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Medication use among pediatric patients with chronic musculoskeletal pain syndromes at initial pain clinic evaluation

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Practice points

- Complex regional pain syndrome, localized and diffuse musculoskeletal pain and other amplified musculoskeletal pain syndromes can lead to debilitating symptoms in pediatric patients.
- There is widespread use of medications to treat chronic pediatric pain despite lack of proven efficacy with evidence of morbidity and cost, especially with opioid pain medications.
- 120 adolescent patients with amplified musculoskeletal pain syndromes were examined and medication use prior to initial evaluation included: 3.2 medications reported on average; 70% used ≥ 1 pain-specific medication including opioids (17%), nonopioids (31%), psychotropic/neuropathic (45%) and other medications (13%).
- On average, adolescents in this sample had made approximately 15 doctor's office visits for pain in the past year and missed 2.6 days of school in the past month.
- Significant correlations were found between number of pain medications used and patient-reported disability, pain duration and number of nonpain medications used.
- Findings indicate that patients who report high levels of physical difficulty due to pain receive prescriptions for medication.
- Disability reports by patient and parent were significantly related to opioid and psychotropic/neuropathic pain medication use.
- It will be important in future research to determine the extent to which a patient's receipt of a prescription for pain medication either facilitates, or potentially undermines, pursuit of other behavioral treatments.

Aim: To characterize medication use by adolescents with chronic musculoskeletal pain syndromes before an initial multidisciplinary clinic visit. **Patients & methods:** A cross-sectional sample of 120 adolescents and parents reported on standardized assessment measures, with medication use data extracted from the medical chart and categorized. **Results:** On average, 3.2 medications were reported; 70% used more than one pain-specific medication including opioids (17%), nonopioids (31%), psychotropics/neuropathics (45%) and other medications (13%). Adolescents with complex regional pain syndrome consistently reported greatest use of opioid, psychotropic/neuropathic and other pain medications. A regression model explained 17% of the variance in pain medication use. Nonpain medication use and disability contributed unique variance – pain duration and intensity did not. **Conclusion:** Greater attention to factors contributing to prescriptive practices, medication use and long-term outcomes is warranted.

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Musculoskeletal pain is a common cause of chronic and recurrent pain in pediatric populations, with prevalence rates as high as 40% [1–4]. Amplified musculoskeletal pain syndromes (AMPS) are characterized by a disproportionate degree of pain and disability originating from a minor trauma, illness or an unidentifiable cause [5–7]. The AMPS spectrum includes such conditions as complex regional pain syndrome (CRPS) [8], localized musculoskeletal pain, diffuse musculoskeletal pain, reflex neurovascular/sympathetic dystrophy and fibromyalgia. The impact of AMPS on a child's life is profound and frequently includes debilitating pain, marked functional limitations, and symptoms of depression and anxiety [9–11]. Multiple somatic symptoms ranging from fatigue and dizziness and occasionally blindness or paralysis may accompany the pain complaint, contributing additional disability.

AMPS can be challenging to diagnose, leading to frustration on the part of the patient and parents, as well as diagnostic and therapeutic difficulties for the provider. While still not fully understood, knowledge regarding the pathophysiology of AMPS is increasing [12,13]. Recent literature implicates dysfunction of the central or peripheral nervous system and the nerves that sense pain and control vascular tone [14,15], resulting in pain hypersensitivity through a process referred to as central sensitization [16].

There is growing support for the importance of an interdisciplinary approach to treatment for AMPS. When identified and treated early, most AMPS in children and adolescent can be treated successfully with a combination of intensive physical therapy [1,5,17–20], cognitive-behavior-based therapy [21–23] and acceptance-based therapies [24,25]. In contrast to physical and behavioral treatment modalities, no single drug or combination of drugs has produced consistent long-lasting improvements in symptoms [15,26,27]. Existing studies on the effectiveness of medications to treat chronic musculoskeletal pain syndromes are limited by factors such as small sample sizes and a focus on adult patients [28,29], making these findings difficult to generalize to a pediatric population [30].

Despite the lack of demonstrated effectiveness, pediatric patients endorse using a variety of medications. Recent studies from other research teams have reported on the quantities and types of medications used for CRPS upon admission to inpatient or day-hospital. Specifically, 56 pediatric patients with CRPS enrolled in a day-hospital-based treatment program reported pain medication use as none (18%), one medication (39%) and more than one medication (43%) at admission [31,32]. Many different types of medications have been reported by patients admitted to inpatient pediatric rehabilitation treatment programs for CRPS [3,7,33,34]. A sample of 32 pediatric patients admitted to an inpatient rehabilitation treatment program for CRPS-reported rates for previous medication treatments including: nonsteroidal anti-inflammatory drugs (66%), opioids (53%), antidepressants (50%), gabapentin (41%), benzodiazepines (31%), muscle relaxants (16%) and oral steroids (9%) [33]. A similarly broad range of medications were endorsed at admission among 17 children with CRPS treated in an inpatient rehabilitation facility (100% of patients reported previous pain medication use) including: nonsteroidal anti-inflammatory drugs (29%), opioid analgesics (59%), antidepressants (53%), anticonvulsants (88%), benzodiazepines (6%), muscle relaxants (12%), antirheumatics (6%), norepinephrine reuptake inhibitors (6%) and stimulants (6%) [34]. Finally, among a sample of 37 pediatric CRPS patients admitted for inpatient therapy [35], an average of 4.4 medications (range 1–10) was reported at admission with the most frequent medications endorsed being gabapentin/pregabalin (65%), low potency opioids (59%) and ibuprofen (59%).

