Daily Assessment of Pain in Adults with Sickle Cell Disease

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Background: Researchers of sickle cell disease have traditionally used health care utilization as a proxy for pain and underlying vaso-occlusion. However, utilization may not completely reflect the amount of self-reported pain or acute, painful episodes (crises).

Objective: To examine the prevalence of self-reported pain and the relationship among pain, crises, and utilization in adults with sickle cell disease.

Design: Prospective cohort study.

Setting: Academic and community practices in Virginia.

Patients: 232 patients age 16 years or older with sickle cell disease.

Measurements: Patients completed a daily diary for up to 6 months, recording their maximum pain (on a scale of 0 to 9); whether they were in a crisis (crisis day); and whether they used hospital, emergency, or unscheduled ambulatory care for pain on the previous day (utilization day). Summary measures included both simple proportions and adjusted probabilities (for repeated measures within patients) of pain days, crisis days, and utilization days, as well as mean pain intensity.

Results: Pain (with or without crisis or utilization of care) was reported on 54.5% of 31 017 analyzed patient-days (adjusted probability, 56%). Crises without utilization were reported on 12.7% of days and utilization on only 3.5% (unadjusted). In total, 29.3% of patients reported pain in greater than 95% of diary days, whereas only 14.2% reported pain in 5% or fewer diary days (adjusted). The frequency of home opiate use varied and independently predicted pain, crises, and utilization. Mean pain intensity on crisis days, noncrisis pain days, and total pain days increased as the percentage of pain days increased ($P < 0.001$). Intensity was significantly higher on utilization days ($P < 0.001$). However, utilization was not an independent predictor of crisis, after controlling for pain intensity.

Limitations: The study was done in a single state. Patients did not always send in their diaries.

Conclusion: Pain in adults with sickle cell disease is the rule rather than the exception and is far more prevalent and severe than previous large-scale studies have portrayed. It is mostly managed at home; therefore, its prevalence is probably underestimated by health care providers, resulting in misclassification, distorted communication, and undertreatment.

Ann Intern Med. 2008;148:94-101. www.annals.org
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Pain may be severe and disabling for patients with sickle cell disease, a genetic erythrocyte disorder affecting persons of African, Mediterranean, or Asian descent (1, 2). Pain typically occurs in long bones, joints, the back, the abdomen, and the chest. Although the pathophysiology of pain and its exacerbations is complex and incompletely understood, a complex cascade of ischemia and vaso-occlusion in the microcirculation is believed to be involved (3–12).

Sickle cell disease vaso-occlusive pain is responsible for most sickle cell disease medical contacts. The often episodic nature of these contacts leads many to conclude that patients do not have pain for most of their days. Caregivers have therefore traditionally used the term *crisis* to describe these contacts and their underlying episodic, acute pain exacerbations and have reserved the term *chronic pain syndrome* to describe pain from sickle cell disease complications, such as ankle ulcers or avascular necrosis (13). Higher-utilizing adults are at higher risk for death, so measuring medical contacts has clinical meaning (14). However, the relationship among daily reported sickle cell disease pain, crises, and utilization has not been described in large-scale, longitudinal epidemiologic studies.

To better understand the epidemiology of daily pain in sickle cell disease, we examined the relationship among self-reported pain, crises, and health care utilization for pain in a cohort study of patients with sickle cell disease.

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METHODS

Study Design

PiSCES (Pain in Sickle Cell Epidemiology Study) is a longitudinal study of pain in sickle cell disease, with particular emphasis on potentially mutable, causal, nonbiological variables. It is also a methodological study of the relationship among measures of pain, crises, and utilization in sickle cell disease. The methods of PiSCES are described in detail elsewhere (15, 16). In brief, we enrolled 308 patients from July 2002 through August 2004. We collected baseline information (including demographic characteristics and medical history), laboratory data (blood and urine samples), and up to 180 daily pain diaries.

We recruited patients 16 years of age or older from across Virginia; most were from the Richmond and Tidewater areas. Sources included statewide sickle cell chapters, clinics and emergency departments, referrals from other

patients and health departments, and direct recruiting through health fairs and radio public service announcements. Both the study and our recruitment methods were approved by the institutional review board of Virginia Commonwealth University, Richmond, Virginia. We invited potentially eligible patients for an enrollment visit, at which time we obtained informed consent.

