Published in final edited form as:

J Pediatr Hematol Oncol. 2015 January ; 37(1): 10–15. doi:10.1097/MPH.0000000000000265.

The Use of Neuropathic Pain Drugs in Children with Sickle Cell Disease is Associated with Older Age, Female Gender and Longer Length of Hospital Stay

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Abstract

Although neuropathic pain is increasingly recognized in sickle cell disease (SCD), it is unknown how neuropathic pain drugs are used in children with SCD. Thus, we investigated use of these drugs and hypothesized older age and female gender are associated with increased neuropathic drug use and the use of these drugs is associated with longer length of stay. We analyzed the Pediatric Health Information System (2004-09) including all inpatient visits 0-18 years with any SCD-related (all genotypes) discharge diagnosis. To limit confounding we excluded psychiatric and seizure visits. Antiepileptics, tricyclic antidepressants, and selective serotonin reuptake inhibitors were drugs of interest. Generalized Estimating Equations determined the impact of age and gender on neuropathic drug use and the impact of neuropathic drug use on length of stay. We analyzed 53,557 visits; 2.9% received 1 neuropathic drugs. The odds of receiving a neuropathic drug increased significantly with age [Reference group 0-4 yrs: 5-10, OR 5.7; 11-14, OR 12.5; 15-18, OR 22.8; all $p < 0.0001$] and female gender [OR 1.5; $p = 0.001$]. Neuropathic drug use was associated with longer length of stay [RR 8.3; $p < 0.0001$]. Neuropathic drug use in children with SCD was associated with older age, female gender, and longer length of stay.

Keywords

sickle cell disease; neuropathic pain

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Conflicts of Interest: The authors declare no competing financial interests.

Authorship Contributions

A.M.B. designed research, performed research, analyzed data, and wrote the manuscript; R.A.F. performed research and critically reviewed the manuscript; M.D. analyzed data; R.G.H. analyzed data; J.A.P. designed research and critically reviewed the manuscript.

Introduction

There is increasing evidence that a component of neuropathic pain contributes to the underlying neurobiology of sickle cell disease (SCD) pain. Neuropathic pain is defined as pain initiated or caused by a lesion or dysfunction of the peripheral or central nervous system affecting the somatosensory system.[1] Neuropathic pain can manifest as *allodynia*, pain due to a non-painful stimulus and/or *hypersensitivity*, exaggerated pain to a painful stimulus.[2, 3] Patients with SCD likely experience allodynia and/or hypersensitivity since epidemiologic data reveal increased wind speed and barometric pressure, colder temperatures, and touch provoke SCD pain.[4-6] The multicenter study of hydroxyurea found that pain intensity was significantly higher in winter and fall and lower temperatures were associated with higher pain frequency and intensity.[5] These precipitating factors suggest patients with SCD have hypersensitivity to tactile stimuli. Further, patients with SCD use pain descriptors including “cold”, “hot”, “shooting”, and “tingling”[7-10] suggestive of neuropathic pain. Through the use of validated tests that measure thermal pain sensitivity, data in both SCD mice and humans provide further evidence that heat and cold pain sensitivity exists supporting a neuropathic pain component in SCD.[11-13]

In chronic pain conditions other than SCD, patient-level factors such as older age and female gender are associated with greater pain frequency and intensity[14-18] and a higher prevalence of neuropathic pain occurs with increasing age in non-SCD painful conditions. [17-20] Older age also significantly contributes to increased hypersensitivity to thermal stimuli, a marker of neuropathic pain in both SCD mice and patients with SCD.[12, 13] These data are consistent with SCD epidemiologic data where health care utilization for pain increases with age and adolescents and adults suffer from chronic pain.[21, 22] Why patients transition from acute to chronic pain is unknown and may be neuropathic in origin. The prevalence of neuropathic pain is higher in females including those with SCD.[10, 17, 18] Thermal hypersensitivity also occurs with a higher frequency in female SCD mice.[12] Despite data supporting the potential for increased neuropathic pain in older and female patients with SCD, the use of neuropathic pain drugs in these patients has not been studied.

Neuropathic pain is associated with longer duration, higher intensity, and is often refractory to conventional analgesics.[17, 20] Neuropathic pain treatment guidelines exist for patients without SCD.[23-25] Anticonvulsants, tricyclic antidepressants, and selective serotonin reuptake inhibitors are first and second line treatments for neuropathic pain.[23-25] Despite the proven effect of these drugs, their use in the treatment of SCD-related pain has not been systematically studied.