While high rates of medication use among patients who require a day-hospital or inpatient admission for pain treatment may be expected due to the severity of symptoms, high rates of medication use have also been documented during new outpatient clinic evaluations. Among 2249 pediatric pain outpatients at a German pediatric multidisciplinary pain clinic setting, 90% reported taking analgesics before they presented to the clinic and 43% were taking analgesics without an indication for pharmacotherapy [55].

As these studies indicate, there is clearly widespread use of medication among pediatric patients with chronic pain syndromes in the hopes of alleviating pain. While the intent to lessen pediatric chronic pain by medication is compelling, it is important to appreciate that use of medication to treat chronic pain is not without risk. The risk of medication overdose and dosage errors at home in children with chronic conditions is significant [36,37]. While there is a role for medication use in the management of musculoskeletal pain [38], there is also growing concern about the use of and greater access to specifically opioid medications and the diversion of unused prescriptions [39,40]. Furthermore, daily medication use imposes a significant financial burden; the average cost of opioid use was US\$22.30 ($\pm$ US\$17.63) a day for adults with chronic pain who completed a pain rehabilitation program [41].

The primary objective of this cross-sectional study is to characterize patterns of medication use in pediatric patients with various forms of AMPS at the time of an initial outpatient multidisciplinary pain clinic evaluation. The high prevalence of medication use, paucity of evidence for its long-term effectiveness and potential risks/costs associated with use prompt a need to understand the scale of this issue among this population and the contributing

factors. We hypothesize that the amount of pain medications a patient endorses is positively associated with pain duration, pain intensity and level of functional disability. We further explore whether different patterns of medication use exist within specific amplified musculoskeletal pain diagnostic subgroups.

Materials & methods

Participants

A total of 127 adolescents and their parents were prospectively enrolled between 2007 and 2010 from a large pediatric institution that provides specialized tertiary care for the management of chronic pain. Patients were contacted prior to their initial outpatient clinic evaluation appointment and consent/assent was provided to participate in an Institutional Review Board-approved protocol exploring multiple aspects of psychosocial functioning in pediatric chronic pain. Additional papers describing participants in this dataset have been published focusing on separate research topics such as: measurement validation [42], treatment expectations [43], readiness to change [44] and parenting behavior [45]. Patients were referred to this multidisciplinary pediatric pain clinic from a variety of medical subspecialties (e.g., orthopedics, rheumatology) and primary care pediatricians, usually after other treatment attempts failed to substantially reduce symptoms.

Patients in this sample were eligible for participation if they were between 11 and 18 years of age and: they had a primary complaint of musculoskeletal pain (e.g., CRPS or idiopathic musculoskeletal pain syndromes) lasting 3 months or longer, their pain was not related to chronic disease, and they were English-speaking and not significantly cognitively impaired. All participating parents lived in the same home as the adolescent. A total of seven participants were excluded after enrollment (six were excluded based on initial pain diagnostic criteria, while only one participant chose to discontinue participation in the study). Thus, a total 120 subjects were included in study analyses.

Procedure

When initially scheduled for an outpatient clinic appointment, families received initial intake questionnaires and a description of the research project. Eligible families were further screened by phone. All questionnaires included in this study were completed prior to the start of the clinical evaluation and further confirmed by the attending physician who also documented all symptoms and diagnoses at the time of the initial evaluation. Medication use data were obtained by clinical staff directly from the patient and parent at the time of the clinical visit. This information was retrospectively and systematically extracted from the completed medical visit documentation from the medical charts for all 120 participants by two authors (MO Lewen and EW Jarvis).

Measures

Medications

Medications were independently reviewed and categorized into groups by two of the physician authors (FW Kraemer and DD Sherry). The complete list of all the medications reported by participants included in the sample was initially categorized as either a pain or a nonpain (e.g., antibiotics, reflux medicines, dietary supplements) medication based on their primary indication. Pain medications were further categorized into four subcategories: opioids (e.g., oxycodone, hydrocodone); nonopioids (e.g., ibuprofen, lidocaine); psychotropic or neuropathic medications (e.g., amitriptyline, gabapentin); or other pain medications with a secondary indication for pain (e.g., clonidine, cyclobenzaprine). When a medication included both opioid and nonopioid agents, the medication was included in only the opioid category. After each physician independently categorized the medications, 91% agreement was reached. Lexicomp [46] was used to clarify the discrepancies of the 14 (out of 149) medications until 100% agreement was reached. The medications were categorized as follows: nonpain medications ($n = 104$) and pain medications (all types [$n = 45$]; opioid analgesics [$n = 11$], nonopioid analgesics [$n = 13$], psychotropic/neuropathic [$n = 12$] and other pain medications [$n = 9$]).

Pain management overview questionnaire

Parents provided information about their adolescent's pain and health history and family demographic information. Variables included sex, ethnicity, grade, pain duration, parent participant, frequency of doctor's visits in the last year, number of persons living in the home and family socioeconomic status [47].

BMI

Patients' height and weight measured at the initial evaluation were extracted from the medical record. BMI percentiles based on sex and age were calculated using the CDC algorithm [48]. Adolescents with scores between the 5th and 85th percentiles were considered to have a healthy weight [48]. We categorized patients into low (<5th percentile), average (5–85th percentiles) or high ($\geq$ 85th percentile) BMI subcategories.

Pain intensity

Adolescent patient self-reports and parent proxy reports of the adolescent's usual, most and least pain intensity during the preceding 2 weeks were assessed using a 100 mm visual analog scale [49,50]. Scores were anchored at 0 = no pain to 100 = unbearable pain. Visual analog scale pain intensity ratings have established reliability and validity [49,51].