Patients received routine care for their sickle cell disease from either community-based physicians or sickle cell specialist physicians associated with academic medical centers (2 physicians at Virginia Commonwealth University serving the Richmond area, and 1 physician associated with Eastern Virginia Medical School, Norfolk, Virginia, serving the Tidewater region). Emergent care for the cohort was provided in emergency departments regardless of the patients' usual source of ambulatory care. No day hospitals for sickle cell disease are located in the region.

Diary Data

Patients filled out daily diaries for up to 6 months. They were encouraged (at the initial baseline visit and with reminder calls by study staff) to complete the diary each day and return it by mail using provided, stamped envelopes. They received payment for each returned diary, with a higher payment in the latter 2 months of the study to encourage study completion. We modeled the diary after that of the Multicenter Study of Hydroxyurea (17). We asked patients to report the following, among other things, about the previous 24 hours in their diary: their worst sickle cell pain intensity, on a scale from 0 (none) to 9 (unbearable), and whether they were in a sickle cell crisis, had taken medication for their pain (and if so, what), or had gone for an unscheduled physician visit or emergency department visit or had been hospitalized because of sickle cell pain. Crises were self-defined by each patient.

Statistical Analysis

For analysis, we defined unplanned health care utilization as an unscheduled clinic visit, emergency department visit, or overnight hospitalization. We defined opiate use on home care days as use of any opiates on days when the patient was not seen at the hospital for their sickle cell pain (in either the emergency department or overnight hospitalization).

We constructed crisis episodes and utilization episodes by counting groups of 1 or more contiguous crisis days as single crisis episodes and contiguous utilization days as single utilization episodes. Missing diary days that were immediately preceded and followed by crisis days or by utilization days were considered part of the same crisis or utilization episode, respectively.

We used generalized estimating equation methods with a logit link (logistic regression, controlling for repeated measures within a patient) to determine whether occurrence of pain, crisis, or unplanned health care utilization varied daily across patient characteristics, controlling for clustering of diary days within patients. We estimated the probability of experiencing the outcomes, along with the 95% CIs, by using the generalized estimating equation parameter estimates and empirical SEs.

To study the relationship between the proportion of pain days experienced by patients and the mean intensity of pain, we grouped patients into 6 categories according to their increasing proportion of pain days (calculated as the proportion of diary days with reported pain intensity greater than 0): 5% or less, 6% to 25%, 26% to 50%, 51% to 75%, 76% to 95%, and 96% to 100%. We used mixed-model analysis of variance to evaluate the differences in pain intensity across these groups, controlling for clustering of diary days within patients, and we performed separate analyses for pain days, crisis days, and noncrisis pain days. Least-squares means are reported.

To understand the relationship among self-reported pain, crises, and utilization, we placed diary days into 1 of 4 mutually exclusive, ordinal categories by severity. From most to least severe, the categories were days with any unplanned health care utilization for sickle cell disease pain, regardless of self-reported crises; days with self-reported crises without unplanned health care utilization; pain days without utilization or crisis; and pain-free days. We calculated the proportion of all days that fell into these 4 categories, estimating and comparing mean pain intensity across the categories by using mixed-model analysis of variance, which controlled for repeated measures (days within patients).

To describe the coincidence of crisis and utilization for each patient, we classified days as to whether the patient had a crisis and whether unplanned health care utilization occurred and computed the percentage of diary days for each of the 4 categories. We then calculated the mean and SD of these percentages over all patients. This method adjusted for the varying number of diaries contributed by each patient. We also used mixed-model regression analysis

Context

Although outpatient, emergency department, and hospital visits have been used as indicators of sickle cell disease severity, the relationship between health care use and pain episodes has not been well described.

Contribution

Two hundred thirty-two patients with sickle cell disease completed a daily diary for 6 months, providing 31 017 patient-days for analysis. Patients reported pain on 56% of total patient-days, crises on 13%, and health care utilization on 4%.

Implication

Patients with sickle cell disease frequently have pain but usually manage even severe pain without an outpatient, emergency department, or hospital visit.

