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Outpatient Pain Management In Children With Chronic Pancreatitis: A Scoping Systematic Review

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Abstract

Objectives: Although pain management is central to pediatric chronic pancreatitis (CP) care, no evidence-based guidelines exist. In this scoping systematic review, we sought promising strategies for chronic pancreatitis (CP) pain treatment in children.

Methods: We systematically reviewed literature on pain management in children and adults with CP, and two conditions with similar pain courses: juvenile idiopathic arthritis and sickle cell disease.

Results: Of 8997 studies identified, 287 met inclusion criteria. There are no published studies of analgesic medications, antioxidants, dietary modification, integrative medicine, or regional nerve blocks in children with CP. In adults with CP, studies of non-opioid analgesics, pancreatic enzymes, and dietary interventions have mixed results. Retrospective studies suggest endoscopic retrograde cholangiopancreatography and surgical procedures, most durably total pancreatectomy with islet auto-transplant, improve pain for children with CP. Follow-up was short relative to a child's life. Large studies in adults also suggest benefit from endoscopic therapy and surgery, but

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Supplemental Digital Content 1, Appendix: Search terms for systematic scoping review

Supplemental Digital Content 2: Table

lack conclusive evidence about optimal procedure or timing. Studies on other painful pediatric chronic illnesses revealed little generalizable to children with CP.

Conclusions: No therapy had sufficient high-quality studies to warrant untempered, evidence-based support for use in children with CP. Multicenter studies are needed to identify pain management "best practices."

Keywords

pediatrics; chronic pancreatitis; acute recurrent pancreatitis; chronic pain

1. INTRODUCTION

Childhood chronic pancreatitis (CP) is an uncommon but severe condition associated with recurrent hospitalizations, absence from school and social activities, risk of pancreatic failure with exocrine or endocrine insufficiency,[1–3] and diminished health-related quality of life (HRQoL).[4,5] Many of the hospitalizations, and much of the psychosocial burden, associated with CP are the result of pain. This pain may be chronic, daily or may present as intermittent exacerbations.[1] Many children with CP have chronic persistent pain that must be managed in an outpatient setting.

Although guidelines exist for adults, there are no evidence-based or consensus "best practice" guidelines for outpatient pain management in children with acute recurrent pancreatitis (ARP) or CP.[6] The INternational Study group of Pediatric Pancreatitis: In search for a cuRE (INSPPIRE)[7] has successfully developed descriptive studies of childhood ARP and CP, improving our understanding of these conditions, their risk factors, and disease course. As INSPPIRE moves toward interventional studies, a thorough analysis of available evidence on interventions that improve pain for CP, ARP and similar chronic illnesses in the outpatient setting has become critical.

This is a scoping systematic review of evidence-based management of outpatient pain in children with CP.[8,9] A scoping review "map[s] the key concepts underpinning a research area and the main sources and types of evidence available."[10] It aims to examine the extent of existing research and to identify gaps in the existing literature. Scoping reviews are intended to highlight research strategies that might expand our knowledge on the topic of interest but do not include evidence grading or meta-analysis.[8]

To assure that we captured all relevant literature, we reviewed evidence on pain management in children and adults with CP, as well as outpatient pain management of two other childhood chronic pain conditions with similar pain course: juvenile idiopathic arthritis (JIA) and sickle cell disease (SCD).

2. MATERIALS AND METHODS

This review was undertaken within Arskey and O'Malley's five-stage methodological framework: identifying the research question, searching for relevant studies, selecting studies, charting the data, and synthesizing and summarizing results.[10] Our objective was to understand the current state of evidence on treatment of pain in children with ARP and

CP (hereafter referred to as “CP”). Of note, articles generally do not specify pain as arising or not arising from the pancreas, rather most appear to assume chronic abdominal pain is related to the existing CP; we have followed this convention.

In accordance with Methodologic Expectations of Cochrane Intervention Reviews guidelines,[11] we conducted a systematic search utilizing both natural language and controlled vocabulary. The search was executed across seven databases: Medline via PubMed and Ovid, Embase and PsycINFO via Ovid, Cochrane Library via Wiley, Web of Science Core Collection, and Global Index Medicus. A complete search strategy is available (see Supplemental Digital Content 1). No restrictions were placed on year of publication or study design. The search is current to July 2020. Results were compiled and deduplicated in EndNote X7.[12]

Utilizing Rayyan, a web-based literature screening tool,[13,14] all identified titles and abstracts of publications were screened by two independent screeners. Conflicts were resolved through consensus or by a third party where necessary. We included studies that focused on children aged 2 to 18 years old being treated primarily in an outpatient or home setting or receiving procedures to improve pain in the outpatient or home setting that had a diagnosis of CP, ARP, JIA, or SCD. We chose JIA and SCD as comparator conditions given that they are also childhood-onset diseases with acute and chronic pain as main disease symptoms and management targets; we wanted to systematically look for successful pain management interventions in children with JIA or SCD that might be relevant to children with CP.

Included studies had to have pain as a measured outcome. We included studies of adults with CP or ARP being treated primarily in an outpatient or home setting or receiving procedures to improve pain in those settings. Since this was a scoping review intended to assess the volume and quality of existing evidence broadly, we excluded studies with less than 20 subjects for adult studies and less than 10 for pediatric studies; these represented case reports or small case series from which generalizable data on pain management could not be reliably drawn, and we felt that including these would introduce bias. We also excluded studies that focused on patients with acute pancreatitis but not CP; who had chronic pain due to malignancy or post-surgical pain; did not include measures of pain; or did not report original data (opinion pieces, review articles).

Full-text screening was subsequently completed by two independent screeners using the same inclusion and exclusion criteria. Reasons for exclusion were recorded and are reported in the PRISMA flow diagram in Figure 1. Since this is a scoping review without meta-analysis, we discuss potential bias in the “Summary” sections and Discussion but did not quantitatively assess for bias. Data extraction forms were developed and piloted prior to refinement and implementation. All data extraction was completed in RedCap.[15] The scoping review protocol was registered in Open Science Framework.[16] A summary of included articles is provided in Supplemental Table 1.