The functional disability inventory

Adolescent patients and parents reported on this 15-item measure to assess the degree to which pain interferes with the adolescent's physical functioning (e.g., eating, sleeping, walking, running) and other age appropriate activities (e.g., attending school, gym/sports, spending time with friends) in the last few days prior to assessment [52]. Items are rated on a 5-point scale ranging from 0 = no trouble to 4 = impossible. Higher scores indicate greater functional disability. The functional disability inventory (FDI) has demonstrated reliability and validity among patients with chronic pain conditions consulting outpatient pediatric multidisciplinary pain clinics [42] and is a measure recommended for use in pediatric chronic/recurrent pain clinical trials [53].

Statistical analysis

Descriptive statistics were computed to describe the sample. Analysis of variance (ANOVAs) were conducted to examine differences between demographic subgroups (i.e., sex, pain diagnosis, medication usage), with post hoc comparisons tested using the Tukey honestly significant difference statistic. χ^2 analyses were conducted to examine whether there were any systematic differences in use of medication overall, specific pain medications and nonpain medications by demographic factors (i.e., sex, pain diagnosis and pain duration). Pearson's and Spearman's correlation coefficients were derived to assess associations among study variables and medication use. Finally, a linear regression analysis was conducted to examine significant predictors of pain medication use. Statistical analysis was performed using the Statistical Package for the Social Sciences (version 17).

Results

There were 544 subjects screened during the study timeframe, of which 138 met criteria. Of the 138 approached for inclusion, 11 initially declined participation, 6 were later found not to meet criteria and 1 withdrew participation. Demographics are presented in Table 1. On average, duration of pain was over 2 years, patients had 15 office visits in the prior year and had consulted four doctors for pain relief. The majority of the patients' BMIs were within the 5–85% range (68.7%); almost a third were above this in the high category and only two patients were in the low category. One-way ANOVAs did not identify any significant group differences for medication use based on low, average or high BMI percentile groupings.

Descriptive data summarizing medication use are presented in Table 2. Patients reported using an average of 3.2 (standard deviation [SD] = 2.7) medications, with an average of 1.3 (SD = 1.3) pain medications and 2.0 (SD = 2.1) nonpain medications at the time of the initial evaluation. One-way ANOVAs did not identify any significant differences based on sex. The CRPS group showed the greatest mean levels of pain medication use for three of the four medication subcategories. Specifically, the use of opioid medications $F(2,119) = 6.63$, $p < 0.01$ (Tukey's honestly significant difference statistic showed CRPS [$M = 0.39$, $SD = 0.56$] differed from both the diffuse [$M = 0.08$, $SD = 0.27$] and localized musculoskeletal pain groups [$M = 0.14$, $SD = 0.35$]). The CRPS group had higher medication use than the localized group for the psychotropic/neuropathic category $F(2,119) = 3.81$, $p < 0.05$ (localized [$M = 0.33$, $SD = 0.54$] vs CRPS [$M = 0.81$, $SD = 0.83$]) and other pain medication category $F(2,119) = 3.45$, $p < 0.05$ (localized [$M = 0.03$, $SD = 0.17$] vs CRPS [$M = 0.26$, $SD = 0.51$]).

Table 3 presents means and SDs reported by adolescent patients and parents for study measures (i.e., pain duration, pain intensity and functional disability) for the total sample. ANOVAs did not identify any significant between-group differences on these measures based on the patient's sex. However, significant differences emerged among musculoskeletal pain subgroups for patient reports of disability, $F(2,119) = 4.86$, $p < 0.01$, with disability

Table 1. Demographic data (n = 120).

Adolescent, parent and family characteristics	Mean or n	(SD) or %
Age at time of initial evaluation (min–max: 11.8–18.6 years)	15.6	(1.5)
Sex: females	96	80%
Ethnicity: Caucasian	107	89%
Grade in school	9.6	(1.6)
Pain duration in months (min–max: 3–148 months)	25.2	(26.2)
BMI percentile (n = 115)	63.2	(27%)
– <5th percentile	2	2%
– 5–85th percentile	79	69%
– ≥85th percentile	34	30%
Parent participant: mother	107	89%
Number of office visits for pain in past year (n = 105; min–max: 0–100 visits)	14.9	(17.6)
Number of doctors seen for pain relief	Mode = 4; 15% of subjects	
Missed days in the last 4 weeks of school (n = 116)	2.6	(2.4)
Family SES – Hollingshead scale (n = 113; min–max: 25–66)	49.7	(10.1)
Patient pain diagnostic category:		
– Diffuse musculoskeletal pain	53	44%
– CRPS – type 1	31	26%
– Localized musculoskeletal pain	36	30%

CRPS: Complex regional pain syndrome; max: Maximum; min: Minimum; n: Number; SD: Standard deviation; SES: Socioeconomic status.

Table 2. Detailed breakdown of mean medication counts by category reported for total sample and demographic subcategories (n = 120).

