Scandinavian Journal of Pain 13 (2016) 156–163

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Clinical pain research

A randomized controlled trial of amitriptyline versus gabapentin for complex regional pain syndrome type I and neuropathic pain in children

Stephen Brown[a,b,*], Bradley Johnston[a,b,c,d], Khush Amaria[e], Jessica Watkins[a,b], Fiona Campbell[a,b], Carolyne Pehora[a], Patricia McGrath[f]

[a] Department of Anesthesia and Pain Medicine, Hospital for Sick Children, Toronto, Ontario, Canada
[b] University of Toronto, Toronto, Ontario, Canada
[c] Child Health Evaluative Services, The Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada
[d] Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
[e] Department of Psychology, The Hospital for Sick Children, Toronto, Ontario, Canada
[f] Pain Innovations Inc., London, Ontario, Canada

HIGHLIGHTS

- 1st paediatric study for amitriptyline and gabapentin for CRPS I and neuropathic pain.
- Amitriptyline and gabapentin proved similarly effective for decreasing pain scores.
- No difference between amitriptyline and gabapentin in decreasing sleep disruption.
- No difference between amitriptyline and gabapentin in adverse events.

ARTICLE INFO

Article history:
Received 15 January 2016
Received in revised form 12 May 2016
Accepted 20 May 2016
Available online 16 June 2016

Keywords:
Neuropathic pain
Adolescents
Paediatrics
Pharmacologic management
Amitriptyline
Gabapentin

ABSTRACT

Background: Treatment of neuropathic pain in children is challenging, and requires a multimodal approach of pharmacologic, physical, and psychological therapies; however there is little evidence to guide practice. Amitriptyline and gabapentin are first-line drugs for treating neuropathic pain in adults, yet no studies have examined their efficacy, or compared them directly, to determine which might be better for pain relief and sleep disturbance in children.

Methods: After informed consent was obtained, 34 patients aged 7–18 years diagnosed with complex regional pain syndrome type I (CRPS I) or a neuropathic pain condition were randomly allocated to receive either amitriptyline or gabapentin. Patients were followed for 6 weeks and assessed for pain intensity, sleep quality and adverse events. We blinded study personnel, including health-care providers, participants, parents, the research coordinator and the data analyst. Patients then completed quantitative sensory testing (QST) and a psychosocial pain assessment with the team psychologist, within 1–3 days of the start of the trial.

Results: At the end of the 6-week trial, patients on both drugs had important reductions in pain, having surpassed the minimally important difference (MID) of 1. The difference between the groups however was not statistically significant. For the secondary outcomes, we found no statistically significant difference between the two drugs in sleep score or adverse events suggesting that both drugs improve sleep score to a similar degree and are equally safe.

Conclusions: Amitriptyline and gabapentin significantly decreased pain intensity scores and improved sleep. There were no significant differences between the two drugs in their effects on pain reduction or sleep disability.

Implications: Although larger, multi-centred trials are needed to confirm our findings, including long-term follow-up, both drugs appear to be safe and effective in treating paediatric patients in the first-line treatment of CRPS I and neuropathic pain over 6-weeks.

DOI of refers to article: http://dx.doi.org/10.1016/j.sjpain.2016.09.001.
* Corresponding author at: Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. Tel.: +1 416 813 7445; fax: +1 416 813 7543.
E-mail address: stephen.brown@sickkids.ca (S.C. Brown).

http://dx.doi.org/10.1016/j.sjpain.2016.05.039

1. Introduction

Chronic pain affects 25% of children and youth of whom 5% have severe pain and pain-related disability. Neuropathic pain is the most predominant form of chronic pain and is associated with significant pain related disability, accounting for up to 40% of referrals to paediatric pain clinics in North America [1,2]. Neuropathic pain may arise as a consequence of a disease or lesion affecting the somatosensory system [3] typically occurring from damage to the nerve pathways from the periphery to the cortical neurons in the brain. Conditions are associated with injury, dysfunction, or altered excitability of portions of the peripheral, central, or autonomic nervous system [4]. The pain sensations are not a result of normal nociceptive neural transmission evoked by acute injury or acute inflammation. Instead, pain persists independent of any ongoing tissue injury or inflammation. Common clinical characteristics include spontaneous and provoked pain, paresthesias and dysethesias, and sensory abnormalities including lowered thresholds to tactile, thermal, and noxious stimulation, allodynia (pain due to a stimulus that does not provoke pain), and hyperalgesia (increased pain from a stimulus that normally provokes pain) [5].

At the Chronic Pain Clinic, The Hospital for Sick Children, complex regional pain syndrome type I (CRPS I) and painful neuropathic disorders comprise approximately 20% of outpatient referrals. The most common conditions of this group include post-surgical and post-traumatic peripheral neuropathic pain, metabolic and toxic neuropathies, neurodegenerative disorders, and CRPS. CRPS types I and II refer to conditions in which there is pain, most commonly in an arm or leg with "neuropathic characteristics" (e.g., spontaneous and evoked pain, warm or heat allodynia, hyperalgesia) and autonomic dysfunction (e.g., cyanosis, mottling, hyperhidrosis, cooler extremity than contralateral by 3 °C, oedema) [6]. CRPS type I refers to conditions with no demonstrable peripheral nerve injury, while CRPS type II refers to conditions with signs of partial or complete nerve injury [6]. The exact incidence of CRPS I and neuropathic pain is unknown in children [6,7]. Clinical studies from two centres indicate a female:male ratio of 6:1, a higher prevalence in the lower extremities (7:1 lower:upper), and an age of onset is typically between 9 and 15 years old [5–8].