—The Editors

to see whether unplanned utilization was predictive of self-reported crisis, after controlling for pain intensity.

To determine whether crisis and utilization episodes overlapped, we compared the dates when each type of episode occurred and counted the overlap. We used crisis episodes as a denominator, determining how often utilization episodes overlapped with them, then did the same by using utilization episodes as denominator. By counting any missing diary days surrounded on both sides by crisis or utilization days as part of a single episode, we maximized the chance of overlap.

Analyses were conducted by using SAS, version 9 for Windows (SAS Institute, Cary, North Carolina).

Role of the Funding Source

The National Heart, Lung, and Blood Institute provided an unrestricted grant for this project. The funding source had no influence on the planning, conduct, analysis, or publication of this study or its results.

RESULTS

Three hundred eight patients enrolled in PiSCES and completed baseline surveys. Twenty-three patients (7.5%) sent in no diaries. Of the remaining 285 patients, we excluded 53 (19%) because they completed fewer than 30 diaries. The remaining 232 patients constitute the analysis sample. Patients in the analysis sample were similar to those excluded except for age; the patients who did not complete sufficient diaries tended to be younger (mean age, 28.3 years vs. 32.6 years; $P = 0.012$). We included a total of 31 017 diaries (patient-days) in this analysis. The median number of diaries completed was 158, about 85% of the diaries requested. When patients were grouped by the number of diaries submitted (30 to 59, 60 to 90, and so on), we found no statistically significant differences among groups in terms of pain, crisis, or utilization.

Table 1 contains a description of the analysis sample ($n = 232$), including probabilities of a pain day, crisis day, and utilization day, adjusted for repeated measures within patients. More than half of studied patients were female, 87% graduated from high school, and 76% either had never married or were otherwise single. Twenty percent of patients were older than 44 years. Most patients (65.9%) had homozygous sickle cell disease. Approximately half of patients were being seen by physicians whom the patients identified as sickle cell disease experts. **Table 1** demonstrates that a patient's adjusted probability of a day with pain, crisis, or unplanned utilization did not differ according to sex, education, genotype, or most self-reported comorbid conditions and sickle cell disease complications. It also demonstrates that, in bivariate analysis, age, marital status, income, frequency of home opiate use, a history of transient ischemic attack, kidney failure status, avascular necrosis, or receipt of care from a community physician each showed some association with the adjusted probability of a pain day, crisis day, or utilization day. In multivariate analysis (not shown), only frequency of home opiate use statistically significantly predicted the adjusted probability of a pain day. Frequency of home opiate use and absence of kidney failure were independent predictors of the adjusted probability of a crisis day, whereas frequency of home opiate use, income, and care of sickle cell disease by an expert were all independent predictors of the adjusted probability of a utilization day.

In **Table 2**, pain intensity is classified by an increasing proportion of pain days experienced. Twenty-nine percent of patients had pain nearly every day, whereas 14% rarely had pain (≤5% days). More than half of patients (54%) reported pain on more than half of days (≥51%). Regardless of which denominator (total pain, noncrisis pain, or crisis days) was used to calculate daily pain intensity, mean pain intensity increased as the percentage of pain days increased (mixed-model analysis of variance, $P < 0.001$).

The **Figure** demonstrates the relationship among self-reported pain, crises, and utilization, by using 4 ordinal, mutually exclusive severity categories, in an analysis that did not adjust for repeated measures within patients. Patients reported no pain on 45.5% of 31 017 analyzed patient-days; thus, they experienced pain on a total of 54.5% of days. On 38.3% of patient-days, they did not describe their pain as a crisis and it was not associated with unplanned health care utilization. On far fewer patient-days (12.7%), patients described their pain as a crisis but managed it at home. Finally, patients reported an unplanned visit to their physician or the emergency department or a hospitalization on only 3.5% of patient-days. Even when we included scheduled visits, utilization days still constituted only 5.1% of all days. The **Figure** also shows statistically significant increases in mean pain intensity (adjusted analysis) by category ($P < 0.001$, with or without consideration of the no-pain category).