3. RESULTS

3.1 Analgesic Medications

3.1.1 Analgesic Medications in CP—Twelve articles on the efficacy of analgesic medications for reducing pain and improving HRQoL met inclusion criteria.[17–27] No studies included children with CP. Six studies explored analgesic medications in adults with CP.[18,22–24,26,27]

We identified 3 randomized controlled trials (RCTs) of analgesic medications for CP pain.[22,26,27] Two were double blinded RCTs of pregabalin in adults with CP.[22,26] Olesen et al demonstrated that pregabalin was associated with more effective pain relief after 3 weeks than placebo (36% vs 24%, $P = 0.02$, n = 64 total).[22] Improved health status was achieved more often in the pregabalin group (44% vs 21%, $P = 0.048$). However, function (self-reported in the Brief Pain Inventory) and HRQoL (self-reported by an instrument developed for adults with cancer, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30) were not significantly different between groups.[28,29,22] Of note, almost half of trial participants had CP likely due to alcohol use.

Talukdar et al also reported that pregabalin led to a significantly higher prevalence of complete pain resolution (48%) compared to placebo (27%) in a trial of 87 adults (75% idiopathic CP, 24% alcohol-related).[26] This study also included antioxidants, as reported below.

One small, short, blinded RCT of tramadol vs morphine showed that both medications improved pain in adults with CP (n = 25), with no significant difference in visual analog scale (VAS) pain scores noted between the two groups.[27]

One retrospective analysis suggested that, for adults with CP and chronic opioid use (n = 53), medical cannabis use (n = 34) was associated with reduced daily opioid use, fewer hospitalizations and ED visits although differences were not statistically significant.[18]

3.1.2 Analgesic Medications in Other Chronic Pain Conditions—There is very limited evidence from other chronic pain conditions on the efficacy of analgesic medications that might be considered in treating children with CP. We identified only one study that addressed the efficacy of analgesics for pain management in SCD patients[20] and 3 studies for children with JIA.[17,21,25] In patients with SCD, one small retrospective study (n = 22) showed reduced hospitalizations due to pain with outpatient methadone use.[20] All 3 studies in children with JIA that met our inclusion criteria evaluated naproxen efficacy. In CP, non-steroidal anti-inflammatory drugs are generally avoided given concern for peptic ulcer disease and resultant gastrointestinal bleeding and because ulcer-related epigastric pain could be confused with a CP exacerbation.[30] Naproxen thus does not seem like a promising therapeutic approach for children with CP.[17,21,25]

We did not identify any studies in adults or children that looked at the impact of other analgesics or other opioids, on the outpatient management of chronic pain in CP, JIA,

and SCD. There were no studies of acetaminophen or other NSAIDs, tricyclic or other anti-depressants, topical anesthetics, ketamine, or benzodiazepines.

3.2 Non-analgesic Medications

Many non-analgesic medications have been evaluated to reduce pain in CP. We found 4 studies of pancreatic enzymes to treat pain in CP,[31–34] 9 studies of anti-oxidants,[26, 35–42] and 3 studies of other medications.[43–45] One study retrospectively reviewed outcomes of several different medications prescribed by treating physicians.[46] Most studies were small and open-label interventions. There were few large studies and limited RCTs.

3.2.1 Pancreatic Enzymes (PE)—Theoretically, exogenous PE (PE) are thought to provide negative feedback that inhibits native pancreatic enzyme secretion, reducing their pancreatic damage and pain.[34]

In the only pediatric study of this approach, Chowdhury et al retrospectively reviewed the effect of enteric-coated PE plus acid suppression in 99 children with CP and abdominal pain.[31] More than 95% of patients were categorized as “idiopathic CP;” subjects averaged 2 previous hospital admissions for pain. Of the 57 children who were assessed over a median of 18 months, 56% had subjective pain relief, as determined by their clinician and chart review. Whether any children were pancreatic insufficient, and if that impacted response to PE, was not discussed.

In a double-blind crossover trial in 20 adults with CP (50% alcohol-related), Halgreen et al examined the effect of an enteric-coated microsphere preparation of PE over 4 weeks.[32] No difference was found in pain relief as evaluated by VAS and use of analgesics with PE versus placebo. Patients with steatorrhea did report improvement in stools on PE.

In a longer-term trial, 26 adults with CP (63% alcohol-associated) were randomized to an enteric-coated microsphere preparation of PE or placebo.[33] Over 8 months, with crossover at 4 months, they found no efficacy of long-term PE on pain presence, intensity, duration or use of analgesic.

In a shorter cross-over trial, Mossner et al treated 47 adults with CP with “acid-protected” pancreatic extracts or placebo, for 14 days each.[34] They found no significant difference between PE and placebo in pain during the study (VAS, analgesics used).

In addition, three prospective, open-label studies examined pancreatic enzyme replacement therapy, doses of medication intended to replace exocrine pancreatic insufficiency, EPI) in patients with CP and pancreatic insufficiency. Treatment with PE did improve abdominal pain in these patients, as measured by questionnaires or physician assessment.[47–49]

3.2.2 Antioxidant Therapy—In CP, free radical-induced acinar cell injury is thought to cause oxidative stress. This injury is thought to be driven by pro-oxidant products that overwhelm antioxidant reserves. Theoretically, antioxidant supplements neutralize free radicals and alleviate pain.[50]

Durgaprasad et al examined the effects of 500 milligrams curcumin (an antioxidant) with 5 milligrams piperine (an alkaloid) in relieving pain in 20 adults with tropical pancreatitis-associated CP over 6 weeks.[37] No clinical effect on pain (as measured by VAS) was found, although red blood cell malonyldialdehyde levels (a marker of oxidative stress) were reduced compared to placebo.

Seven placebo-controlled trials examined the efficacy of antioxidants that contained selenium, vitamin C, beta-carotene, vitamin E, and methionine—although formulation and dosing was not uniform across trials. Three found that antioxidants improved pain more than placebo; four found no difference in pain between groups.

In the largest study, Bhardwaj et al performed a placebo-controlled double-blind trial of antioxidants versus placebo in adults with CP over 6 months (n = 127).[35] The antioxidant group had a significant reduction in number of painful days per month and a significantly greater reduction in analgesic dose per month than those taking placebo.

Two smaller, shorter cross-over trial reported benefit, although trial dropout was substantial. Udenet al performed a 20-week double-blind crossover trial in 28 adults with ARP or CP; twenty patients were fully analyzed.[42] Six had an AP attack while on placebo, vs none on antioxidant; pain was reported as improved, but no measures were provided. Kirk et al performed a randomized double-blind 20-week crossover trial of a commercial antioxidant combination product versus placebo in adults with CP.[38] Although 36 enrolled, only 19 completed the study (cause for withdrawal not noted). Those treated with the antioxidants reported improvement in pain (by 36-item Short Form Survey, SF-36)[51] and improvement in functioning.

In a second randomized placebo-controlled trial of antioxidants in 61 adult patients with CP over 3 months,[36] pain reduction and analgesic requirement were not significantly different in the two groups.