The management of CRPS I and neuropathic pain requires a multimodal approach typically combining pharmacologic, physical, and psychological therapies [9–11]. Pharmacologically, amitriptyline, a tricyclic antidepressant (TCA), and gabapentin, an anticonvulsant, are two of the first-line drugs for treating neuropathic pain in adults [12]. Most of the evidence on the pharmacologic treatment of neuropathic pain in children and adolescents is based on extrapolation from adult studies, case reports or clinical series from specialized paediatric pain centres [5–7,13]. Not surprisingly, the downward extensions of adult interventions are identified as questionable [6]. Well-designed, pharmacological trials for children examining the outcome of pain reduction are lacking [6,7]. Furthermore, the impact of treatment on other core domains of impairment in individuals with chronic pain is required. Specifically, the PedIMMPACT statement [14] recommends including sleep as a core outcome domain in paediatric chronic pain trials.

This study is the first prospective randomized controlled trial directly comparing gabapentin and amitriptyline for the treatment of CRPS I and neuropathic pain in a paediatric population. In addition to pain, our secondary objective was to evaluate disruption in children's sleep, which can be common in patients with chronic pain [15] and the safety of the two drugs.

2. Methods

2.1. Participants and recruitment

Consecutive paediatric patient referrals to an interdisciplinary Chronic Pain Clinic (The Hospital for Sick Children, Toronto, Canada) were screened for eligibility between April 2006 and July 2010. Enrollment criteria included children aged 8–17 years, CRPS I or neuropathic pain and recommendation for pharmacological treatment with gabapentin or amitriptyline by a clinic physician during the patients' intake appointment.

Children were not eligible if they were: unable to speak English, lactose intolerant, pregnant, previously using either gabapentin or amitriptyline for the treatment of CRPS I or neuropathic pain or if they were unable to swallow a size "0" gelatin capsule. Children were also excluded if study medications were contraindicated by additional health conditions or the treatment of such conditions, including the regular use of any of the following medications or classes of medications: anticholinergics, antihypertensives, anticonvulsants, H2 receptor antagonists, antidepressants, sympathomimetics, thyroid replacements, antacids and analgesics.

2.2. Study design

This was a 6-week single-centred, blinded (health-care providers, participants, parents, research coordinators, data analyst) randomized controlled trial stratified by sex. The study received Health Canada approval, Institutional Review Board approval of protocol and consent forms, and adhered to ongoing Institutional Safety Review Board's adverse monitoring and Good Clinical Practice guidelines. The study was registered on clinicaltrials.gov (clinicaltrials.gov identifier: NCT00312260). Reporting of this study adheres to CONSORT guidelines [16].

Patients who met eligibility criteria were informed about the study by the clinic physician. If interested in hearing more about the study, a research coordinator explained the study protocol privately to families and for those agreeing to participate, obtained consent from patients and/or parents. Patients were informed that the clinical management for children who agreed to participate in the study was the same as for children who did not consent, and typically included one of the two study medications with an individualized physiotherapy and/or a cognitive-behavioural therapy programme as recommended by the team physiotherapist or psychologist, respectively.

Patients who consented were then randomly allocated to receive either gabapentin or amitriptyline (see dosing schedule below) and received an ECG (to rule out any unknown cardiac arrhythmias or prolongation of the QTc interval), typically on the same day or within 1 day of their intake appointment. Most participants began study medication within 1 day of their intake appointment after review of ECG results. Patients then completed quantitative sensory testing (QST) (approximately 45 min) and a psychosocial pain assessment (90 min) with team psychologist, within 1–3 days of the start of the trial.

Participants were asked to complete daily journal entries documenting pain, sleep disability and any adverse events. The research coordinator phoned parents within the first 3 days of the trial and then weekly to obtain pain intensity and sleep disability ratings, and to inquire about any adverse events. In keeping with chronic pain continuity of care, parents were also invited to complete 2-, 4- and 6-week post-trial interviews with the study coordinator to report on their child's pain intensity and sleep disability levels, and report on any adverse events of current medications. A modification in protocol was made to include the use of journals for pain

and sleep disability scores. In the event that data from the 6-week clinic visit was missing, patient journals were used for pain and sleep disability scores and the last observation was carried forward.

2.3. Randomization and allocation concealment

Participants were randomly assigned to receive either gabapentin or amitriptyline. The randomization sequence generation was completed by the research support service pharmacist (not involved in patient care) and the allocation list was concealed from the participants and the study team. The research support pharmacy held the allocation sequence schedule, with a copy of participant-specific medications in sealed manila envelopes available to the research coordinator for emergency purposes or unblinding at the end of the study period. Since some neuropathic pain conditions disproportionately affect boys and girls, randomization was stratified by sex to ensure that equivalent numbers of boys and girls were randomized to each treatment group. The randomization sequence of 1:1 ratio of amitriptyline to gabapentin was a block 4 design with the possible sequence combinations (e.g., AABB, ABAB) assigned a number and then a point on a page of printed random numbers picked.