Table 3 reports the mean proportion of days on which crises or utilization were reported. On average, for more than three quarters of their days, patients reported neither crisis nor utilization. In contrast, on average, patients reported a crisis but did not seek medical treatment for it on 13% of days. Finally, patients either reported a crisis and utilized care for their pain or sought unplanned medical care but did not report experiencing a pain crisis on fewer than 2% of days, on average. In multivariate, repeated-measures logistic regression, unplanned utilization was not significantly associated with crisis when controlling for pain intensity. Because pain and utilization may be proximate with only some overlap, we performed an analysis by episodes. Patients experienced a total of 1254 crisis episodes and 502 utilization episodes during the study period. Utilization episodes occurred within or overlapped with only 21.1% of crisis episodes, and crisis episodes occurred within or overlapped with only 57.2% of utilization episodes.

DISCUSSION

We believe this PiSCES report is the most detailed large study to date of the epidemiology of pain in relatively

Table 1. **PiSCES Study Cohort**

Characteristic	Patients, *n**	Probability of a Day with Pain (95% CI)†	Probability of a Day with Crisis (95% CI)†	Probability of a Day with Utilization (95% CI)†
All participants	232	0.56 (0.51–0.61)	0.15 (0.13–0.19)	0.04 (0.03–0.05)
Demographic characteristics				
Sex				
Female	143	0.56 (0.50–0.62)	0.15 (0.12–0.19)	0.03 (0.03–0.05)
Male	89	0.56 (0.48–0.64)	0.16 (0.12–0.22)	0.04 (0.02–0.07)
Education				
Less than high school	28	0.54 (0.40–0.69)	0.11 (0.05–0.22)	0.02 (0.01–0.04)
High school graduate	88	0.52 (0.44–0.60)	0.13 (0.10–0.18)	0.04 (0.03–0.07)
Some college	82	0.60 (0.52–0.68)	0.18 (0.14–0.25)	0.04 (0.03–0.07)
College graduate	34	0.58 (0.45–0.71)	0.16 (0.09–0.26)	0.02 (0.01–0.04)
Age‡§				
16–24 y	51	0.32 (0.23–0.42)	0.09 (0.06–0.14)	0.03 (0.02–0.05)
25–34 y	69	0.64 (0.55–0.72)	0.17 (0.12–0.23)	0.05 (0.03–0.09)
35–44 y	66	0.67 (0.58–0.75)	0.20 (0.14–0.27)	0.03 (0.02–0.04)
45–54 y	35	0.55 (0.42–0.68)	0.16 (0.09–0.25)	0.04 (0.02–0.08)
55–64 y	11	0.57 (0.33–0.79)	0.04 (0.02–0.08)	0.02 (0.01–0.04)
Marital status‡				
Married	55	0.70 (0.59–0.79)	0.15 (0.10–0.22)	0.04 (0.02–0.06)
Never married	144	0.51 (0.45–0.58)	0.14 (0.11–0.19)	0.03 (0.02–0.05)
Divorced/separated/widowed	33	0.54 (0.41–0.66)	0.19 (0.12–0.30)	0.05 (0.02–0.09)
Annual income‖				
<$10 000	88	0.62 (0.53–0.69)	0.14 (0.10–0.20)	0.04 (0.03–0.07)
$10 001–$20 000	52	0.61 (0.50–0.70)	0.23 (0.16–0.31)	0.04 (0.03–0.08)
$20 001–$30 000	34	0.58 (0.45–0.70)	0.15 (0.10–0.23)	0.04 (0.03–0.06)
>$30 000	53	0.44 (0.35–0.54)	0.10 (0.06–0.16)	0.01 (0.01–0.02)
Sickle cell disease characteristics				
Genotype				
B-thal or SS	169	0.57 (0.51–0.62)	0.15 (0.12–0.19)	0.04 (0.03–0.05)
SB + thal or SC	62	0.53 (0.43–0.63)	0.16 (0.11–0.23)	0.03 (0.02–0.05)
Treated by specialist‖				
Yes	110	0.57 (0.50–0.64)	0.15 (0.11–0.21)	0.02 (0.01–0.03)
No	117	0.56 (0.49–0.63)	0.15 (0.12–0.20)	0.05 (0.04–0.08)
Days at home using opiates‡§‖				
0%	39	0.12 (0.07–0.22)	0.01 (0.01–0.02)	0.01 (0.00–0.01)
0%–49%	88	0.37 (0.31–0.43)	0.09 (0.07–0.12)	0.02 (0.02–0.04)
≥50%	104	0.89 (0.85–0.91)	0.25 (0.20–0.31)	0.06 (0.04–0.08)
Self-reported comorbid condition				
Avascular necrosis‡				
Yes	48	0.73 (0.63–0.81)	0.20 (0.13–0.28)	0.05 (0.03–0.07)
No	183	0.52 (0.46–0.57)	0.14 (0.11–0.18)	0.03 (0.02–0.05)
Priapism or impotence (men only)				
Yes	15	0.57 (0.37–0.75)	0.14 (0.06–0.28)	0.06 (0.02–0.15)
No	74	0.56 (0.47–0.65)	0.16 (0.12–0.23)	0.04 (0.02–0.06)
Ischemic ankle ulcers				
Yes	26	0.69 (0.54–0.80)	0.17 (0.11–0.26)	0.06 (0.03–0.14)
No	205	0.55 (0.49–0.60)	0.15 (0.12–0.19)	0.03 (0.03–0.04)
Asthma				
Yes	29	0.54 (0.41–0.68)	0.13 (0.07–0.23)	0.03 (0.02–0.05)
No	202	0.57 (0.51–0.62)	0.16 (0.13–0.19)	0.04 (0.03–0.05)
Autoimmune diseases (lupus, rheumatoid arthritis, sarcoidosis)				
Yes	29	0.61 (0.48–0.73)	0.16 (0.09–0.27)	0.04 (0.01–0.10)
No	202	0.55 (0.50–0.61)	0.15 (0.12–0.19)	0.04 (0.03–0.05)
Hypertension				
Yes	21	0.55 (0.39–0.70)	0.09 (0.05–0.17)	0.06 (0.03–0.13)
No	211	0.56 (0.51–0.61)	0.16 (0.13–0.19)	0.03 (0.03–0.05)
Transient ischemic attack§				
Yes	27	0.51 (0.36–0.65)	0.10 (0.06–0.16)	0.06 (0.03–0.12)
No	204	0.57 (0.52–0.62)	0.16 (0.13–0.20)	0.03 (0.03–0.05)
Osteomyelitis				
Yes	11	0.49 (0.29–0.69)	0.12 (0.06–0.22)	0.03 (0.01–0.07)
No	220	0.57 (0.51–0.62)	0.16 (0.13–0.19)	0.04 (0.03–0.05)

