Treatment of Complex Regional Pain Syndrome in Children and Adolescents: A Systematic Review

Andrea Vescio

Università degli Studi di Catania

Gianluca Testa (✉ gianpavel@hotmail.com)

Università degli Studi di Catania <https://orcid.org/0000-0001-5246-9714>

Annalisa Culmone

Università degli Studi di Catania

Marco Sapienza

Università degli Studi di Catania

Fabiana Valenti

Università degli Studi di Catania

Fabrizio Di Maria

Università degli Studi di Catania

Vito Pavone

Università degli Studi di Catania

Research article

Keywords: Paediatric, Growing Age, Complex regional pain syndrome, Reflex sympathetic dystrophy, Multidisciplinary, Physical therapy, Cognitive Behavioural Therapy, Drugs, Pharmacological treatment, Occupational Therapy

Posted Date: May 12th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-28127/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Complex Regional Pain Syndrome (CRPS), as known as Reflex Sympathetic Dystrophy, is characterized by chronic, spontaneous and provoked pain of the distal extremities, whose severity is disproportionate to the triggering event. In growing age, CRPS affects most commonly women aged 5 to 17 years, with a maximum incidence peak around the 13th year of age. Among the orthopedics, diagnosis remains challenging, as well as, the treatment is still debated and multidisciplinary. The purpose of this systematic review is to analyze the available literature to provide an update on the latest evidence related to the treatment of CRPS in growing age.

Methods: Three reviewers searched Pubmed and Web of Science databases from their date of inception to the 20th September 2019 in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses guidelines. Data extraction was performed independently by 3 reviewers based on predefined criteria and the methodologic quality of included studies was quantified by the the Newcastle-Ottawa Quality Assessment Scale Cohort Studies.

Results: A total of n = 264 articles were found. At the end of the first screening, following the previously described selection criteria, we selected n = 103 articles eligible for full-text reading. Ultimately, after full-text reading and a reference list check, we selected n = 6. The articles focused on physical (PT), cognitive-behavioral (CBT) and pharmacological (PhT) treatments. The combination of PT+CBT is the most efficacy and suggested, but a commonly accepted protocol has been not developed. Despite the good patients outcome, several are the adverse events recorded in PT.

Conclusions: Physical therapy in association with occupational, and cognitive behavioral treatment is the recommended option in the management of pediatric CRPS. Pharmacological therapy should be reserved for refractory and selected patients. The design and development of a standard protocol are strongly suggested.

Background

First described in the 17th century as "causalgia"[1], complex regional pain syndrome (CRPS) is characterized by chronic, spontaneous and provoked pain of the distal extremities, whose severity is disproportionate to the triggering event [2]. Three different CRPS subtypes have been distinguished:

Type 1, previously known as reflex sympathetic dystrophy (RSD), whose cause is not always known.
Type 2, which results from nerve damage.
Type 3 or not otherwise specified CRPS, which partly shares clinical and diagnostic aspects with the previous types [2].

CRPS type 1 affects children and adolescents aged 5 to 17 years, with a peak incidence around the 13th year of age, and it is more frequently found in women (70% of cases) [3, 4]. The pathogenic mechanism is still unclear, although several hypotheses have been proposed. Genetic factors, altered microcirculation, and traumas, such as sprains, fractures and surgical procedures, contribute to pain symptoms. Anxiety,

somatization, and familial and school problems could also play a role. Chronic pain, generally unilateral and limb localized, autonomic and motor dysfunction and trophic disorders are the main symptoms of CRPS type 1. There are two presentations of the syndrome: the “warm” one, with red, warm, swollen skin that usually occurs in the acute phase, and the “cold” one, with blue/purple, cold, sweaty skin, which is usually associated with the chronic phase [3–6]. The diagnosis of CRPS type 1 is clinical and based on the Budapest diagnostic criteria [4]. However, diagnosis remains challenging due to the lack of validated diagnostic tests and the difficulty of differential diagnosis. Laboratory and imaging tests can be helpful in the event of diagnostic doubt [1]. Treatment is multidisciplinary, and it is mostly based on physical and psychological therapy and medications; only in selected subjects is treatment invasive [7]. The purpose of this systematic review was to analyse the available literature to provide an update on the latest evidence related to the treatment of CRPS type 1 in children and adolescents, highlighting the multidisciplinary approach.