2.4. Study medication and blinding

Dosing schedules were selected based on our "best practice" recommendations for treating CRPS I and neuropathic pain in children at the time of study design [5] The doses and titration schedules were the same for all children treated in the Chronic Pain Clinic, independent of their enrolment in this trial. Amitriptyline was prescribed at a dose of 10 mg (at bedtime) and gabapentin was prescribed at 900 mg/d (300 mg three times per day). To maintain blinding due to differences in dosing frequency for the two study drugs, participants were prescribed one capsule at night (~20:00 h) for the first 3 days, then added a second capsule in the morning (~08:00 h) for the next 3 days and then added a third capsule mid-afternoon (~14:00 h) for the remainder of the trial. Children randomized to the amitriptyline group received amitriptyline in the evening pill and placebo in the morning and afternoon pills; while children randomized to gabapentin received 300 mg of gabapentin in each pill. If untoward adverse events (e.g., nausea, vomiting, activity-limiting sedation) developed at the start of trial, the patient's dose was decreased by removing the last pill added until adverse events remitted and the patient was returned to the study dosing schedule. Additional pain medications were not allowed during the trial.

Both study and placebo medications were made to be similar in composition, odour, colour and taste by over encapsulating the untouched original dosage form with a larger opaque hard gelatin capsule (7.34 ml in length) and filling any space with lactose powder. The powder stopped the capsule from rattling and made sure no shape of the original dosage form could be seen if the study capsule was held up to light. Study medications for the morning/afternoon doses were bottled separately (Bottle A, 90 capsules) from the evening medication (Bottle B, 45 capsules) and extra pills were provided in case of misplacement or if patients' 6-week follow-up appointment was delayed. Adherence/medication compliance was confirmed by parental report of medication consumption and confirmed by assessing pill usage from standardized bottles at the end of the study trial.

2.5. Measures and outcomes

Our primary outcome measure was change in usual pain intensity (i.e., past week) from baseline to 6-weeks post-trial start, as measured by the Coloured Analogue Scale (CAS) [17]. Our secondary outcomes were sleep disability as measured on an internally developed 5-point Likert scale [18] and the occurrence of adverse events. All baseline outcomes were measured before any study drugs were administered.

For pain intensity, children were instructed on using the Coloured Analogue Scale [19] for completing all study pain intensity ratings prior to start of the trial. The CAS is a visual analogue scale and scored from 0 to 10 (0.25 increments), and is considered a valid and reliable tool for the measurement of pain in children [19]. Patients rated their current pain, usual pain in the last week, and their lowest (min) and strongest (max) pain levels at baseline and end of trial. If CAS ratings were incomplete, 0–10 numerical rating scale (NRS) scores (where 0 equals "no pain" and 10 equals "the worst pain you can imagine") were used as substitutes if available (e.g., from clinic intake or follow-up appointment). In the event that NRS scores were not available from clinic visits, pain scores from journals or parent interviews were used. As identified by McGrath et al.; pain diaries are a frequently used tool in chronic pain clinical trials of children and adolescents [14].

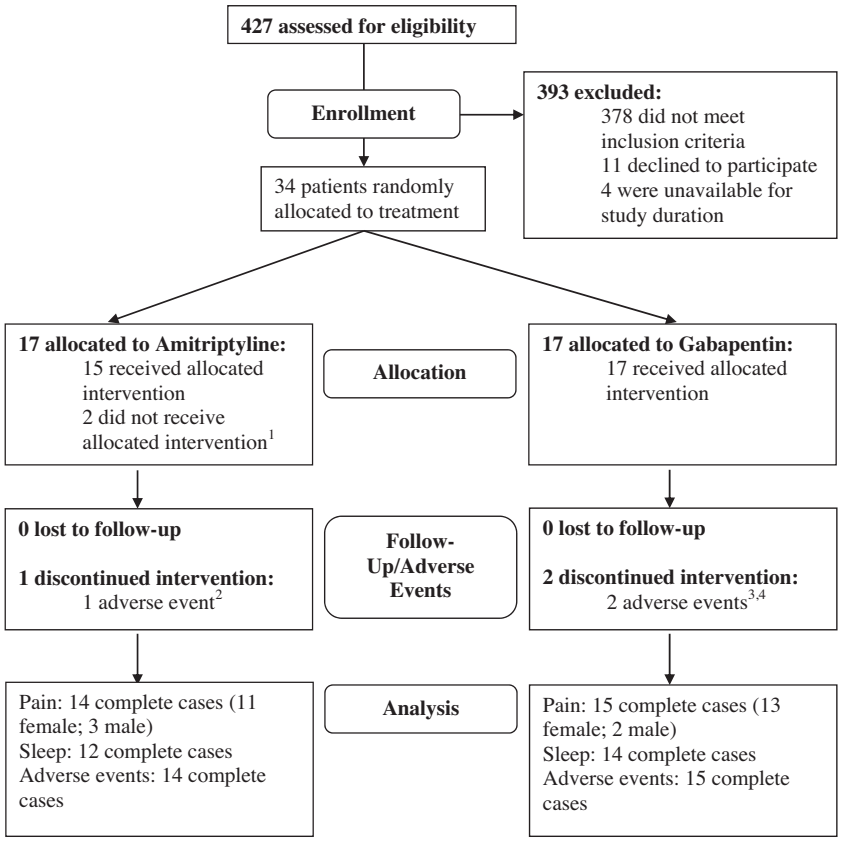
Prior to commencement of study medications, secondary outcomes were measured, including disruption of sleep, school, social and sports. These patient reported outcomes were collected by clinicians and a research coordinator using clear, objective criteria on 5-point Likert scales developed at The Hospital for Sick Children. For the sleep scale, 0 equals no disruption of regular sleep, 1 equals mild or difficulty falling/staying asleep 1–2 nights per week, 2 equals moderate disruption or difficulty falling/staying asleep 2–4 nights per week, 3 equals major disruption or difficulty falling/staying asleep 5–6 nights per week and 4 equals severe disruption or difficulty falling/staying asleep daily. To assess school, social and sports, 0 equals "regular attendance" and 4 equals "complete withdrawal for at least 1 week" to evaluate children's level of disability at clinic intake and follow-up appointments [18]. Parents also provided disruption ratings for their children at baseline and during weekly telephone interviews using our standardized questionnaires rated by interviewer using the 5-point criteria described above. When patient or parent questionnaire data was unavailable for disability ratings, patient journals were used.