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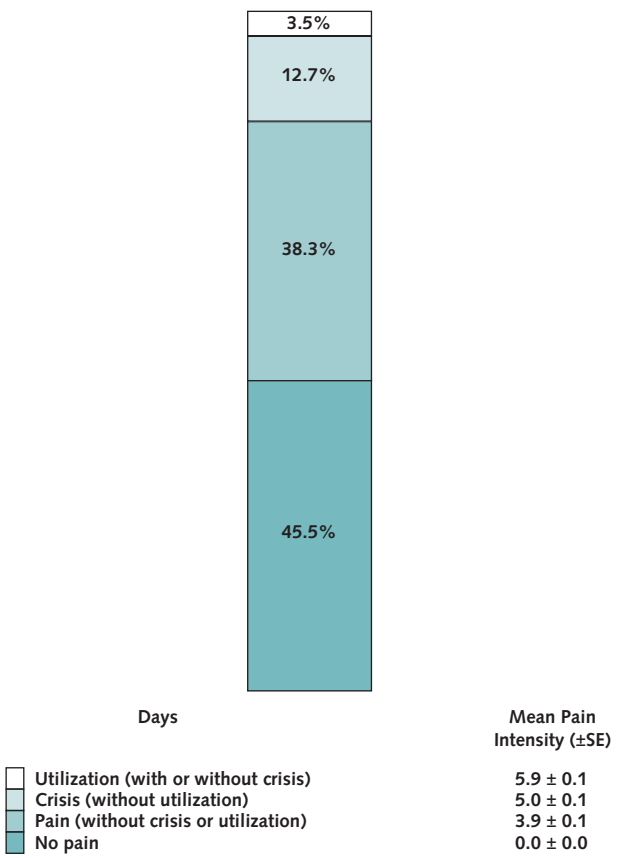
Table 1—Continued