Two longer placebo-controlled RCTs reported no benefit of antioxidants during 6-month follow-up. Sirwardenaet al performed a 6-month double-blind, trial in 70 adult patients with CP, predominantly of alcoholic origin.[41] After 6 months, there were no significant differences between the two groups in pain scores (numeric rating scale, Brief Pain Inventory), average daily pain, validated HRQoL measures, opioid use, hospital admissions or outpatient visits. Singhet al examined the effect of antioxidants on development of diabetes in CP, but secondarily examined their impact on pain.[40] They randomized 107 patients to antioxidants or placebo for 6 months. No effect on pain was seen, assessed by VAS, number of pain days, and use of analgesics.

Rupasinghe et al and Siriwardena et al reported the effect of long-term of antioxidant therapy in CP (median, 3.5 years, up to 10 years).[39] In their cohort of 30, with CP predominantly related to alcohol, no difference in opiate use at last recorded visit was noted compared to baseline.

Finally, Talukdar et al examined the combination of antioxidants and pregabalin in ameliorating pain in chronic calcific pancreatitis in a 2 month RCT, followed by a 4-month

open-label study (n = 87).[26] After 2 months, the treatment group had significantly improved pain scores (VAS, Izbicki). A further significant improvement in VAS was seen in both groups during the open-label period.

3.2.3 Other Medications—Vitamin D plays an important role in modulating the immune system by regulating inflammatory cytokines and inhibiting pro-inflammatory cell proliferation.[52] There are no studies of Vitamin D to treat pain in children or adults with CP. In a randomized pilot trial, in children with SCD (n = 32),[53] high-dose vitamin D supplementation led to fewer pain days and higher physical activity HRQoL scores (measured by PedsQL™). In a cross-sectional study Adegokeet al noted that amongst Nigerian children with SCD (n = 123) all of those with low vitamin D levels (n = 14) had pain episodes, compared to 70% of those with normal vitamin D levels ($P = 0.04$).[54]

Trypsin plays a key role in the development of pancreatitis.[55] Chlorophyll and trasylol are tryspin inhibitors. In an open-label study, an intravenous infusion of chlorophyll-a (dose of 5–20 milligrams daily for 1–2 weeks) improved abdominal pain in 66% of adults with CP (n = 34).[44] However, pain was assessed by the research teams' clinical judgement only, and repeated infusions were required.

Shiratori et al performed a multicenter dose-response controlled trial of loxiglumide (a cholecystokinin receptor antagonist) to reduce pain in CP.[43] Patients (n = 207, 110 centers, 45% alcohol-related) were randomized to receive loxiglumide or placebo for 4 weeks. The treated group had a significant improvement in pain compared to placebo, as measured by physician grading of pain on a three-point scale.

Pujahari randomized 121 adults with CP to high-dose omeprazole or no omeprazole; most were males with alcohol-related CP.[45] Pain relief (by VAS) was significantly better in the group receiving omeprazole after 2 weeks (97% vs 68%) and 3 months (96% vs 83%) although this difference disappeared by 1 year (96% vs 94%). After one year on therapy, there was greater weight gain in the omeprazole group.

Mehta et al randomized 50 adults with idiopathic CP or ARP to simvastatin or standard therapy (proton-pump inhibitor with antioxidant) in a single-center, open-label trial.[56] Patients on simvastatin had a significantly greater decrease in pain from baseline (by VAS) than those in standard therapy.

Burton et al reported on the frequency and perceived efficacy of non-analgesic medical therapies in the North American Pancreatitis Study 2 (NAPS2) study of CP in 516 adults, most with CP thought to be related to alcohol or smoking.[46] The most commonly used pain medication was PE, which was perceived as effective by treating physicians in patients who had associated pancreatic insufficiency. Antioxidants were used in 14% of patients and were noted to be more effective in patients with idiopathic and obstructive causes of CP rather than alcoholic CP (25% vs 4%, P = 0.03). Perceived efficacy of octreotide was highly variable.

Summary

There is some evidence, albeit single-center and in adults, for pregabalin efficacy in CP pain. Available trials do not suggest that enteric-coated PE reduces pain in CP, except in those with EPI. Some trials suggest that antioxidants may improve pain in CP by reducing oxidative stress, but results are mixed. Assessing trials is complicated by the variation in antioxidants used and the study structure. There are no studies of antioxidants in children. Studies from children with pain associated with SCD suggest that adequate vitamin D levels may reduce pain.

3.3 Integrative Medicine

Integrative medicine is the use of evidence-based complementary and alternative medicine in conjunction with conventional medical therapy.[57] In children with CP, the literature on integrative medicine to treat pain is limited. Not all integrative pain methodologies were represented in studies that met our criteria.

3.3.1 Yoga—Yoga is a mind-body modality that combines mindfulness, breathwork and physical poses.[58] There are no studies in children with CP. In one small trial, adults with CP and pain (n = 24) were randomized to an Iyengar yoga intervention or a control group.[59] Yoga decreased self-reported pain levels by 62% and self-reported use of pain medication by 36%, but no comparison to the control group was provided. Yoga participants reported significantly improved HRQoL (by SF-36), mood, and stress scores, compared to no change over time in controls.[60]

3.3.2 Acupuncture—Acupuncture is a component of Traditional Chinese Medicine (TCM). There are no studies of this therapy in children with CP. In adults with CP (n = 23), Ballegaard et al evaluated electro-acupuncture versus transcutaneous electric nerve stimulation (TENS). They found no pain reduction, as measured by VAS and amount of analgesia used, for either intervention.[61]

3.3.3 Pain Tolerance and Coping—Thastum et al evaluated the impact of pain tolerance and coping in 16 children with JIA and one parent, compared to a group of healthy children and one parent.[62] Children with JIA used more behavioral distraction than healthy children. Pain coping techniques (cognitive and behavioral distraction) in children with JIA correlated with those of their parents for both experimental and clinical pain episodes.

3.3.4 Sleep—Pain can cause poor sleep, which can lead to poor functioning and exacerbate pain. In 20 children with SCD aged 8–12 years, poor sleep quality was associated with high pain scores (measured by VAS) the following day.[63] Pain medication use attenuated the impact of pain on sleep quality.

3.3.5 Exercise—Tarakci et al reported that a 12-week customized exercise program in children with JIA led to an improvement in pain by VAS, functioning and HRQoL (Peds QL™).[64] Of note, specific location of pain improved (joint vs. abdominal or other) was not specified.