2.6. Sample size calculation

A sample size of 17 subjects per group, or 34 in total, was calculated to achieve 80% power to detect a difference between the null hypothesis that both group means on change in pain intensity score (final-baseline) are 1.0 and the alternative hypothesis that the difference of the mean (final-baseline) of one of the groups is 2.0 with estimated group standard deviations of 1.0 and with a significance (alpha) level of 0.05 using a two-sided two-sample *t*-test. The calculation was based on data from eight previous patients who had received either amitriptyline ($n = 2$) or gabapentin ($n = 6$) during standard treatment in the Chronic Pain Clinic. The original study design included a plan to recruit 20 patients per group as randomization was being completed in blocks of four.

2.7. Statistical analysis

For our primary outcome we explored separately completed cases and all randomized cases. For all randomized cases missing values were imputed using either the last-data entry in the participants journal or the participants baseline data. Normality of primary outcome pain data was verified by exploring histograms as well as by running Shapiro–Wilk test. All pain variables (pre-trial, post-trial, decrease) for complete and all cases did not deviate from normality. Since variables were normal, the comparison was performed by running an independent sample *t*-tests.



[1] Patients consented and were allocated to treatment group, however were subsequently withdrawn due to new medical information identifying a contraindicated health condition of prolonged QT Syndrome (1 patient prior to commencing treatment; 1 patient within the first 2 days of trial).

[2] Adverse symptoms developed at day 27 in trial and patient withdrew trial. Adverse event (development of secondary pain site) was not believed to be related to study medication.

[3] Secondary pain site developed and patient withdrew from trial at day 6 in trial. Adverse event was not believed to be related to study medication.

[4] Unexpected foreign body was found at pain site requiring surgery. Patient withdrew from trial.

Fig. 1. Study flow diagram.

Secondary outcome data for sleep disturbance were analyzed in a similar manner. Normality was verified by running Shapiro–Wilk test for three sleep score variables using complete cases. However, normality was violated when all cases data were used. Therefore, to compare drug groups we used independent samples *t*-tests for complete cases and *t*-tests plus non-parametric Mann–Whitney tests for all cases. For our adverse event data, we used the Fisher's exact test given our small sample size to compare the proportion of events between groups.

2.8. Missing data

The baseline usual pain score was missing for one patient. To replace this data, the median baseline score among all patients was used. End of trial 6-week usual pain scores were missing for five patients, all of whom withdrew from the study. Sleep score data at six weeks was also missing for seven patients. Using patient journals we carried the last observation forward for missing outcome data (using data ranging from week 1 to week 4). If journal data was not available we carried forward the baseline observation.

3. Results

3.1. Patient characteristics

A total of 427 patients were seen in the Chronic Pain Clinic and screened for eligibility between April 2006 and July 2010 (Fig. 1). Forty-nine patients were eligible, with 11 declining (e.g., anxious about swallowing any type of medications, too busy) and four being unavailable for study duration. A total of 34 patients were allocated to treatment.

Patient characteristics, diagnosis, pain location, duration and frequency and disruption ratings from baseline are shown in Table 1. The two groups had similar compositions in demographic (age, sex, ethnicity) and baseline clinical characteristics (pain intensity and frequency, disruption, and physiotherapy recommendations) with the exception of participants in the amitriptyline group having both higher sleep disruption scores and recommendations for psychological therapy. We found no statistically significant difference in pre-trial pain intensity ($p = 0.10$ for complete cases, $p = 0.08$ for all cases) indicating that randomization resulted in two groups with similar pain levels (Table 2a). We found

Table 1
Baseline demographic and clinical characteristics by group.