Characteristic	Patients, *n**	Probability of a Day with Pain (95% CI)†	Probability of a Day with Crisis (95% CI)†	Probability of a Day with Utilization (95% CI)†
Gout				
Yes	23	0.66 (0.50–0.80)	0.17 (0.10–0.29)	0.03 (0.02–0.06)
No	208	0.55 (0.50–0.60)	0.15 (0.12–0.19)	0.04 (0.03–0.05)
Gallstones or cholecystitis				
Yes	121	0.58 (0.52–0.65)	0.15 (0.12–0.19)	0.04 (0.03–0.05)
No	110	0.54 (0.46–0.61)	0.16 (0.12–0.21)	0.04 (0.02–0.06)
Kidney failure§				
Yes	10	0.65 (0.41–0.83)	0.07 (0.04–0.13)	0.10 (0.03–0.31)
No	221	0.56 (0.51–0.61)	0.16 (0.13–0.19)	0.03 (0.03–0.04)

* Totals <232 reflect missing values.
† Probability of a pain, crisis, or utilization day was adjusted for repeated measures within patients.
‡ $P < 0.05$ for percentage of pain days.
§ $P < 0.05$ for percentage of crisis days.
‖ $P < 0.05$ for percentage of utilization days.

unselected adults with sickle cell disease. Our results are both surprising and striking: Pain in adults with sickle cell disease is far more prevalent and severe than previous studies have portrayed, and it is mostly managed at home; therefore, it is vastly underestimated when measured by using only health care utilization.

Figure. **Breakdown of diary days.**



Total diary days ($n = 31\,017$) are reported by percentage in 4 mutually exclusive categories of pain severity, and mean pain intensity is reported by category. Percentages of days in each category are unadjusted for repeated measures within patients. Mean pain intensity scores are adjusted.

First, we found that more than one half of patients with adult sickle cell disease completing up to 6 months of pain diaries reported having pain, crises, or utilization on more than half of days. Almost one third (29%) had pain nearly every day. In contrast, only about 15% rarely had pain. Second, we found that on days when patients reported pain, the mean reported intensity was in the middle range, rather than the lower, of our severity scale. Self-reported pain intensity was even higher on the days when patients reported pain that was either severe enough that they called it a crisis or went for treatment in a health care facility. Third, we found that reported crisis days and utilization days were far less common than reported pain days. In fact, pain days that were not associated with a crisis occurred 10 times more often as pain days associated with health care utilization. Similarly, even crisis days occurred nearly 4 times as often as utilization days. Fourth, we found that crisis days or episodes were not usually coincident with utilization days or episodes. Not surprisingly, the frequency of home opiate use varied, and patients who required more opiates also had more pain, crises, and utilization.

Our epidemiologic findings provide useful new information about sickle cell disease, but their explanations lie in the fields of vascular biology, pain neurobiology, behavioral medicine, and health services research.

First, our finding of frequent, often severe daily pain in sickle cell disease can be explained by emerging evidence of the chronicity of the sickle erythrocyte vaso-occlusive phenomenon and its relationship to ischemic pain. Sickle vaso-occlusion is due in part to adhesins expressed on the erythrocyte membrane (18, 19). Evidence is mounting for the chronicity of this vaso-occlusion. Clinically, vaso-occlusion seems chronic: It results in chronic hemolysis, ischemia, and ultimately organ damage (20). Endothelial function in sickle cell disease is impaired both during and

after painful episodes (21). The increased expression of vascular adhesins on sickle erythrocytes seems to be stable over time within a given patient, but differences in expression between children are correlated with differences in ischemic pain frequency (22). In contrast to the constancy of expressed vascular adhesins, evidence shows that microvascular hemodynamic forces within patients constantly change, mediating widely variant adherence of sickle cells to the vascular endothelium (23). This could account for sudden painful episodes within patients.

Our results extend the conclusion from these data that home-managed and hospital-managed sickle cell disease pain are at opposite extremes of a varying continuum of pain frequency and severity caused by correspondingly varying but chronic underlying vaso-occlusion. They suggest that chronic vaso-occlusion may result in chronic baseline ischemic pain as a frequent, even usual, manifestation of sickle cell disease.

