The Impact of Sickle Cell Anemia and Mental Health Diagnoses on Healthcare Use and Preventive Care among Children Enrolled in Medicaid, 2005-2012

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Objective To examine mental health diagnoses, healthcare use, and receipt of age-appropriate preventive care, including antibiotic prophylaxis, hydroxyurea therapy, and transcranial Doppler screenings, among children with sickle cell anemia (SCA).

Study design Children aged 1-17 years with SCA from 6 states having 3 or more Medicaid claims with a SCA diagnosis within a year (2005-2012) were included. Children with mental health diagnoses were identified with 1 or more mental health encounters. Poisson and logistic regression models with general estimating equations assessed the relationship between mental health diagnoses, healthcare use, and receipt of age-appropriate preventive care.

Results In total, 7963 children with SCA were identified (22 424 person-years); 1593 person-years (7.1%) included 1 or more mental health diagnoses. Children with a mental health diagnosis were more likely to have inpatient admissions (incidence rate ratio [IRR] 1.46, 95% CI 1.36-1.56) and outpatient (IRR 1.27, 95% CI 1.21-1.34), emergency department (IRR 1.39, 95% CI 1.30-1.48), and well-child visits (IRR 1.19, 95% CI 1.11-1.29). Those with a mental health diagnosis were more likely to receive hydroxyurea therapy (odds ration [OR] 1.17, 95% CI 1.03-1.33) and less likely to receive transcranial Doppler screenings (OR 0.79, 95% CI 0.68-0.93).

Conclusions Children with SCA do not receive adequate age-appropriate preventive care. Further research is necessary to identify key points of coordination between mental health and SCA services throughout the life course. This approach may help to increase receipt of age-appropriate preventive care and decrease reliance on acute care. *(J Pediatr 2020;224:79-86)*.

Sickle cell disease, an inherited red blood cell disorder, disproportionately occurs in minority populations in the US and affects 1 of every 365 black births.[1,2] There are numerous subtypes of sickle cell disease, which confer differing levels of morbidity; children with the subtype sickle cell anemia (SCA), which includes HbSS and HbS beta^0 thalassemia, experience serious physical complications, including infection, pain, and stroke.[1-3] Given the significant morbidity experienced by children with SCA, the National Heart, Lung, and Blood Institute (NHLBI) developed guidelines for age-appropriate preventive care among this population, including penicillin prophylaxis to prevent infections for ages 0-5 years, hydroxyurea therapy to reduce the frequency of painful episodes for ages 9 months and older, and transcranial Doppler (TCD) screening to detect those at high risk for stroke for ages 2-16 years.[4] However, rates of each of these age-appropriate preventive care measures remain low; previous studies have demonstrated that 18% of children with SCA adhere to antibiotic prophylaxis recommendations, whereas 35% adhere to hydroxyurea therapy recommendations, and 44% adhere to TCD screening recommendations.[5-9]

In addition to these physical manifestations, many children with SCA also experience comorbid mental health diagnoses, such as depressive symptoms, social isolation, feelings of helplessness, and depressed mood and suicidality.[10] The occurrence of both SCA and mental health diagnoses impacts healthcare use among these children; for example, children with a mental health diagnosis tend to have more sickle cell pain–related hospital admissions and longer hospital stays compared with children without a mental health diagnosis.[11-13] Yet, little is known about the receipt of age-appropriate preventive care among children with concurrent SCA and mental health diagnoses. Therefore, we assessed how concurrent SCA and mental health diagnoses relate to healthcare use and the receipt of age-appropriate preventive care.

ADHD	Attention deficit and hyperactivity disorder
ED	Emergency department
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
IRR	Incidence rate ratio
MAX	Medicaid Analytic eXtract
NDC	National Drug Code
NHLBI	National Heart, Lung, and Blood Institute
SCA	Sickle cell anemia
TCD	Transcranial Doppler

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The authors declare no conflicts of interest.

Portions of this study were presented at the Michigan Public Health Association's Epidemiology Section Conference, March 29, 2019, Lansing, Michigan.

https://doi.org/10.1016/j.jpeds.2020.05.027

Methods

We conducted a multistate analysis of healthcare use and receipt of age-appropriate preventive care among children with SCA using administrative claims data. Our target population was drawn from Medicaid programs in 6 states with an average to high prevalence of SCA: Florida, Illinois, Louisiana, Michigan, South Carolina, and Texas.[14] Administrative claims data from Medicaid Analytic eXtract (MAX) files for the years 2005 to 2012 were acquired from the Centers for Medicare and Medicaid Services. At the time of the study, this was the most recent and complete data. This dataset includes enrollment history and all claims for all received health services, including inpatient, outpatient, emergency department (ED), laboratory, and pharmacy claims.

