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Current Concepts in Physiatric Pain Management

Managing Chronic Pain in Children and Adolescents: A Clinical Review

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Abstract

Chronic pain in children and adolescents can be difficult for a single provider to manage in a busy clinical setting. Part of this difficulty is that pediatric chronic pain not only impacts the child but also the families of these children. In this review article, we discuss etiology and pathophysiology of chronic pain, along with variables that impact the severity of chronic pain and functional loss. We review diagnosis and management of selected chronic pain conditions in pediatric patients, including headache, low back pain, hypermobility, chronic fatigue, postural orthostatic tachycardia syndrome, abdominal pain, fibromyalgia, and complex regional pain syndrome. For each condition, we create a road map that contains therapy prescriptions, exercise recommendations, and variables that may influence pain severity. Potential medications for these pain conditions and associated symptoms are reviewed. A multidisciplinary approach for managing children with these conditions, including pediatric pain rehabilitation programs, is emphasized. Lastly, we discuss psychological factors and interventions for pediatric chronic pain and potential complementary and alternative natural products and interventions.

Introduction

A clinical review of pediatric chronic pain requires an understanding of etiology, biology, and current clinical management perspectives in treating children and adolescents with variable presenting features associated with chronic pain. Even though the focus of this article is on the pediatric patient with chronic pain, there are limited empirical data related to the treatment of many chronic pain conditions in this population. Therefore, this review is not systematic but represents the clinical expertise of the authors, combined with the current available data when the greatest level of evidence was limited or extrapolated from the adult literature. The purpose of this review is to help guide the clinician in improving the pain and function of the pediatric patient with chronic pain. Emerging evidence regarding the lack of effectiveness in medication-based treatments alone emphasizes the role of a multidisciplinary approach and continues to expand our understanding of the challenges facing the management of chronic pain in children and adolescents.

Prevalence of Pain in Children

Pain is common in children and adolescents, with estimates ranging from 20% to 46% of children worldwide affected by varying types of chronic pain [2,3]. In adults, it is estimated that 19%, or 39.4 million, of Americans suffer from chronic pain, with two-thirds of those reporting their pain as "constantly present," and 50% as "unbearable and excruciating" [4]. In children and adolescents, Mikkelsson et al [5] found that as many as one-third experience some manner of weekly musculoskeletal pain. The greatest risk of developing persistent pain was seen in individuals with day-time fatigue, headache, or those participating in vigorous activity and hence more likely to experience some sort of traumatic event [6].

The reason for any perceived or actual increase in the rate of childhood chronic pain is unclear but probably multifactorial. Increased pain identification, stress and anxiety, poor role-modeling, and maladaptive pain behaviors and attitudes are all areas of concern. The Institute of Medicine's report in 2011 on chronic pain

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proposed that, in many cases, chronic pain is a disease in its own right and therefore demands direct, appropriate treatment [7]. Perhaps a greater recognition of chronic pain syndromes by the public together with the development of new treatments is triggering families to seek potential solutions for conditions that historically were considered untreatable.

Impact of Pain on Children and Families

Many of these children experience significant physical, psychological, and social sequelae that affect not only themselves but also family and friends. There is a substantial financial burden on the individual and family, with direct and indirect costs of health care use and lost wages. The economic impact on society as a whole is large. A 2014 report estimation of total health care costs for adolescents with moderate-to-severe chronic pain to be around $19.5 billion annually in the United States [8]. In comparison, estimates for adults with chronic pain reach upwards of $500-600 billion annually [7]. In addition, childhood pain is not necessarily an isolated event of growth and development that improves with age. Convincing evidence exists that childhood chronic pain predisposes an individual, not only for continuation of pain, but also for development of new and different types of pain into adulthood [9].

Etiology and Pathophysiology of Chronic Pain

Various concepts have emerged that begin to explain the clinical presentation of chronic pain. There exists a complex interaction between primary afferent nerves, dorsal horn neurons, spinal glia, neurotransmitters, and other factors that propagate and perpetuate the symptoms of chronic pain. Many individuals present with chronic pain well after the damage from an acute injury has resolved. During an acute injury, damaged or inflamed tissues release growth factors and procytokines among other neuromediators. The release of similar mediators in the spinal cord is triggered, which then activates and up-regulates certain phenotypes of spinal glia, thus altering their activity and leading to an overall increase in excitability [10]. Central sensitization with wind-up phenomenon describes this state of dysregulated nociception with increased dorsal horn activity, which then triggers an exaggerated response to both painful (hyperpathia) and nonpainful (allodynia) stimuli over a wide anatomic field. This process may not only happen with direct physical injury but also after illness, significantly traumatic psychological events, uncontrolled stress, and even physical inactivity [11-14].

Changes in neurotransmitter function may play a role in chronic pain as increased levels of substance P and glutamate increase sensitivity to pain, whereas decreased levels of inhibitory serotonin and noradrenaline seem to limit the body's ability to diminish the pain response [15-17]. Brain-derived neurotrophic factor is of potential interest because of its presence in and proposed impact on peripheral and central nervous systems. Brain-derived neurotrophic factor has been found to initiate neuronal repair but unfortunately also causes increased pain by both increasing the excitatory and reducing the inhibitory transmission in the dorsal horn [10]. Alterations in neurotransmitter regulation in the spinal cord appear to correlate with other changes along the hypothalamus-pituitary axis and are influenced, or affected by, stress, physical activity level, illness, sleep patterns, and more [13,16-20]. There are perhaps even epigenetic factors influencing an individual's response to stress and pain that are related to significant early life stressors or abuse [11,21].

Variables That Perpetuate Chronic Pain

In addition to the biology of chronic pain, there are psychological characteristics such as emotional, cognitive, and behavioral factors that also influence pain. The emotional and cognitive factors include fear and avoidance of pain, maladaptive strategies for coping with pain, and influences of anxiousness and depressive symptoms. Other potential confounders of chronic pain for children and adolescents are parental behaviors regarding pain and cultural expectations about pain (Figure 1).

Although some youth with chronic pain have premorbid anxiety and depression, many develop anxiety and depression as a result of their pain. When a child has chronic pain that prevents him or her from participating in preferred activities such as sports and extracurricular activities, the loss of activities can also lead to a loss of positive reinforcement, friendships, and lower self-esteem, which can result in depression. Similarly, youth who have missed school and social opportunities may develop anxiety related to the stress of returning to school and other activities.

Pediatric patients with chronic pain often have older relatives with chronic pain and thus learn the meaning of pain and acceptable coping strategies in part by watching family members' response to pain [22]. A teenager who watches a parent cope with his chronic migraines by resting, staying home from work, and complaining may develop a different understanding of pain than a teenager who observers his parent cope with pain by using strategies such as relaxation, moderation, and continuing responsibilities. In addition to modeling pain coping strategies, parents' own distress and cognitions regarding their child's pain as well as their reaction to their child's pain influences pain intensity, expression, and disability [22]. For example, parental solicitous responses increased sick-role and pain behaviors in youth with recurrent abdominal pain [23,24].

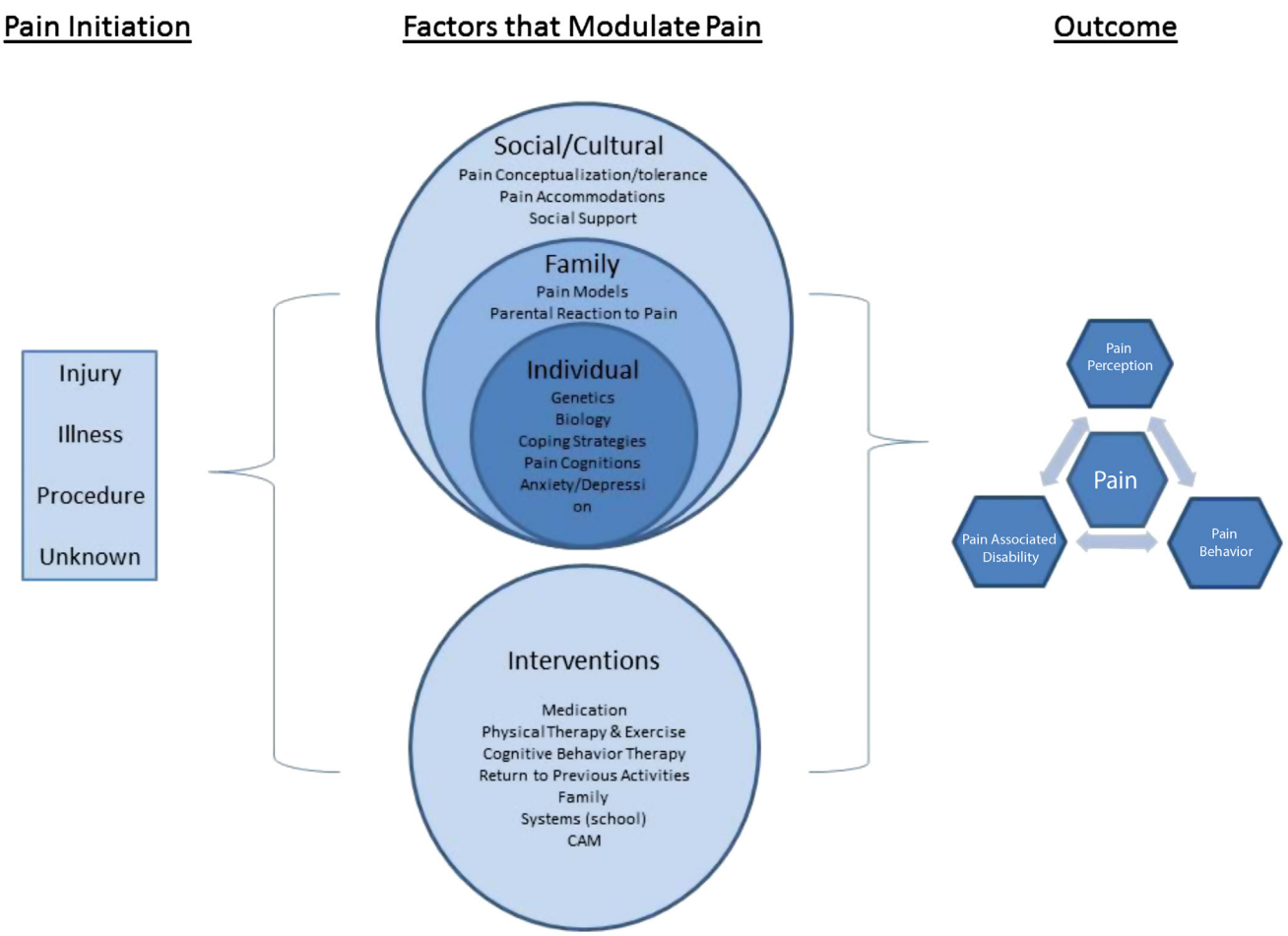

Figure 1. Variables that modulate pain.

Furthermore, parental protective behaviors such as allowing a child to miss school increased functional disability, particularly in anxious children [23-25].

A final factor that perpetuates chronic pain goes beyond the family system to consider the larger culture that surrounds the youth with pain. Over time, Western culture's conceptualization of pain has changed from one of "integrated pain" in which pain is considered a natural part of human life to "naked pain," in which pain is regarded as a neurogenic phenomenon that belongs in the medical world [26]. Perhaps as our ability to treat pain has increased, our tolerance for pain has changed as well.