Medication categories	Total sample mean (SD)	Sex		Pain diagnosis		
		Female, n = 96	Male, n = 24	Diffuse, n = 53	CRPS, n = 31	Localized, n = 36
Total medications (min–max: 0–13)	3.2 (2.7)	3.2 (2.7)	3.4 (3.0)	3.4 (3.1)	3.6 (2.9)	2.7 (1.9)
Nonpain medications (0–10)	2.0 (2.1)	1.9 (2.0)	2.1 (2.2)	2.3 (2.3)	1.9 (2.0)	1.7 (1.7)
Pain medications (0–8)	1.3 (1.3)	1.3 (1.3)	1.3 (1.3)	1.2 (1.2)	1.7 (1.5)	1.0 (1.1)
– Opioid analgesics (0–2)	0.2 (0.4)	0.2 (0.4)	0.1 (0.3)	0.1 (0.3)*	0.4 (0.6)*	0.1 (0.4)*
– Nonopioid analgesics (0–4)	0.4 (0.7)	0.4 (0.7)	0.3 (0.6)	0.4 (0.6)	0.2 (0.6)	0.5 (0.8)
– Psychotropic or neuropathic medications (0–3)	0.6 (0.7)	0.5 (0.7)	0.7 (0.8)	0.6 (0.7)*	0.8 (0.8)*	0.3 (0.5)*
– Other medications with secondary indication for pain (0–2)	0.1 (0.4)	0.1 (0.4)	0.2 (0.4)	0.1 (0.3)*	0.3 (0.5)*	0.0 (0.2)*

*Significant between group differences within each demographic category.

CRPS: Complex regional pain syndrome; max: Maximum; min: Minimum; n: Number; SD: Standard deviation.

levels reported for the localized pain group ($M = 21.64$, $SD = 11.81$) significantly lower than both the CRPS ($M = 29.29$, $SD = 11.40$) and Diffuse pain group ($M = 28.26$, $SD = 11.05$). Subjects who used any pain medication, compared with those who took none, reported higher levels of usual pain intensity ($F[1119] = 4.55$, $p < 0.05$) and their parent reported significantly higher FDI scores ($F[1119] = 4.15$, $p < 0.05$).

We further examined the percentages of patients reporting one or more medications. Almost all patients ($n = 107$) reported using a medication at the initial evaluation; 70% reported using one or more pain-specific medication with psychotropic/neuropathic medications (45%) being most common. χ^2 analyses were used to examine potential differences in medication use. No significant group differences were found based on patient sex. Patients with CRPS were significantly more likely to use opioid analgesics (χ^2 [2 degrees of freedom (df)] = 11.28, $p < 0.01$) and other pain medications (χ^2 [2 df] = 6.02, $p < 0.05$), with the CRPS group reporting the highest use. Significant group differences also emerged for pain duration subgroups (coded as 3–11.9, 12–23.9 and ≥ 24 months) for use of nonpain medication use (χ^2 [2 df] = 9.48, $p < 0.01$). The highest percentages of patients endorsing both nonpain medication (93%) and any pain medication (78%) use occurred when pain duration lasted within 12–23.9 months.

Spearman rank-order correlations supported that consulting a greater number of doctors for pain relief was related to older patient age ($r = 0.22$, $p < 0.05$), pain duration ($r = 0.33$, $p < 0.01$) and use of pain medication

Table 3. Patient and parent reports of patient pain and disability for total sample and within demographic subgroups (n = 120).

Adolescent pain and functional disability reports	Mean (SD)	Sex		Pain diagnosis			Medication use		Pain medication use	
		Female, n = 96	Male, n = 24	Diffuse, n = 53	CRPS, n = 31	Localized, n = 36	None, n = 13	≥1, n = 107	None, n = 36	≥1, n = 84
Adolescent pain duration (months; 3–148)	25.2 (26.2)	24.1 (24.4)	29.8 (32.8)	30.0 (27.5)	18.4 (21.8)	24.9 (27.3)	20.5 (19.3)	25.8 (27.0)	23.0 (18.5)	26.2 (29.0)
Adolescent report										
– Least pain (0–91)	37.2 (22.8)	36.6 (22.4)	39.5 (24.6)	38.0 (24.2)	41.5 (22.8)	32.9 (20.4)	35.2 (22.4)	37.4 (23.0)	32.4 (25.7)	39.3 (21.3)
– Usual pain (0–100)	58.9 (21.8)	59.6 (20.1)	56.2 (26.9)	56.1 (20.8)	64.5 (20.5)	58.2 (23.0)	55.4 (25.9)	59.3 (21.0)	52.6 (30.2)*	61.6 (15.9)*
– Most pain (5–100)	85.2 (18.1)	85.9 (16.2)	82.1 (24.6)	82.2 (20.9)	87.2 (15.3)	87.9 (15.6)	85.9 (19.3)	85.1 (18.1)	82.3 (25.1)	86.4 (14.1)
– Disability (FDI; 0–53)	26.6 (11.7)	26.7 (11.6)	26.0 (12.4)	28.3 (11.0)*	29.3 (11.4)*	21.6 (11.8)*	26.0 (12.6)	26.6 (11.7)	24.4 (14.8)	24.4 (10.1)
Parent report										
– Least pain (0–100)	39.1 (23.5)	38.4 (22.5)	41.9 (28.0)	38.9 (24.4)	41.8 (21.5)	37.1 (24.3)	41.6 (29.6)	38.8 (22.8)	34.6 (28.7)	41.0 (20.8)
– Usual pain (1–100)	53.8 (22.5)	53.8 (22.3)	53.8 (24.0)	51.6 (21.0)	59.0 (23.3)	52.5 (24.0)	53.5 (23.7)	53.8 (22.5)	50.8 (28.2)	55.1 (19.7)
– Most pain (10–100)	81.0 (20.1)	81.9 (19.6)	77.3 (22.0)	78.5 (23.2)	80.4 (19.1)	85.2 (15.0)	72.8 (24.0)	82.0 (19.4)	77.1 (24.1)	82.7 (18.0)
– Disability (FDI; 0–51)	24.8 (12.6)	24.5 (13.2)	25.9 (10.5)	26.4 (12.9)	26.2 (11.8)	21.2 (12.4)	24.6 (11.5)	24.8 (12.8)	21.3 (13.8)*	26.3 (11.9)*

*Significant between-group differences within each demographic category.