Our study population included only children with SCA, including both HbSS and HbS beta^0 thalassemia, because the age-appropriate preventive care recommended by the NHLBI target this specific subtype of sickle cell disease.[3,4] We identified our study population using a previously-validated method with a high level of accuracy for identifying children with SCA: children with 3 or more claims within a year with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnoses for SCA (282.61, 282.62).[15] This method has a sensitivity of 91.4% and specificity of 80% in comparison with the gold standard, newborn screening records.[9,15] We then obtained administrative claims data for all services provided to these children for 2005 to 2012.

Children aged 1-17 years as of December 31 of each respective year were eligible to be in the study population and were required to be continuously enrolled in Medicaid for at least 1 calendar year from 2005 to 2012. In addition, we restricted our analysis to children with no other forms of health insurance during the study period to maximize the completeness of claims available. Children were eligible to contribute multiple nonsequential years to the study population (eg, 2008 and 2010).

Exposure: Childhood Mental Health Diagnoses

Childhood mental health diagnoses refer to all diagnoses for mental health conditions that can begin in childhood.[16] This study considered the following mental health diagnoses: depression, anxiety, bipolar disorder, attention deficit and hyperactivity disorder (ADHD), conduct disorder, and oppositional defiant disorder. Frayne et al estimated the validity of algorithms for identifying mental health diagnoses and demonstrated that researchers should consider their research question and population in defining algorithms for mental health conditions.[17] Studies have suggested that the administrative claims contained within the MAX dataset may underestimate the true prevalence of mental health and that black children generally are less likely to use healthcare services relating to a mental health diagnosis or be diagnosed with a mental health diagnosis; therefore, we took a conservative approach in defining our algorithm.[10,12,13,17-19] Children were classified as having a mental health diagnosis if there was at least 1 ED, outpatient, or inpatient encounter for any of the mental health diagnoses listed previously. Encounters for mental health diagnoses were identified using ICD-9-CM codes (**Table I**; available at www.jpeds.com).[20] Children could have multiple diagnoses across the study period.

Outcomes

Two sets of outcomes were considered in this study: healthcare use and receipt of age-appropriate preventive care.

Healthcare Use. Healthcare use variables included the annual number of inpatient admissions, ED visits discharged home, outpatient visits, and well-child visits.[21] These encounters were defined using the Healthcare Effectiveness Data and Information Set definitions, which include Healthcare Common Procedure Coding System, Current Procedural Terminology codes, and ICD-9-CM codes.[21] Distinctly, well-child visits follow the American Academy of Pediatrics schedule, and outpatient visits refer to an issue that requires more attention and addresses the key components of a problem-oriented evaluation and management service.[22]

Receipt of Age-Appropriate Preventive Care. Receipt of age-appropriate preventive care included antibiotic prophylaxis, hydroxyurea therapy, and TCD screening. These measures of care were defined based on the NHLBI's established evidenced-based guidelines for specific age groups of children with SCA.[4]

Antibiotic Prophylaxis. Daily antibiotic prophylaxis is recommended to protect children ages 0-5 years with SCA against invasive pneumococcal disease; this prophylaxis has been shown to reduce the risk of infection by more than 80%.[23,24] Among children aged 1-5 years in this study, antibiotic prophylaxis was defined as a filled prescription for oral penicillin, erythromycin, or amoxicillin, which were identified in pharmacy claims by using National Drug Codes (NDCs) associated with an antibiotic.[9] To identify all the associated claims for antibiotics, a list of NDCs was produced and confirmed using RxNorm, a normalized naming system for all drugs made and maintained by the National Library of Medicine.[25] The number of days' supply of antibiotics within a year was determined by summing the days' supply reported within each filled prescription.[4,9] Adequate antibiotic prophylaxis was defined dichotomously (yes/no) as having filled antibiotic prescriptions that would cover 300 days or more of the year.[9]

Hydroxyurea Therapy. Hydroxyurea therapy reduces the frequency of sickle cell–related pain and incidence of acute chest syndrome, and since 2014, it has been recommended that it be offered to children with SCA starting at 9 months of age regardless of disease severity.[4] Before 2014, the NHLBI recommended hydroxyurea use for children and adolescents with specific complications, such as frequent pain episodes, acute chest syndrome, vaso-occlusive events, or symptomatic anemia.[26] Among children at least 1 year old, hydroxyurea was identified through pharmacy claims for a filled hydroxyurea prescription, including all forms for oral administration. To identify all the associated claims for hydroxyurea therapy, a list of NDCs was produced and

confirmed using RxNorm.[25] The number of days' supply was summed annually; hydroxyurea use was defined dichotomously (yes/no) as having greater than 30 days of filled prescriptions within a year to account for 1 refill, suggesting that the child may be using the medication as opposed to obtaining 1 prescription.