	Amitriptyline ($n = 17$)	Gabapentin ($n = 17$)	Comparison test
Age (years)	13.5 ± 2.35	12.6 ± 2.52	$t(32) = 1.08$, $p = 0.29$
Sex (female)	14 (82%)	14 (82%)	$\chi^2(1) = 0.00$, $p = 1.00$
Ethnic origin (self-reported)			$\chi^2(4) = 4.67$, $p = 0.32$
White	5 (29.4%)	9 (52.9%)	
Black	0 (0.0%)	1 (5.9%)	
South Asian	1 (5.9%)	0 (0.0%)	
Other	1 (5.9%)	0 (0.0%)	
Not assessed	10 (58.8%)	7 (41.2%)	
Diagnosis and location (# of patients)			$\chi^2(4) = 0.53$, $p = 0.97$
CRPS-I	10 (58.8%)	10 (58.8%)	
Upper limb	2 (20.0%)	2 (20.0%)	
Lower limb	8 (80.0%)	8 (80.0%)	
Neuropathic pain – other			
Upper limb	1 (14.3%)	2 (28.6%)	
Lower limb	3 (42.9%)	3 (42.9%)	
Other[a]	3 (42.9%)	2 (28.6%)	
Pain duration (months)			
Mean ± SD	23.9 ± 44.29	10.0 ± 12.10	$t(32) = 1.25$, $p = 0.22$
Range, median	1–180, 5	1–48, 5	
<6 months	9 (52.9%)	9 (52.9%)	$\chi^2(2) = 0.00$, $p = 1.00$
≥6 and <12 months	3 (17.6%)	3 (17.6%)	
≥12 months	5 (29.4%)	5 (29.4%)	
Pain frequency (# of patients)			$\chi^2(1) = 1.41$, $p = 0.23$
Constant	14 (82.4%)	12 (70.6%)	
Episodic	2 (11.8%)	5 (29.4%)	
Disruption (0–4)			
Sleep[b]	2.77 ± 1.44	1.65 ± 1.50	$t(32) = 1.75$, $p = 0.09$
Psychological treatment status (# of patients)[c]			
Enrolled at trial onset	0 of 17	2 of 17	$\chi^2(1) = 2.13$, $p = 0.14$
Therapy recommended	15 of 17	5 of 17	$\chi^2(1) = 12.14$, $p < 0.001$
Physiotherapy treatment status (# of patients)[c]			
Enrolled at trial onset	8 of 17	8 of 14	$\chi^2(1) = 0.31$, $p = 0.58$
Therapy recommended	10 of 13	12 of 12	$\chi^2(1) = 3.15$, $p = 0.08$

Data are means ± SD or counts (%).
[a] Other included abdomen, shoulder and scrotum.
[b] Severity of pre-trial sleep disruption was assessed during intake by clinic team member using the following criteria on a 5-point Likert scale [where 0 = no disruption or regular sleep; 1 = mild or 1–2 nights/week of difficulty falling or staying asleep; 2 = moderate disruption or difficulty falling/staying asleep 3–4/nights per week; 3 = major disruption or difficulty falling/staying asleep 5–6/nights per week and 4 = severe disruption or difficulty falling/staying asleep daily].
[c] Accounts for missing pre-trial data or patient withdrawn at trial onset.

a statistically significant difference in pre-trial sleep score between the two drug groups, with patients allocated to amitriptyline having higher sleep score than patients assigned to gabapentin ($p = 0.04$ for complete cases, $p = 0.03$ for all cases) (Table 3). This suggests that randomization resulted in two groups with unequal sleep scores.

3.2. Primary outcome

At the end of the 6-week trial, we found no statistically significant difference between two the drugs in pain intensity decrease ($p = 0.77$ for complete cases, $p = 0.62$ for all cases) suggesting that both drugs were similarly effective in reducing pain level among patients. However, patients on both drugs had important reductions in pain (greater than the minimally important difference [MID] of 1) [12].

We also dichotomized decrease in pain intensity values by using MID (a decrease in pain of 1 or more) (Table 2b) [22]. Although there is some indication of gabapentin being slightly more effective than amitriptyline as the percentage decrease in pain intensity above MID for gabapentin (60%) was higher than amitriptyline (46.2%), we found no statistically significant difference between the two drugs ($p = 0.71$ for complete cases, $p = 0.73$ for all cases).

3.3. Secondary outcomes

We found no statistically significant difference between the two drugs in sleep score ($p = 0.26$ for complete cases, $p = 0.36$ for all cases), suggesting that both drugs impacted sleep scores similarly (Table 3). We found no statistically significant difference in the

Table 2a
Analysis of pain intensity (continuous values).

Primary outcome	Drug 1 (amitriptyline)	Drug 2 (gabapentin)	Comparison tests
Complete cases	$n = 14$	$n = 15$	
Pre-trial pain intensity (usual pain 0–10 CAS score)	6.50 ± 1.46	5.00 ± 3.15	$t(21.86) = 1.74$, $p = 0.10$
Post-trial pain intensity (usual pain 0–10 CAS score)	5.00 ± 3.15	3.30 ± 2.38	$t(26) = 1.62$, $p = 0.12$
Decrease in pain intensity (usual pain 0–10 CAS score)	1.50 ± 2.49	1.77 ± 2.34	$t(26) = -0.30$, $p = 0.77$
All cases (with assumptions – missing values imputed)	$n = 17$	$n = 17$	
Pre-trial pain intensity (usual pain 0–10 CAS score)	6.46 ± 1.34	5.13 ± 2.67	$t(23.52) = 1.84$, $p = 0.08$
Post-trial pain intensity (usual pain 0–10 CAS score)	5.29 ± 2.86	3.57 ± 2.47	$t(32) = 1.88$, $p = 0.07$
Decrease in pain intensity (usual pain 0–10 CAS score)	1.16 ± 2.26	1.56 ± 2.27	$t(32) = -0.51$, $p = 0.62$

Note: Values reported as mean ± standard deviation.
Though current, lowest, highest and usual pain was recorded, usual pain is reported here.

Table 2b
Analysis of pain intensity (dichotomized values).

