73 y) 	<ul style="list-style-type: none"> • Dextromethorphan (20) • Memantine (20) • Placebo (20) 	Pain intensity at 1 month	“Oral dextromethorphan temporarily extended ketamine pain relief over one month and future studies should include larger populations and pharmacogenetics screening. Cognitive-affective dimensions were improved with dextromethorphan and memantine suggesting these drugs could help patients to establish pain-coping strategies.”
McConaghy et al, 1998, UK ⁶⁵	Randomized double-blind placebo-controlled study	60 Patients undergoing total abdominal hysterectomy <ul style="list-style-type: none"> • Dextromethorphan (0%, mean 45 y, range 30-58 y) • Placebo (0%, mean 45 y, range 37-63 y) 	<ul style="list-style-type: none"> • Dextromethorphan (27) • Placebo (26) 	Pain scores, postoperative morphine consumption	“In summary we have shown that the perioperative use of the NMDA antagonist dextromethorphan did not offer any benefit to patients undergoing abdominal hysterectomy within the confines of the study methodology.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
McQuay et al, 1994, UK ⁶⁶	Double-blind randomized controlled crossover trial	19 Patients with chronic neuropathic pain (60%, mean 57.6 y, range 28-80 y)	<ul style="list-style-type: none"> Dextromethorphan and placebo (19) 	Pain intensity, pain relief, adverse effects, mood, sleep, and global rating of treatment	"Dextromethorphan at either 40.5 or 81 mg daily did not relieve neuropathic pain."
Mecoli and McSoley, 2017, US ¹⁰⁶	Case report	23-Year-old female patient with epidermolysis bullosa scheduled for cancer-related foot amputation	<ul style="list-style-type: none"> Continuous peripheral femoral and sciatic nerve blockade with gabapentin, dextromethorphan, acetaminophen, and breakthrough oxycodone (1) 	Controlled pain, no residual skin breakdown or blistering at catheter sites	"Our case demonstrates the effectiveness of continuous peripheral nerve blockade as a viable option for postoperative pain control in a patient with EB [epidermolysis bullosa]. With attention to skin assessment careful catheter securement and vigilant site monitoring this technique can be safely utilized in these complex patients."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Mercadante et al, 1998, Italy ⁶⁷	Open-label randomized trial	<p>60 Cancer patients with pain</p> <p>Group 1:</p> <ul style="list-style-type: none"> • Dextromethorphan (50%, mean 62.5 y) • Conventional treatment (60%, mean 62.7 y) <p>Group 2:</p> <ul style="list-style-type: none"> • Dextromethorphan (60%, mean 63.4 y) • Conventional treatment (50%, mean 63.7 y) <p>Group 3:</p> <ul style="list-style-type: none"> • Dextromethorphan (50%, mean 63.9 y) • Conventional treatment (50%, mean 60.9 y) 	<p>Group 1: Patients treated with non-steroidal anti-inflammatory drugs requiring the next step of the analgesic ladder (opioids) received:</p> <ul style="list-style-type: none"> • Dextromethorphan for 2 days, then conventional treatment consisting of dextropropoxyphene if poor pain control (10) • Conventional treatment (10) <p>Group 2: Patients treated with opioids for moderate pain and needed strong opioids received:</p> <ul style="list-style-type: none"> • Dextromethorphan for 2 days, then conventional treatment consisting of morphine if poor pain control (10) • Conventional: conventional treatment (10) <p>Group 3: Patients on morphine therapy who required an increase in dose received:</p> <ul style="list-style-type: none"> • Dextromethorphan for 2 days, then conventional treatment consisting of increase of morphine dose if poor pain control (10) • Conventional treatment (10) 	Pain intensity, symptom intensity, opioid escalation index	<p>“These observations are the first on the use of DM [dextromethorphan] in cancer pain. Despite the potentially useful role derived from experimental work no clinical advantage could be found when DM at doses of 90 mg daily was combined with the drugs of the analgesic ladder.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Mueller et al, 2021, US ⁶⁸	Longitudinal single-blind placebo-controlled pilot trial	14 Patients with fibromyalgia (0%, range 23-65 y)	<ul style="list-style-type: none"> • Placebo and dextromethorphan (14) 	Symptom report	<p>“In this pilot study we did not find strong evidence to support DXM [dextromethorphan] as an important treatment for FM [fibromyalgia]. Future studies exploring DXM as a treatment for chronic pain may consider different dosages and dosing schedules. This study does not change guidance to clinicians on treating FM. Experimental medications including DXM should not be used as a first-line treatment due to the limited amount of evidence that currently supports their use in these populations. Considerably more research would need to be conducted before DXM can be considered as a viable FM treatment option.”</p>