TCD Screening. TCD screening measures the velocity of the blood flow in cerebral vessels, which identifies children at the greatest risk of stroke.[4] These children should begin stroke prevention efforts in the form of chronic blood transfusions, which reduce the risk of stroke by more than 90%.[27] From ages 2 to 16, children with SCA are recommended to have a TCD screening on an annual basis.[4] Receipt of at least 1 TCD screening within a year was assessed among those aged 2 to 16 years old using Current Procedural Terminology codes (93886, 93888, 93890, 93892, and 93893) and was classified dichotomously (yes/no).[8] This approach has been previously validated; Medicaid administrative claims for receipt of TCD screening have a specificity of 100% (95% CI 91%-100%) and a sensitivity of 94% (95% CI 83%-99%) as compared with medical record review.[8] Although chronic blood transfusions may be indicative of previous stroke, we did not exclude children who received transfusions; however, we anticipate that the proportion receiving 7 or more in a year would be low (less than 2%).[8]

Statistical Analyses

Demographics of the study population (sex, median age) were summarized by state and calendar year of enrollment. We determined the frequency and proportion of children with mental health diagnoses among our study population of children with SCA, both overall and by each category of diagnosis (depression, anxiety, bipolar disorder, ADHD, conduct disorder, and oppositional defiant disorder) across the entire study period and by calendar year.

Next, the median and IQR of the number of annual healthcare encounters (inpatient admissions and ED, outpatient, and well-child visits) among children in the study population, both overall and stratified by the presence of a mental health diagnosis, were computed. The frequency and percent of children with at least 1 of each type of healthcare encounter were also determined. We used *t* tests to compare the mean number of each type of healthcare encounter between children with and without a mental health diagnosis. Then, we used independent Poisson regression models for each type of healthcare encounter to assess the relationship between the number of encounters and the presence of a mental health diagnosis.

Additionally, the frequency and percent of children who received each age-appropriate preventive care measure (antibiotic prophylaxis, hydroxyurea therapy, and TCD screening) were calculated. The proportion of children who received each type of age-appropriate preventive care was assessed both overall in the study population and stratified by the presence of a mental health diagnosis. We used χ^2 tests to compare the counts of receipt of each age-appropriate care measure between children with and without a mental health diagnosis. Separate logistic regression models were used to analyze the relationship between receipt of each type of age-appropriate preventive care measure and the presence of a mental health diagnosis.

All regression models were adjusted for age, sex, and calendar year of enrollment. We also adjusted the models for state of residence as a proxy for health-related policies that may differ between states, as receipt of each type of age-appropriate preventive care has been shown to vary across these states in previous studies.[8] In addition, because multiple periods of enrollment were allowed for each child, generalized estimating equations with robust SEs were used to account for any correlation among children contributing multiple time intervals.

Mental health diagnoses can be unreliable, especially when developmentally appropriate behaviors can be mistaken for symptoms of a diagnosis; this risk is increased among younger children.[28] To address this potential bias, we performed a sensitivity analysis by running the same models described previously for hydroxyurea therapy and TCD screening, but only among children 5 years of age and older. We then compared the results for the restricted age groups to the results with the full study population to assess for any differences in results.

All analyses were done with SAS 9.4 (SAS Institute, Cary, North Carolina). This study was approved by the University of Michigan institutional review board (HUM#00120422).

Results

A total of 7963 children with SCA were identified during the study period, contributing 22 424 person-years of enrollment. In total, 3846 (48.3%) female and 4117 (51.7%) male patients were included in the study. The median age of each sex was 8 years. States varied in the total number of person-years contributed to the study population: Florida with 6816 person-years (30.4%), Illinois with 3298 person-years (14.7%), Louisiana with 3753 person-years (16.7%), Michigan with 2708 person-years (12.1%), South Carolina with 2122 person-years (9.5%), and Texas with 3727 person-years (16.6%). Enrollment by calendar year varied with the fewest children enrolled in 2006 and the most enrolled in 2012 (**Table II**).