Clearly, chronic pain in children and adolescents is multifactorial and multidimensional. Therefore, a multidisciplinary approach for addressing chronic pain in this population is important. In this article, we will first discuss 8 of the more common pediatric chronic pain conditions, outlining a road map of therapeutic interventions for each condition. This road map offers input on various treatments to consider when evaluating a child with chronic pain in your rehabilitation practice. For some conditions, we discuss medications and pediatric dosing for managing the pain disorder, such as migraines, or associated symptoms, such as poor sleep. We will then discuss the psychological aspects of chronic pain in children and adolescents, multidisciplinary pediatric pain rehabilitation programs, and lastly use of complimentary and integrative medicine interventions. Figure 2 is a general physical therapy prescription for the child with chronic pain. For each of the 8 chronic pain conditions we discuss, a "Therapeutic Opportunities" figure follows. These boxes are meant to serve as a reference for symptom specific treatment approaches based on the clinical presentation.

Clinical Presentation and Biologic Treatment of Specific Chronic Pain Conditions

Abdominal Pain

Abdominal pain-related functional (ie, without an identifiable organic disorder) disorders affect 20% of the world's children [27]. Irritable bowel syndrome is diagnosed in approximately half of these children, and functional dyspepsia and abdominal migraines represent other diagnoses [27]. Affected children and adolescents have decreased quality of life, increased signs of

Therapy Prescription:

- Review aerobic exercise principles with an ultimate goal of 60 minutes or more of developmentally appropriate and varied aerobic activity daily. This activity should include at least moderate-intensity aerobic physical exercise every day, with at least 3 days per week at a vigorous-intensity level.
- Assessment of biomechanics in functional activities that may be pain or symptom producing.
- Progress to sports-specific functional activities such as drills, plyometrics, etc., when able.
- Limited use of modalities such as heat, ice, TENS, or manual therapy can be applied as a means to facilitate increased participation in functional exercises.
- Promote long term compliance through use of diaries, pedometers or fitness trackers.
- Education on consistent activity level and pacing as it relates to prolonged positioning and ergonomics at home and school.

* Moderate intensity exercise = 3-6 METs (Metabolic Equivalents). Vigorous intensity exercise = >6 METs

Figure 2. General therapy prescription for a child with chronic pain.

depression, social isolation, and frequent school absences [28]. Diagnostic evaluation costs an average of $6000 per child [28]. The diagnosis of functional abdominal pain usually is made with Rome III criteria, which include: (1) episodic or continuous abdominal pain; (2) insufficient criteria for other functional gastrointestinal disorders; and (3) no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the symptoms [29].

Chronic idiopathic nausea can occur without significant pain and seems to be more severe, more frequent, and more likely to occur in older adolescent females than the nausea associated with functional abdominal pain [30]. Interestingly, abdominal pain also can increase in the upright (versus supine) position in adolescents with postural orthostatic tachycardia syndrome, or POTS, which is discussed later in this paper; this may relate to positional alterations in gastric electrical activity [31].

Underlying organ-specific causes of abdominal pain deserve specific treatment, and associated aggravators of chronic abdominal pain also should be treated as appropriate for individual patients, including acid-related disorders (antacids), dysmotility (possibly pro-motility agents), food intolerances (dietary restriction if lactose- or fructose-intolerant, gluten restriction if celiac disease), and bacterial overgrowth (appropriate antibiotic). However, the mainstay of treatment of abdominal pain is a rehabilitative approach with restoration of regular meal schedules, physical therapy (Figure 3), daily exercise and physical activity, and healthy sleep schedules [32].

Cognitive behavioral therapy (CBT) is effective for abdominal pain as well as for other specific chronic pains [28]. Transcutaneous electrical nerve stimulation units also can help diminish transmission of pain signals and improve abdominal pain in some children [33]. Pharmacologic agents often are used, although a real

Therapeutic Opportunities: Refer to generalized therapy prescription (Figure 2). Consider also including:

- Core stability assessment and training.
- Work to improve control & decrease reflex over-activation of abdominal muscles at rest then dynamically. If applicable, can consider ultrasound assisted neuromuscular re-education of transversus abdominis.
- Cross-fiber massage, myofascial release, or desensitization massage to myofascial trigger point.
- Biofeedback for posture re-education.
- Review posture principles and exercises to encourage upright posture maintenance during activities and at rest (i.e. neutral cervicothoracic posture, keep shoulders back).
- Educate on lifting biomechanics.

Figure 3. Therapeutic opportunities for chronic abdominal pain.

evidence base is lacking for many abdominal pain medications [27,29]. Tricyclic agents such as amitriptyline (starting dose 0.5 mg/kg/day, with a target dose typically 1-2 mg/kg/day) seem to help some patients [34] but are not uniformly helpful [35]. Selective serotonin reuptake inhibitors such as citalopram (starting dose 10 mg/day, target dose 40 mg/day maximum) similarly seem useful for some people [36], but larger more definitive studies are lacking [29]. Other widely tried measures do not seem to be helpful, based on limited studies, including probiotics [27] and fiber supplements [37]. Narcotics can aggravate chronic abdominal pain, have side effects, and should be avoided [38].

Low Back Pain

The true prevalence of low back pain in children is difficult to determine and depends on the definition used and data collection methodology. Pellise et al [39] reported a 1-month prevalence of low back pain in 40% of adolescents. Most had mild pain, but those who also had whole-body pain experienced more significant impairment. Girls were more likely to experience low back pain with whole-body pain than boys. In a longitudinal cohort study, Kjaer et al [40] estimated the 1-month back pain prevalence in 9-year-olds to be 4%, 13-year-olds to be 22%, and 15-year-olds to be 36%. Those who previously reported back pain were more likely to report it on a subsequent survey. After a systematic literature review, Jeffries et al [41] concluded that prevalence of low back pain increases during the adolescent period and reaches adult levels around age 18. Girls were noted to have earlier onset and greater prevalence than boys. Wirth et al [42] found risk factors to include parental reports of back pain and spinal asymmetry in girls and parental smoking in both genders.

The evaluation of back pain in a child or adolescent should always include questions about inciting event, quality, duration and location of pain, and "red flag" symptoms as well as a thorough musculoskeletal and neurological exam. Constant, night, persistent or severe pain, abnormal neurological examination findings, fever, weight loss, malaise, stiffness, rapidly progressive scoliosis, and trauma should prompt further investigation. Radiographs and single-photon emission computed tomography bone scans may identify etiologies such as spondylolysis/listhesis, Scheuermann disease, and other bony lesions. The extra radiation with obliques is typically avoided in children. Magnetic resonance imaging is helpful in identifying infectious, inflammatory, or mass lesions.

Treatments and prevention for low back pain in this population include postural education and hygiene, the practice of physical therapy exercise and regular physical activity (Figure 4). Physical therapy conditioning and supervised exercise has been shown to be effective for improving back pain in this population [43,44]. Aerobic exercise recommendations are similar to the typical adolescent population with working towards 30-60 minutes per day of continuous activity. Greater-intensity aerobic exercise has been shown to improve chronic low back pain over passive modalities [45].

In a meta-analysis, Michaleff et al [44] found moderate quality evidence to support a short-term exercise program in reducing back pain in children and adolescents (perhaps a better effect in the pediatric population compared with adults) but no evidence to support back education programs for prevention of back pain.

Chronic Fatigue

Chronic pain and chronic fatigue are each common, with the 2 symptoms often co-existing. In a population-based study of early adolescents, 24% had back pain, 29% had headache, 21% had stomachache, and 31% had morning fatigue at least 2 mornings each week [46]. Longer-lasting, more severe fatigue also is fairly common. In a study from Holland, 21% of adolescent girls and 7% of adolescents boys have severe fatigue, with nearly 47% of the severely fatigued girls and 35% of the severely fatigued boys describing long-term fatigue of

Therapeutic Opportunities: Refer to generalized therapy prescription (Figure 2). Consider also including:

- Manual therapy for low back and hip range of motion.
- Core stability assessment and training.
- Direction-specific stretching to enhance trunk and hip range of motion but does not increase back pain.
    - Two minutes per muscle group, hold position for 30 seconds
- Strengthening of lumbar extensors. Begin at 10-15 reps per day.
- Review posture principles and exercises to encourage upright posture maintenance during activities and at rest (i.e. neutral cervicothoracic posture, keep shoulders back).

Figure 4. Therapeutic opportunities for chronic back pain.

greater than 3 months [47]. In the United Kingdom, 1.1% of adolescents are significantly impaired with chronic fatigue [48].

Fatigue can occur with nonpainful medical conditions during adolescence, such as hypothyroidism, celiac disease, inflammatory disorders, renal insufficiency, and infections. Chronic fatigue was defined in 1994 for research purposes as clinically evaluated, unexplained, persistent, or relapsing fatigue of known onset (not lifelong) that is not simply related to exertion and that is not fully alleviated by rest while resulting in significant reduction in previous levels of activity [49]. This definition also includes the presence of associated symptoms such as memory impairment, sore throat, lymphadenopathy, and non-restorative sleep [49]. More recently, chronic fatigue syndrome was relabeled systemic exertion intolerance disorder in an attempt to better link research definitions and clinical descriptions [50]. Many patients with chronic fatigue, however, also seem to have significant autonomic dysfunction, and many have POTS (discussed later in this paper) [32,51].

A variety of treatments have been proposed for chronic fatigue in adolescents, but most have not been subjected to rigorous evaluation. Some treatments, however, are known to be useful. Scheduled incrementally increasing exercise programs are more effective than exercise programs that are "paced" according to what the patient feels like (Figure 5) [52]. CBT is effective in decreasing fatigue, increasing school participation, and improving physical functioning, with the gains sustained over months [52,53]. CBT is effective for at least 60% of chronically fatigued adolescents [54]. Interestingly, CBT is effective whether in face-to-face or internet settings [52]. Thus, the often common approaches to fatigue (rest, affirmation of the patient's disability) appear to be counter with commitment to exercise and psychological approaches.

Complex Regional Pain Syndrome (CRPS)

CRPS is a distinct disorder of a localized region that is characterized by pain, allodynia, swelling, limited range of motion, vasomotor instability, changes in skin texture or color, and bone demineralization. It often begins after an inciting event such as injury or surgery, and typically follows a course of various stages, although the presentation and clinical course is perhaps not as defined or severe in children [55-57]. The changes in nosology over the years, with varied presentations, emphasizes the importance to understanding alternative diagnoses when an individual's pain cannot be accurately described by this specific label.

CRPS has numerous expressions in addition to pain including autonomic dysfunction, disordered sleep, increased stress, conversion symptoms, eating disorders, and even self-injurious behaviors [58,59]. Identification and management of each of these is essential in returning the individual to a prior level of function and may require further consultation with the appropriate specialists in psychiatry or sleep medicine.

Children may have a better outcome and be more responsive to conservative measures than adults. Treatment in adolescents should be initiated with physical therapy, occupational therapy, and CBT [60]. Medications and other adjunctive therapies are facilitatory and are seldom, if ever, adequate as sole treatment options for CRPS rehabilitation for adolescents with CRPS (Figure 6) typically entails desensitization to

Therapeutic Opportunities: Refer to generalized therapy prescription (Figure 2). Consider also including:

- Focus on aerobic activities to prevent deconditioning and maintain functional work capacity. [1]
  - RPE 9-12/20
  - Intensity not main focus
  - 3-5 days/week
  - 1-2 session per day
  - 5 minutes/session progressing to 60 minutes/session as tolerated
- Flexibility exercises to maintain range of motion.
- Review posture principles and exercises to encourage upright posture maintenance during activities and at rest (i.e. neutral cervicothoracic posture, keep shoulders back).
- Core stability assessment and training.
- Functional exercises of upper and lower extremities to promote strengthening in non-pain-provoking manner. Can begin with isometrics and progress to isotonics as tolerated using bands or light weights. Focus should be on proper technique and not significantly increasing weight. Distinction also needs to be made between training-related pain and exacerbation of typical pain.