In summary, although neuropathic pain is an increasingly recognized component of SCD pain, national data regarding the use of neuropathic pain drugs in patients with SCD do not exist. Furthermore, patient-level factors associated with the development of neuropathic pain in SCD are not well characterized. Thus, the objectives of our study were to: 1) Describe the use of neuropathic pain drugs in children with SCD, 2) Determine patient-level factors associated with the use of these drugs, and 3) Determine the association between the use of neuropathic drugs and length of hospital stay. We hypothesized older age and female gender

are associated with increased use of neuropathic pain drugs and the use of neuropathic pain drugs is associated with longer length of hospital stay.

Materials and Methods

Data Source

Data for this retrospective cohort study were obtained from the Pediatric Health Information System (PHIS), an administrative database containing inpatient, emergency department, ambulatory surgery and observation data from 43 tertiary care US pediatric hospitals. These hospitals are affiliated with the Children's Hospital Association (Overland Park, KS). Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals. The data warehouse function for the PHIS database is managed by Truven Health Analytics (Ann Arbor, MI). For external benchmarking, participating hospitals provide discharge/encounter data including demographics, diagnoses, and procedures. Forty-two of these hospitals also submit resource utilization data (e.g. pharmaceuticals). Data are de-identified and subjected to reliability and validity checks before database inclusion. For this study, data from 42 hospitals from years 2004-09 were included. The study was approved by the Institutional Review Board of the Children's Hospital of Wisconsin.

Study Population

All inpatient visits from patients age 0-18 years with any SCD-related inpatient discharge diagnosis between January 1, 2004-December 31, 2009 were identified. A SCD visit was defined as an International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic code of SCD (282.41, 282.42, 282.60, 282.61, 282.62, 282.63, 282.64, 282.68, 282.69). Visits included any SCD primary, secondary, or tertiary diagnosis. All SCD genotypes were included. A single inpatient visit with a SCD diagnosis was sufficient to define that patient as having SCD.[26, 27] To limit confounding, patient visits that also included any ICD-9 diagnosis of depression, anxiety or seizure disorder, or headache diagnosis were excluded since neuropathic drugs also treat these disorders. Visits were included for an individual patient until one of these confounding diagnoses were made then all subsequent visits for that patient were excluded after this diagnosis even if it was not coded in the database.

Neuropathic Pain Drugs of Interest

Visits meeting inclusion criteria were analyzed for the receipt of the following neuropathic drugs during hospital admission: 1) antiepileptics (gabapentin, pregabalin, phenytoin, valproate), 2) tricyclic antidepressants (amitriptyline, nortriptyline), and 3) selective serotonin reuptake inhibitors (fluoxetine, paroxetine, venlafaxine). These drugs of interest were based on neuropathic pain treatment guidelines for patients without SCD.[23-25] There were 4254 visits with incomplete data for gabapentin use thus these visits were completely excluded from the study to be the most conservative in our approach.

Outcomes

The primary outcomes were: 1) Receipt of a neuropathic pain drug during hospital admission including the total number of neuropathic drugs received and 2) The association between neuropathic drug use and age, gender, and length of hospital stay.

Data Analysis

Data were analyzed at the visit level. Descriptive statistics revealed frequencies and percentages, means with standard deviations or standard error, and medians with interquartile ranges. Since the number of patient visits including more than one neuropathic drug was small (n=95), the receipt of a neuropathic drug was dichotomized (yes/no) rather than using total number of drugs received as an outcome. For univariate analyses, independent samples t-test and chi-square were used to analyze differences between continuous or categorical variables respectively. Since this was a visit-level analysis and the same patient could have multiple visits, Generalized Estimating Equations (GEE) were used to determine the impact of age and gender on the use of neuropathic pain drugs to account for multiple visits by the same patients by including a correlation over time which ensures that subjects with more visits do not contribute too much to the results. The receipt of a neuropathic drug during hospital admission (yes/no) was the dependent variable and age and gender were predictor variables. Age was classified into 4 groups (0-4, 5-10, 11-14, and 15-18 years). GEEs were also used to determine the impact of the receipt of a neuropathic drug on length of stay with receipt of a neuropathic drug (yes/no) as the predictor variable and length of hospital stay (days) as the dependent variable. Due to the large sample size and risk of finding statistically significant differences that were not clinically relevant, we chose $p=0.01$ as the critical value. This makes statistical and clinical significance more closely aligned in the analysis. All analyses used SAS 9.3 (SAS Institute, Inc., Cary, NC).

Results

Study Population

A total of 53,557 patient visits were identified across 12,371 individual patients. The mean age of these visits was 9.6 (± 5.7) years. The remainder of the demographics and characteristics of the study population are in Table I.