Naeem et al, 2016, Saudi Arabia ⁶⁹	Double-blind randomized controlled trial	36 Patients requiring analgesia <ul style="list-style-type: none"> • Dextromethorphan (56.3%, median 9.7 y) • Placebo (76.9%, median 5.54 y) 	<ul style="list-style-type: none"> • Dextromethorphan (16) • Placebo (13) 	Pain scores	<p>“Dextromethorphan has no effect on opioid requirement for control of acute pain in children admitted with acute critical care illness in PICU [pediatric intensive care unit] ... In the future we suggest a randomized controlled trial using higher doses of dextromethorphan preferably administered intravenously.”</p>
Nelson et al, 1997, US ⁹⁵	Randomized double-blind crossover study	14 Patients with diabetic neuropathy (76.9%, median 54 y, range 35-75 y) 13 Patients with postherpetic neuralgia (84.6%, median 65 y, range 40-74 y)	Patients in each group had a washout period of 1 week before crossover to the second arm of study <ul style="list-style-type: none"> • Dextromethorphan (27) • Placebo (27) 	Global pain relief scale	<p>“The results of this study suggest that dextromethorphan may be effective for the treatment of painful diabetic peripheral neuropathy... Until this result is confirmed in additional studies, however, we cannot recommend widespread use of high-dose dextromethorphan for chronic neuropathic pain particularly since the drug is sold in combination with many other ingredients.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
<p>Nosotti et al, 2014, Italy³⁰</p> <p>Nosotti et al, 2015, Italy³¹</p>	<p>Randomized double-blinded placebo-controlled study</p>	<p>395 Thoracotomy patients receiving preoperative or postoperative intercostal block with levobupivacaine</p> <ul style="list-style-type: none"> • Group A (54%, mean 59 y ± 11.1) • Group B (56.5%, mean 60.1 y ± 11.1) • Group C (59.8%, mean 61.5 y ± 10.2) • Group D (61%, mean 57.2 y ± 13.5) 	<ul style="list-style-type: none"> • Group A: Dextromethorphan (99) • Group B: Placebo (99) • Group C: Placebo (97) • Group D: Placebo (100) 	<p>Morphine consumption, pain intensity on pain scale</p>	<p>“In conclusion our results demonstrate that preoperative use of dextromethorphan associated with intercostal nerve block with levobupivacaine for thoracotomy patients provides preventive analgesic effects decreasing postoperative analgesic consumption.”</p>
<p>Olesen et al, 2007, UK¹⁰⁷</p>	<p>Single-center, double-blind, randomized, three-way cross-over study</p>	<p>20 Healthy volunteers receiving treatment for experimental muscle and skin pain (60%, range 22.5–27.7 y)</p> <p>18 Volunteers completed the study</p>	<ul style="list-style-type: none"> • Paracetamol plus dextromethorphan (18) • Paracetamol (18) • Placebo (18) 	<p>Pain score</p>	<p>“The acute pain models were not sufficiently sensitive to detect an analgesic effect of paracetamol or the combination with dextromethorphan. The selected dose of dextromethorphan was low as the aim was to use commonly used doses, and a higher dose of dextromethorphan is most likely needed to attenuate the selected pain measures.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Plesan et al, 2000, Sweden ⁹⁷	Double-blind crossover and randomized study	19 Healthy volunteers (47%, range 19-43 y)	<p>Experiments carried out on 9 different occasions for each subject with at least 1 week between tests:</p> <ul style="list-style-type: none"> • Run-in (19) • Oral placebo (19) • Oral dextromethorphan 30 mg (10) • Oral dextromethorphan 90 mg (10) • Intravenous ketamine (10) • Intravenous morphine (19) • Oral dextromethorphan 30 mg + intravenous morphine (19) • Oral dextromethorphan 90 mg + intravenous morphine (19) • Intravenous ketamine + morphine (10) 	Pain on visual analog scale	<p>“In conclusion oral DEX [dextromethorphan] in doses of 30 and 90 mg in single treatment does not reduce experimental ischemic pain. The addition of DEX to MO [morphine] did not further improve MO-induced analgesia. Further studies are warranted in other pain modalities as well as in models allowing for longer exposure to the drug before final evaluation of the analgesic effects of DEX.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Price et al, 1994, US ⁹⁸	Double-blind quasi-random crossover experiment	6 Healthy volunteers (100%, range 22-51 y)	Four sessions with different doses of dextromethorphan: <ul style="list-style-type: none"> • Oral vehicle only (control, 6) • Oral dextromethorphan 15 mg (6) • Oral dextromethorphan 30 mg (6) • Oral dextromethorphan 45 mg (6) 	Reduction in temporal summation of second pain, intensity of first and second pain according to visual analog score	<p>“These results clearly demonstrate that oral doses of DM [dextromethorphan] selectively reduce slow temporal summation of electrically and thermally evoked second pain in a dose-dependent manner. These effects are selective in that only temporal summation of second pain and not the magnitude of first pain or the magnitude of second pain evoked by the first (or a single) stimulus is reduced by DM. That DM reduced only temporal summation of second pain and not the magnitudes of first or second pain in general further distinguishes effects of NMDA [N-methyl-D-aspartate] antagonists such as DM from those of morphine.”</p>