Primary outcome	Drug 1 (amitriptyline)	Drug 2 (gabapentin)	Comparison tests
Complete cases	$n = 14$	$n = 15$	
Decrease in pain intensity, usual pain, ≥MID	6 (46.2%)	9 (60.0%)	Fisher's exact test, $p = 0.71$
All cases (missing values imputed)	$n = 17$	$n = 17$	
Decrease in pain intensity, usual pain, ≥MID	7 (41.2%)	9 (52.9%)	Fisher's exact test, $p = 0.73$

MID, minimally important difference.

Table 3
Analysis of sleep score.

Secondary outcome	Drug 1 (amitriptyline)	Drug 2 (gabapentin)	Comparison tests
Complete cases	$n = 12$	$n = 14$	
Pre-trial sleep score	2.83 ± 1.40	1.64 ± 1.45	$t(24) = 2.12$, $p = 0.04$
Post-trial sleep score	1.58 ± 1.83	1.18 ± 1.30	$t(24) = 0.66$, $p = 0.52$
Decrease in sleep score	1.25 ± 1.86	0.46 ± 1.60	$t(24) = 1.16$, $p = 0.26$
All cases (missing values imputed)	$n = 17$	$n = 17$	
Pre-trial sleep score	2.77 ± 1.44	1.65 ± 1.50	$t(32) = 2.22$, $p = 0.03$ Mann–Whitney, $p = 0.04$
Post-trial sleep score	1.88 ± 1.80	1.27 ± 1.39	$t(30.12) = 1.12$, $p = 0.27$ Mann–Whitney, $p = 0.34$
Decrease in sleep score	0.88 ± 1.69	0.38 ± 1.45	$t(32) = -0.93$, $p = 0.36$ Mann–Whitney, $p = 0.50$

Note: Values reported as mean ± standard deviation.

Table 4
Analysis of adverse events.

Outcome	Drug 1 (amitriptyline)	Drug 2 (gabapentin)	Comparison tests
Complete cases	$n = 14$	$n = 15$	
Adverse events	2 (14.2%)	1 (6.6%)	Fisher's exact test, $p = 0.75$
All cases (with missing values imputed)	$n = 17$	$n = 17$	
Adverse events	2 (11.7%)	1 (5.9%)	Fisher's exact test, $p = 0.77$

Complete case: RR 2.14, 95% CI (0.22–21.10); all cases: RR 2.00, 95% CI (0.20–20.04).
RR, risk ratio; CI, confidence interval.

proportion of adverse events between groups (all cases $p = 0.77$; Table 4).

3.4. Adverse events/withdrawals

Among the 5 reportable adverse events as per Health Canada criteria, 1 participant suffered an adverse event prior to commencing treatment, 1 participant withdrew from trial when surgery was required in the area of pain and 3 were considered adverse events potentially related to the study medications (1 in amitriptyline; 2 in gabapentin).

The participant withdrawn prior to commencing the trial was noted to have a prolonged QT interval (a contraindicated study condition) on ECG prior to starting the study medication (which was noted to be amitriptyline when unblinded). One participant on the 2nd day of the trial was noted to have a prolonged QT syndrome on ECG and was withdrawn from the study (which was also noted to be amitriptyline when unblinded). Both participants with prolonged QT were withdrawn and referred to cardiology. Two participants discontinued the intervention on days 6 and 27 respectively due to development of additional pain sites that were deemed unrelated to the study medication. When unblinded, it was noted that one patient was from each drug group. The final patient discontinued the intervention on day 33 when surgery was required in the area of pain on their foot. When unblinded, it was noted that they had been on the study medication gabapentin. Finally, two patients experienced adverse events that were also deemed to be unrelated to study medication and continued in the study to completion.

There was no significant difference in adverse events between groups ($p = 0.77$).

4. Discussion

This study is the first prospective randomized trial comparing the efficacy of amitriptyline versus gabapentin for alleviating pain and improving sleep in children with CRPS I or neuropathic pain. We did not find a statistically significant difference in reduction in pain scores between amitriptyline 10 mg and gabapentin 900 mg. Furthermore, while both drugs decreased pain scores greater than the MID for patients in each group, there was no statistically significant difference between the two drugs in terms of percentage decrease in pain intensity greater than the MID. While both drugs also improved quality of sleep, there was no statistically significant difference in sleep score improvements between the two drugs.

This trial was conducted in a large tertiary paediatric hospital with a comprehensive chronic pain outpatient treatment programme. Patients were frequently referred when not responding to conventional measures or their cases were too complex for management by a general practitioner or paediatrician. This may have impacted their propensity to respond to our treatment drugs. Although gabapentin and amitriptyline are well recognized as agents in the treatment algorithm for CRPS I and neuropathic pain, our results may not be generalized to other agents in these pharmacological categories, such as pregabalin and nortriptyline, until further studies are completed.

Not surprisingly, most of the literature regarding the treatment of paediatric CRPS I and neuropathic pain is extrapolated from adult studies and recommendations. Recent recommendations for the pharmacologic management of neuropathic pain in adults suggest the use of a tricyclic antidepressant or a calcium channel alpha-2-delta ligand such as gabapentin [12]. The use of nortriptyline

and gabapentin in combination has also met with success in adults [20]. When used in mice, gabapentin and nortriptyline also has a synergistic effect in antinociception [21]. A systematic review and meta-analysis of the Special Interest Group on Neuropathic Pain's (NeuPSIG) recommendations for the pharmacotherapy of neuropathic pain also found a strong recommendation for the use of tricyclic antidepressants, gabapentin and pregabalin [11]. Recommendations are published for children [22,23], but these recommendations are based on the adult literature. Previous studies in adults have shown a similar efficacy of gabapentin versus amitriptyline suffering from diabetic peripheral neuropathy pain [24] and neuropathic pain in malignancy [25].