Less than 3% of patient visits were prescribed a neuropathic pain drug

We found a neuropathic pain drug was prescribed in 2.9% (n=1566) of patient visits from 531 patients (Table II). The majority of these visits (2.8%) were prescribed a single drug. Table II displays the most commonly used drugs. There was no difference in the use of neuropathic pain drugs over the study time period (2004-09).

The use of neuropathic pain drugs is associated with older age

The mean age of patient visits that received a neuropathic drug was significantly higher than those that did not receive a neuropathic drug [Table I]. Neuropathic drug use also increased significantly with age [Table I]. Of the total number of patient visits that received a

neuropathic drug, 2% were 0-4 years, 12.8% were 5-10 years, 25.3% were 11-14 years and 59.9% were 15-18 years.

The use of neuropathic pain drugs is associated with female gender

A significantly higher proportion of visits for females received neuropathic pain drugs while hospitalized compared to visits for males [Table I].

Older age and female gender are independent predictors of neuropathic pain drug use

In multivariate analysis, compared to the reference group of 0-4 years, the odds of receiving a neuropathic pain drug increased significantly and sequentially for each older age group and visits for females were more likely to have received a neuropathic drug [Table III]. There was no significant interaction between age and gender.

The use of neuropathic pain drugs is associated with longer length of hospital stay

The mean length of stay for patient visits that included a neuropathic drug was significantly longer than those not receiving a neuropathic drug for all ages [9 days (SE=0.32) vs. 3.5 days (SE=0.02); $p<0.0001$, t-test]. The length of stay was also greater for those taking neuropathic drugs compared to those that were not in each age group [0-4 years: 27.5 (SE=4.14) vs. 3 (SE=0.04); 5-10 years: 12.1 (SE=1.2) vs. 3.2 (SE=0.03); 11-14 years: 8.2 (SE=0.65) vs. 3.7 (SE=0.05); and 15-18 years: 7.9 (SE=0.34) vs. 4.1 (SE=0.05); $p<0.0015$ for each comparison]. In multivariate analysis adjusting for older age and gender, the use of a neuropathic drug was found to be an independent predictor for longer length of stay [Table IV]. A significant interaction between neuropathic drug use and age also existed [Table IV]. In patient visits prescribed a neuropathic pain drug, this interaction revealed length of stay decreased markedly with age [27.5 (SE=4.1) days for those 0-4 years; 12.1 (SE=1.2) days for those 5-10 years; 8.2 (SE=0.65) days for those 11-14 years; 7.9 (SE=0.34) days for those 15-18 years; p -value <0.0001]. Conversely, if a neuropathic drug was not prescribed, the length of stay increased slightly with age [3.0 days for those 0-4 years to 4.1 days for those 15-18 years].

Discussion

As hypothesized, based on a visit level analysis we found older age and female gender were significant independent predictors of neuropathic pain drug use in children with SCD. We also found that patient visits receiving neuropathic pain drugs during a SCD-related hospitalization had longer length of hospital stay compared to those not receiving these drugs suggesting these patients have more prolonged pain. Lastly, we found that neuropathic drugs were infrequently used with less than 3% of patient visits receiving a neuropathic drug during a hospital stay. This pattern did not significantly change over time from 2004-09.

Visits from older patients with SCD were more likely to have been prescribed a neuropathic drug during hospitalization. Specifically, the odds of receiving a neuropathic drug increased significantly and sequentially for each older age group with adolescents being almost 20 times more likely to be prescribed one of these drugs. Our findings are supported by data in non-SCD pain populations where older age is associated with an increased prevalence of

neuropathic pain.[18-21] These data are also supported by data in both patients with SCD and non-SCD pain populations that reveal older age is associated with increased thermal pain sensitivity, a marker of neuropathic pain.[14] Specifically, through the use of quantitative sensory testing, our prior work[13] and that of O'Leary et al.[28] found that older patients with SCD have increased thermal pain sensitivity. The relationship between age and use of neuropathic pain drugs suggests that SCD may have an effect on pain processing that worsens with age.[18-21]

Also in agreement with our hypothesis, female gender was a significant independent predictor of neuropathic pain drug use with visits from females being 1.5 times more likely to be prescribed a neuropathic drug. In general pain conditions, data reveal females have greater pain-related distress and report more acute and chronic pain conditions (i.e. fibromyalgia, arthritis, headaches).[29, 30] Females also experience greater sensitivity to experimentally induced pain (thermal, pressure) than males[31-33] and in non-SCD pain populations have increased use of neuropathic pain drugs.[18, 19] Female patients with SCD are more likely to report scores consistent with neuropathic pain on a screening questionnaire specifically designed to differentiate a neuropathic pain phenotype[24] and are more likely referred to a multidisciplinary pain clinic suggesting more refractory pain.[34]