Rafiei et al, 2012, Iran ⁹⁹	Double-blind randomized clinical trial	60 Patients scheduled for bilateral tonsillectomy <ul style="list-style-type: none"> • Oral dextromethorphan (45%, mean 40.6 y ± 6.6) • Gargling dextromethorphan (60%, mean 39.7 y ± 6.7) • Placebo (50%, mean 41.8 y ± 4.3) 	<ul style="list-style-type: none"> • Oral dextromethorphan (20) • Gargling dextromethorphan (20) • Placebo (20) 	Pain-free period, severity of post-operative pain at rest and during swallowing saliva (Visual Analog Scale score), satisfaction after 24 hours, adverse effects	<p>“Preemptive analgesia by eating or gargling dextromethorphan can effectively attenuate post-operative tonsillectomy pain.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Rose et al, 1999, US ⁷⁰	Randomized double-blinded placebo-controlled prospective study	57 Patients scheduled for adenotonsillectomy <ul style="list-style-type: none"> • Placebo (53%, mean 7.9 y ± 1.6) • Dextromethorphan 0.5 (58%, mean 7.8 y ± 1.7) • Dextromethorphan 1.0 (42%, mean 7.9 y ± 1.6) 	<ul style="list-style-type: none"> • Placebo (19) • Dextromethorphan 0.5 mg/kg (19) • Dextromethorphan 1.0 mg/kg (19) 	Pain scores	“In conclusion dextromethorphan 0.5 and 1.0 mg/kg PO [orally] administered 1 h before adenotonsillectomy in 6- to 12-yr-old children whose general anesthetic was supplemented with morphine 0.075 mg/kg IV [intravenous] and acetaminophen 25–35 mg/kg PR [per rectum] had no effect on postoperative morphine requirements pain and behavior scores or parental satisfaction with postoperative analgesia in the first 24 h after surgery.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sang et al, 2002, US ³²	Randomized placebo-controlled double-blinded trials Trial 1: Efficacy trial Trial 2: Dose-response trial	44 Patients with neuropathic pain <ul style="list-style-type: none"> Diabetic neuropathy (52%, median 55 y, range 40-64 y) Postherpetic neuralgia (55%, median 69 y, range 36-78 y) 	<ul style="list-style-type: none"> Trial 1: Three period three treatment design comparing maximally tolerated dose of dextromethorphan, memantine, and active placebo (lorazepam) (36*) Trial 2: Four period four treatment design in responders comparing 25, 50, and 100% of maximally tolerated dose of preferred drug from first study to active placebo; preferred drug: <ul style="list-style-type: none"> Dextromethorphan (15) Memantine (2) <p>*19/23 Patients with diabetic neuropathy completed at least 3 weeks of each of the 3 treatments; 17/21 patients with postherpetic neuralgia completed at least 1 week of each of the 3 treatments</p>	Pain relief scale	“Dextromethorphan is effective in a dose-related fashion in selected patients with DN [diabetic neuropathy]. This was not true of PN [postherpetic neuralgia] suggesting a difference in pain mechanisms. Selective approaches to pain-relevant N-methyl-D-aspartate receptors are warranted.”
Sriprajittichai et al, 2009, Thailand ⁷¹	–	66 Patients undergoing laparoscopic surgery (sex, age not provided)	<ul style="list-style-type: none"> Dextromethorphan (not provided) Etoricoxib (not provided) Dextromethorphan and etoricoxib (not provided) 	Morphine used over 24 hours, numerical pain rating scale	“Oral DM [dextromethorphan], 60 mg etoricoxib 120 mg and their combination before LS [laparoscopic surgery] did not alter the 24-hour postoperative morphine consumption significantly. NRS [numerical rating scale] at rest on coughing and other adverse events were not statistically different except dizziness which was less in etoricoxib group.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Suski et al, 2010, Poland ³⁵	Double-blinded placebo-controlled randomized study	60 Patients undergoing spine surgery <ul style="list-style-type: none"> • Placebo (16.7%, mean 16.5 y ± 2.7) • Dextromethorphan (23.3%, mean 15.9 y ± 2.4) 	<ul style="list-style-type: none"> • Placebo (30) • Dextromethorphan (30) 	Pain scale	“In conclusion in young patients subjected to spine surgery addition of dextromethorphan to morphine reduced pain only in early post-operative period. In such patients co-analgesic action of dextromethorphan was not associated with significant changes in plasma levels of morphine metabolites.”