3.3.6 Spirituality—In 50 adult African-American patients with SCD, attending church once or more per week was associated with lower pain scores Short Form McGill Pain Questionnaire and VAS.[65]

Summary

We identified only two small studies on integrative medicine techniques to control CP pain, both in adults, with mixed results. We identified no studies on the utility of other integrative, holistic, or wellness techniques for treating pain in children or adults with CP.

3.4 Dietary Interventions

Modifying or decreasing fat intake is often recommended in CP management, based on the concept that fat intake stimulates secretion of endogenous PE, which may trigger or exacerbate intra-pancreatic inflammation and pain. In a cross-sectional study, Castineira-Alvarino et al evaluated the impact of consuming a high-fat diet (>30% of total caloric intake, n = 24) versus a non-high fat diet (n = 144) in CP.[66] Most patients had alcohol-related CP and were smokers; genetic causes were not evaluated. Patients with CP on a high-fat diet reported significantly more continuous abdominal pain.

Maruki et al prospectively evaluated efficacy of a low-fat diet (<20 grams of fat/day for 4 weeks) in 54 adults with non-alcohol related CP.[67] Patients with endoscopic ultrasound (EUS) findings suggestive of CP had the most improvement in their pain scores (by VAS), and had significantly improved VAS scores compared to those without definite EUS-detected changes of CP.

In a multicenter, prospective study, Kataoka et al evaluated 594 adults with CP (mostly alcohol related) who ate a regular diet plus an elemental formula supplement (average 600 kcal daily of Elental™, Ajinomoto Pharmaceuticals, Tokyo, Japan).[68] Patients' reported improvement in pain scores (by VAS) was significant at 1 week into intervention and throughout the 12-week study, compared to baseline. However, of the 132 patients using analgesia during the study, only 22 patients decreased their dosing (97 no change, 13 increased). In a smaller case-control study (n = 30) using the same elemental formula supplement (80 g/day) for 2 months, pain scores (by VAS) were lower in those on the supplement.[69] These studies do not directly address the question of reducing dietary fat content as a means of controlling pain in CP.

Skipworth et al evaluated the effect of nasojejunal (NJ) feeding of a semi-elemental formula in 58 adults with CP (most alcohol-related).[70] Resolution of abdominal pain and discontinuation of all opioid analgesia occurred in forty-six patients (79.3%). There was no control group. Forty-two (72.4%) patients reported good tolerance of NJ feeds.

In a retrospective study, Stanga et al evaluated percutaneous gastrojejunostomy and or jejunostomy placement followed by enteral feeds (n = 57 adults, 28% with alcohol-related CP) with polypeptide or elemental formula.[71] Abdominal pain was present in 96% of patients at study initiation, and only 23% at 6-month follow-up (n = 48). Narcotic use dropped significantly. Exocrine pancreatic insufficiency and PE use was not discussed.

Summary

There is limited observational but not RCT evidence that fat ingestion exacerbates pain in CP. No RCTs of low-fat diets to control pain in ARP or CP were identified. Uncontrolled studies suggest that an elemental supplement or jejunal delivery of formula reduces pain in adults with CP. Most studies did not test for EPI. We identified no trials of nutrition interventions to treat pain in children with CP.

3.5 Multi-disciplinary Approach to Pain Management

One large prospective study in India examined a step-up intervention.[72] Adults with CP (n = 313, 72% idiopathic, 26% alcohol-related, 92% with chronic pain) initially received medical management (diet with 25–30% fat, antioxidants, pancreatic enzymes, smoking and alcohol cessation counseling). Interventional therapy (endoscopy or surgery) was offered to those without pain improvement. Of the 21% that had an endoscopic retrograde pancreatography (ERCP), 72% experienced pain relief (improvement in a 12-point pain score) but 39% required subsequent surgical intervention. Of the 26 patients who had surgery (lateral pancreatojejunostomy, Whipple's procedure [pancreaticoduodenectomy] or Frey's procedure [pancreatic head resection + lateral pancreatojejunostomy]), 85% had symptom relief.

Brandow et al reported retrospectively on multi-disciplinary, multi-modal pain management in 19 children (median age 15 years) with SCD who were on opioids and had frequent pain admissions.[73] Their team included a pain management physician, psychologist, social worker and nurse. Interventions included medications for pain and SCD, psychologist assessment, cognitive behavioral therapy, evaluation and treatment of depression, and social work support including an individualized education program. An individualized formal pain management plan was developed for each patient, given to the family and included in the medical record. Pain was measured as number of admissions to the hospital for pain and use of opioids. The intervention led to decreased hospital admissions for pain and transition to the majority of patients using non-opioid pain management techniques.

3.6 Nerve Blocks and Regional Anesthesia

Seven studies, all in adults, evaluated the efficacy of celiac plexus block for pain relief in chronic pancreatitis. Basinski et al evaluated the impact of neurolytic celiac plexus block (n = 30) versus videothoracoscopic splanchnicectomy (n = 18) in adults with CP in a prospective, non-randomized study.[74] Both techniques significantly improved pain (by VAS) and decreased opioid use compared to a control group who underwent no intervention. Celiac plexus block was associated with temporary orthostatic hypotension (30%) and diarrhea (13%), and splanchnicectomy with intercostal pain (22%).

Imaging techniques to assist with nerve blockade using various approaches and medications have been used to guide delivery of celiac plexus blocks to adults with CP. In a prospective, single-arm study of 90 adults with CP (38% alcohol-related),[75] EUS-guided injection using bupivacaine and triamcinolone led to improvement in 55% (based on VAS); however, only 26% of patients still had reduced pain at 12 weeks. In a smaller study using the same type

of medication (n = 22), the efficacy of computed tomography (CT) versus EUS-directed approach was compared.[76] Thirty percent with EUS-directed block had enduring pain relief (by VAS) at 24 weeks. In contrast, 75% of patients with a CT-directed block had recurrent pain by 6 weeks. No complications were reported.

In a randomized study of 1 versus 2 bupivicaine/triamcinolone EUS-directed blocks in 51 adults with CP,[77] no difference in pain relief was noted. Pain relief lasted a median 28 days (range, 1–203 days). In a retrospective study comparing unilateral to bilateral celiac blocks (100% alcohol) in adults with CP,[78] a significant reduction in pain (by VAS) on day 7 after intervention was reported only by patients who underwent bilateral block. Adrenal artery hemorrhage in 1 patient.

Endoscopic ultrasound-guided celiac plexus block was compared to fluoroscopic-guided celiac block in a randomized trial in adults with CP; twenty-seven received an EUS-guided injection and 29 a fluoroscopic-guided injection.[79] Endoscopic ultrasound-guided injections were associated with significantly more pain relief (self-reported improvement on VAS, $P = 0.044$) than fluoroscopic-guided celiac block. However, most patients returned to pre-block pain scores by 24 weeks.