Second, the human biological response to both chronic pain stimuli and treatment may partly explain our results of infrequent health care utilization in response to frequent, severe pain, as well as the relatively infrequent characterization of even severe pain as a crisis. We did not attempt to document alterations in pain tolerance, which may have occurred in our patients. Such laboratory-measured alterations, including hyperalgesia and hypoalgesia, have been well described in other painful conditions (24, 25). Some propose a special cause of hyperalgesia known as central sensitization—central nervous system neuroreceptive pain, even without a continuing local pain stimulus (26)—as a cause of chronic pain in sickle cell disease (13). Conceivably, chronic nociceptive pain could have led to central sensitization in our patients. In addition, patients could have experienced opioid-induced hyperalgesia, which was recently recognized as a potential form of central sensitization. In this condition, a patient's pain level increases in parallel with elevation of his or her opioid dose and decreases with detoxification (27). We did see a correlation between the proportion of pain days and both the pain intensity on pain days or crisis days and opiate use. This correlation confirms that patients with more frequent pain both experience more intense pain and use more opiates, and it is consistent with either of the types of central sensitization described.

Table 2. **Pain Intensity, by Percentage of Pain Days***

Pain Days	Patients, *n* (%)	Mean Pain Intensity (±SE)†		
		Pain Days	Noncrisis Pain Days	Crisis Days
≤5%	33 (14.2)	3.5 ± 0.4	3.3 ± 0.4	4.5 ± 0.6
6%–25%	42 (18.1)	3.7 ± 0.2	3.5 ± 0.2	4.4 ± 0.3
26%–50%	32 (13.8)	3.6 ± 0.3	3.3 ± 0.3	4.6 ± 0.3
51%–75%	21 (9.1)	4.3 ± 0.3	4.0 ± 0.3	5.4 ± 0.3
76%–95%	36 (15.5)	4.4 ± 0.2	4.0 ± 0.2	6.2 ± 0.3
96%–100%	68 (29.3)	5.1 ± 0.2	4.8 ± 0.2	6.2 ± 0.2

* Results were adjusted for repeated measures within patients.
† Mean pain intensity statistically significantly increased as percentage of pain days increased ($P < 0.001$).

Table 3. **Mean Percentage of Days When Each Patient Reported Crises, Utilization, or Both**

Crisis	Mean Days per Patient (SD), %	
	No Utilization	Utilization
No	83.0 (24.2)	1.7 (4.9)
Yes	13.4 (21.7)	1.9 (4.7)

Third, our finding of relatively infrequent utilization of health care in response to even severe pain may be explained by general human behavioral responses to pain and by factors governing interaction with the health care system. Behavioral theories suggest that many factors besides pain influence the pain response (28–31). Like other adults with sickle cell disease, our patients may have weighed carefully the decision to come to a busy emergency department for treatment of even severe pain. Some may have preferred to manage their pain at home, not simply because it wasn't severe enough to warrant a health care visit, but also because they succumbed to pressing obstacles to care, were afraid their pain would not be managed better by a professional, or were forced to manage competing life priorities instead. Evidence of each of these may be found in behavioral studies of sickle cell disease (32–36), many of which we have reviewed (37).

In our review of English-language literature listed in MEDLINE from 1966 to January 2007, we found several smaller pain diary studies in sickle cell disease that are consistent with our results but are not as extensive. Longitudinal studies measuring daily pain in children (22, 38–41) and adults (36, 42–44) have found that pain was most often managed at home rather than within health care facilities. However, none reported whether patients assessed pain as a crisis, nor did the studies completely distinguish the pain–crisis–utilization relationship. To our knowledge, our study is the first to measure these distinctions.

We believe our findings prove that, contrary to commonly held belief, pain in sickle cell disease is the rule rather than the exception—at least in adults. Together, our findings suggest a vast, mostly submerged iceberg of sickle cell pain that is not seen by most professionals, but rather is managed outside of medical facilities. The extremely low proportion of sickle cell disease pain that is managed within medical facilities explains why treating physicians might believe that sickle cell pain is the exception rather than the rule.