Talakoub and Molaeinasab, 2005, Iran ³⁷	–	40 Patients undergoing elective laparotomy <ul style="list-style-type: none"> • Dextromethorphan (60%, mean 46.2 y ± 15.93) • Placebo (55%, mean 50.45 y ± 14.57) 	<ul style="list-style-type: none"> • Dextromethorphan (20) • Placebo (20) 	Morphine requirement	“Oral dextromethorphan premedication may decrease intra-operative morphine requirement and reduce maximal increase in systolic and mean arterial blood pressure during surgery.”
Verne et al, 2012, US ³⁹	Double-blind placebo-controlled crossover study	23 Patients with irritable bowel syndrome (sex, age not provided)	<ul style="list-style-type: none"> • Dextromethorphan (23) • Diphenhydramine (placebo, 23) 	Pain sensitivity	“The results showed that 1) a subset of IBS [irritable bowel syndrome] patients had increased visceral/cutaneous hypersensitivity following a series of repetitive nociceptive stimuli and that 2) this increased pain sensitivity was blocked by administration of dextromethorphan.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Wadhwa et al, 2001, Australia ⁷²	Prospective randomized double-blinded comparison study	56 Patients undergoing knee surgery <ul style="list-style-type: none"> • Placebo reconstructions (72%, mean 32.9 y) • Placebo replacements (56%, mean 64.4 y) • Dextromethorphan reconstruction (82%, mean 27.7 y) • Dextromethorphan replacements (73%, mean 66.2 y) 	<ul style="list-style-type: none"> • Placebo reconstructions (18) • Placebo replacements (16) • Dextromethorphan reconstruction (11) • Dextromethorphan replacements (11) 	Postoperative pain	<p>“We conclude that increasing orally administered dextromethorphan to near maximum tolerated doses does not provide greater morphine sparing than 20-40 mg given 6-8 hourly as in previous studies. Furthermore, we conclude that dextromethorphan does not improve pain scores in a manner expected of a drug with NMDA antagonist properties.”</p>
Weinbroum, 2002, Israel ⁴⁰	Double-blinded placebo-controlled randomized study	80 Patients undergoing inguinal herniorrhaphy or diagnostic surgical arthroscopy <ul style="list-style-type: none"> • Lidocaine-epidural + placebo (sex not provided, mean 58 y ± 17) • Lidocaine-epidural + dextromethorphan (sex not provided, mean 53 y ± 20) • General anesthesia + placebo (sex not provided, mean 51 y ± 15) • General anesthesia + dextromethorphan (sex not provided, mean 52 y ± 16) 	<ul style="list-style-type: none"> • Lidocaine-epidural + placebo (20) • Lidocaine-epidural + dextromethorphan (20) • General anesthesia + placebo (20) • General anesthesia + dextromethorphan (20) 	Pain score	<p>“We conclude that oral DM [dextromethorphan] 90 mg in patients undergoing surgery under LA [epidural lidocaine anesthesia] or GA [general anesthesia] reduces morphine and diclofenac use by ~50% in the immediate and late postoperative period compared with placebo. Subjectively scored levels of pain sedation and well-being were better as well.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Weinbroum et al, 2003, Israel ⁴¹	Randomized placebo-controlled double-blind study	<p>60 Patients who underwent lower body bone and soft tissue cancer surgery</p> <ul style="list-style-type: none"> • Dextromethorphan (53.3%, mean 50 y ± 21) • Placebo (56.7%, mean 42 y ± 19) 	<ul style="list-style-type: none"> • Dextromethorphan (30) • Placebo (30) 	Pain score, rescue drugs	<p>“A 3-day DM [dextromethorphan] administration is associated with better pain reduction in patients undergoing surgery for bone malignancy under combined general and epidural anesthesia with postoperative PCEA [patient-controlled epidural anesthesia] compared with placebo without increasing side effects.”</p>
Weinbroum et al, 2004, Israel ⁴²	Randomized placebo-controlled double-blinded study	<p>120 Patients who underwent lower body bone and soft-tissue cancer surgery</p> <ul style="list-style-type: none"> • Patient-controlled epidural analgesia (PCEA) + Dextromethorphan (53.3%, mean 50 y ± 21) • PCEA + placebo (56.7%, mean 42 y ± 19) • IV-Patient-controlled analgesia (PCA) + Dextromethorphan (50%, mean 45 y ± 22) • IV-PCA + Placebo (43.3%, mean 47 y ± 17) 	<ul style="list-style-type: none"> • PCEA + Dextromethorphan (30) • PCEA + placebo (30) • IV-PCA + Dextromethorphan (30) • IV-PCA + Placebo (30) 	Pain intensity	<p>“In conclusion oral DM [dextromethorphan] 90 mg given once preoperatively and for 2 additional days postoperatively helped to reduce pain intensity.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Weinbroum et al, 2002, Israel ⁴³	Randomized placebo-controlled double-blind study	<p>75 Patients who underwent surgery for bone and soft tissue malignancies</p> <ul style="list-style-type: none"> • Dextromethorphan 60 mg (60%, mean 43 y +/- 16) • Dextromethorphan 90 mg (60%, mean 42 y +/- 16) • Placebo (56%, mean 41 y +/- 16) 	<ul style="list-style-type: none"> • Dextromethorphan 60 mg (25) • Dextromethorphan 90 mg (25) • Placebo (25) 	Pain intensity	<p>“Dextromethorphan (DM) is associated with reduced pain intensity sedation and analgesic requirements even in patients undergoing surgery for bone and soft tissue malignancies. A 3-day DM administration neither increased the incidence of side effects nor accelerated ambulation and discharge home.”</p>