As hypothesized, we found receipt of a neuropathic drug during hospital admission was associated with a significantly longer length of hospital stay and this effect persisted when adjusted for age, a patient-level factor known to be associated with longer length of stay, and gender.[22] The reason for the longer length of stay may be because neuropathic pain is more chronic and more refractory to conventional analgesics.[18] Thus, those patient visits that were prescribed neuropathic drugs may reflect patients with more refractory pain requiring a longer hospital stay for pain management. However, this is a proposed hypothesis since we cannot determine cause and effect due to the nature of the data. Specifically, we cannot determine if longer length of stay led to starting a neuropathic drug since the patient was experiencing refractory pain and alternative pain treatments were tried. On the contrary, patients could have already been on a neuropathic drug at home and patients with a history of neuropathic pain have refractory pain requiring longer length of stay. Nevertheless, although cause and effect cannot be determined, the use of a neuropathic drug is clearly a marker for longer length of stay suggesting more severe and perhaps refractory SCD pain.

A significant interaction existed between neuropathic drug use and age that impacted length of stay. In the cohort of patients who received a neuropathic drug, as age increased, length of stay decreased as shown by the decreasing Rate Ratio in Table IV. This suggests that neuropathic drugs may be appropriately treating neuropathic pain and shortening length of stay in the most at-risk patients as older age is shown to be a risk factor for neuropathic pain. [17-20] However, these data are not designed to answer this specific question as the data are limited to only those patient visits that received neuropathic drugs and we do not have length of stay data for those patient visits that have neuropathic pain and are not treated with neuropathic drugs. In addition, since the mean length of stay in the 0-4 age group was very long, it is possible that these children were taking neuropathic drugs for another indication as their hospitalization may have been complicated by factors other than pain.

The infrequent use of neuropathic drugs in our population could reflect the lack of awareness of neuropathic pain in SCD during the time frame of the study. A PubMed search reveals the majority of literature about SCD pain neurobiology and neuropathic pain is published after 2009. A repeat analysis with updated data may inform whether the surge of recent literature on the neurobiology of SCD pain is reflected in clinical use. However, it is well known that it takes ten years or more before research findings are well adopted into clinical practice. Moreover, the limited use of these drugs suggests the need for systematic screening to diagnose neuropathic pain in patients with SCD which likely is under recognized.

Our study is limited by the retrospective nature of the data. However, these data allow for a comprehensive evaluation of the use of neuropathic pain drugs in children with SCD in real practice. These data were extracted in 2011 thus differences may exist today due to an increased understanding of neuropathic pain in SCD. The PHIS data are generated from claims data making the data subject to inaccurate reporting. However, the data have undergone numerous reliability and validity checks to provide the most accurate representation of what actually occurred during each hospital admission. It is possible that secondary diagnoses such as anxiety or chronic headache may not be accurately coded for during an inpatient admission for an acute problem thus patients may be inappropriately included. Gabapentin use was an incomplete variable for 4254 visits. The reason for this is unclear and is a limitation of the dataset. We excluded all of these visits from the analysis to be the most conservative in our approach. The receipt of neuropathic drugs during hospital admission was used as a proxy for the presence of neuropathic pain. As a result, we cannot know with certainty why the patient was receiving the neuropathic drug, however, we tried to comprehensively exclude other reasons that patients could be on these drugs to limit confounding. The use of a neuropathic pain drug may be a surrogate for a more comprehensive approach to pain management including psychological support and care coordination; however these data are not captured in the database so their contribution cannot be determined. Rare comorbid conditions in patients with SCD (i.e. fibromyalgia) were not excluded, however if these diseases did exist as a comorbid condition they are still associated with neuropathic pain, the primary outcome of the study. Data for patient visits in the 0-4 year age group have limitations due to small numbers (n=10). Currently, the PHIS is largely limited to inpatient data; there could be increased use of neuropathic drugs in patients with SCD in the outpatient setting and these data are not captured in our study. In general, the ability to obtain reliable comprehensive outpatient medication data is limited, thus these data provide a good starting point for evaluating the use of neuropathic drugs. Finally, we present data from a visit level analysis. A patient-level analysis would also be important to perform, however this type of analysis is most appropriate for a separate study.