Methods

Literature search strategy

A systematic review of the current literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8]. On 20th September 2019, three independent authors (SM, VF and DiMF) performed a systematic review of two different medical electronic databases (PubMed and Web of Science). To achieve the maximum sensitivity of the search strategy, a search string was used (“(complex regional pain syndrome OR reflex sympathetic dystrophy OR Sudeck’s atrophy) AND (pediatric) AND (treatment)”).

Selection criteria

The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies, and the articles were assessed using the inclusion and exclusion criteria. The following inclusion criteria were used when screening titles and abstracts:

- a. Studies of any level of evidence.
- b. Studies written in the English-language.
- c. Studies reporting clinical or preclinical results.
- d. Studies on the treatment of complex regional pain syndrome type 1.

The exclusion criteria were as follows:

1. Review articles.
2. Case reports.
3. Articles written in other languages.
4. Diagnosis or differential diagnosis of complex regional pain syndrome type 1.

Duplicates and articles on other topics, with poor scientific methodology, or without an accessible abstract were not included in the study; abstracts, case reports, conference presentations, editorials and expert opinions were also excluded.

Data extraction and criteria appraisal

All data were extracted from article texts, tables and figures. Three investigators (SM, VF and DMF) independently reviewed each article. Discrepancies between the two reviewers were resolved by discussion and consensus. The final results and any remaining controversy on the reviewed article were reviewed and discussed with the senior investigators (VA and CA), who served as independent reviewers and assessed study quality. Conflicts about data were resolved by the senior surgeon (PV). Reference lists from the selected papers were also screened. The PRISMA flowchart for the selection and screening method is provided in Fig. 1.

Risk of bias assessment

A risk of bias assessment of all selected full-text articles was performed according to the Newcastle-Ottawa Quality Assessment Scale Cohort Studies (NOS) [9]. The NOS contains eight items, categorized into three dimensions including selection, comparability, and depending on the study type, outcome (cohort studies) or exposure (case-control studies). For each item, a series of response options is provided. A star system is used to perform a semi-quantitative assessment of study quality, such that the highest quality studies are awarded a maximum of one star for each item with the exception of the item related to comparability that allows the assignment of two stars. The NOS ranges between zero and nine stars. The assessments were performed by two authors (VA and CA) independently. Any discrepancy was discussed with the senior investigator for the final decision. All the raters agreed on the final result of every stage of the assessment (Appendix). In the systematic review, studies classified with more than six stars were included.

Results

Study Selection

From the search of PubMed and Web of Science, 264 articles were included in the review, and 240 studies were selected after duplicate exclusion. Following the inclusion and exclusion criteria, the first screening was performed. A total of 103 papers were considered eligible. Finally, after the full-text reading, reference list check and risk of bias assessment, 6 studies were included. A PRISMA[8] flowchart of the method of selection and screening is provided (Fig. 1). The main focus of the included studies was related to physical (PT), cognitive behavioural (CBT) and pharmacological (PhT) treatments. A summary of the results is provided in Table 1.

Table 1
Main findings of the included article

Author	Subjects	Assessment	Treatment	Results	Limits
Brown et al. 2016	14 patients (11 F; 3 M) Amitriptyline Gabapentin 15 patients (13 F; 2)	Coloured Analogue Scale (CAS) Pain 6-weeks post-trial start; Sleep disability as measured on an inter-nally developed 5-point Likert scale Adverse events.	Amitriptylin 10 mg (at bedtime) Gabapentin at 900 mg/d (300 mg three times per day)	CAS p = 0.77. Sleep p = 0.26. Adverse events p = 0.75	Small sample size. No randomization. No placebo group. No medium and long follow up.
Petje et al. 2003	7 female patients	Visual analog scale VAS (0–10 points).	Intermittent intravenous infusion of Iloprost at 2 ng/kg/minute for approximately 6 hours per day on 3 consecutive days. + physiotherapy and psychologic	All patients were pain free after the infusion trial as assessed on VAS. All patients had headache at the first day of infusion. 3 patients had flushing. 2 patients had vomiting. 86% of the sample had a decrease of systolic blood pressure with an average of 7 mm Hg (5–15 mm Hg) in the first 30 minutes after administration of Iloprost.	No control group Retrospective series. Small number of cases.