Finally, Stevens et al randomized 40 adults with CP (50% alcohol-related) to EUS-guided injections of bupivacaine with triamcinolone or bupivacaine with saline.[80] No difference in pain or HRQoL outcomes was noted between the groups (VAS, McGill pain score, Short-Form 12). The block improved pain in 85% of each group, but mean duration of response was 5.3 months in the combined group and only 0.6 months in the bupivicaine group.

We identified 10 studies that reported on the efficacy of thoracic splanchnicectomy (TS) in adults with CP.[81–90] None included pediatric patients. Only one study included a control group (32 TS, 32 controls all alcohol-related CP).[89] Average pain scores improved significantly after TS and remained below baseline for 12 months, vs. no change from baseline in controls. Self-reported functional scores were stable to slightly increased over 12 months for TS, but decreased for controls.

Among the nine uncontrolled cohort studies of TS, including 2 groups that reported early and later results from the same cohort, all reported that it led to significant pain improvement.[81–88,90] Cohort size ranged from 20 to 75. Length of follow-up and pain outcome measures varied widely. In the 5 cohorts that reported overall response rate, 46–95% of patients had sustained pain relief—most commonly reported at 12–15 months. Decreased narcotic prescriptions and improved HRQoL (self-reported via various questionnaires) were most commonly reported in conjunction with improved pain scores. Pain relief decreased with time, from 52% at 12 months to 28% at 48 months in Buscher et al's 2008 cohort (n = 75).[81] In the Leksowki et al cohort, 33% had pain recurrence after the initial intervention,[88] and in the Davis et al 2008 study, 44% of patients went on to require pancreatic surgery.[83]

Complications were inconsistently reported. Buscher et al reported persistent pain at the trochar insertion site in 7.5% and pneumothorax in 5% of procedures.[81] Ihse et al reported that 9% of their patients required thoracotomy for procedure-related bleeding.[86]

Recently, less invasive blocks have been explored for CP pain. In a study of 54 adults with chronic pain and CP, ultrasound-guided subcostal transversus abdominis plan block (using bupivacaine and methylprednisolone) was studied retrospectively.[91] Of 21 patients thought to have “abdominal myofascial pain” (focused within the abdominal wall), 95% reported pain relief that lasted at least 3 months, and 62% for 6 months. Of those with reports of deeper visceral pain, the superficial block was ineffective.

Two studies suggest that nerve block during pancreatic drainage procedures may improve pain relief. In a double-blind, placebo-controlled RCT of intraoperative celiac plexus block during pancreatic head resection (Frey procedure, n = 136), celiac plexus block was associated with a higher prevalence of pain relief (99% vs 83% at 2 years post intervention), lower opioid requirements and a better HRQoL.[92] In a smaller retrospective study, adults with CP had lateral pancreaticojejunostomy for CP with (n = 18) or without (n = 16) a concurrent intraoperative celiac axis plexus block using 50% alcohol.[93] Significantly more patients who received celiac axis block reported complete pain cessation and cessation of narcotic use. There was no difference in operative complications.

Summary

Nerve blockade for CP appears to be effective in the short-term in adults. Endoscopic ultrasound-guided blockade seems to have an increased likelihood of pain relief. The addition of steroids (triamcinolone) to injection protocols has not been shown to improve efficacy. In adults undergoing drainage procedures, concurrent nerve block may improve pain control. No pediatric studies using nerve or regional blocks were identified.

3.7 Endoscopic Interventions

Endoscopic and surgical interventions are often considered as therapeutic options when conventional medical therapy fails to alleviate pain associated with CP. Therapeutic ERCP can be used for ductal decompression and drainage, which may improve CP-related pain.

3.7.1 ERCP in Children—Although the pediatric literature is limited, several retrospective observational studies have shown ERCP’s potential to improve pain in children with CP. In the only multi-center study of pediatric patients, Troendle et al reported that 45% of the cohort (n = 177) had an ERCP.[94] By physician report, 43.6% of patients felt ERCP was “helpful” for pain.

In a single-center study from India, Agarwal et al. reviewed 143 children with pancreatic disease who underwent ERCP, mostly for chronic pain due to CP.[95] Interventions included major and minor papilla sphincterotomy, pancreatic duct stenting and stone retrieval with and without extracorporeal shock wave lithotripsy (ESWL). In children with available follow-up (mean 13 months), 64% reported no pain (5-point Likert scale) and no analgesic use (tramadol, NSAIDs). Those who required analgesic more than 10 times/month decreased

from 20% to 4% of the cohort. Adverse events were rare (n = 6: pancreatitis, abdominal pain). Two ultimately required surgical intervention for refractory stricture or calculi.

In a single-center study from Italy, Kohoutova et al. reported on 158 ERCP procedures in 38 children with CP.[96] All had a sphincterotomy, 66% also had stone/plug removal (3/38 with ESWL) and 29% had stricture stenting/dilation. Median pain severity improved from 8.5 pre-ERCP (0–10 patient-reported scale) to 1.0 at follow-up ($P < 0.001$). During a median of 10.5 years of follow-up, 66% of patients were pain-free after completing endoscopic therapy. Analgesic use significantly improved, decreasing from 100% non-opioid and 68% opioid use at baseline to 34% and 3% post-ERCPs (both $P < 0.001$). Adverse events (n = 5) included bleeding, AP, cholangitis and cholecystitis.

In a single-center study from China, Li et al reviewed 110 ERCPs in 42 children.[97] Interventions included sphincterotomy (56%), papillotomy (23%), dilation (36%), and stenting (76%). Over an average follow-up of 61 months, 81% of patients reported improvement in pain (5-point Likert Scale), including 65% with complete pain relief. However, 17% of patients had complications, including pancreatitis and cholangitis. Five underwent surgery for persistent or recurrent pain.

Finally, Wen et al reviewed 38 children with pancreas divisum and ARP/CP who underwent 74 therapeutic ERCPs.[98] Over a median follow-up of 57 months, 56% of children with CP were pain-free and 35% reported improvement (5-point Likert scale). Of note, 48% had recurrent pain or AP, and 26% required repeat ERCP.