Gabapentin acts by inhibiting neurotransmitter release by binding voltage-gated calcium channels [12]. Its use in children with reflex sympathetic dystrophy was first mentioned in two case studies of 9-year-old girls in the year 2000 [26]. Since then, it has become a standard component of the multimodal treatment of paediatric CRPS I and neuropathic pain, which also includes amitriptyline, physical therapy, cognitive-behavioural therapy, TENS, and nerve blocks [6]. Although frequently used, it requires careful dose titration once initiated, cautious dosing in patients with impaired renal function, and can cause adverse reactions such as dizziness and sedation.

In the adult population with various types of neuropathic pain, tricyclic antidepressants are repeatedly demonstrated to be efficacious analgesics in placebo-controlled randomized trials [27,28]. Their treatment effect can be expected after 6–8 weeks. Despite their low cost and ease of administration, their frequent anticholinergic side effects may not be tolerated by some patients [12]. In addition, they should be used with caution in patients with ventricular conduction abnormalities such as a prolonged QT interval. Tricyclic antidepressants (of which amitriptyline is classed) are linked by case reports with QT prolongation, torsade de pointes and sudden cardiac death [12]. In a recent rat model, chronic amitriptyline administration prevented the increased expression of GFAP, IL-10 and CCL5, and enhanced the expression of TNFalpha, in the prefrontal cortex of OB-SNL rats. This data demonstrates that chronic amitriptyline differentially may alter somatic nociceptive responding, following peripheral nerve injury [29].

Our paper has a number of limitations. Firstly, there were numerous etiologies for neuropathic pain in our study. As we reviewed cases from this study and our clinic database, etiologies ranged from a simple paper cut injury to post surgical trauma. While we were concerned that this diverse source resulting in CRPS I and neuropathic pain may not all be equally responsive to our pharmacologic interventions, work done in our clinic has shown otherwise. Secondly, the initial intent of the study was to include secondary outcome measures of disability in sleep, school, sports and social functioning during the study period. However, due to small sample size, and for simplification and as per PedIMMPACT recommendations, we ultimately limited our initial analysis of secondary outcomes to adverse events and sleep disability (see Table 1, footnote b for sleep disruption rating scale). Thirdly, we had difficulty with recruitment and terminated the study before reaching our target sample size of 40 in July 2010 due to decreases in eligible patients over the course of the study period. Despite a similar number of new patients seen in clinic each year (average of 105 new referrals per year), the percentage of eligible patients significantly declined during the latter year (2010) of recruitment to 2.5% from an average of 12.7% in previous years (2008 and 2009). Given we had reached our minimum sample of $N = 34$ based on a priori sample size calculation, we closed recruitment before reaching 20 patients per group. Our study is also limited by a small sample size with missing data for 5 (15%) patients for pain intensity and 7 (21%) patients for sleep disturbance. To test the robustness of the complete case analysis for pain and sleep, we substituted missing data using an "all randomized cases" analysis. We found consistent results for both complete and all case analyses, which is reassuring and reduced the risk of a misinterpretation of treatment effect. A placebo was not included in our trial. Our research team, after a discussion with our research ethics board felt it was not ethical in children experiencing chronic pain to receive a placebo in place of active treatment since amitriptyline and gabapentin had become first-line drugs in the treatment of chronic pain in adults. Thus due to ethical concerns and lack of resources, a placebo arm with acute rescue medication was not possible. We acknowledge that the lack of placebo arm may have caused the positive effect to both study drugs.

While patients were followed by the chronic pain clinic after completion of the trial, subsequent data was not assessed after the 6-week mark. Thus, it is possible that patients had a more (or less) profound response to their medication at a later time-point or undocumented adverse events. In addition, although medication bottles were checked for the correct number of remaining pills and parental confirmation of administration of medication was sought, it is possible that with a paediatric study population, some children did not in fact ingest the medication as prescribed.

5. Conclusion

Despite our trial's stated limitations, this is the first prospective randomized trial comparing amitriptyline and gabapentin in the paediatric population for use in CRPS I and neuropathic pain. It reveals that while both drugs significantly decreased pain scores beyond the MID and improved sleep, there were no significant differences between the two drugs in their effect. Although pain reduction was small but important (surpassing the MID), the amount of pain reduction was not moderate or large on average (i.e. 2 to 3× the MID). In light of these findings, both drugs may be considered in the first-line treatment of paediatric CRPS I and neuropathic pain, with specific potential contraindications (e.g. prolonged QT syndrome) and adverse events (e.g. sedation) taken into consideration. Given the prevalence and impact of chronic pain in children, further research into the pharmacological treatment of neuropathic pain and CRPS I is urgently required.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgement

This research was funded by a Canadian Institutes of Health Research (CIHR) New Emerging Team (NET) Grant (GHL-63209).