Author	Subjects	Assessment	Treatment	Results	Limits
Donado et al. 2017	102(82F;20M)	Preadmission, discharge and 4 months follow-up Pain Score (PS), Pain-related Functional Disability (PFD) and Sleep disturbances (SD)	Continuous regional anesthesia (epidural or peripheral catheter)	PS preadmission median = 7.0; IQR, 5.8–8.2. PS discharge = 3.1; IQR, 1.5–5.4; (P < 0.0001). PS 4 months follow-up = 4.3; IQR, 2.0–6.0; (P < 0.0001). PFD at the admission had a moderate positive correlation with PDF at discharge (r, 0.5; P < 0.0001) SD = Yes 48.04%	Retrospective design. Completed a full course of cognitive behavioral therapy
Logan et al 2012	56 patients	At admission and at the discharge. Numeric ratings scale (NRS). Functional Disability Inventory (FDI). Lower extremity functional scale: (LEFS). Canadian Occupational Performance Measure: (COPM). Multidimensional Anxiety Scale for Children (MASC). Children's Depression Inventory (CDI). Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition (BOT-2)	Patients participated in daily physical therapy, occupational therapy and psychological treatment and received nursing and medical care as necessary	NRS = p < 0.001 FDI = p < 0.001 LEFS = p < 0.001 COPM = < 0.001 MASC = p < 0.001 CDI p = 0.003 All BOT-2 domains = p < .001 No patients underwent any procedures (e.g. nerve blocks) during or immediately prior to participation in the rehabilitation program.	No randomization. No control group. No isolate treatment effects. Uncontrolled prior treatment history in analyses

Author	Subjects	Assessment	Treatment	Results	Limits
Sherry et al. 1999	103 children (87 F, 16M).	Visual analog scale (VAS) and Brief Symptom Inventory (BSI) at admission and remission	An intensive exercise program (most received a daily program of 4 hours of aerobic, functionally directed exercises, 1–2 hours of hydrotherapy, and desensitization). No medications or modalities were used. All had a screening psychological evaluation,.	VAS = $p = 0.021$. BSI depression $p = 0.037$ BSI paranoid ideation $p = 0.048$. 1 child (2%) was dysfunctional with CRPS pain, and 5 (10%) had persistent mild pain but were fully functional. Median time between remission of the first episode of CRPS and the start of the second episode = 2 months (range =: 2 weeks to 4 years). Predictors of recurrent episodes: Previous suicide attempts ($p = 0.026$), History of an eating disorder ($p = 0.028$).	No long-term follow-up. No control group.

Author	Subjects	Assessment	Treatment	Results	Limits
Lee et al. 2002	28 patients randomly assigned to either group A (PT once per week for 6 weeks) or group B (PT 3 times per week for 6 weeks) Both groups received 6 sessions of cognitive-behavioral treatment.	Pretreatment; at completion of the treatment program; and (3) long-term follow-up at 6 to 12 months. Visual analog scale (VAS), Standardized gait impairment score (SGIS), Child Health Questionnaire (CHQ-CF87), Child Depression Inventory (CDI), Revised Children's Manifest Anxiety Scale (CMAS), Compliance	Individualized physical therapy. Individualized 6 weekly sessions cognitive-behavioral therapy. Standard educational program	At the short-term follow-up, both groups showed improvement in all five outcome measures related to pain and physical functioning ($P < .001$ for all measures with a change in median values. There were no between-group differences in any of these measures at baseline or at either follow-up assessment. 79% Compliance good.	Small sample. No Standardized after the 6-week protocol.

Physical Therapy and Cognitive Behavioural Treatment

Three included studies contained a combination of physical therapy and cognitive treatment. Sherry et al [10] reported the complete resolution of pain symptoms in 74.7% of the sample. Seven subjects did not have remission. One child was dysfunctional with CRPS pain, and 5 had persistent mild pain but were fully functional. The authors highlighted suicide attempts ($p = 0.026$), an eating disorder ($p = 0.028$), reporting less pain initially ($p = 0.021$), and scoring higher on the Brief Symptom Inventory subsets for depression and paranoid ideation ($p = 0.037$ and 0.048 , respectively) as predictors of recurrence. Lee et al. [11] divided patients into 2 different groups: PT + CBT for 3 weeks vs PT + CBT for 6 weeks. Both the cohorts showed improvement in all pain and physical functioning outcome measures with short and long follow-up, without differences in pain scores, recurrent episodes of CRPS, or participation in school or activities.