Figure 5. Therapeutic opportunities in chronic fatigue.

Therapeutic Opportunities: Refer to generalized therapy prescription box above. Consider also including:

- Desensitization, reactivation.
- Flexibility and strengthening of affected muscle groups.
- Ergonomics, movement therapy, normalization of use with functional rehab.
- Graded exposure through all therapeutic interventions.
- Education on avoiding overexertion and instruct in pacing strategies.
- Distraction with functional activities while using affected body part to promote desensitization and proper use.
- Progress to return to functional activity such as sports.

Figure 6. Therapeutic opportunities in complex regional pain syndrome.

the affected limb, gradually increasing exposure to functional activities with strengthening, stretching for affected muscle groups, weight-bearing and then neuromuscular re-education to return to normal functional movement of the affected area [60]. This can typically take between a few sessions to a few weeks and varies between patients, but initial exercise intensive therapy has been shown effective for treating CRPS in children [55,61,62].

Juvenile-Onset Fibromyalgia (JFM)

The identification of JFM is controversial and remains a clinical diagnosis. Both the American College of Rheumatology guidelines on diagnosis of fibromyalgia and Yunus and Masi classification have been used in JFM [63-65]. Both of these systems include widespread pain and acknowledge associated symptoms, including fatigue and sleep disturbances. JFM is estimated to impact 2.1%-6.1% of children, with the majority being female adolescents [17]. The etiology of JFM is not known, but similar to adult fibromyalgia, is thought to involve central sensitization in combination with peripheral nervous system factors, genetic and biochemical predisposition, and psychosocial and environmental influences. Adding to the complexity of JFM are the many associated symptoms including fatigue, cognitive fogginess, sleep difficulties, mood disturbances, migraines, irritable bowel syndrome, and dysautonomias [17]. Individuals with JFM may have difficulties with physical function caused by pain, decreased quality of life, and greater time spent sedentary [66-69]. They have difficulty with school attendance with high rates of absenteeism or inability to attend school altogether [70].

Regardless of what the underlying mechanistic cause is, exercise can improve aerobic function, mood, and global well-being in addition to possibly decreasing tender points and pain [71]. Recommendations for aerobic exercise have suggested more benefit in pain reduction than just resistance training in patients suffering from fibromyalgia [72]. Aerobic exercise can be land or water-based and should be tailored to the individual's interests to maintain enjoyment and compliance in the program (Figures 2 and 7). Häuser et al [73] conducted a meta-analysis and systematic review in 2010 investigating patients ages 13-59. They did not delineate between the age groups and ultimately recommended beginning with an aerobic exercise program for 2-3 days per week of slight to moderate

Therapeutic Opportunities: Refer to generalized therapy prescription (Figure 2). Consider also including:

- Beginning with low impact, closed kinetic chair aerobic exercises, 2-3 days per week.
- Core stability assessment and training.
- Functional exercises of upper and lower extremities to promote strengthening in non-pain-provoking manner. Can begin with isometrics and progress to concentrics as tolerated using bands or light weights. Minimize eccentric contractions. Focus should be on proper technique and not significantly increasing weight. Distinction also needs to be made between training-related pain and exacerbation of typical pain.
- Review posture principles and exercises to encourage upright posture maintenance during activities and at rest (i.e. neutral cervicothoracic posture, keep shoulders back).

Figure 7. Therapeutic opportunities in juvenile-onset fibromyalgia.

intensity for 4 weeks in all patients with fibromyalgia. Although this is notably less than the current recommendations for 1 hour of moderate-to-vigorous aerobic-based exercise per day for healthy children, excessive bouts of exercise could possibly exacerbate the problem. In studies in adults, it appears that more intense exercise may worsen symptoms, although a supervised moderate-intensity exercise program appears to be reasonable without increasing symptoms in children [74]. The benefits of improvement in physical function, JFM symptoms, quality of life, and pain from this more conservative level of activity seem to be short-lived, as long term benefits have not been demonstrated and adherence to an exercise program can be poor [17]. A multidisciplinary treatment program may be helpful in motivating a young patient to actively participate in exercise.

Headache

Headache is present at all ages in childhood; 4% of preschool children, 10% of school-aged children, and 16% of young women experience headache. Chronic headache defined as greater than 15 days with headache per month for more than 3 months occurs in 1% of early school-aged children, 0.8% of middle-school boys, 2.4% of middle-school girls, 2% of men, and 4% of women [75-77]. The most common forms of headache to present to the physician's office are typically migraine.

Diagnostically, children with papilledema, focal neurologic deficits, or a recent history of seizures should be referred to the appropriate specialist or emergency department for consideration of advanced imaging of the head, such as computed tomography or magnetic resonance imaging. Blood and urine tests are rarely useful when headache is the sole presentation [78,79].

Therapy is divided into 5 categories of interventions. First, lifestyle changes are reviewed, because sleep deprivation, missing meals (particularly breakfast), and busy schedules are often triggers. Anxiety is a frequent co-morbid factor.

Second, acute pain relief is offered for the most severe headache. With migraines, most patients will do well with ibuprofen (10 mg/kg/dose), acetaminophen (15 mg/kg/dose), or a triptan [80]. Opioid and barbiturate containing drugs should be avoided, as these are generally believed to lead to the chronification of migraine [81].

Third, prevention can be accomplished with the use of a daily medicine (Table 1) [82-84]. High-quality evidence currently is lacking as to which approach is the best, but most headache experts will start with either amitriptyline (starting dose 0.5 mg/kg/day, with a target dose typically 1-2 mg/kg/day), topiramate (starting dose 0.5 mg/kg/day, target dose of 2 mg/kg/day), or propranolol (starting dose 1 mg/kg/day, target 1-3 mg/kg/day). The goals are a reduction in days of severe headache, although completely headache freedom is infrequently achieved [83]. Additional medications can be tried if side effects, lack of efficacy, or allergy occur with use of these first-line medications.

Fourth, biobehavioral approaches are useful. There is high-quality evidence that shows that CBT is effective [85]. Biofeedback, relaxation therapy, treatment of anxiety, improved sleep hygiene, and increased school attendance are all useful goals of therapy.

Fifth, physical therapy can be a helpful discipline for headache management (Figure 8). The focus of intervention should be toward more active approaches over passive activities or interventions. Activities should be guided by the child's or adolescent's activity tolerance with gradual progression in difficulty. Aerobic exercise programs that are enjoyable are more favorable for patient compliance. Starting with a few minutes of aerobic exercise a day may be appropriate, with a goal of working up to between 30 and 60 minutes of continuous activity [86]. The use of a perceived exertion scale (such as the Borg Rating of Perceived Exertion Scale) can be useful for self-pacing while the patient performs the aerobic activities.

Often the symptoms of sleep and anxiety need to improve first before significant progress is made in controlling the headache. It is a challenge, as worsening headaches often exacerbate sleep problems and anxiety. The preventative medications are most useful to decrease the number of severe headache days. Lifestyle change, behavioral techniques and exercise seem to be most helpful when a daily headache is present. Most patients seem to have a reduced headache burden in the summer, although the start of a new school semester (either in September or January), seems to usher in worsening headache control [83].

Hypermobility With Pain

Joint hypermobility often is a relatively benign familial phenotypic trait, but it can also be seen in connective tissue disorders such as Marfan or Loeys-Dietz syndrome, or aneuploidies such as Down or Turner syndrome. The relationship between hypermobile joints and pain is unclear [87,88]. Even though many studies have shown an increased incidence of pain or injury in certain populations with hypermobility [89-91], others have shown no such increase in individuals with generalized joint hypermobility or joint pain [92,93]. Still there is other evidence that demonstrates a protective aspect of hypermobility with regards to certain types of arthritis or injury [94,95].

The clinical presentation of a child with hypermobility and pain is quite variable, but evidence indicates that decreased muscle strength, reduced endurance, impaired functional performance, increased fatigue, and impaired quality of life are common [96,97]. Although many children are instructed to limit or cease

Table 1
Chronic pain medications

Class	Generic Name	Mechanism of Action [82]	Common Indications [82]	Dosing Considerations [32,83]	Notable Side Effects [82]	Additional Information [32,82-84]
Antidepressant	Amitriptyline	Tricyclic antidepressant; may block serotonin and norepinephrine uptake	FDA approved: • Depression* Off label: • Neuropathic pain • Headache • Sleep disturbance • Fibromyalgia • Postherpetic neuralgia	• Start with 10 mg (or 0.2 mg/kg for patient smaller than 50 kg) 2 hours before bedtime • Increase by 10 mg every week • Target dose is typically 0.5-1 mg/kg/d, although some may need up to 3 mg/kg/d • Typical adult dose is up to 150 mg/d	• Black box warning: increased risk of suicidal thinking and behavior • Dry mouth • May prolong QT interval • Morning sleepiness • Weight gain	• Consider ECG before initiation (QT interval) and at greater doses (~1 mg/kg/dose) • Check blood level at doses of 50 mg and again at 100 mg (total therapeutic concentration for amitriptyline and nortriptyline 80 to 120 ng/mL) • Encourage trial of 6 mo • Not available in oral solution • Available intravenously
	Nortriptyline	Tricyclic antidepressant; may block serotonin and norepinephrine uptake	FDA approved: • Depression† Off label: • Headache • Irritable bowel syndrome • Low back pain • Neuropathic pain • Sleep disturbance • Post-herpetic neuralgia	• Starting dose, titration, and target dose same as amitriptyline	• Side effects similar (although typically less severe) to amitriptyline	• Same as amitriptyline • Available as oral solution • Comes as capsules, not tablets, so cannot be cut
	Duloxetine	Serotonin and norepinephrine reuptake inhibitor; weak inhibitor of dopamine reuptake	FDA approved: • Diabetic peripheral neuropathic pain‡ • Generalized anxiety disorder§ • Generalized musculoskeletal pain‡ • Fibromyalgia‡ • Major depression‡	• May start at 20-30 mg/d increasing to 60 mg/d maximum (doses for depression are up to 120 mg/d)	• Black box warning: Increased risk of suicidal thinking and behavior • Dizziness • Dry mouth • Nausea • Orthostatic hypotension at initiation • Sleepiness	• Once-daily dosing may help compliance • Avoid in liver and end-stage kidney disease • Not available in oral solution
	Citalopram	Selective serotonin reuptake inhibitor, minimal effect on norepinephrine and dopamine reuptake	FDA approved • Depression‡ Off label: • Chronic fatigue syndrome • Abdominal pain • Body dysmorphic disorder • Depression (pediatric)	• Starting dose 10 mg/d, increasing to 40 mg/d maximum	• Similar to duloxetine • Black box warning: increased risk of suicidal thinking and behavior • Ejaculatory disorder and decreased libido	• Monitor for QT prolongation • Avoid in liver and end-stage kidney disease
Anticonvulsant	Gabapentin	Exact mechanism unknown; may act on voltage-gated calcium channel	FDA approved: • Postherpetic neuralgia‡ • Seizure‖ Off label: • Diabetic peripheral neuropathy • Fibromyalgia • Headache • Neuropathic pain	• For young children, start at 10 mg/kg/d in 3 divided doses; we start with bedtime dose and titrate up to 3 doses/d; increasing every 3-5 d • For older children and adolescents, start with 300 mg at night ×3 d, then 300 mg	• Increased suicidal thinking • Joint swelling • Mood swings • Sedation	• Adequate therapeutic trial is six months • Available in oral solution of 250 mg/5 mL