3.7.2 ERCP in Adults—Endoscopic therapy has been well-studied in adult CP. This literature demonstrates the potential efficacy of ERCP in specific patient groups and intervention types. Generalizability to pediatric patients is cautioned as the disease etiology and phenotype in adults is different. Many retrospective adult studies demonstrate improvement in pain with endoscopic therapy.[99,100] In a large retrospective review of 1000 adult patients receiving endoscopic therapy for painful CP (72% alcohol-associated) with ductal obstruction, 65% experienced significant pain relief after almost 5 years of follow-up. Pain-free status at follow-up was reported in 63% of patients with strictures; 73% with pancreatic stones and 66% with both. However, 24% went on to require pancreatic surgery.[101] Other studies have demonstrated improved pain outcomes with specific indications including management of ductal strictures[102–107] and pancreatic calculi[108,109]; however, not all interventions have been noted to be beneficial. For example, Lehman et al found pancreas divisum patients receiving minor sphincterotomy had improved symptom scores (summary of pain severity, opioid use, pain-related hospitalizations) if they had ARP but not CP.[110] Kahl et al found endoscopic stenting of biliary strictures did not improve pain scores (VAS) or analgesic use in CP.[111]

A number of adult studies have demonstrated efficacy of ESWL alone[112] or in combination with ERCP[113–118] for management of pancreatic calculi; however, two different, small studies found no significant improvement in number of patients receiving narcotics post procedure.[119, 120] Dumonceau et al conducted a randomized controlled trial of adult patients with both painful CP and calcifications obstructing the main pancreatic duct who were

randomized to receive ESWL alone or ESWL combined with ERCP for stone extraction.[121] Both groups had similar decreased in the number of patient-reported pain episodes in the year following intervention (mean decrease 3.8 episodes in ESWL only, 3.7 ESWL + endoscopy).

3.7.3 Endoscopic Versus Surgical Therapy in Children—No prospective studies or randomized controlled trials of children with CP compare endoscopic to surgical therapy. There is one retrospective review of 98 children with CP and abdominal pain, in which 10 underwent endoscopic therapy (2 ESWL, 8 sphincterotomy, and stenting) and 15 had surgery (10 lateral pancreatojejunostomy, 5 Frey procedure).[31] Of those patients with follow-up, 62.5% receiving ERCP had pain relief, by physician report, compared to 27% after surgery.

3.7.4 Endoscopic Versus Surgical Therapy in Adults—In four RCTs of adults with CP, surgical resection and drainage procedures led to more sustained pain relief than endoscopic management.[122–125] Dite et al randomized 72 adults with CP, pain, and duct obstruction to surgery or endotherapy. Complete pain resolution was more frequent after surgery (34% vs 15% with ERCP, $P = 0.002$); prevalence of partial pain relief was similar (reduction in pain by ≥3 points on Melzack score; 52% vs 49%) at 5 year follow-up.[124] Cahen et al randomized 39 adults to endoscopic drainage or surgical pancreaticojejunostomy. At 24 months, pain scores (Izbicki) were significantly lower in patients who had surgery.[123] At five-years, the mean difference in pain score was no longer significant but surgery patients were more likely to report pain relief (decrease > 50%; 80% vs 38%, $P = 0.042$). Notably, 68% of the endoscopic group required future procedures, compared to only 5% of surgical patients ($P = 0.001$). Nearly half the endoscopic group needed surgery within 5 years of follow-up.

More recently, Issa et al randomized 88 adult patients with obstructive painful CP (69% alcohol-induced) in a multicenter trial to early surgery (lateral pancreatojejunostomy or duodenum-preserving pancreatic head resection) versus endoscopy-first approach (therapeutic ERCP +/− ESWL).[125] After 18 months, the surgical group had a significantly lower pain score (Izbicki) (37 vs 49, $P = 0.02$); however, complete or partial pain relief was not significantly different (58% vs 39%). Treatment complications, hospital admissions and HRQoL (by SF-36) were similar.

The potential role of interim endoscopic therapy, to optimize the patient's condition prior to surgery, was demonstrated by Kwon et al. They found that patients with endoscopic pancreatic stent placement who then achieved narcotic independence within 2 months were more likely achieve narcotic independence after lateral pancreaticojejunostomy (80% vs 10%, odds ratio 38, $P = 0.0025$).[126]

Summary

To date, there are no prospective studies or randomized controlled trials of endoscopic therapies in pediatric patients. Furthermore, characteristics of which pediatric patients may benefit from endoscopic interventions, and which specific interventions (e.g.,

sphincterotomy, stone/plug removal, stenting and dilation) can be helpful remain unclear. While studies in adults demonstrate improvement in CP pain with ERCP, generalizability to children, who usually have different CP etiology than adults, may be limited.

3.8 Pancreatic Surgery

3.8.1 Pancreatic Surgery in Children—Within this scoping review, our review of pancreatic surgery in CP is focused on relief of pain and reduction in hospitalization. Seven single-center, retrospective, observational studies examine the impact of surgical intervention on CP in children.[31, 127–132] Chowdhury et al[31] is described above.

Ray et al reviewed 54 children with CP who underwent surgery (26 Puestow [lateral pancreaticojejunostomy], 25 Frey, 3 Izbicki procedures [a drainage procedure adapted for patients with small duct disease[133]]).[129] More than 90% underwent operations for pain, as assessed clinically. Median duration of follow-up was 48 months; 83% had resolution of pain, per patient report, during this time.

Sacco Casamassima et al reported on 20 pediatric patients with CP; the majority with obstructive disease.[130] A variety of procedures (including 11 total pancreatectomies) were performed. Reduction or elimination of analgesics (opioids and NSAIDs) was achieved in 60%. No factors predicted pain relief in multivariate analysis. Weber et al reviewed 18 children with CP, 9 with hereditary pancreatitis, with mean follow-up of 7.5 years.[131] Children underwent a variety of drainage procedures. Two who had Puestow procedures underwent distal pancreatectomies within one year. Five (28%) continued to report pain, although 72% had no further hospitalizations. Wang et al reviewed 12 patients who had a Puestow or Duval procedure at a single center.[132] During follow-up of 1.5–4.5 years, all reported good outcomes, but no specific measurement of pain was recorded.

Two studies focused on surgery in children with specific risk factors for CP. Neblett et al reviewed 8 children having surgery for CP associated with pancreas divisum.[128] All had ductal drainage procedures, for a total of 12 procedures. Three (38%) reported no episodes of pain after intervention. DuBay et al examined results of the Puestow procedure on 12 children with hereditary CP.[127] Eleven patients reported their surgical outcome as “excellent” or “good,” but 8 continued to have pancreatitis symptoms, for which 6 had been hospitalized.