Weinbroum et al, 2001, Israel ⁴⁴	Prospective double-blind study	<p>30 Patients undergoing laparoscopic cholecystectomy or inguinal hernioplasty</p> <ul style="list-style-type: none"> • Dextromethorphan (53.3%, mean 35 y ± 1) • Placebo (60%, mean 35 y ± 3) 	<ul style="list-style-type: none"> • Dextromethorphan (15) • Placebo (15) 	Pain score	<p>“Compared with placebo DM [dextromethorphan] enabled reduction of postoperative analgesics consumption improved well-being and reduced sedation pain intensity and primary and secondary thermal hyperalgesia.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Weinbroum et al, 2001, Israel ⁴⁵	Random and double-blind study	60 Patients scheduled for inguinal herniorrhaphy or surgical arthroscopy <ul style="list-style-type: none"> Dextromethorphan 60 mg (sex not provided, mean 55 y +/- 8) Dextromethorphan 90 mg (sex not provided, mean 51 y +/- 7) Placebo (sex not provided, mean 59 y +/- 9) 	<ul style="list-style-type: none"> Dextromethorphan 60 mg (20) Dextromethorphan 90 mg (20) Placebo (20) 	Pain score	“In conclusion pre-incisional oral dextromethorphan at doses of 60 or 90 mg reduced the analgesic requirement following lower body surgical procedures under epidural lidocaine anaesthesia both immediately (first 6 h) and for 3 days afterwards.”
Zhou et al, 2011, US ¹¹⁶	Randomized double-blind study	10 Patients with irritable bowel syndrome (IBS) and significant pain (sex, age not provided)	<ul style="list-style-type: none"> Dextromethorphan (10) Placebo (10) 	Sensory experiences, pain scale	“The results of our present study suggest that enhanced temporal summation and central sensitization are chronically present in a subset of IBS patients and that both the summation and the sensitization are blocked by administration of dextromethorphan.”
Indication 13: Pseudobulbar affect (PBA)					
McGrane et al, 2017, US ⁹³	–	57-Year-old female with relapsing-remitting multiple sclerosis presenting with PBA	<ul style="list-style-type: none"> Dextromethorphan (1) 	PBA symptoms	“Taking the available literature together, it is clear that more safety and efficacy data are needed prior to routinely utilizing dextromethorphan/fluoxetine in patients with PBA. Monitoring for nystagmus, diarrhea, nausea, distorted vision, feeling “drunk,” ataxia, dizziness, serotonin syndrome, and other adverse events should be performed when utilizing any combination of dextromethorphan and a CYP2D6 inhibitor.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Morrone et al, 2020, US ⁹⁴	Case	42-Year-old female with PBA	<ul style="list-style-type: none"> Dextromethorphan and bupropion (1) 	Center for Neurologic Study Lability Scale (CNS-LS), Pathological Laughter and Crying Scale (PLCS)	"Further evidence is needed to confirm the efficacy of Dextromethorphan/Bupropion combination for the treatment of PBA. The combination of two inexpensive generics, if proved effective, will also add to cost containment."
Indication 14: Rett syndrome					
Naidu, 2018, US ¹¹⁷	Randomized quadruple-blinding placebo-controlled study	52 Patients who are MECP2 mutation positive <ul style="list-style-type: none"> Dextromethorphan (0%, mean 4.75 y ± 2.52) Placebo (0%, mean 4.91 y ± 1.91) 	<ul style="list-style-type: none"> Dextromethorphan (26) Placebo (26) 	Change in Mullen Scales of Early Learning	Clinical trial, results available on ClinicalTrials.gov, no author's conclusions
Smith-Hicks et al, 2017, US ¹⁰² Gupta et al, 2014, US ⁸⁴	Prospective, randomized, open-label trial	35 Pediatric patients with Rett Syndrome (0%, age not provided)	Dextromethorphan at varying doses: <ul style="list-style-type: none"> 0.25 mg/kg/day (13) 2.5 mg/kg/day (12) 5 mg/kg/day (10) 	Seizure occurrence, clinical severity of Rett Syndrome	"Randomized clinical trials of DM [dextromethorphan] in girls with RTT [Rett syndrome] are rare. Our results demonstrate that DM is not only safe in young children but may be of therapeutic value in the treatment of some core features of RTT. Thus, it seems appropriate to conduct additional trials initiating DM soon after diagnosis in younger patients with RTT."