References

[1] Perquin CW, Hazebroek-Kampschreur AA, Hunfeld JA, Bohnen AM, van Suijlekom-Smit LW, Passchier J, van der Wouden JC. Pain in children and adolescents: a common experience. Pain 2010;87:51–8.
[2] Huguet A, Miro J. The severity of chronic pediatric pain: an epidemiological study. J Pain 2008;9:226–36.
[3] Treede RD, Jensen TS, Campbell JN, Crucco G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008;70:1630–5.
[4] Bennett G. Neuropathic pain: an overview. In: Borsook D, editor. Molecular neurobiology. Seattle: IASP Press; 1997. p. 109–13.
[5] Berde CB, Lebel AA, Olsson G. Neuropathic pain in children. In: Schechter NL, Berde CB, Yaster M, editors. Pain in infants, children, and adolescents. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2003. p. 620–41.
[6] Walco GA, Dworkin RH, Krane EJ, LeBel AA, Treede RD. Neuropathic pain in children: special considerations. Mayo Clin Proc 2010;85(Suppl. 3):33–41.

[7] Howard RF, Wiener S, Walker SM. Neuropathic pain in children. Arch Dis Child 2014;99:84–9.
[8] Olsson G. Neuropathic pain in children. In: McGrath PJ, Finley GA, editors. Chronic and recurrent pain in children and adolescents. Seattle: IASP Press; 1999. p. 75–98.
[9] Attal N, Finnerup NB. Pharmacological management of neuropathic pain. IASP Pain Clin Updates 2010;18:1–8.
[10] Turner-Stokes L, Andreas G. Complex regional pain syndrome in adults: concise guidance on behalf of the guideline development group. Clin Med 2011;11:596–600.
[11] Finnerup NB, Attal N, Haroutaunian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jenson TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice ASC, Rowbotham M, Sena E, Siddal P, Smith BH, Wallace M. Pharmacology for neuropathic pain in adults: a systematic review and meta-analysis. Lancet 2015;14:162–73.
[12] Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmader KE, Stacey B, Stanos S, Treede RD, Turk DC, Walco GA, Wells CD. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc 2010;85(Suppl. 3): 3–14.
[13] Kachko L, Ben Ami S, Lieberman A, Shor R, Tzeitlin E, Efrat R. Neuropathic pain other than CRPS in children and adolescents: incidence, referral, clinical characteristics, management, and clinical outcomes. Paediatr Anaesth 2014;4:608–13.
[14] McGrath PJ, Walco GA, Turk DC, Dworkin RH, Brown MT, Davidson K, Eccleston C, Finley GA, Goldschneider K, Haverkos L, Hertz SH, Ljungman G, Palermo T, Rappaport BA, Rhodes T, Schechter N, Scott J, Sethna N, Svensson OK, Stinson J, von Baeyer CL, Walker L, Weisman S, White RE, Zajicek A, Zeltzer L. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. J Pain 2008;9:771–83.
[15] Casarett D, Karlawish J, Sankar P, Hirschman K, Asch DA. Designing pain research from the patient's perspective: what trial end points are important to patients with chronic pain. Pain Med 2001;2:309–16.
[16] Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
[17] McGrath PA, Seifert CE, Speechley KN, Booth JC, Stitt L, Gibson MC. A new analogue scale for assessing children's pain: an initial validation study. Pain 1996;64:435–43.
[18] Ruskin DA, Amaria K, Warnock F, McGrath PA. Pain assessment: infants, children and adolescents. In: Turk DC, Melzack R, editors. Handbook of pain assessment. 3rd ed. New York: The Gilford Press; 2011. p. 213–41.
[19] Bulloch B, Garcia-Filion P, Notricia D. Reliability of the color analog scale: repeatability of scores in traumatic and nontraumatic injuries. Acad Emerg Med 2009;16:465–9.
[20] Gilron I, Bailey J, Tu D, Holden RR, Jackson AC, Houlden L. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomized controlled crossover trial. Lancet 2009;374:1252–61.
[21] Miranda HF, Noriega V, Zepeda R, Zanetta P, Prieto-Rayo J, Sierralta F. Antinociception synergism of gabapentin and nortriptyline in mice with partial sciatic nerve ligation. Pharmacology 2015;95:59–64.
[22] Brown SC, Taddio A, McGrath PA. Pharmacological considerations in infants and children. In: Pharmacology of pain. IASP Press; 2010. p. 529–47.
[23] Brown SC. Analgesic guidelines for infants and children. In: Gebhart GF, Schmidt RF, editors. Encyclopedia of pain. 2nd ed. New York: Springer-Verlag Berlin and Heidelberg; 2013. p. 133–40.
[24] Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Shagian GA. Randomized double-blind study comparing the efficacy of gabapentin and amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med 1999;159:1931–7.
[25] Banerjee M, Pal S, Bhattacharya B, Ghosh B, Monday S, Basu J. A comparative study of efficacy and safety of gabapentin versus amitriptyline as coanalgesics in patients receiving opioid analgesics for neuropathic pain in malignancy. Indian J Pharmacol 2013;45:334–8.
[26] Wheeler DS, Vaux KK, Tam DA. Use of gabapentin in the treatment of childhood reflex sympathetic dystrophy. Pediatr Neurol 2000;22:220–1.
[27] Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005;118:289–305.
[28] Max MB, Culnane M, Schafer SC, Gracely RH, Walther DJ, Smoller B, Dubner R. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology 1987;37:589–96.
[29] Burke NN, Finn DP, Roche M. Chronic administration of amitriptyline differentially alters neuropathic pain-related behaviour in the presence and absence of a depressive-like phenotype. Behav Brain Res 2015;278:193–201.