Overall, 1593 person-years (7.1%) contributed by 430 children (5.4%) contained a mental health diagnosis, with the most person-years contributed by ADHD (n = 687) followed by depression (n = 613), anxiety (n = 342), conduct disorders (n = 200), bipolar disorder (n = 153), and oppositional defiant disorder (n = 145). Among the 1593 person-years with at least 1 mental health diagnosis, 32.9% (n = 524) of person-years had 1 mental health diagnosis within the study period, and 67.1% (n = 1069) had more than 1 diagnosis during the study period. The proportion of children with each category of mental health diagnosis varied across state and year; however, these variations were not substantial nor clinically relevant (**Table III**).

Among all children in the study population, the annual median number of inpatient admissions was 1 (IQR = 2), and there were an annual median number of 3 (IQR = 4) ED visits, 7 (IQR = 7) outpatient visits, and 1 (IQR = 1) well-child visits. Further, 76.2% (n = 17 087) of person-years had

Table II. Demographic characteristics of children aged 1-17 with SCA enrolled in Medicaid by year, 2005-2012

Characteristics	2005 n = 2545	2006 n = 2470	2007 n = 2513	2008 n = 2586	2009 n = 2959	2010 n = 2916	2011 n = 3132	2012 n = 3303
Age, y, median	9	9	9	8	8	7	8	8
Sex								
Female, n (%)	1214 (47.7)	1167 (47.3)	1242 (49.4)	1261 (48.8)	1476 (49.9)	1438 (49.3)	1527 (48.8)	1609 (48.7)
Male, n (%)	1331 (52.3)	1303 (52.8)	1271 (50.6)	1325 (51.2)	1483 (50.1)	1478 (50.7)	1605 (51.3)	1694 (51.3)
State								
Florida, n (%)	711 (27.9)	678 (27.5)	619 (24.6)	709 (27.4)	980 (33.1)	1017 (34.9)	1017 (32.5)	1085 (32.9)
Illinois, n (%)	358 (14.1)	393 (15.9)	383 (15.2)	394 (15.2)	474 (16.0)	417 (14.3)	422 (13.5)	457 (13.8)
Louisiana, n (%)	500 (19.7)	433 (17.5)	463 (18.4)	469 (18.1)	485 (16.4)	462 (15.8)	496 (15.8)	445 (13.5)
Michigan, n (%)	309 (12.1)	309 (12.5)	347 (13.8)	339 (13.1)	378 (12.8)	350 (12.0)	346 (11.1)	330 (10.0)
South Carolina, n (%)	292 (11.5)	280 (11.3)	269 (10.7)	203 (7.9)	144 (4.9)	181 (6.2)	310 (9.9)	443 (13.4)
Texas, n (%)	375 (14.7)	377 (15.3)	432 (17.2)	472 (18.3)	498 (16.8)	489 (16.8)	541 (17.3)	543 (16.4)

at least 1 inpatient admission, 86.3% (n = 19 348) had at least 1 ED visit, 97.6% (n = 21 885) had at least 1 outpatient visit, and 53.14% (n = 11 916) had at least 1 well-child visit. When stratified by the presence of a mental health diagnosis, the mean number of inpatient admissions and ED and outpatient visits tended to be greater for children with a mental health diagnosis compared with those without a mental health diagnosis (all $P < .0001$), and the mean number of well-child visits tended to be lower for children with a mental health diagnosis than those without a mental health diagnosis ($P < .0001$) (Table IV). Regression analysis revealed that among children with SCA, those with a mental health diagnosis are more likely to have inpatient admissions (incidence rate ratio [IRR] 1.46, 95% CI 1.36-1.56) and ED (IRR 1.39, 95% CI 1.30-1.48), outpatient (IRR 1.27, 95% CI 1.21-1.34), and well-child visits (IRR 1.19, 95% CI 1.11-1.29) than those without a mental health diagnosis when adjusting for age, sex, geographic residence, and calendar year (Table V).