Conclusions

In summary, we found older age and female gender were both significant independent predictors of neuropathic pain drug use with adolescents being about 20 times more likely to be prescribed one of these drugs. This relationship suggests that SCD may have an effect on pain processing that worsens with age and also suggests that older patients have refractory pain requiring alternative drugs to opioids. Neuropathic drug use was also significantly

associated with a longer length of hospital stay suggesting the use of these drugs may be a marker for more severe SCD pain. Neuropathic drugs were infrequently prescribed which could reflect the lack of awareness of neuropathic pain in SCD during the study's time frame. The underlying reason for the relationship between age, gender and neuropathic pain in SCD warrants further investigation and may provide clues to the underlying neurobiology of SCD pain and help target treatment to the most at risk patients.

Acknowledgments

The authors would like to thank John Grantham and Kyle Steffen for their help with data abstraction.

Source of Funding: This work was supported in part by grants from the National Institutes of Health National Heart, Lung, and Blood Institute 1K23 HL114636-01A1 (AMB) and the Midwest Athletes Against Childhood Cancer and Blood Diseases Fund (AMB).

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Table I

Demographics and Clinical Characteristics of Study Population (n=53,557)

	Neuropathic Drug Usage			p-value
	Total (n=53,557)	Yes (n=1,566)	No (n=51,991)	
Variable	mean (SD)			
Age	9.6 (±5.7)	14.3 (±3.5)	9.5 (±5.7)	p<0.0001
Length of Hospital Stay (days)	3.7 (±5.2)	9 (±12.7)	3.5 (±4.6)	p<0.0001

	n (% of total)	n (% of total in age group)	n (% of total in age group)
Age Group			
0-4 yrs	13345 (24.9)	31 (0.23)	13314 (99.8)
5-10 yrs	14054 (26.2)	201 (1.4)	13853 (98.6)
11-14 yrs	11793 (22.0)	396 (3.4)	11397 (96.6)
15-18 yrs	14365 (26.8)	938 (6.5) *	13427 (93.5)
Gender: Female	26291 (49.1)	970 (3.7) #	25321 (96.3)
Male	27266 (50.9)	596 (2.2)	26670 (97.8)

* use of neuropathic pain drugs increases significantly with age; p<0.0001, ordinal chi-square

significantly more females than males prescribed neuropathic pain drugs; p<0.0001, chi-square

Table II

Neuropathic Pain Drug Use During Hospital Admission for Children with Sickle Cell Disease

Number of Drugs	n (%)	Drug	n (%)
0	51,991 (97.1)	amitriptyline	783 (50)
1	1471 (2.8)	gabapentin	471 (30.1)
2	88 (0.2)	fluoxetine	165 (10.5)
3	6 (0.01)	phenytoin	123 (7.9)
4	1 (0)	pregabalin	47 (3)
		venlafaxine	52 (3.3)
		paroxetine	21 (1.3)
		nortriptyline	7 (0.5)

Table III

Impact of Age and Gender on Receipt of a Neuropathic Pain Drug in Sickle Cell Disease Patients During Hospital Admission

Parameter	Odds Ratio (OR)	95% CI (OR)	p-value [#]
Age Group (years)			
0-4 (Reference)	1.0	-	-
5-10	5.7	3.8 -8.6	p<0.0001
11-14	12.5	8.3 - 18.7	p<0.0001
15-18	22.8	15.1 -34.3	p<0.0001
Gender			
Male (Reference)	1.0	-	-
Female	1.5	1.2 -1.9	p=0.0013

[#] Using General Estimating Equations (GEE)

Table IV

Impact of Neuropathic Pain Drug Use, Age, and Gender on Hospital Length of Stay in Children with Sickle Cell Disease

Parameter		Rate Ratio (RR) (Length of Stay)	95% CI (RR)	p-value [#]
Neuropathic Pain Drug (Yes/No)	Yes	8.31	5.74 -12.05	<0.0001
Age Group (years)	0-4 (Reference)	1.0	-	-
	5-10	1.07	1.03 – 1.12	0.0003
	11-14	1.22	1.17 – 1.28	<0.0001
	15-18	1.37	1.30 – 1.44	<0.0001
Gender (Male is Reference)	Female	1.01	0.97 – 1.05	0.65
Interaction between Neuropathic Pain Drug (Yes/No) and Age Group	Yes and 0-4 (Reference)	1.0	-	-
	Yes and 5-10	0.47	0.30 – 0.73	0.0007
	Yes and 11-14	0.27	0.18 – 0.40	<0.0001
	Yes and 15-18	0.23	0.15 – 0.34	<0.0001

[#] Using General Estimating Equations (GEE)