Logan et al. [12] assessed 56 patients aged 8–18 years at admission and at discharge, and every parameter evaluated had statistically significant improvements. Thirty-two percent of patients required an assistive device at admission, while none required one at discharge

Pharmacological Treatment

Petje et al. [13] assessed functional outcome in patients treated with an intravenous infusion of iloprost, a prostacyclin analogue. The drug was administered 6 hours per day on 3 consecutive days. Among the side

effects noted were headache on the first day of infusion in all patients and flushing, and vomiting on the second day in three patients. A decrease in systolic blood pressure of an average of 7 mm Hg (5–15 mm Hg) in the first 30 minutes after administration was detected in almost the entire cohort. Improvement of the visual analogue scale (VAS) score was found ($p < 0.05$). Relapse of CRPS was experienced by two patients, the first after 3 months. Brown et al. [14] analysed the outcome of 29 patients refractory to PT + CBT. Fourteen subjects underwent amitriptyline administration, and 15 underwent gabapentin administration. After the 6-week trial, both cohorts showed improvement in pain symptoms, sleep disturbances and functionality. No statistically significant differences were found ($p = 0.77$) between the drugs. Similar adverse events were recorded ($p = 0.77$). Donado and colleagues [15] investigated the use of continuous regional anaesthesia (epidural or peripheral catheter) in subjects refractory to PT + CBT. Their data showed significant changes between admission and discharge for pain ($p < 0.0001$), without significant changes throughout the 4-month period after admission ($p > 0.05$).

Discussion

CRPS is a common disorder not completely understood, with no data available regarding the incidence of paediatric CRPS [5] because the diagnosis is uncertain and underestimated. Clinical evaluation, including a neurologic exam, combined with a thorough history collection is mandatory [4] to rule out other possible reasons for chronic pain, such as orthopaedic, neurological and rheumatologic conditions [5]. Early diagnosis is as important as or more than treatment; in fact, a longer disease course and sequelae [2] are associated with late identification. Unfortunately, no specific diagnostic tools have been developed for children and adolescents, so the adult criteria are used [5]. Orthopaedists have a key role in the recognition of the disease due to very little evidence, no common consensus among the physicians, and a lack of guidelines [6]. As reported by Berde and Lebel [16], often the choice of treatment may vary according to the experience and resources of the clinician. Several treatments have been described [2], including acupuncture, transcranial magnetic stimulation, and invasive procedures, but the efficacy has been proven for the combination of physical and cognitive behavioural therapy and some pharmacological treatments only. The most established treatment is a programme of physical rehabilitation and cognitive behavioural therapy [15]. The goal is to restore normal function, increase the joint motion range, load tolerance and strength, and concurrently assist the child in accepting and managing the pain [2]. Different protocols were illustrated in selected studies, highlighting the absence of a standard treatment protocol. Sherry and colleagues [10] suggested aerobic training and progressive resistive exercises, in addition to hydrotherapy, desensitization with towel rubbing, hand massage, textured fabric rubs, and contrast baths (2 °C and 38 °C). During the patient's hospitalization, 5–6 hours of daily exercise therapy and 45 minutes to 3 hours of home exercise programmes (HEPs) were performed. In the Logan et al. trial [12], the patients underwent open-chain and closed-chain activities and an individualized HEP, and each child's functional goals, such as playing a specific sport, were incorporated into the physical schedule. In addition, this multidisciplinary rehabilitation approach addresses the entire pain experience, incorporating desensitization, exposure to feared activities, skills for coping with pain, and changes to social responses to pain. Lee et al. [11] designed a protocol including transcutaneous electrical nerve stimulation, progressive weight bearing, tactile desensitization, massage, contrast baths and an HEP. Six weekly sessions of individual CBT