3.8.2 Total Pancreatectomy With Islet Cell Auto-Transplant—Total pancreatectomy with islet cell auto-transplant (TPIAT) involves removal of the entire pancreas, as well as the spleen and gallbladder. The insulin-producing islet cells are isolated and returned to the patient, usually into the liver via the portal vein, but sometimes in peritoneal or subcutaneous locations. The islets may prevent or mitigate diabetes.[134] The indication for TPIAT in children with ARP or CP is disability from pain, which may include loss of time in school, loss of time with friends, exclusion from sports, and frequent hospital admissions for pain.

We will focus on the data in children where possible, although several large studies include both children and adults. The TPIAT literature is dominated by relatively large, single-center

retrospective reviews of adults, in whom the most common risk factor for CP is excessive alcohol ingestion. Many also include patients with acute pancreatitis and surgical procedures generally performed in that condition, such as pseudocyst drainage. These findings cannot be extrapolated reliably to children.

In a review of children (n = 30) and adults (n = 185) with 10 years of survival after TPIAT, overall pain symptoms (by SF-36), were reported as better or improved in 77.1% at one year and 81.5% at 10 years.[135] The pain improvement in children was comparable or better to that reported in adults. Opioid use declined from 54% at one-year post operatively to 37% at 10 years. In the subset of these patients who completed the SF-36 before and at 5 years or later post-TPIAT, all 8 subscales were significantly higher after TPIAT, suggesting long-term pain relief. A later retrospective report from the same group focused on 17 children ages 3–8 years old with painful ARP or CP.[136] At a median 2.2 years post-TPIAT, all reported pain relief, and all were off opioids. Hospitalizations decreased significantly, from 5.0 per person-year before TPIAT to 0.35 per person-year after TPIAT. Other retrospective studies combining adults and children consistently support these findings that, after TPIAT, patient-reported pain and opioid use both decrease.[137–141]

Summary

Conventional surgical approaches provide pain relief in some children, but available evidence does not answer which children get durable pain relief, which procedures are superior, and what their impact is on functioning. Variation in surgery performed, lack of standardized pain questionnaires, and short follow-up relative to the life of a child make it difficult to draw conclusions. There is evidence that conventional surgical procedures (pancreatojejunostomy, pancreatic head resection) may reduce the success of a TPIAT by affecting the ability to sufficiently harvest islet cells.[140,141] This is a potential a concern for children, who often have genetic risk factors for CP.

Pain relief from TPIAT has been studied only retrospectively. However, data from children shows it to be effective and durable in relieving pain. It should be noted that TPIAT is a major, complex operation with significant risks, including diabetes and life-threatening infection associated with splenectomy.[142] But among children with severe pain and reduced quality of life from CP, TPIAT appears to be effective at reducing hospitalization, relieving pain, and improving QoL.

4. DISCUSSION

Pain is disruptive and debilitating in children with chronic pancreatitis. Almost half of children with CP report constant pain of varying severity, and the remainder have episodic pain[1]. Despite pain being the predominant symptom of CP, and pain control being central to its management,[143] there is scant evidence on how to do this optimally in children with CP. In this comprehensive review of the literature on pain management in CP, we identified no published studies of analgesic medications, antioxidants or other supplements, dietary modification, integrative medicine or other wellness interventions, or regional nerve blocks in children with CP. Sizeable retrospective, observational studies suggest that ERCP

and surgical procedures can improve pain for these children, with TPIAT having the most durable results. But these studies offer little to no insight into optimal timing, frequency or goal endpoint for these therapies. While many studies reported some improvement in pain from medications or procedures, most reported a varying number of patients were still reporting pain episodes. Duration of follow-up was short relative to a child's life.

Amongst trials and observational studies in adults with CP, the majority of studies were single-center and retrospective. Surprisingly, few studies investigated the use of opiates or adjunct pain medications for pain in CP. In addition, the generalizability of studies in adults with CP to children are limited, as the risk factors associated with pediatric CP are typically different.[1] Review of pain management for children with conditions that can cause similar pain—chronic with acute exacerbations—like SCD and JIA also revealed very little evidence generalizable to children with CP.

No therapy we reviewed had sufficient high-quality studies to warrant untempered, evidence-based guidelines for its use in children with CP. There are a few therapies that had enough data to consider more extensive study in future trials. In regards to medications, pregabalin demonstrated effective pain relief in adult patients with CP, reducing the use of opioids and potentially leading to decreased addiction and other side effects.[22,26,144] However, there are no data in children, with CP or other painful conditions. Pancreatic enzymes appear to have no benefit in improving pain in adults with CP except in those with EPI; but again, there are no prospective studies in children.

The use of regional anesthesia and celiac plexus blocks to control CP pain has been limited to adult studies. In general, they appear to be effective but provide only short-term relief. Studies using this modality often demonstrate pain recurrence within 12 months. Regional anesthesia may play a palliative role or a bridge to surgery for children with intractable CP pain but is unlikely to provide long-term pain relief.

Interventions using integrative medicine or dietary changes have limited supporting data. The impact Vitamin D on pain in children with SCD is intriguing.[53,54] Nutritional interventions (low fat, elemental formula, direct jejunal feeds) may be beneficial in pain control, although studies are few and often small, all open label, and in adults with no long-term outcomes or acceptability to patients reported. Additional studies in pediatric CP could be considered.

Pediatric data exist for the effectiveness of endoscopic interventions, and results are often favorable. But published studies are all retrospective. Additionally, although many studies show initial improvement in pain after therapeutic ERCP, pain may recur long-term. For many children, especially with genetic causes of CP, ERCP may best serve as a bridge to surgical intervention.

There is evidence that surgical interventions improve pain control in children and adults with CP, although with significant risk of complications. Pediatric data suggest that most children have some pain relief after surgery, but pain persists in others and often recurs. It is not clear if specific procedures have benefit over others. A major concern with drainage procedures is that children often have genetic causes of CP, such that pancreatic injury and islet loss likely

continue even if obstruction and pain are surgically relieved. Previous pancreatic surgery impacts insulin independence after a subsequent TPIAT.[145] Data from pediatric TPIAT demonstrates good pain control and reduction in opiate use from this procedure, despite the known risks.

A limitation of this scoping review is that we have not included psychologic interventions. This critical arm of multi-disciplinary support for children with CP and pain has been systematically reviewed in other recent publications.[146,147] Of note, however, there are published studies on psychologic interventions for pain in children with CP. A trial currently underway of remotely-delivered cognitive behavioral therapy will provide more information on this approach.[148] Cystic fibrosis transmembrane regulator modulators have shown impact on numbers of episodes of pancreatitis in people with CF and ARP.[149] There are theoretical reasons to consider studies of these modulators, as the CFTR may be the pathway by which tobacco smoking and alcohol increase the risk of pancreatitis.[150] However, no study of these medications met our criteria for review.