(*continued on next page*)

Table 1 (*continued*)

Class	Generic Name	Mechanism of Action [82]	Common Indications [82]	Dosing Considerations [32,83]	Notable Side Effects [82]	Additional Information [32,82-84]
			• Restless legs syndrome	BID ×3 d, then 300 mg TID ×3 d; maximum is 3600 mg/d. • Consider slower titration if there is a history of intolerances of other medications due to side effects.		
	Pregabalin	Exact mechanism unknown; may act on voltage-gated calcium channel	FDA approved: • Fibromyalgia‡ • Neuropathic pain‡ • Postherpetic neuralgia‡ Off label: • Generalized anxiety disorder • Headache • Restless legs syndrome	• Start with 50 mg at night then increase to BID dosing as tolerated • Alternate dosing schedule: 75 mg BID for 1 wk, 150 mg BID for 1 wk, 225 mg BID for 1 wk, then 300 BID thereafter • Maximum dose 600 mg/d in 2 divided doses	• Increased suicidal thinking • Increased appetite/ weight gain • Lower-extremity swelling • Sedation	• Most insurance companies require gabapentin trial before pregabalin Available as oral solution 20 mg/mL • A consideration for patients who had no improvement on gabapentin as it is more potent, has faster absorption, and greater bioavailability.
	Topiramate	Exact mechanism unknown; may bind voltage-gaited sodium channel; increase neuronal GABA; antagonize AMPA subtype of glutamate receptor; inhibit carbonic anhydrase enzyme	FDA approved: • Migraine prophylaxis* • Seizure¶ Off label: • Eating disorder • Obesity	• Start with 0.5 mg/kg and titrate over 3-4 wk • Target dose for migraines in children is 1-2 mg/kg/d • Typical adult dose is 100-200 mg/d	• Decreased appetite • Decreased sweating • Difficulty thinking and word finding • Kidney stones	• Watch for heat sensitivity or decreased sweating in those taking topiramate alone or in combination with other anticholinergic medications • Available as sprinkles
	Valproic acid	Exact mechanism unknown; increases concentration of GABA in brain	FDA approved: • Manic bipolar disorder‡ • Migraine prophylaxis‡ • Seizure**	• Start with 10 mg/kg/d • Target dose for migraines in children is 10-30 mg/kg/d • Typical adult dose is 500-1500 mg/d	• Mood swings • Rare liver and pancreatic problems • Teratogenic • Weight gain	• Females of childbearing age should use a method of birth control • Available in oral solution of 250 mg/5 mL
Anti-hypertensives	Metoprolol	Beta-adrenergic blocker with selective activity on beta-1 adrenoreceptors; may block beta-2 receptors at greater doses	FDA approved: • Cardiac disturbances‡(FDA approved for children 6 and older for hypertension only) Off label: • Migraine prophylaxis • POTS	• Dosing for POTS; 25 mg by mouth in morning and midday; smaller adolescents consider starting at 12.5 mg/dose; can titrate up to 50 mg per dose and up to TID • Target dose for migraines in children is 1-2 mg/kg/d	• Asthma exacerbation • Depression • Fatigue • Occasional exercise intolerance	• Anecdotally, long-acting forms are less effective for POTS symptoms • Can be compounded as an oral suspension
	Propranolol	Nonselective beta-adrenergic blocker; competitively binds beta-adrenergic receptors	FDA approved: • Cardiac disturbances‡ Off label: • Anxiety • Migraine prophylaxis	• Start with 1 mg/kg/d • Target dose for migraines in children is 1-3 mg/kg/d • Typical adult dose is 60-120 mg/d.	• Asthma exacerbation • Irritability • Nightmares • Occasional exercise intolerance	• Available in oral solution of 20 mg/5 mL, 40 mg/5 mL

	Verapamil	Calcium-channel inhibitor; specifically L-type calcium channel inhibitor (slow-channel blocker)	FDA approved: • Cardiac disturbances† Off label: • Arterial spasm in sub-arachnoid hemorrhage • Cluster headaches • Migraine prophylaxis	• Start with 1-2 mg/kg/d • Target dose for migraines in children is 1-6 mg/kg/d • Typical adult dose is 120-480 mg/d	• Constipation • Dizziness • May prolong QT interval • Need to follow QT interval on ECG at greater doses
Other	Midodrine	Alpha(1)- Agonist	FDA approved: • Orthostatic hypotension‡ Off label: • POTS • Syncope	• Dosing for POTS; 2.5 mg by mouth TID, increase to 10 mg per dose as needed	• Itchy scalp with rapid dose initiation • Supine headache if dose within 3-4 h of lying down

FDA = Food and Drug Administration; ECG = electrocardiogram; BID, twice per day; TID, 3 times per day; GABA = (gamma aminobutyric acid; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; POTS = postural orthostatic tachycardia syndrome.
Indicates FDA-approved Indications: *children 12 years through adults, †children and adults (age not specified), ‡adults only, §children 7 years through adults, ‖children 3 years through adults, ¶children 2 years through adults, and **children 10 years and older.

participation in high-impact activities, avoid resistance training, use assistive devices or braces, undergo corrective or stabilization orthopedic surgery, and follow-up with maintenance screening with expensive testing such as echocardiograms or dual-energy X-ray absorptiometry (DEXA) scans, there is limited evidence to support this approach. Recent evidence suggests that individuals who participate in an exercise program demonstrate improvements in pain, ratings of the impact of hypermobility, walking distance, quality of life, proprioception, balance, and strength [88,98]. Perhaps more important is the fact that individuals with hypermobility and pain who participate in an exercise program improve over time without any significant adverse effects [88]. As with all recommended training in the pediatric population, instruction under a licensed practitioner and practice under supervision should be encouraged to decrease the risk of injury.

There remains a significant dearth of understanding with regard to specific types of exercises that are most effective. In general, it seems that the most effective programs focus on strengthening the stabilizing muscles around the hypermobile joints, enhancing proprioception, improving coordination and balance, and enhancing the neural pathways and movement patterns that can encourage compensation reactions and possibly prevent joint movement into extreme ranges [88]; however, there is also some benefit seen from more generalized exercise programs that address cardiorespiratory fitness or the musculoskeletal aspects of movement and neurologic function (Figure 9) [99]. Given the prevalent comorbidities often seen in patients with hypermobility including pain, autonomic symptoms, and psychosocial difficulties, a multidisciplinary model of care may be most beneficial [100,101].

Postural Orthostatic Tachycardia Syndrome

POTS was first described in adults in 1993 [102] and first reported in adolescents in 1999, even though there are retrospectively accurate descriptions of the condition from the mid-1800s [32]. Increasingly recognized during the past decade, POTS has its typical onset around the beginning of puberty and is most common in high-achieving women [103], many of who also have hyperflexibility [104]. It often begins after a significant illness such as mononucleosis or after an injury such as a concussion [103,104]. POTS is characterized by chronic fatigue, dizziness, nausea, and abdominal discomfort. Psychological disorders, nonrestorative sleep, and pain are common comorbidities [32,105]. The diagnosis is based on typical symptoms, excessive postural tachycardia (at least a 40-beat per minute increase in heart rate between supine and standing positions), and the absence of any other primary condition to account for the findings [32,106].

Therapeutic Opportunities: Refer to generalized therapy prescription (Figure 2). Consider also including:

- Biofeedback for postural re-education and/or muscle relaxation.
- Educate on avoiding overexertion and instruct in pacing strategies.
- Review postural principles and encourage upright posture maintenance during rest, sitting, and standing and exercise (i.e. thoracic extension to neutral, scapular retraction, and chin-tuck to avoid hyperlordosis).
- Review sleeping position & pillow for neutral spine.
- Stretching exercises for the cervical paraspinals, trapezius, levator scapulae, and pectorals.
- Strengthening of thoracic spine extensors and cervical paraspinals with direction specific exercises toward a pain relieving position.
- Core stability assessment and training.
- Manual therapy if not contraindicated by age or diagnosis.
- Massage as child or adolescent feels comfortable with.

Figure 8. Therapeutic opportunities in headache.

In general, the treatment of POTS centers on restoring circulatory volume (increased fluid and salt intake), reconditioning aerobic exercise, CBT, treatment of comorbidities, and, often, medication (such as beta blockers and an alpha agonist, midodrine). With treatment, improvement in daily functional ability and eventual full recovery are likely [32,107]. POTS is an entity that typically presents with pain that appears amplified (with central sensitization) and where, in addition to exercise, diet and improved sleep can make a difference, especially in the initial management. Because patients with POTS exhibit lower-than-normal stroke volume during exercise, graded physical training may improve stroke volume and thus systemic perfusion even as it facilitates reconditioning [108]. The active "muscle pump" in the legs is thought to help force venous blood back up to the heart. This may be part of the body's intrinsic venoregulatory system, preventing pooling in the extremities. The stronger the pump, the more likely that signs and symptoms of POTS will be reduced, specifically those of dizziness, lightheadedness, edema, and acrocyanosis.

Medications also are effective in the treatment of POTS (see Table 1 for further details). Beta blockers (such as metoprolol, 25 mg by mouth first thing in the morning and then again at mid-day) and/or an alpha agonist such as midodrine (2.5 mg by mouth 3 times daily with incremental increases as needed and

Therapeutic Opportunities: Refer to generalized therapy prescription (Figure 2). Consider also including:

- Dynamic joint strengthening up to, but not into, the hypermobile range. Focus on proper motor control techniques first before progressing resistance. Distinction may need to be made between training-related pain and exacerbation of typical pain.
- Progressive balance training to focus on proprioception & neuromuscular re-education to recruit supporting muscles within safe motion. Begin with static balance activities, i.e. sitting, standing and four-point kneeling on the floor, and progress to a stability trainer such as a foam pad, Bosu ball, wobble board, Bongo board, etc when able. Active exercises can eventually be added through the use of a weighted ball or sports specific positioning. Advancement towards dynamic balance activities can eventually be considered with an emphasis on agility and coordination through sport-specific movements, drills, plyometrics, etc.
- Posture re-education and improved joint awareness through biofeedback, manual guidance, joint approximation techniques, mirrors, and the use of tape to facilitate proprioception.
- Avoid splints and braces if possible. Only use with active dislocation/subluxations and limit to at-risk activities.
- Core stability assessment and training.

Figure 9. Therapeutic opportunities in hypermobility with pain.

tolerated to 10 mg 3 times daily, avoiding dosing within 4 hours of lying down to sleep) are commonly used. Some physicians like to build vascular volume with fludrocortisone (0.1 mg by mouth once or twice daily), whereas others prefer to rely on increased oral fluid and salt intake alone. Selective serotonin reuptake inhibitors such as citalopram (starting dose 10 mg/day, target dose 40 mg/day maximum) seem to play an adjunctive role in treatment of POTS, especially when there is significant abdominal pain or concurrent depression. Selective serotonin and norepinephrine reuptake inhibitors such as duloxetine (starting dose 20-30 mg/day, maximum 60 mg/day) seem to be useful for the chronic pain associated with POTS but seem anecdotally to have less direct benefit to the autonomic-based symptoms.