incorporating pain management strategies, including relaxation training, deep breathing exercises, biofeedback, and guided imagery, were also included. Patient compliance, nurse care and parent treatment programmes [17] are mandatory to promote successful remission from pain and restoration of functional ability. Despite a rigorous rehabilitation programme, Sherry et al. described their patients as a motivated and eager to please sample [10]. Lee et al. [11] recorded compliance varying between 78 and 82%. No adverse events were recorded in the three studies, but the remission rate varied between 79% and 100% [10–12]. Several authors have investigated the role of PT + CBT in paediatric CRPS type 1, especially the brain and neurological changes and treatment action on the central nervous system. Frot et al. found evidence of emotional integration of pain in CRPS patients [18]. Lebel et al. [19] concluded that some changes in the brain persist, especially in the amygdala and basal ganglia, even after symptomatic recovery [20]. Diers et al. [21] demonstrated that behavioural extinction training reduces the emotional involvement in processing painful stimuli and induces a shift to a more sensory-discriminative way of pain processing post-treatment. Kregel et al. [22] emphasize that conservative treatments for patients with chronic musculoskeletal pain may induce both functional and morphological changes in predominantly prefrontal brain regions. For these reasons, non-invasive treatments are often recommended, even in recurrent forms [2, 4]. On the other hand, the literature presents evidence of good outcomes after intravenous infusion of drugs and regional nerve blockades. Three pharmacological trials were selected in the study, and different molecules were investigated. Petje et al. [13] assessed the outcome of iloprost intravenous infusion, an analogue of prostacyclin, which induces transitory complete sympathicolysis and avoids the anxiety associated with a lumbar sympathetic blockade. Despite the good rate of response, relevant adverse reactions such as headache, flushing, vomiting, and a decrease in systolic blood pressure were recorded in all cohorts; consequently, the same authors do not suggest iloprost as primary therapy. Other drugs proposed for treating neuropathic pain were gabapentin and amitriptyline. The first avoids the release of neurotransmitters acting on voltage-gated calcium channels [23], and the latter reinforces the serotonin transporter [24]. Brown et al. compared the two molecules in a refractory PT + CBT schedule. The series revealed that both drugs are effective in reducing pain scores and improving sleep, without significant differences. However, ventricular conduction abnormalities were noted in the gabapentin group, while amitriptyline was linked to QT prolongation, torsade de pointes and sudden cardiac death. For these reasons, the use of both drugs in selected patients and with proper monitoring may be considered. Several invasive options have been proposed, including the use of continuous regional anaesthesia with epidural or peripheral catheters, which demonstrate a reduction in pain score and improvement in function score at short- and long-term follow-up. On the other hand, in the Donado et al. series [15], 39% of the sample did not clinically improve the pain symptoms, and 43% had no functional advantages. Nevertheless, the authors suggested the treatment in addition to an active PT + CBT protocol. All the studies included in the systematic review emphasized the utility of PT + CBT, even when additional approaches were undertaken. The comparison of management with versus without rehabilitation was considered ethically unacceptable [2]; however, the outcome can be not related to a single treatment, and the results have been influenced by conservative treatment even in pharmacologic protocol studies. Future research directions should focus on the identification of disease onset mechanisms and the development of more defined, proper and easy-to-use diagnostic tools. The design of high-quality, prospective, large-

cohort, long-term follow-up studies is strongly encouraged, as is design of a specific assessment score. The heterogeneity of the scores utilized in the objective clinical assessment of the patients, the absence of standard protocols, and the lack of randomized, blinded prospective trials are the main limits in the comparison of study results.

Conclusion

In conclusion, conservative treatment (physical, occupational, and cognitive behavioural therapy) is the recommended option in the management of paediatric CPRS. Pharmacological therapy should be reserved for refractory and selected patients. The design and development of standard protocols are strongly suggested.

Abbreviations

Complex regional pain syndrome = CRPS; reflex sympathetic dystrophy = RSD; Preferred Reporting Items for Systematic Reviews and Meta-Analyses = PRISMA; Newcastle-Ottawa Quality Assessment Scale Cohort Studies = NOS; physical therapy = PT; cognitive behavioural therapy = CBT; pharmacological treatment = PhT

Declarations

Ethics approval and consent to participate.

Not applicable

Consent for publication.

Not applicable

Availability of data and materials.

The datasets used and/or analyzed during the current study are available from authors on reasonable request.

Competing interests.

The author GT declares to be a member of the editorial board of BMC Musculoskeletal disease. Other authors declare that they have no competing interests.

Funding.

None declared.

Authors' contributions.

AV: Study idea, Study design, Data analysis, Manuscript preparation and review, Final approval of manuscript. GT: Study idea, Study design, Manuscript review, Final approval of manuscript. AC: Data collection, Data analysis, Final approval of manuscript. MS: Data collection, Final approval of manuscript. FV: Data collection, Final approval of manuscript. FDM: Data collection, Final approval of manuscript. VP: Study idea, Study design, Manuscript review, Final approval of manuscript. All authors have read and approved the manuscript.

Acknowledgements.