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 15: Tourniquet-associated hypertension					
Honarmand and Safavi, 2007, Iran ⁵⁹	Randomized double-blind prospective study	75 Patients undergoing lower limb surgery under general anesthesia <ul style="list-style-type: none"> • Dextromethorphan (76%, mean 39.7 y ± 17.1) • Clonidine (76%, mean 31.6 y ± 10.6) • Control (80%, mean 34.1 y ± 12.7) 	<ul style="list-style-type: none"> • Dextromethorphan (25) • Clonidine (25) • Control (25) 	Systolic, diastolic, and mean arterial pressure	“In conclusion, preoperative oral clonidine significantly blunts BP [blood pressure] and HR [heart rate] responses to prolonged tourniquet inflation of the lower limbs under general anaesthesia in ASA I and II patients better than oral DM [dextromethorphan].”
Yamashita et al, 2004, Japan ⁴⁷	Randomized double-blinded prospective study	74 Patients undergoing knee cruciate ligament reconstruction with tourniquet inflation under general anesthesia <ul style="list-style-type: none"> • Dextromethorphan (67.6%, mean 29.6 y ± 9.3) • Placebo (70.3%, mean 28.2 y ± 10.9) 	<ul style="list-style-type: none"> • Dextromethorphan (37) • Placebo (37) 	Blood pressure, heart rate	“In conclusion preoperative oral DM [dextromethorphan] 30 mg significantly attenuated arterial blood pressure and heart rate increases during tourniquet inflation under general anesthesia.”