Typical recommendations for nonpharmacologic treatment include [32]:

- hydration: >2 L/day (Enough water to produce >4 daily urinations with clear-colored urine (not including first morning void);
- increased salt intake as tolerated: can assess if needed via output >170 mmol/day on a 24-hour urinary sodium excretion;
- graded aerobic and lower extremity strengthening exercises seven days per week (Figure 10);
- supportive elastic hose of 15-30 mm Hg;
- family education and CBT; and
- attention to adequate sleep, regular meals and school schedule, and good social support

Psychology of Pediatric Chronic Pain

Psychosocial Treatments

Several meta-analytic reviews have documented the effectiveness of psychological treatments for chronic pain. In a review of 25 randomly controlled trials that included both multicomponent CBT packages and relaxation/biofeedback therapies involving children with headache, abdominal pain and fibromyalgia, a large positive effect on pain reduction both immediately after treatment (odds ratio = 5.92) and 3 months later (odds ratio = 9.88) was found [109]. The type of treatment (multicomponent CBT, relaxation, or biofeedback) did not influence results, suggesting CBT is effective using different modes of treatment delivery. More recently, a review of 35 studies determined that psychological therapies can significantly reduce pain in youth with headache, decrease pain and disability in youth with abdominal pain, and decrease pain, disability and depression in youth with musculoskeletal pain [110].

Treatments Targeting the Child/Adolescent

Relaxation. Training in relaxation has long been a core component of pain management treatment, and recent meta-analytic reviews reinforce its efficacy for pain reduction [109,110]. Relaxation strategies work by helping the child achieve a relaxation response in the body that may slow the heart rate, slow breathing, and decrease muscle tension. These changes in the body may reduce the discomfort, stress, and anxiety associated with the pain experience. Second, learning and using relaxation strategies may help the child develop a sense of mastery over the pain, again reducing the stress and anxiety associated with the pain. Children and teenagers can be taught to practice diaphragmatic breathing, progressive muscle relaxation, and imagery as strategies to obtain a state of relaxation fairly quickly, often in only one or a few sessions [111]. However, they need to be reminded to practice the relaxation daily in order to achieve an effective and long-term response.

Biofeedback. Biofeedback is an effective tool for helping children and adolescents learn to achieve a

Therapeutic Opportunities: Refer to generalized therapy prescription (Figure 2). Consider also including:

- Patient should begin slowly with as little as 5 minutes or less of aerobic activity or that which does not produce symptoms, increasing by only 1-2 minutes every 4-7 days as tolerated. Upright activity should be trialed first over reclined or horizontal activity, but can consider aquatic aerobic fitness program if land-based program problematic.
- Review posture principles and exercises to encourage upright posture maintenance during activities and at rest (i.e. neutral cervicothoracic posture, keep shoulders back).
- Core stability assessment and training.
- Functional exercises of upper and lower extremities to promote strengthening in non-pain-provoking manner. Can begin with isometrics and progress to isotonics as tolerated using bands or light weights. Focus should be on proper technique and not significantly increasing weight. Distinction also needs to be made between training-related pain and exacerbation of typical pain.

Figure 10. Therapeutic opportunities in postural orthostatic tachycardia syndrome.

relaxation response. Biofeedback uses electronic equipment to measure and provide information back to the patient about specific physiological functions, so they can use this information to produce a relaxation response. Typically, fingertip skin temperature, breathing, pulse, and heart-rate variability are measured while the patient sees the information on the computer screen and is coached to use the information to increase relaxation. Most research supporting the use of biofeedback has combined the use of biofeedback equipment and coaching by a professional such as a psychologist or physical/occupational therapist. Currently, biofeedback software is readily available for desktop computers and tablets, but the efficacy of using the software alone has not been well studied [111].

Other strategies may also promote relaxation but at this point have less empirical support in the treatment of chronic pain. Strategies such as yoga and aromatherapy have some initial evidence whereas others such as Healing Touch may have little to no current empirical support [111,112].

As noted previously, meta-analytic reviews demonstrate the efficacy of multicomponent CBT programs. These typically include components of cognitive therapy, which targets thoughts that serve to increase the anxiety and discomfort associated with the pain. For example, when children feel helpless about their pain and exhibit catastrophic thinking regarding their pain, it can increase their disability associated with the pain experience. Cognitive therapy helps a child understand the links between their thoughts, feelings, and behaviors. Children are taught to become more aware of their thoughts and reframe (in cognitive behavioral therapy [113]) or accept (in acceptance and commitment therapy [26]) their thoughts. Positive self-talk is another strategy that is a frequent component of CBT treatments.

Stress Management, Anxiety, and Depression. For some children, the pain experienced leads to significant anxiety and depression. For those children, addressing the anxiety and depression may help the child recover from their pain more quickly. This treatment may include both pharmacotherapy as well as psychotherapy such as CBT. Stress management skills help the child identify both cognitive and behavioral strategies to manage both the stress of the pain itself as well as associated stressors.

Treatments That Include Parents

Behavior Therapy. Parental cognitions and behaviors have a significant impact on the pain perception and expression of youth with chronic pain, as discussed earlier. Treatment that uses operant techniques is a common component of chronic pain treatment programs. Parents are taught to minimize their attention to the child's pain (eg, no more pain logs, questions about the pain, reassurance), and instead provide attention for their child's coping attempts (eg, using relaxation, attending school). Clear expectations for functioning are established, and parents may be taught to use a token economy (point system) to reward their child with concrete rewards (eg, sleepover, computer time) for their age-appropriate functioning. Parents also remove privileges (computer, TV, smartphone) if their child is unable to meet expectations such as school attendance and require the child to rest without access to enjoyable activities if they are unable to attend school [25,114-116].

Multidisciplinary Pain Rehabilitation Programs

For some children with chronic pain, the pain leads to significant disability, often resulting in missed school, extracurricular activities, and age-appropriate activities, such as chores and dating. For children who do not respond to the approaches outlined in the previous section, an intensive and coordinated interdisciplinary treatment program should be considered [117-120]. These programs typically include both patients and parents and use a CBT model. The focus is primarily on helping the patient return to age-appropriate functioning rather than reducing pain. Patients are taught the aforementioned strategies discussed such as relaxation, positive thinking, sleep hygiene, and stress management. Physical therapy and occupational therapy aim to help the patient become more physically active as well as return to homework, chores and other age appropriate activities. These programs occur in both a day-treatment setting as well as an inpatient setting. Day-treatment settings typically include parental participation, whereas inpatient settings may separate the parent and child for part of the rehabilitation process, thus reducing secondary gain for the pain and allowing the patient to learn new strategies without parental influence. Although limited data in the pediatric population is available, data suggests that patients attending these programs report significantly improved functioning, decreased depression, and healthier thoughts about their pain [121-123].

Although these programs can be expensive, a cost-analysis study in 2002 revealed that pain-rehabilitation programs for adults provided comparable reduction in pain with greater cost-effectiveness than other pain treatment modalities (including implantation of spinal cord stimulators or drug delivery systems, conservative care, or surgery) [124]. These programs also showed significantly better outcomes for functional improvement, health care use, medication use, return to work, closure of disability claims, and with substantially fewer adverse events than other pain treatment modalities [124].

Although a similar cost analysis has not been published for pediatric pain rehabilitation programs,

Table 2
Herbal supplements

Name	Class	Indications	Notable Side Effects	Dose	Notes
Coenzyme Q10 (CoQ10)	Antioxidant	• Chronic fatigue • Fibromyalgia • Migraine		• 1-3 mg/kg daily in pediatrics • 150-300 mg daily in in adults	• In pediatric migraine study, most effective in those with low CoQ10 values [127].
Melatonin	Hormone	• Sleep disturbance	• Persistent drowsiness (consider lower dose, altering timing, or changing formulation) • Possible irritability or hyperactivity in children with autism	• 0.5-1 mg approximately 5 h before desired sleep time (sleep induction) • 1-9 mg a half hour before bedtime (sleep maintenance)	• Although still under study, consider use of immediate-release if goal is sleep induction and controlled-release if goal is sleep maintenance [128,129].
Calcium	Mineral	• Menstrual migraine			• No randomized studies in pediatrics [130] • May work best in combination with other supplements [131].
Magnesium	Mineral	• Menstrual migraine • Migraine	• Diarrhea if taken in excess	• 350-500 mg daily (adolescents)	• Combine with calcium to help optimize intake of both [130] • Iron or zinc supplements can increase magnesium absorption. • L-lactate dehydrogenase is most effective form [130]. • Excreted renally. Caution with use in those with renal impairments as could cause toxicity [132].
Fish oil	Omega-3 fatty acid	• Migraine		• Two capsules per day (Each capsule consisted of EPA [378 mg], DHA [249 mg], and tocopherol [2 mg])	• Not shown to be more effective than placebo (olive oil) in adolescents [133].
Butterbur (Petastites hybridus)	Plant extract	• Migraine	• Constipation • Diarrhea • Nausea • Vomiting	• 50-200 mg daily	• In randomized placebo controlled trial (Butterbur — Placebo-music therapy) in children and adolescents, only superior to placebo at long-term follow up. Not superior to music therapy at any time point [134]. • In adult systematic review, greater effectiveness found at doses >150 mg [135].
Cannabis (cannabinoid family)	Plant extract	• Fibromyalgia • Neuropathic pain • Rheumatoid arthritis • Spasticity related pain	• Dizziness • Drowsiness • Fatigue • Legal	• Dosing and preparation varies in adults	• In adults, may have benefit for refractory chronic pain including neuropathic pain, fibromyalgia, rheumatoid arthritis, spasticity, and mixed pain syndromes [136-138]. • Safety and efficacy for chronic pain conditions in children is not known. Studies underway for use of cannabinoids for pediatric epilepsy [139,140].
Capsaicin/Cayenne (Capsicum family)	Plant extract	• Acute postoperative pain • Low back pain • Osteoarthritis	• Stinging or burning at site of application	• Topical (plaster or cream)	• In children, may be effective for acute post-operative pain and emergence agitation when applied topically at specific accupoints [141,142] • No studies evaluating use in pediatric chronic pain. • In adults, appears better than placebo for low back pain [143,144]
Devil's Claw (Harpagophytum procumbens)	Plant extract	• Back and neck pain • Osteoarthritis	• May increase risk of bleeding • May lower blood sugar • Stomach upset	• 600-1200 mg 3 times a day (contains 50-100 mg of harpagoside) in adults	• Dosing and safety in children not known. • Moderate to good evidence to support use in adults with certain chronic pain conditions [143-145]

(*continued on next page*)

Table 2 (*continued*)

Name	Class	Indications	Notable Side Effects	Dose	Notes
Feverfew (Tanacetum parthenium)	Plant extract	• Migraine	• Aphthous stomatitis • Upset stomach	• Variable	• Systematic review revealed insufficient evidence that feverfew is superior to placebo for migraine [146]. • Can get rebound headaches with discontinuation [130].
Peppermint oil	Plant extract	• Functional abdominal pain • Irritable bowel syndrome		• Two capsules (187 mg per capsule) 3 times a day if >45 kg • 1 capsule 3 times a day if 30-45 kg	• One RCT showed significant improvement in abdominal pain compared with placebo in children 8-17 years old [147].
White Willow Bark (Salix Alba)	Plant extract	• Low back pain • Osteoarthritis	• Allergic reaction • Possibly unsafe in children when taken during viral infection (due to risk of Reye's syndrome)	• 120-240 mg in adults	• Dosing and safety in children not known. Because of the risk of Reye syndrome, recommend avoiding use. • For adults, appears to reduce symptoms of low back pain better than placebo [144].
5-Hydroxytryptophan	Serotonin precursor	• Anxiety • Migraine • Mood		• 400 mg daily	• May reduce migraine severity in adults [148,149] • No controlled trials in pediatrics.
B2 (riboflavin)	Vitamin	• Migraine	• Bright yellow urine	• 200 mg BID	• No randomized control trials in pediatrics [130].