Not applicable

References

1. Chang C, McDonnell P, Gershwin ME. Complex regional pain syndrome - False hopes and miscommunications. *Autoimmun Rev.* 2019;18(Suppl 3):270–8.
2. Lascombes P, Mamie C. Complex regional pain syndrome type I in children: What is new? *Orthop Traumatol Surg Res.* 2017;103(Suppl 1):135–42.
3. Barrett MJ, Barnett PLJ. Complex regional pain type 1. *Pediatr Emerg Care.* 2016;32(Suppl 3):185–9.
4. Rabin J, Brown M, Alexander S. Update in the Treatment of Chronic Pain within Pediatric Patients. *Curr Probl Pediatr Adolesc Health Care.* 2017;47(Suppl 7):167–72.
5. Weissmann R, Uziel Y. Pediatric complex regional pain syndrome: a review. *Pediatr Rheumatol Online J.* 2016;14 Suppl 1:29.
6. Williams G, Howard R. The Pharmacological Management of Complex Regional Pain Syndrome in Pediatric Patients. *Paediatr Drugs.* 2016;18(Suppl 4):243–50.
7. Xu J, Yang J, Lin P, Rosenquist E, Cheng J. Intravenous Therapies for Complex Regional Pain Syndrome: A Systematic Review. *Anesth Analg.* 2016;122(Suppl 3):843–56.
8. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
9. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;25(Suppl 9):603–5.
10. Sherry DD, Wallace CA, Kelley C, Kidder M, Sapp L. Short- and long-term outcomes of children with complex regional pain syndrome type I treated with exercise therapy. *Clin J Pain.* 1999;15(Suppl 3):218–23.

11. Lee BH, Scharff L, Sethna NF, et al. Physical therapy and cognitive-behavioral treatment for complex regional pain syndromes. *J Pediatr*. 2002;141(Suppl 1):135–40.
12. Logan DE, Carpino EA, Chiang G, Condon M, Firn E, Gaughan VJ. A day-hospital approach to treatment of pediatric complex regional pain syndrome: initial functional outcomes. *Clin J Pain*. 2012;28 Suppl 9.
13. Petje G, Radler C, Aigner N, Walik N, Kriegs Au G, Grill F. Treatment of reflex sympathetic dystrophy in children using a prostacyclin analog: preliminary results. *Clin Orthop Relat Res*. 2005;(433):178–82.
14. Brown S, Johnston B, Amaria K, Watkins J, Campbell F, Pehora C, McGrath P. A randomized controlled trial of amitriptyline versus gabapentin for complex regional pain syndrome type I and neuropathic pain in children. *Scand J Pain*. 2016;13(Suppl 1):156–63.
15. Donado C, Lobo K, Velarde-Álvarez MF, et al. Continuous Regional Anesthesia and Inpatient Rehabilitation for Pediatric Complex Regional Pain Syndrome. *Reg Anesth Pain Med*. 2017;42(Suppl 4):527–34.
16. Berde CB, Lebel A. Complex regional pain syndromes in children and adolescents. *Anesthesiology*. 2005;102(Suppl 2):252–5.
17. Dickson SK. Including Parents in the Treatment of Pediatric Complex Regional Pain Syndrome. *Pediatr Nurs*. 2017;43(Suppl 1):16–21.
18. Frot M, Faillenot I, Mauguière F. Processing of nociceptive input from posterior to anterior insula in humans. *Hum Brain Mapp*. 2014;35(Suppl 11):5486–99.
19. Lebel A, Becerra L, Wallin D, Moulton EA, Morris S, Pendse G, Jasciewicz J, Stein M, Aiello-Lammens M, Grant E, Berde C, Borsook D. fMRI reveals distinct CNS processing during symptomatic and recovered complex regional pain syndrome in children. *Brain*. 2008;131(Pt 7):1854–79.
20. Linnman C, Becerra L, Lebel A, Berde C, Grant PE, Borsook D. Transient and persistent pain induced connectivity alterations in pediatric complex regional pain syndrome. *PLoS One*. 2013;8(Suppl 3):e57205.
21. Diers M, Yilmaz P, Rance M, Thieme K, Gracely RH, Rolko C, Schley MT, Kiessling U, Wang H, Flor H. Treatment-related changes in brain activation in patients with fibromyalgia syndrome. *Exp Brain Res*. 2012;218(Suppl 4):619–28.
22. Kregel J, Coppieters I, DePauw R, Malfliet A, Danneels L, Nijs J, Cagnie B, Meeus M. Does Conservative Treatment Change the Brain in Patients with Chronic Musculoskeletal Pain? A Systematic Review. *Pain Physician*. 2017;20(Suppl 3):139–54.
23. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmader KE, Stacey B, Stanos S, Treede RD, Turk DC, Walco GA, Wells CD. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. 2010;85 Suppl 3:3–14.
24. Kremer M, Salvat E, Muller A, Yalcin I, Barrot M. Antidepressants and gabapentinoids in neuropathic pain: Mechanistic insights. *Neuroscience*. 2016;338:183–206.

Figures

Figure 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart of the systematic literature review

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Editingcertification.pdf](#)