CRPS: Complex regional pain syndrome; FDI: Functional disability inventory; n: Number; SD: Standard deviation.

Table 4. Correlations between medication use, pain intensity and functional measures.

Study variables	1	2	3	4	5	6	7	8	9	10	11	12
1. Total medications	1.0	0.898**	0.700**	0.304**	0.293**	0.592**	0.388**	0.261**	0.121	0.183*	0.016	0.243**
2. Nonpain medications			0.315**	0.096	0.079	0.350**	0.150	0.236**	0.025	0.074	-0.043	0.104
3. Pain medications				0.500**	0.503**	0.709**	0.594**	0.180*	0.221*	0.275**	0.105	0.356**
4. Opioid pain medications					-0.069	0.206*	0.354**	0.064	0.146	0.284**	0.223*	0.309**
5. Nonopioid pain medications						-0.028	0.025	0.018	0.008	-0.053	-0.121	0.002
6. Psychotropic/neuropathic pain medications							0.318**	0.261**	0.249**	0.257**	0.137	0.321**
7. 'Other' pain medications								0.007	0.101	0.236**	0.072	0.259**
8. Pain duration									0.042	-0.094	0.079	0.119
9. Usual pain (adolescent report)										0.481**	0.727**	0.411**
10. Disability (adolescent report)											0.430**	0.807**
11. Usual pain (parent report)												0.436**
12. Disability (parent report)												1.0

*p < 0.05.

**p < 0.01.

Variables 1–7 each represent the raw count of the number of medications used within each category.

($r = 0.19$, $p < 0.05$) – specifically, psychotropic/neuropathic pain medications ($r = 0.21$, $p < 0.05$) and other pain medication use ($r = 0.020$, $p < 0.05$). Table 4 presents Pearson's correlations between medication use, pain and functional disability measures. Significant correlations were found between number of pain medications used and patient-reported disability ($r = 0.28$, $p < 0.01$), usual pain ($r = 0.22$, $p < 0.02$), pain duration ($r = 0.18$, $p < 0.05$) and number of nonpain medications used ($r = 0.32$, $p < 0.01$). While the number of pain medications used was not related to parent reports of the patient's usual pain, it was significantly related to parent reports of the patient's disability ($r = 0.36$, $p < 0.01$). Both adolescent and parent reports of patient disability were significantly related to all pain medication subcategories except nonopioid medication. However, pain intensity reports were only significantly related between patient self-reported pain and use of psychotropic/neuropathic pain medication ($r = 0.25$, $p < 0.01$) and between parent reports of patient pain and opioid pain medication ($r = 0.22$, $p < 0.05$).

Table 5 presents results of the regression model exploring four variables entered as separate steps (in sequential order: pain duration, nonpain medication use, usual pain intensity and adolescent report of disability) that explained 17% of the variance in pain medication use ($F[4|114] = 6.93$, $p < 0.01$), with each step contributing significant incremental variance. However, only nonpain medication use ($\beta = 0.27$) and disability ($\beta = 0.23$) contributed

Table 5. Regression model of predictors of patient pain medication use.

Variable	β (95% CI)	SE	Std β	t (signif.)	R ² for step	Adj. R ² for step	R ² change (signif.)
Step 1: pain duration	0.007 (-0.002, 0.015)	0.004	0.138	1.582	0.034	0.025	0.034*
Step 2: nonpain medication count	0.164 (0.058, 0.270)	0.053	0.266	3.067**	0.113	0.098	0.080**
Step 3: patient-reported pain	0.006 (-0.005, 0.017)	0.006	0.100	1.038	0.157	0.135	0.044*
Step 4: patient-reported disability	0.024 (0.004, 0.045)	0.011	0.226	2.329*	0.195	0.167	0.038*
*p < 0.05. **p < 0.01. SE: Standard error; signif.: Significance.							

unique variance to the final model, suggesting that factors such as pain duration and pain intensity explain a relatively small amount of variance in adolescent pain medication use.

Discussion

This cross-sectional study provides a detailed description of the incidence and type of medication use among a sample of adolescent patients with chronic musculoskeletal pain syndromes during an initial evaluation at an outpatient pain clinic. These data expand the knowledge base for this rigorously characterized sample by providing new information about the type of medications and correlates of use with pain duration, intensity and functional disability for CRPS, diffuse and localized musculoskeletal pain subgroups. Consistent with past findings about medication use being prevalent in pediatric outpatient settings [31,34,54,55], 89% of the total sample reported using at least one medication, with an average use of 3.2 medications. Results identified that 70% of the sample reported using more than one pain medication, including opioid analgesics (17%), nonopioid analgesics (31%), psychotropic/neuropathic (45%) and/or other medications with a secondary indication for pain (13%). Adolescents diagnosed with CRPS were more likely to use opioid, psychotropic/neuropathic and other pain medications than the localized or diffuse diagnostic subgroups.

Overall pain medication use was significantly correlated with increased pain duration and higher levels of intensity and functional disability. However, a regression model explained only 17% of the variance in the use of pain medication. In this model, pain duration and intensity did not contribute unique variance whereas nonpain medication use and disability did. Collectively, these findings indicate that those who report high levels of physical difficulty due to pain receive prescriptions for medication. However, it remains unclear the extent to which these recommendations for medication were also coupled with recommendations for counseling or physical therapy (and if so, whether these other treatment modalities were pursued prior to the multidisciplinary pain clinic assessment). It will be important in future research to determine the extent to which a patient's receipt of a prescription for pain medication either facilitates, or potentially undermines, pursuit of other behavioral treatments.