Our results are also methodologically important. First, they further support construct validity of the numeric pain intensity scale in sickle cell disease. The range in daily pain intensity among our patients was similar to that found in pain diary studies of other chronic pain conditions, such as rheumatoid arthritis and osteoarthritis (35, 45). Also, the relative

intensities of reported pain outside of crises, during crises, and associated with utilization varied as we expected—pain not judged by patients as a crisis was less intense than crisis pain that patients chose to manage at home, which in turn was less intense than pain managed in health care facilities.

Second, our results are methodologically important because they show that measures of sickle cell pain based only on utilization are biased. Utilization counts underestimate pain by excluding pain episodes that are short or are self-treated. Thus, our findings illustrate the measurement bias of previous large sickle cell disease studies. The CSSCD (Cooperative Study of Sickle Cell Disease), the largest cohort study of sickle cell disease to date (14, 46), conservatively defined a painful episode as utilization in a health care facility. However, all utilization that occurred within 2 weeks was counted as 1 episode. Furthermore, 74 patients were excluded from the analyses of counts of episodes because they had "more than ten closely spaced [utilization] episodes" (46) making it difficult to determine an accurate rate. Similar to the CSSCD, the Multicenter Study of Hydroxyurea required a visit to a medical facility of at least 4 hours' duration and receipt of analgesics as evidence of a painful episode (17, 47, 48). Although both studies have yielded many important, valid findings, they seem to have vastly undermeasured sickle cell disease pain.

Despite the high completion rate of studied patients, we had to use imputation strategies because of missing data to determine crisis and utilization episodes, as discussed in the Methods section. For this reason, we used conservative methods to identify episodes and maximize possible overlap. We excluded 76 of the 308 enrolled PiSCES patients for this analysis because of poor diary response. However, except for age, excluded patients did not differ from included patients on baseline variables, so a significant response bias is unlikely. Our sample was heavily drawn from patients already having sought care and from Richmond, Virginia. We cannot exclude that pain intensity and frequency are lower for most community-dwelling patients with sickle cell disease in Virginia, some of whom may not seek care. However, we found no differences in pain between patients treated by sickle cell experts in academic facilities and those treated by other physicians in community facilities.

Our study may be criticized for neither capturing detailed qualitative descriptions of pain on a daily basis, nor distinguishing between pain from complications of sickle cell disease, such as avascular necrosis, and direct, vaso-occlusive, ischemic pain. We chose to conduct an epidemiologic study that minimized daily respondent burden; however, our approach to measuring daily pain is consistent with the concept of pain as multidimensional and is composed of both pain and responses to pain (49).

From this longitudinal sickle cell disease cohort study, which collected in-depth pain diary information daily for 6 months, we conclude that patients with sickle cell disease experience pain far more frequently than previously reported, with significant methodological and treatment implications. Our results support calls to trust reports of pain in patients with sickle cell disease and not to withhold opiates and other therapies (50). They underline the importance of attending to sickle cell disease pain not only when patients present acutely for treatment, but also in the ambulatory setting, where home pain management regimens are prescribed. They both underline the preeminent need for more remittive therapies that halt the underlying chronic vaso-occlusion that causes sickle cell pain and suggest new ways to measure response to these remittive therapies.

Finally, our results imply that terminology for describing sickle cell disease pain may be used differently by patients with sickle cell disease than by health care providers. For example, providers and researchers may define *crisis* as necessitating a visit for short-term treatment, whereas patients may not. Thus, misclassification, distorted communication, and undertreatment may result. It is time to reconsider how we use this terminology and to recognize sickle cell disease as a chronic pain syndrome.

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Grant Support: By the National Heart, Lung, and Blood Institute (1R01HL64122-01A1).

Potential Financial Conflicts of Interest: *Consultancies*: W.R. Smith (Purdue Pharma). *Grants received*: W.R. Smith (National Heart, Lung, and Blood Institute), L.T. Penberthy (National Heart, Lung, and Blood Institute), D.K. McClish (National Heart, Lung, and Blood Institute), I.P. Aisiku (National Heart, Lung, and Blood Institute), S.D. Roseff (National Heart, Lung, and Blood Institute). *Grants pending*: W.R. Smith (National Heart, Lung, and Blood Institute), L.T. Penberthy (National Heart, Lung, and Blood Institute).

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