Abbreviations: –, not provided; ADHD, attention-deficit/hyperactivity disorder; ALS, amyotrophic lateral sclerosis; CRPS, complex regional pain syndrome; NKH, nonketotic hyperglycinemia; NMDA, N-methyl-D-aspartate; PBA, pseudobulbar affect.

^aAs defined by authors.

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

2. Do you prescribe or administer dextromethorphan hydrobromide to your patients?

- Yes
- No

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

- Oral products
- None of the above

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

- Dementia
- Multiple sclerosis
- Muscle pain/spasms
- Traumatic brain injury
- Other (please explain) _____

5. I prescribe or administer dextromethorphan hydrobromide with my patients as the following: (check all that apply)

- FDA-approved drug product
- Compounded drug product
- Over-the-counter drug product
- Other (please explain) _____

6. I use compounded dextromethorphan hydrobromide 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 dextromethorphan hydrobromide
- Other (please explain) _____

7. Do you stock non-patient-specific compounded dextromethorphan hydrobromide at your practice?
- Yes
 - No
 - I'm not sure
8. I obtain compounded dextromethorphan hydrobromide from the following: (check all that apply)
- Compound myself at my practice
 - Have the product compounded by an in-house pharmacy
 - Purchase, or have a patient purchase, from a compounding pharmacy
 - Purchase, or have a patient purchase, from an outsourcing facility
 - Other (please explain) _____
9. What is your practice setting? (check all that apply)
- Physician office/private practice
 - Outpatient clinic
 - Hospital/health system
 - Academic medical center
 - Emergency room
 - Operating room
 - Other (please describe) _____
10. What degree do you hold? (check all that apply)
- Doctor of Medicine (MD)
 - Doctor of Osteopathic Medicine (DO)
 - Doctor of Medicine in Dentistry (DMD/DDS)
 - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
 - Naturopathic Doctor (ND)
 - Nurse Practitioner (NP)
 - Physician Assistant (PA)
 - Other (please describe) _____

Appendix 3.2. Survey instrument for 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

^aAssociations that declined in Year 1 and/or Year 2 were not contacted in Year 3.