Additional limitations of this manuscript relate to its design as a scoping review, intended to identify gaps and opportunities from the existing literature but not lead to definitive, quantitatively-supported conclusions about best practices for pain management. We excluded some studies for feasibility, for example those in languages other than English and small case series. We also did not attempt any quantitative meta-analysis or bias assessment.

Based on our scoping review, we suggest that focused multi-center RCTs be developed to build an evidence basis for pain management in pediatric CP. The total population of children with CP is relatively small, and there will be a limit on the number of such studies the population can support. Coordinating studies is also important to ensure standardized pain and other outcomes measures, as utilization of different pain and quality of life scores is a significant limitation in comparing data across smaller studies. Where retrospective studies have shown no or very small impact on pain, there is unlikely to be a large enough number of pediatric patients with CP to demonstrate efficacy, even in a multi-center trial. Potential targets, based on our review, would pregabalin and vitamin D, and studies directed at the characteristics of pediatric patients most likely to benefit from endoscopic interventions. Optimal pain management in children with CP will also most likely involve targeting both peripheral nociception from the inflamed pancreas and centrally-mediated hyperalgesia (a heightened response to noxious stimuli) and allodynia (reduced threshold for nociceptive propagation from the periphery to the central nervous system).[151,152]

Our findings match prior research initiatives that note the lack of good quality studies for many serious pediatric diseases.[153] This scoping review reveals that medical therapies for pain in CP have very little high-quality supporting data. Endoscopic and surgical interventions having a stronger foundation of evidence for efficacy, but details of how to optimize their use are still scant. None have enough data, particularly in children, to recommend without reservation, making the development of evidence-based guidelines for pain in children with CP difficult. We are hopeful that prospective research consortiums such as INSPPIRE[7] and the Hungarian Pediatric study[154] will provide the coordination necessary

to build an evidence basis and allow development of best practices—to optimize outcomes for all children and families living with CP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

ARP	Acute recurrent pancreatitis
CP	Chronic pancreatitis
CT	Computed tomography
EPI	Exocrine pancreatic insufficiency
ERCP	Endoscopic retrograde cholangiopancreatography
ESWL	Extracorporeal shockwave lithotripsy
EUS	Endoscopic ultrasound
HRQoL	Health related quality of life
INSPPIRE	INternational Study group of Pediatric Pancreatitis: In search for a cuRE
JIA	Juvenile idiopathic arthritis
PE	Pancreatic enzymes
RCT	Randomized controlled trials
SCD	Sickle cell disease
SF-36	36-item Short Form Survey
TS	Thoracic splanchnicectomy
VAS	Visual analog scale

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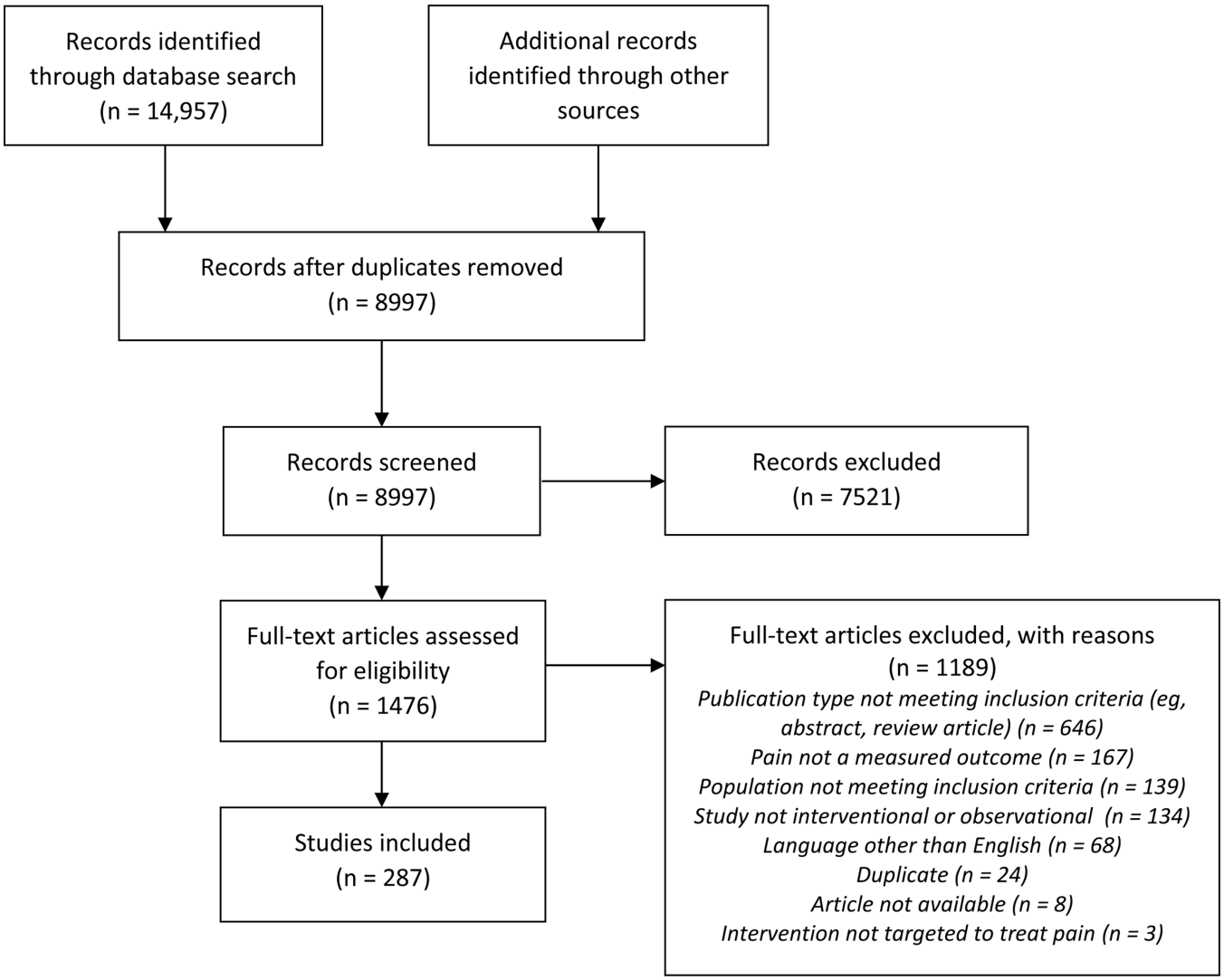

FIGURE 1.
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.