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; RCT = randomized controlled trial; BID = twice daily.

preliminary research suggests significant cost-savings post treatment due to decreased medical utilization as well as decreased lost work days for parents, yielding an estimated average savings of $27,118 per family in the year after program participation [125].

Complementary and Alternative Medicine (CAM)

Some families may seek alternative interventions for their child's chronic pain. Chronic neck and back pain are among the most common reasons children participate in CAM treatments [124]. According to the 2012 National Health Interview Survey, 11.6% of children in the United States had used a CAM intervention in the past year [126]. The most common CAM intervention children used, regardless of health status, was nonvitamin, nonmineral medications. Of these fish oil, melatonin, and pre/probiotics were most commonly used. CAM interventions were more likely in children who were older (12-17 years old), had parents who participated in CAM treatments, and whose parents had greater than a high school education [126].

Supplements may be an adjunct to a child's comprehensive pain management plan (Table 2) [127-149]. Asking families about supplements is important too, as some supplements may interact with other prescribed medications, may have evidence of ineffectiveness, or have the potential to be harmful to the child (Table 2). Other CAM interventions including acupuncture, hypnosis, massage, music therapy, pet therapy, and osteopathic or chiropractic manipulation could be considered as part of the comprehensive pain management program, though randomized controlled trials in pediatrics are limited, particularly for those not involving direct physical touch (hypnosis, music therapy, and pet therapy) [130,150]. Acupuncture can provide benefit and be well tolerated in children as young as 6 years of age with varying pain conditions, including migraines, abdominal pain, fibromyalgia, and CRPS type 1 [151,152]. Intolerance, including anxiety about the acupuncture procedure, may be reduced when combined with hypnosis [152]. For those with concerns regarding needles, noninvasive acupuncture techniques, including transcutaneous electrical acupoint stimulation and laser acupuncture, may be an alternative [151].

Massage interventions are more challenging to study systematically as types of massage vary. However, in a review of randomized trials evaluating massage in children, a common positive outcome was anxiety reduction with either single or multiple-session massage [153]. One prospective cohort trial on chiropractic interventions in children and adolescents with chronic low back pain reported improved low back pain symptoms and no adverse events [154]. A prospective, single-blind randomized controlled trial using a single episode of manual therapy for cervicogenic headaches in children showed no significant difference between those who

underwent sham manual therapy (light touch to specific spinal segments) and spinal manipulative therapy (high velocity, low amplitude), with both groups experiencing improvement in headache frequency [155]. Although this study had strict inclusion criteria, which limited recruitment, it appears that some type of manual intervention may be helpful for cervicogenic headaches.

CAM interventions that do not use direct physical contact include hypnosis, music therapy, and pet therapy. Many of these have been explored in pediatric acute pain interventions and cancer pain but have not been as thoroughly explored in chronic pain. For children with functional abdominal pain and irritable bowel syndrome, hypnosis therapy appears to provide significant pain improvement [156]. Music therapy also shows promise in chronic pediatric pain conditions both when administered by a music therapist and when part of a singing program in a multidisciplinary pain program [157,158]. Pet therapy, or animal-assisted therapy, provides pain improvement for hospitalized children with acute pain [135] and an improvement in pain, mood, and distress in adults in a comprehensive pain management program [159]. Extrapolating from these studies, integration of animal-assisted therapy in pediatric chronic pain programs, may provide benefit for multiple pain symptoms. In general, when considering CAM interventions, caution should be used when selecting practitioners to ensure proper practices and familiarity with these practices in children and adolescents. Overall, as children with chronic pain conditions are using CAM, practitioners should be mindful to inquire about CAM use in children and adolescents with chronic pain.

Conclusion

The road to wellness through appropriate management of pediatric chronic pain remains complex. Clinical variations in how individual pediatric patients present with chronic pain conditions are likely based on a complex relationship of predisposing biological, psychological, genetic, and social features, while at the same time patients demonstrate consistent responsiveness to a multidisciplinary approach of care. Specific protocols may be lacking but successful programs seem to follow a similar road map focused on exercise, physical and occupational therapy, CBT, and family involvement. The biopsychosocial model also endorses school reintegration, promotes self-management, provides education on appropriate parental interactions, helps with improvement of sleep disturbances, advocates a healthy diet, inspires regular daily exercise, encourages social interaction, and supports opportunities for personal and emotional growth. The biological and psychological aspects of chronic pain management may be addressed most effectively through integrated multimodal programs that serve to validate the patient's and family's concerns, mitigate the symptoms, and help prevent future setbacks.

References

1. Bailey S. Chronic fatigue syndrome. In: Durstine JL, Moore G, Painter PL, Roberts SO, eds. ACSM's Exercise Management for Persons with Chronic Diseases and Disabilities. 3rd ed. Champaign, IL: Human Kinetics; 2009; 233-238.
2. King S, Chambers CT, Huguet A, et al. The epidemiology of chronic pain in children and adolescents revisited: A systematic review. Pain 2011;152:2729-2738.
3. Perquin CW, Hazebroek-Kampschreur AA, Hunfeld JA, et al. Pain in children and adolescents: A common experience. Pain 2000;87:51-58.
4. Kennedy J, Roll JM, Schraudner T, Murphy S, McPherson S. Prevalence of persistent pain in the U.S. Adult population: New data from the 2010 national health interview survey. J Pain 2014;15:979-984.
5. Mikkelsson M, Salminen JJ, Kautiainen H. Non-specific musculoskeletal pain in preadolescents. Prevalence and 1-year persistence. Pain 1997;73:29-35.
6. El-Metwally A, Salminen JJ, Auvinen A, Macfarlane G, Mikkelsson M. Risk factors for development of non-specific musculoskeletal pain in preteens and early adolescents: A prospective 1-year follow-up study. BMC Musculoskelet Disord 2007;8:46.
7. Committee on Advancing Pain Research, Care, and Education, Board on Health Sciences Policy. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press; 2011.
8. Groenewald CB, Essner BS, Wright D, Fesinmeyer MD, Palermo TM. The economic costs of chronic pain among a cohort of treatment-seeking adolescents in the United States. J Pain 2014;15:925-933.
9. Walker LS, Dengler-Crish CM, Rippel S, Bruehl S. Functional abdominal pain in childhood and adolescence increases risk for chronic pain in adulthood. Pain 2010;150:568-572.
10. Smith PA. BDNF: No gain without pain? Neuroscience 2014;283:107-123.
11. Heim C, Newport DJ, Bonsall R, Miller AH, Nemeroff CB. Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. Am J Psychiatry 2001;158:575-581.
12. Jiao J, Vincent A, Cha SS, Luedtke CA, Kim CH, Oh TH. Physical trauma and infection as precipitating factors in patients with fibromyalgia. Am J Phys Med Rehabil Apr 16. [Epub ahead of print].
13. Sluka KA, O'Donnell JM, Danielson J, Rasmussen LA. Regular physical activity prevents development of chronic pain and activation of central neurons. J Appl Physiol (1985) 2013;114:725-733.
14. Van Houdenhove B, Luyten P. Stress, depression and fibromyalgia. Acta Neurol Belg 2006;106:149-156.
15. Cohen SP, Mao J. Neuropathic pain: Mechanisms and their clinical implications. BMJ 2014;348:f7656.
16. Hoffart CM, Wallace DP. Amplified pain syndromes in children: Treatment and new insights into disease pathogenesis. Curr Opin Rheumatol 2014;26:592-603.
17. Kashikar-Zuck S, Ting TV. Juvenile fibromyalgia: Current status of research and future developments. Nat Rev Rheumatol 2014;10:89-96.
18. Goldfarb AH, Jamurtas AZ. Beta-endorphin response to exercise. An update. Sports Med 1997;24:8-16.
19. Jennings EM, Okine BN, Roche M, Finn DP. Stress-induced hyperalgesia. Prog Neurobiol 2014;121:1-18.
20. Stagg NJ, Mata HP, Ibrahim MM, et al. Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: Role of endogenous opioids. Anesthesiology 2011;114:940-948.