Functional disability and use of nonpain medication were statistically correlated with use of overall pain medications. Specifically, opioid pain medication use was significantly correlated with patient reports of disability and parent reports of patient disability and pain. The use of neuropathic or psychotropic pain medications was significantly correlated with pain duration, patient reports of pain and the patient and parent report of the patient's disability. In contrast, no significant correlations were found between nonopioid pain medication use and patient disability and reports of pain. It may be that patients who are more functionally disabled (e.g., sleeping poorly, missing school, etc.) are more noticeably distressed by their pain, thereby eliciting both parents and treatment providers to depend on medications to provide relief. This may also be consistent with the finding that patients with CRPS consistently had the greatest mean pain medication use for each pain medication type. It may be that patients with abnormal physical features associated with CRPS appear 'more believable' to providers compared with those with allodynia alone.

Our findings document that patients arrive with wide range of treatment recommendations received by multiple providers prior to their initial pain clinic evaluation. We found an association between the number of doctors consulted for pain relief and use of pain medication, specifically, psychotropic/neuropathic pain medications and other pain medication. While there is clearly a role for medications for acute pain and symptoms, long-term medication use for chronic pediatric pain is not an optimal solution. Availability of medications, long-term can increase the chances of misuse [40], and can have untoward consequences for youth at greater risk for substance abuse [56,57]. Access to medication may be more commonplace in part due to medications frequently being the

most readily available and heavily marketed treatment options for both primary care and the majority of medical specialists not connected with academic teaching hospitals. Medications are considered among the less invasive treatments for conditions such as CRPS in a recent review by Katholi *et al.*; nevertheless, this review and promising intervention research findings emphasize an increased need for behavioral approaches to optimally manage this painful condition [31,58,59].

Intensive treatment programs have shown great promise in treating longer-standing amplified musculoskeletal pain conditions without an emphasis on medications [6,18–20,31]. Using an interdisciplinary approach of 5 h of daily physical therapy and occupational therapy, along with psychotherapy, art therapy and music therapy, and without pain medications, has proven efficacious [5,18–20,54,60].

These findings must be considered with respect to its limitations. These cross-sectional data do not allow us to determine the extent to which medication use may help to improve or potentially inhibit the functional progress of pediatric patients. Findings of significance can only reflect a correlation not a causal relationship. The majority of our sample was female, so this may have precluded our ability to detect any significant patterns of sex differences for medication use. Patients attending this outpatient multidisciplinary pain clinic are among the more severely disabled pediatric chronic pain patients. Thus, our findings may not be generalizable to youth with chronic pain who do not consult tertiary care pediatric pain treatment centers. Future research is needed to systematically monitor and assess medication use in the outpatient setting in order to clarify the role of specific pain medications and their efficacy, or not, for this population. In addition, future studies should examine additional factors that may contribute to medication use, as well as the effectiveness of this treatment modality alone or combined with other treatments on long-term outcomes.

Conclusion & future perspective

In conclusion, we found that the level of adolescent disability explains medication use over and above the contribution of pain duration, nonpain medications and pain intensity. The experience of pain is a confluence of biological and behavioral factors; thus, a single treatment modality is generally not effective. The results of this descriptive study clearly indicate the need for an interdisciplinary approach to AMPS, which is consistent with previous studies on the treatment of pediatric patients with AMPS. Further research is warranted to understand the role of timing and duration of medication-based treatment recommendations for this population in relation to other treatment modalities to ensure optimal well-being for patients and their families. Mounting concerns about inappropriate access and use of pain management medications highlight the need for greater attention to complex factors that contribute to prescriptive practices, medication use and long-term functioning for youth with chronic pain syndromes to ensure optimal outcomes.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

- 1 Connolly M, Schanberg L. Latest developments in the assessment and management of chronic musculoskeletal pain syndromes in children. *Curr. Opin. Rheumatol.* 18(5), 496–502 (2006).
- 2 El-Metwally A, Salminen JJ, Auvinen A, Kautiainen H, Mikkelsson M. Prognosis of non-specific musculoskeletal pain in preadolescents: a prospective 4-year follow-up study till adolescence. *Pain* 110(3), 550–559 (2004).
- 3 King S, Chambers CT, Huguet A *et al.* The epidemiology of chronic pain in children and adolescents revisited: a systematic review. *Pain* 152(12), 2729–2738 (2011).
- 4 Perquin CW, Hazebroek Kampschreur AA, Hunfeld JA *et al.* Pain in children and adolescents: a common experience. *Pain* 87, 51–58 (2000).
- 5 Sherry DD. An overview of amplified musculoskeletal pain syndromes. *J. Rheumatol.* 27(58), 44–48 (2000).
- 6 Hoffart CM, Wallace DP. Amplified pain syndromes in children: treatment and new insights into disease pathogenesis. *Curr. Rheumatol. Rep.* 26(5), 592–603 (2014).
- 7 Binkley KE. Improving the diagnosis and treatment of CRPS: insights from a clinical immunologist's personal experience with an underrecognized neuroinflammatory disorder. *J. Neuroimmune. Pharmacol.* 8(3), 477–488 (2013).
- 8 Meresky H, Bogduk N. *Classification of Chronic Pain: Description of Chronic Pain Syndromes and Definitions of Pain Terms.* IASP Press, Seattle, WA, USA (1994).
- 9 Roth-Isigkeit A, Thyen U, Stöven H, Schwarzenberger J, Schmucker P. Pain among children and adolescents: restrictions in daily living and triggering factors. *Pediatrics* 115(2), e152–e162 (2005).
- 10 Kashikar-Zuck S, Vaught MH, Goldschneider KR, Graham TB, Miller JC. Depression, coping, and functional disability in juvenile primary fibromyalgia syndrome. *J. Pain* 3(5), 412–419 (2002).
- 11 Eccleston C, Crombez G, Scotford A, Clinch J, Connell H. Adolescent chronic pain: patterns and predictors of emotional distress in adolescents with chronic pain and their parents. *Pain* 108(3), 221–229 (2004).
- 12 Huguet A, Tougas ME, Hayden J, McGrath PJ, Stinson JN, Chambers CT. Systematic review with meta-analysis of childhood and adolescent risk and prognostic factors for musculoskeletal pain. *Pain* 157(12), 2640–2656 (2016).
- 13 Jussila L, Paananen M, Näyhä S *et al.* Psychosocial and lifestyle correlates of musculoskeletal pain patterns in adolescence: a 2-year follow-up study. *Eur. J. Pain* 18(1), 139–146 (2014).
- 14 Marinus J, Moseley GL, Birklein F *et al.* Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurol.* 10(7), 637–648 (2011).
- 15 Clauw DJ. Diagnosing and treating chronic musculoskeletal pain based on the underlying mechanism(s). *Best Pract. Res. Clin. Rheumatol.* 29(1), 6–19 (2015).
- 16 Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 152(3, Suppl.), S2–S15 (2011).
- 17 Malleson PN, Connell H, Bennett SM, Eccleston C. Chronic musculoskeletal and other idiopathic pain syndromes. *Arch. Dis. Child* 84, 189–192 (2001).
- 18 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* 15(3), 218–223 (1999).
- 19 Sherry DD. Amplified musculoskeletal pain: treatment approach and outcomes. *J. Pediatr. Gastroenterol. Nutr.* 47(5), 693–694 (2008).
- 20 Sherry DD, Brake L, Tress JL *et al.* The treatment of juvenile fibromyalgia with an intensive physical and psychosocial program. *J. Pediatr.* 167(3), 731–737 (2015).
- 21 Logan DE, Conroy C, Sieberg CB, Simons LE. Changes in willingness to self-manage pain among children and adolescents and their parents enrolled in an intensive interdisciplinary pediatric pain treatment program. *Pain* 153(9), 1863–1870 (2012).
- 22 Simons LE, Basch MC. State of the art in biobehavioral approaches to the management of chronic pain in childhood. *Pain Manag.* 6(1), 49–61 (2015).
- 23 Kashikar-Zuck S, Ting TV, Arnold LM *et al.* Cognitive behavioral therapy for the treatment of juvenile fibromyalgia: a multisite, single-blind, randomized, controlled clinical trial. *Arthritis Rheum.* 64(1), 297–305 (2012).
- 24 Gauntlett-Gilbert J, Connell H, Clinch J, McCracken LM. Acceptance and values-based treatment of adolescents with chronic pain: outcomes and their relationship to acceptance. *J. Pediatr. Psychol.* 38(1), 72–81 (2013).