21. Flinn MV, Nepomnaschy PA, Muehlenbein MP, Ponzi D. Evolutionary functions of early social modulation of hypothalamic-pituitary-adrenal axis development in humans. Neurosci Biobehav Rev 2011;35:1611-1629.
22. Wilson AC, Moss A, Palermo TM, Fales JL. Parent pain and catastrophizing are associated with pain, somatic symptoms, and pain-related disability among early adolescents. J Pediatr Psychol 2014;39:418-426.
23. Walker LS, Williams SE, Smith CA, Garber J, Van Slyke DA, Lipani TA. Parent attention versus distraction: Impact on symptom complaints by children with and without chronic functional abdominal pain. Pain 2006;122:43-52.
24. Walker LS, Garber J, Greene JW. Psychosocial correlates of recurrent childhood pain: A comparison of pediatric patients with recurrent abdominal pain, organic illness, and psychiatric disorders. J Abnorm Psychol 1993;102:248-258.
25. Claar RL, Simons LE, Logan DE. Parental response to children's pain: The moderating impact of children's emotional distress on symptoms and disability. Pain 2008;138:172-179.
26. Dahl JC, Wilson KG, Luciano C, Hayes SC. Acceptance and Commitment Therapy for Chronic Pain. Reno, NV: Context Press; 2005.
27. Korterink JJ, Ockeloen L, Benninga MA, Tabbers MM, Hilbink M, Deckers-Kocken JM. Probiotics for childhood functional gastrointestinal disorders: A systematic review and meta-analysis. Acta Paediatr 2014;103:365-372.
28. Korterink JJ, Rutten JM, Venmans L, Benninga MA, Tabbers MM. Pharmacologic treatment in pediatric functional abdominal pain disorders: A systematic review. J Pediatr 2015;166:424-431.e426.
29. Chiou E, Nurko S. Management of functional abdominal pain and irritable bowel syndrome in children and adolescents. Expert Rev Gastroenterol Hepatol 2010;4:293-304.
30. Kovacic K, Miranda A, Chelimsky G, Williams S, Simpson P, Li BU. Chronic idiopathic nausea of childhood. J Pediatr 2014;164:1104-1109.
31. Safder S, Chelimsky TC, O'Riordan MA, Chelimsky G. Gastric electrical activity becomes abnormal in the upright position in patients with postural tachycardia syndrome. J Pediatr Gastroenterol Nutr 2010;51:314-318.
32. Kizilbash SJ, Ahrens SP, Bruce BK, et al. Adolescent fatigue, POTS, and recovery: A guide for clinicians. Curr Probl Pediatr Adolesc Health Care 2014;44:108-133.
33. Yik YI, Ismail KA, Hutson JM, Southwell BR. Home transcutaneous electrical stimulation to treat children with slow-transit constipation. J Pediatr Surg 2012;47:1285-1290.
34. Teitelbaum JE, Arora R. Long-term efficacy of low-dose tricyclic antidepressants for children with functional gastrointestinal disorders. J Pediatr Gastroenterol Nutr 2011;53:260-264.
35. Kaminski A, Kamper A, Thaler K, Chapman A, Gartlehner G. Antidepressants for the treatment of abdominal pain-related functional gastrointestinal disorders in children and adolescents. Cochrane Database Syst Rev 2011;7:CD008013.
36. Campo JV, Perel J, Lucas A, et al. Citalopram treatment of pediatric recurrent abdominal pain and comorbid internalizing disorders: An exploratory study. J Am Acad Child Adolesc Psychiatry 2004;43:1234-1242.
37. Horvath A, Dziechciarz P, Szajewska H. Systematic review of randomized controlled trials: fiber supplements for abdominal pain-related functional gastrointestinal disorders in childhood. Ann Nutr Metab 2012;61:95-101.
38. Camilleri M. Management of patients with chronic abdominal pain in clinical practice. Neurogastroenterol Motil 2006;18:499-506.
39. Pellise F, Balague F, Rajmil L, et al. Prevalence of low back pain and its effect on health-related quality of life in adolescents. Arch Pediatr Adolesc Med 2009;163:65-71.
40. Kjaer P, Wedderkopp N, Korsholm L, Leboeuf-Yde C. Prevalence and tracking of back pain from childhood to adolescence. BMC Musculoskelet Disord 2011;12:98.
41. Jeffries LJ, Milanese SF, Grimmer-Somers KA. Epidemiology of adolescent spinal pain: A systematic overview of the research literature. Spine (Phila Pa 1976) 2007;32:2630-2637.
42. Wirth B, Knecht C, Humphreys K. Spine Day 2012: Spinal pain in Swiss school children- epidemiology and risk factors. BMC Pediatr 2013;13:159.
43. Calvo-Munoz I, Gomez-Conesa A, Sanchez-Meca J. Physical therapy treatments for low back pain in children and adolescents: A meta-analysis. BMC Musculoskelet Disord 2013;14:55.
44. Michaleff ZA, Kamper SJ, Maher CG, Evans R, Broderick C, Henschke N. Low back pain in children and adolescents: A systematic review and meta-analysis evaluating the effectiveness of conservative interventions. Eur Spine J 2014;23:2046-2058.
45. Chatzitheodorou D, Kabitsis C, Malliou P, Mougios V. A pilot study of the effects of high-intensity aerobic exercise versus passive interventions on pain, disability, psychological strain, and serum cortisol concentrations in people with chronic low back pain. Phys Ther 2007;87:304-312.
46. Ghandour RM, Overpeck MD, Huang ZJ, Kogan MD, Scheidt PC. Headache, stomachache, backache, and morning fatigue among adolescent girls in the United States: Associations with behavioral, sociodemographic, and environmental factors. Arch Pediatr Adolesc Med 2004;158:797-803.
47. ter Wolbeek M, van Doornen LJ, Kavelaars A, Heijnen CJ. Severe fatigue in adolescents: A common phenomenon? Pediatrics 2006;117:e1078-e1086.
48. Rimes KA, Goodman R, Hotopf M, Wessely S, Meltzer H, Chalder T. Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: A prospective community study. Pediatrics 2007;119:e603-e609.
49. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121:953-959.
50. Clayton EW. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: An IOM report on redefining an illness. JAMA 2015;313:1101-1102.
51. Wyller VB, Helland IB. Relationship between autonomic cardiovascular control, case definition, clinical symptoms, and functional disability in adolescent chronic fatigue syndrome: An exploratory study. Biopsychosoc Med 2013;7:5.
52. Knight SJ, Scheinberg A, Harvey AR. Interventions in pediatric chronic fatigue syndrome/myalgic encephalomyelitis: A systematic review. J Adolesc Health 2013;53:154-165.
53. Smith SN, Crawley E. Is there effective behavioural treatment for children with chronic fatigue syndrome/myalgic encephalomyelitis? Arch Dis Child 2013;98:561-563.
54. Werker CL, Nijhof SL, van de Putte EM. Clinical practice: Chronic fatigue syndrome. Eur J Pediatr 2013;172:1293-1298.
55. Wilder RT, Berde CB, Wolohan M, Vieyra MA, Masek BJ, Micheli LJ. Reflex sympathetic dystrophy in children. Clinical characteristics and follow-up of seventy patients. J Bone Joint Surg Am 1992;74:910-919.
56. Barbier O, Allington N, Rombouts JJ. Reflex sympathetic dystrophy in children: Review of a clinical series and description of the particularities in children. Acta Orthop Belg 1999;65:91-97.
57. Tan EC, Zijlstra B, Essink ML, Goris RJ, Severijnen RS. Complex regional pain syndrome type I in children. Acta Paediatr 2008;97:875-879.
58. Sherry DD, Weisman R. Psychologic aspects of childhood reflex neurovascular dystrophy. Pediatrics 1988;81:572-578.
59. Silber TJ. Eating disorders and reflex sympathetic dystrophy syndrome: Is there a common pathway? Med Hypotheses 1997;48:197-200.
60. Stanton-Hicks M, Baron R, Boas R, et al. Complex regional pain syndromes: Guidelines for therapy. Clin J Pain 1998;14:155-166.
61. 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; 15:218-223.
62. Wilder RT. Management of pediatric patients with complex regional pain syndrome. Clin J Pain 2006;22:443-448.
63. Mikkelsson M, Sourander A, Piha J, Salminen JJ. Psychiatric symptoms in preadolescents with musculoskeletal pain and fibromyalgia. Pediatrics 1997;100:220-227.
64. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-172.
65. Yunus MB, Masi AT. Juvenile primary fibromyalgia syndrome. A clinical study of thirty-three patients and matched normal controls. Arthritis Rheum 1985;28:138-145.
66. Kashikar-Zuck S, Flowers SR, Verkamp E, et al. Actigraphy-based physical activity monitoring in adolescents with juvenile primary fibromyalgia syndrome. J Pain 2010;11:885-893.
67. Kashikar-Zuck S, Vaught MH, Goldschneider KR, Graham TB, Miller JC. Depression, coping, and functional disability in juvenile primary fibromyalgia syndrome. J Pain 2002;3:412-419.
68. Kashikar-Zuck S, Zafar M, Barnett KA, et al. Quality of life and emotional functioning in youth with chronic migraine and juvenile fibromyalgia. Clin J Pain 2013;29:1066-1072.
69. Varni JW, Burwinkle TM, Limbers CA, Szer IS. The PedsQL as a patient-reported outcome in children and adolescents with fibromyalgia: An analysis of OMERACT domains. Health Qual Life Outcomes 2007;5:9.
70. Kashikar-Zuck S, Johnston M, Ting TV, et al. Relationship between school absenteeism and depressive symptoms among adolescents with juvenile fibromyalgia. J Pediatr Psychol 2010;35:996-1004.
71. Busch AJ, Barber KA, Overend TJ, Peloso PM, Schachter CL. Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev 2007:CD003786.
72. Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. Cochrane Database Syst Rev 2013;12: CD010884.
73. Hauser W, Klose P, Langhorst J, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: A systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther 2010;12:R79.
74. Stephens S, Feldman BM, Bradley N, et al. Feasibility and effectiveness of an aerobic exercise program in children with fibromyalgia: Results of a randomized controlled pilot trial. Arthritis Rheum 2008;59:1399-1406.
75. Abu-Arefeh I, Russell G. Prevalence of headache and migraine in school children. BMJ 1994;309:765-769.
76. Alp R, Alp SI, Palanci Y, et al. Use of the International Classification of Headache Disorders, Second Edition, criteria in the diagnosis of primary headache in school children: epidemiology study from eastern Turkey. Cephalalgia 2010;30:868-877.
77. Aromaa M, Sillanpaa ML, Rautava P, Helenius H. Childhood headache at school entry: A controlled clinical study. Neurology 1998;50:1729-1736.
78. Carville S, Padhi S, Reason T, Underwood M. Diagnosis and management of headaches in young people and adults: Summary of NICE guidance. BMJ 2012;345:e5765.
79. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: Report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology 2004;63:2215-2224.
80. Damen L, Bruijn JK, Verhagen AP, Berger MY, Passchier J, Koes BW. Symptomatic treatment of migraine in children: A systematic review of medication trials. Pediatrics 2005;116:e295-302.
81. Bigal ME, Lipton RB. Migraine chronification. Curr Neurol Neurosci Rep 2011;11:139-148.
82. Micromedex® 2.0 (electronic version). Truven Health Analytics; 2015. Available at: http://www.micromedexsolutions.com/. Accessed May 7, 2015.
83. Mack KJ. Chronic Daily Headache in Children. Evansville, IL: Mead Johnson & Company; 2011.
84. Mayo Medical Laboratories (electronic version). Mayo Foundation for Medical Education and Research; 2015. Available at: http://www.mayomedicallaboratories.com/. Accessed May 7, 2015.
85. Powers SW, Kashikar-Zuck SM, Allen JR, et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: A randomized clinical trial. JAMA 2013;310: 2622-2630.
86. Varkey E, Cider A, Carlsson J, Linde M. Exercise as migraine prophylaxis: A randomized study using relaxation and topiramate as controls. Cephalalgia 2011;31:1428-1438.
87. Keer R, Simmonds J. Joint protection and physical rehabilitation of the adult with hypermobility syndrome. Curr Opin Rheumatol 2011;23:131-136.
88. Palmer S, Bailey S, Barker L, Barney L, Elliott A. The effectiveness of therapeutic exercise for joint hypermobility syndrome: A systematic review. Physiotherapy 2014;100:220-227.
89. Konopinski MD, Jones GJ, Johnson MI. The effect of hypermobility on the incidence of injuries in elite-level professional soccer players: A cohort study. Am J Sports Med 2012;40: 763-769.
90. Pacey V, Nicholson LL, Adams RD, Munn J, Munns CF. Generalized joint hypermobility and risk of lower limb joint injury during sport: A systematic review with meta-analysis. Am J Sports Med 2010;38:1487-1497.
91. Stewart DR, Burden SB. Does generalised ligamentous laxity increase seasonal incidence of injuries in male first division club rugby players? Br J Sports Med 2004;38:457-460.
92. McCluskey G, O'Kane E, Hann D, Weekes J, Rooney M. Hypermobility and musculoskeletal pain in children: A systematic review. Scand J Rheumatol 2012;41:329-338.
93. Russek LN, Errico DM. Prevalence, injury rate and, symptom frequency in generalized joint laxity and joint hypermobility syndrome in a "healthy" college population. Clin Rheumatol 2015 May 1. [Epub ahead of print].
94. Dolan AL, Hart DJ, Doyle DV, Grahame R, Spector TD. The relationship of joint hypermobility, bone mineral density, and osteoarthritis in the general population: The Chingford Study. J Rheumatol 2003;30:799-803.
95. Kraus VB, Li YJ, Martin ER, et al. Articular hypermobility is a protective factor for hand osteoarthritis. Arthritis Rheum 2004; 50:2178-2183.
96. Fatoye F, Palmer S, Macmillan F, Rowe P, van der Linden M. Pain intensity and quality of life perception in children with hypermobility syndrome. Rheumatol Int 2012;32:1277-1284.
97. Rombaut L, Malfait F, De Wandele I, et al. Muscle mass, muscle strength, functional performance, and physical impairment in women with the hypermobility type of Ehlers-Danlos syndrome. Arthritis Care Res (Hoboken) 2012;64:1584-1592.
98. Smith TO, Bacon H, Jerman E, et al. Physiotherapy and occupational therapy interventions for people with benign joint hypermobility syndrome: A systematic review of clinical trials. Disabil Rehabil 2014;36:797-803.
99. Kemp S, Roberts I, Gamble C, et al. A randomized comparative trial of generalized vs targeted physiotherapy in the management of childhood hypermobility. Rheumatology (Oxford) 2010; 49:315-325.
100. Castori M. Joint hypermobility syndrome (a.k.a. Ehlers-Danlos Syndrome, Hypermobility Type): An updated critique. G Ital Dermatol Venereol 2013;148:13-36.
101. Pacey V, Tofts L, Wesley A, Collins F, Singh-Grewal D. Joint hypermobility syndrome: A review for clinicians. J Paediatr Child Health 2015;51:373-380.

102. Schondorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: An attenuated form of acute pandysautonomia? Neurology 1993;43:132-137.
103. Johnson JN, Mack KJ, Kuntz NL, Brands CK, Porter CJ, Fischer PR. Postural orthostatic tachycardia syndrome: A clinical review. Pediatr Neurol 2010;42:77-85.
104. Jarjour IT. Postural tachycardia syndrome in children and adolescents. Semin Pediatr Neurol 2013;20:18-26.
105. Ojha A, Chelimsky TC, Chelimsky G. Comorbidities in pediatric patients with postural orthostatic tachycardia syndrome. J Pediatr 2011;158:20-23.
106. Singer W, Sletten DM, Opfer-Gehrking TL, Brands CK, Fischer PR, Low PA. Postural tachycardia in children and adolescents: What is abnormal? J Pediatr 2012;160:222-226.
107. Kimpinski K, Figueroa JJ, Singer W, et al. A prospective, 1-year follow-up study of postural tachycardia syndrome. Mayo Clin Proc 2012;87:746-752.
108. Burkhardt BE, Fischer PR, Brands CK, et al. Exercise performance in adolescents with autonomic dysfunction. J Pediatr 2011;158: 15-19.19 e11.
109. Palermo TM, Eccleston C, Lewandowski AS, Williams AC, Morley S. Randomized controlled trials of psychological therapies for management of chronic pain in children and adolescents: An updated meta-analytic review. Pain 2010;148:387-397.
110. Fisher E, Heathcote L, Palermo TM, de C Williams AC, Lau J, Eccleston C. Systematic review and meta-analysis of psychological therapies for children with chronic pain. J Pediatr Psychol 2014;39:763-782.
111. Lee C, Crawford C, Hickey A. Mind-body therapies for the self-management of chronic pain symptoms. Pain Med 2014; 15(Suppl 1):S21-S39.
112. Cramer H, Lauche R, Haller H, Dobos G. A systematic review and meta-analysis of yoga for low back pain. Clin J Pain 2013;29: 450-460.
113. Palermo TM. Cognitive Behavioral Therapy for Chronic Pain in Children and Adolescents. New York: Oxford University Press; 2012.
114. Caes L, Vervoort T, Eccleston C, Vandenhende M, Goubert L. Parental catastrophizing about child's pain and its relationship with activity restriction: The mediating role of parental distress. Pain 2011;152:212-222.
115. Sieberg CB, Williams S, Simons LE. Do parent protective responses mediate the relation between parent distress and child functional disability among children with chronic pain? J Pediatr Psychol 2011;36:1043-1051.
116. Simons LE, Claar RL, Logan DL. Chronic pain in adolescence: Parental responses, adolescent coping, and their impact on adolescent's pain behaviors. J Pediatr Psychol 2008;33:894-904.
117. Boonstra AM, Reneman MF, Schiphorst Preuper HR, Waaksma BR, Stewart RE. Differences between patients with chronic musculoskeletal pain treated in an inpatient or an outpatient multidisciplinary rehabilitation program. Int J Rehabil Res 2014;37: 187-191.
118. Eccleston C, Malleson PN, Clinch J, Connell H, Sourbut C. Chronic pain in adolescents: Evaluation of a programme of interdisciplinary cognitive behaviour therapy. Arch Dis Child 2003;88: 881-885.
119. Katholi BR, Daghstani SS, Banez GA, Brady KK. Noninvasive treatments for pediatric complex regional pain syndrome: A focused review. PM R 2014;6:926-933.
120. Maynard CS, Amari A, Wieczorek B, Christensen JR, Slifer KJ. Interdisciplinary behavioral rehabilitation of pediatric pain-associated disability: Retrospective review of an inpatient treatment protocol. J Pediatr Psychol 2010;35:128-137.
121. Banez GA, Frazier TW, Wojtowicz AA, Buchannan K, Henry DE, Benore E. Chronic pain in children and adolescents: 24-42 month outcomes of an inpatient/day hospital interdisciplinary pain rehabilitation program. J Pediatr Rehabil Med 2014;7:197-206.
122. Hechler T, Dobe M, Kosfelder J, et al. Effectiveness of a 3-week multimodal inpatient pain treatment for adolescents suffering from chronic pain: Statistical and clinical significance. Clin J Pain 2009;25:156-166.
123. Weiss KE, Hahn A, Wallace DP, Biggs B, Bruce BK, Harrison TE. Acceptance of pain: Associations with depression, catastrophizing, and functional disability among children and adolescents in an interdisciplinary chronic pain rehabilitation program. J Pediatr Psychol 2013;38:756-765.
124. Turk DC. Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain. Clin J Pain 2002;18:355-365.
125. Evans J BE, Banez G. The cost-effectiveness of intensive pain rehabilitation for the treatment of chronic pain: From admission to one year follow-up. Presented at the 10th Annual International Symposium on Pediatric Pain. May 31-June 4, 2015, Seattle, WA.
126. Black LI, Clarke TC, Barnes PM, Stussman BJ, Nahin RL. Use of complementary health approaches among children aged 4-17 years in the United States: National Health Interview Survey, 2007-2012. Natl Health Stat Rep 2015;78:1-19.
127. Hershey AD, Powers SW, Vockell AL, et al. Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. Headache 2007;47:73-80.
128. Guenole F, Godbout R, Nicolas A, Franco P, Claustrat B, Baleyte JM. Melatonin for disordered sleep in individuals with autism spectrum disorders: Systematic review and discussion. Sleep Med Rev 2011;15:379-387.
129. Sanchez-Barcelo EJ, Mediavilla MD, Reiter RJ. Clinical uses of melatonin in pediatrics. Int J Pediatr 2011;2011:892624.
130. Kemper KJ, Breuner CC. Complementary, holistic, and integrative medicine: Headaches. Pediatr Rev 2010;31:e17-e23.
131. Gedye A. Hypothesized treatment for migraines using low doses of tryptophan, niacin, calcium, caffeine, and acetylsalicylic acid. Med Hypotheses 2001;56:91-94.
132. Schetzek S, Heinen F, Kruse S, et al. Headache in children: Update on complementary treatments. Neuropediatrics 2013;44: 25-33.
133. Harel Z, Gascon G, Riggs S, Vaz R, Brown W, Exil G. Supplementation with omega-3 polyunsaturated fatty acids in the management of recurrent migraines in adolescents. J Adolesc Health 2002;31:154-161.
134. Oelkers-Ax R, Leins A, Parzer P, et al. Butterbur root extract and music therapy in the prevention of childhood migraine: An explorative study. Eur J Pain 2008;12:301-313.
135. Agosti R, Duke RK, Chrubasik JE, Chrubasik S. Effectiveness of petasites hybridus preparations in the prophylaxis of migraine: A systematic review. Phytomedicine 2006;13:743-746.
136. Boychuk DG, Goddard G, Mauro G, Orellana MF. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: A systematic review. J Oral Facial Pain Headache 2015;29:7-14.
137. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; A systematic review of randomized trials. Br J Clin Pharmacol 2011;72:735-744.
138. Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: An updated systematic review of randomized controlled trials. J Neuroimmune Pharmacol 2015;10:293-301.
139. Ammerman S. Marijuana. Adolesc Med State Art Rev 2014;25: 70-88.
140. Sharp GB, Samanta D, Willis E. Options for pharmacoresistant epilepsy in children: When medications don't work. Pediatr Ann 2015;44:e43-e48.
141. Acar HV, Yilmaz A, Demir G, Gunal Eruyar S, Dikmen B. Capsicum plasters on acupoints decrease the incidence of emergence agitation in pediatric patients. Paediatr Anaesth 2012;22: 1105-1109.
142. Kim KS, Kim DW, Yu YK. The effect of capsicum plaster in pain after inguinal hernia repair in children. Paediatr Anaesth 2006; 16:1036-1041.

143. Gagnier JJ, van Tulder MW, Berman B, Bombardier C. Herbal medicine for low back pain: A Cochrane review. Spine (Phila Pa 1976) 2007;32:82-92.
144. Oltean H, Robbins C, van Tulder MW, Berman BM, Bombardier C, Gagnier JJ. Herbal medicine for low-back pain. Cochrane Database Syst Rev 2014;12:CD004504.
145. Denner SS. A review of the efficacy and safety of devil's claw for pain associated with degenerative musculoskeletal diseases, rheumatoid, and osteoarthritis. Holist Nurs Pract 2007;21:203-207.
146. Pittler MH, Ernst E. Feverfew for preventing migraine. Cochrane Database Syst Rev 2004;1:CD002286.
147. Kline RM, Kline JJ, Di Palma J, Barbero GJ. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. J Pediatr 2001;138:125-128.
148. De Benedittis G, Massei R. Serotonin precursors in chronic primary headache. A double-blind cross-over study with L-5-hydroxytryptophan vs. placebo. J Neurosurg Sci 1985;29:239-248.
149. Nicolodi M, Sicuteri F. L-5-hydroxytryptophan can prevent nociceptive disorders in man. Adv Exp Med Biol 1999;467:177-182.
150. Hestbaek L, Stochkendahl MJ. The evidence base for chiropractic treatment of musculoskeletal conditions in children and adolescents: The emperor's new suit? Chiropr Osteopat 2010;18:15.
151. Golianu B, Ming Yeh A, Brooks M. Acupuncture for pediatric pain. Children 2014;1:134-138.
152. Zeltzer LK, Tsao JC, Stelling C, Powers M, Levy S, Waterhouse M. A phase I study on the feasibility and acceptability of an acupuncture/hypnosis intervention for chronic pediatric pain. J Pain Symptom Manage 2002;24:437-446.
153. Beider S, Moyer CA. Randomized controlled trials of pediatric massage: A review. Evid Based Complement Alternat Med 2007;4:23-34.
154. Hayden JA, Mior SA, Verhoef MJ. Evaluation of chiropractic management of pediatric patients with low back pain: A prospective cohort study. J Manipulative Physiol Ther 2003;26:1-8.
155. Borusiak P, Biedermann H, Bosserhoff S, Opp J. Lack of efficacy of manual therapy in children and adolescents with suspected cervicogenic headache: Results of a prospective, randomized, placebo-controlled, and blinded trial. Headache 2010;50:224-230.
156. Vlieger AM, Menko-Frankenhuis C, Wolfkamp SC, Tromp E, Benninga MA. Hypnotherapy for children with functional abdominal pain or irritable bowel syndrome: A randomized controlled trial. Gastroenterology 2007;133:1430-1436.
157. Kenny DT, Faunce G. The impact of group singing on mood, coping, and perceived pain in chronic pain patients attending a multidisciplinary pain clinic. J Music Ther 2004;41:241-258.
158. Braun C, Stangler T, Narveson J, Pettingell S. Animal-assisted therapy as a pain relief intervention for children. Complement Ther Clin Pract 2009;15:105-109.
159. Marcus DA, Bernstein CD, Constantin JM, Kunkel FA, Breuer P, Hanlon RB. Animal-assisted therapy at an outpatient pain management clinic. Pain Med 2012;13:45-57.

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