- 25 Wicksell RK, Greco LA. Acceptance and commitment therapy for pediatric chronic pain. In: *Acceptance and Mindfulness Treatments for Children and Adolescents: A Practitioner's Guide*. Greco LA, Hayes SC (Eds). New Harbinger Publications, Oakland, CA, USA, 89–113 (2008).
- 26 NIH National Institute of Neurological Disorders and Stroke NINDS. NINDS Complex Regional Pain Syndrome Information Page. www.ninds.nih.gov/disorders/reflex_sympathetic_dystrophy/reflex_sympathetic_dystrophy.htm
- 27 Arnold LM, Schikler KN, Bateman L *et al*. Safety and efficacy of pregabalin in adolescents with fibromyalgia: a randomized, double-blind, placebo-controlled trial and a 6-month open-label extension study. *Pediatr. Rheumatol.* 14(1), 46 (2016).
- 28 Mellick GA, Mellick LB. Reflex sympathetic dystrophy treated with gabapentin. *Arch. Phys. Med. Rehabil.* 78(1), 98–105 (1997).
- 29 van de Vusse AC, Stomp-van den Berg SG, Kessels AH, Weber WE. Randomised controlled trial of gabapentin in complex regional pain syndrome type 1 [ISRCTN84121379]. *BMC Neurol.* 4(1), 1 (2004).
- 30 Wilder RT. Management of pediatric patients with complex regional pain syndrome. *Clin. J. Pain* 22(5), 443–448 (2006).
- 31 Logan DE, Carpino EA, Chiang G *et al*. A day-hospital approach to treatment of pediatric complex regional pain syndrome: initial functional outcomes. *Clin. J. Pain* 28(9), 766–774 (2012).
- 32 Kaufman EL, Tress J, Sherry DD. Trends in medicalization of children with amplified musculoskeletal pain syndrome. *Pain Med.* 18(5), 825–831 (2017).
- 33 Bovend'Eerdt TJH, Botell RE, Wade DT. Writing SMART rehabilitation goals and achieving goal attainment scaling: a practical guide. *Clin. Rehabil.* 23(4), 352–361 (2009).
- 34 Cruz N, O'Reilly J, Slomine BS, Salorio CF. Emotional and neuropsychological profiles of children with complex regional pain syndrome type-I in an inpatient rehabilitation setting. *Clin. J. Pain* 27(1), 27–34 (2011).
- 35 Zernikow B, Dobe M, Hirschfeld G, Blankenburg M, Reuther M, Maier C. Please don't hurt me!: A plea against invasive procedures in children and adolescents with complex regional pain syndrome (CRPS). *Schmerz* 26(4), 389–395 (2012).
- 36 Ogilvie JD, Rieder MJ, Lim R. Acetaminophen overdose in children. *CMAJ* 184(13), 1492–1496 (2012).
- 37 Walsh KE, Mazor KM, Stille CJ *et al*. Medication errors in the homes of children with chronic conditions. *Arch. Dis. Child* 96(6), 581–586 (2011).
- 38 Selanne H, Ryba TV, Siekkinen K *et al*. The prevalence of musculoskeletal pain and use of painkillers among adolescent male ice hockey players in Finland. *Health Psychol. Behav. Med.* 2(1), 448–454 (2014).
- 39 Mazer-Amirshahi M, Mullins PM, Rasooly IR, van den Anker J, Pines JM. Trends in prescription opioid use in pediatric emergency department patients. *Pediatr. Emerg. Care* 30(4), 230–235 (2014).
- 40 Groenewald CB, Rabbitts JA, Gebert JT, Palermo TM. Trends in opioid prescriptions among children and adolescents in the United States: a nationally representative study from 1996 to 2012. *Pain* 157(5), 1021–1027 (2016).
- 41 Cunningham JL, Rome JD, Kerkvliet JL, Townsend CO. Reduction in medication costs for patients with chronic nonmalignant pain completing a pain rehabilitation program: a prospective analysis of admission, discharge, and 6-month follow-up medication costs. *Pain Med.* 10(5), 787–796 (2009).
- 42 Kashikar-Zuck S, Flowers SR, Claar RL *et al*. Clinical utility and validity of the functional disability inventory among a multicenter sample of youth with chronic pain. *Pain* 152(7), 1600–1607 (2011).
- 43 Guite JW, Kim S, Chen C-P *et al*. Treatment expectations among adolescents with chronic musculoskeletal pain and their parents before an initial pain clinic evaluation. *Clin. J. Pain* 30(1), 17–26 (2014).
- 44 Guite JW, Kim S, Chen C-P *et al*. Pain beliefs and readiness to change among adolescents with chronic musculoskeletal pain and their parents before an initial pain clinic evaluation. *Clin. J. Pain* 30(1), 27–35 (2014).
- 45 Welkom JS, Hwang WT, Guite JW. Adolescent pain catastrophizing mediates the relationship between protective parental responses to pain and disability over time. *J. Pediatr. Psychol.* 38(5), 541–550 (2013).
- 46 Lexi-CompOnlineTM. *Pediatric & Neonatal Lexi-Drugs OnlineTM*. Lexi-Comp, Inc., Hudson, OH, USA (2011).
- 47 Hollingshead AB. *Four-factor Index of Social Status*. Yale University, Department of Sociology, New Haven, CN, USA (1975).
- 48 CDC. Body mass index-for-age percentiles. Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic Disease Prevention and Health Promotion. <http://apps.nccd.cdc.gov/dnpabmi/>
- 49 Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 17(1), 45–56 (1983).
- 50 Varni JW, Thompson KL, Hanson V. The Varni/Thompson Pediatric Pain Questionnaire: I. Chronic musculoskeletal pain in juvenile rheumatoid arthritis. *Pain* 28(1), 27–38 (1987).
- 51 McGrath PA. *Pain in Children: Nature, Assessment, and Treatment*. Guilford Press, New York, NY, USA (1990).
- 52 Walker LS, Greene JW. The Functional Disability Inventory: measuring neglected dimension of child health status. *J. Pediatr. Psychol.* 16(1), 39–58 (1991).

- 53 McGrath PJ, Walco GA, Turk D *et al.* Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. *J. Pain* 9(9), 771–783 (2008).
- 54 Brooke V, Janselewitz S. Outcomes of children with complex regional pain syndrome after intensive inpatient rehabilitation. *PMR* 4(5), 349–354 (2012).
- 55 Zernikow B, Wager J, Hechler T, Hasan C, Rohr U, Dobe M. Characteristics of highly impaired children with severe chronic pain: a 5-year retrospective study on 2249 pediatric pain patients. *BMC Pediatrics* 12(54), doi:10.1186/1471-2431-12-54 (2012).
- 56 Vosburg SK, Eaton TA, Sokolowska M *et al.* Prescription opioid abuse, prescription opioid addiction, and heroin abuse among adolescents in a recovery high school: a pilot study. *J. Child Adolesc. Subst.* 25(2), 105–112 (2016).
- 57 Russell BS, Trudeau JJ, Leland AJ. Social influence on adolescent polysubstance use: the escalation to opioid use. *Subst. Use Misuse* 50(10), 1325–1331 (2015).
- 58 Nilsson S, Rosvall P-Å, Jonsson A. Adolescent-centered pain management in school when adolescents have chronic pain—a qualitative study. *Glob. J. Health Sci.* 9(4), 8 (2016).
- 59 Katholi BR, Daghestani SS, Banez GA, Brady KK. Noninvasive treatments for pediatric complex regional pain syndrome: a focused review. *PMR* 6(10), 926–933 (2014).
- 60 Sherry DD. An overview of amplified musculoskeletal pain syndromes. *J. Rheumatol. Suppl.* 58, 44–48 (2000).