Within the recommended age groups for each type of age-appropriate preventive care, 15.8% (N = 1253) of person-years received antibiotic prophylaxis, whereas 23.4% (N = 4885) received hydroxyurea therapy, and 34.6% (N = 5854) received TCD screening. When stratifying by the presence of a mental health diagnosis, we found a greater percent of children with a mental health diagnosis received hydroxyurea therapy ($P < .0001$) and a lower percent of children with a mental health diagnosis received TCD screenings compared with those without a mental health diagnosis ($P < .0001$); there was no difference in the proportion of children that received antibiotics ($P = .83$) (Table IV). Regression analysis demonstrated that among children with SCA, those with a mental health diagnosis were more likely to receive hydroxyurea therapy (OR 1.17, 95% CI 1.03-1.33) and less likely to receive TCD screenings (OR 0.79, 95% CI 0.68-0.93) than those without a mental health diagnosis when adjusting for age, sex, geographic residence, and calendar year enrolled in Medicaid (Table V); there was no association between having a mental health diagnosis and receipt of antibiotic prophylaxis (OR 1.17, 95% CI 0.70-1.90).

The sensitivity analysis yielded comparable results to the original models. As before, the analysis showed that among children with SCA, those with a mental health diagnosis were more likely to receive hydroxyurea therapy and less likely to receive TCD screenings than those without a mental health diagnosis when adjusting for restricted age, sex, geographic residence, and calendar year enrolled in Medicaid.

Table III. Mental health diagnoses among children aged 1-17 with SCA enrolled in Medicaid 2005-2012 by diagnosis and by year, n = 22 424 person-years*

Diagnoses	2005 n = 2545	2006 n = 2470	2007 n = 2513	2008 n = 2586	2009 n = 2586	2010 n = 2916	2011 n = 3132	2012 n = 3303
All mental health diagnosis, n (%) n = 1593 p-y	180 (7.1)	176 (7.1)	170 (6.8)	176 (6.8)	200 (6.8)	185 (6.3)	247 (7.9)	259 (7.8)
Depression, n (%) n = 613 p-y	88 (3.5)	72 (2.9)	67 (2.7)	70 (2.7)	69 (2.3)	61 (2.1)	100 (3.2)	86 (2.6)
Anxiety, n (%) n = 342 p-y	35 (1.4)	25 (1.0)	33 (1.3)	46 (1.8)	36 (1.2)	47 (1.6)	46 (1.5)	74 (2.2)
Bipolar disorder, n (%) n = 153 p-y	9 (0.4)	16 (0.7)	11 (0.4)	13 (0.5)	28 (1.0)	19 (0.7)	34 (1.1)	23 (0.7)
ADHD, n (%) n = 687 p-y	59 (2.3)	75 (3.0)	71 (2.8)	66 (2.6)	91 (3.1)	88 (3.0)	123 (3.9)	114 (3.5)
Conduct disorders, n (%) n = 200 p-y	21 (0.8)	21 (0.9)	22 (0.9)	24 (0.9)	33 (1.1)	22 (0.8)	30 (1.0)	27 (0.8)
Oppositional defiant disorder, n (%) n = 145 p-y	20 (0.8)	17 (0.7)	19 (0.8)	19 (0.7)	12 (0.4)	18 (0.6)	23 (0.7)	17 (0.5)

p-y, person-years.
*Any mention of a mental health diagnosis; children could contribute multiple p-y of enrollment. Percentages are column-wise.

Table IV. Healthcare use and receipt of age-appropriate preventive care among children aged 1-17 with SCA and a mental health diagnosis enrolled in Medicaid from 2005 to 2012, n = 22 242 person years

Healthcare use and age-appropriate preventive care	Overall Mean (SD)	Presence of a mental health diagnosis: Yes n = 1593 Mean (SD)	Presence of a mental health diagnosis: No n = 20 831 Mean (SD)	*P* value
Type of healthcare encounter*				
Inpatient	1.98 (2.27)	3.10 (3.55)	1.90 (2.12)	<.001
Outpatient	8.25 (7.15)	11.24 (11.91)	8.02 (6.59)	<.001
ED	3.64 (4.03)	5.50 (6.55)	3.50 (3.73)	<.001
Well-child	0.88 (1.29)	0.63 (0.86)	0.89 (1.31)	<.001
	Frequency (%)	**Frequency (%)**	**Frequency (%)**	
Preventive care measure†				
Received antibiotics (aged 1-5 y) n = 7942	1253 (15.8)	19 (15.1)	1234 (15.8)	.92
Received hydroxyurea (aged 1-17 y) n = 20 901	4885 (23.4)	568 (35.8)	4317 (22.4)	<.001
Received TCD screening (aged 2-16 y) n = 16 905	5854 (34.6)	326 (26.5)	5528 (35.3)	<.001

*t tests were used to compare the mean number of healthcare encounters of children with and without mental health diagnoses.
†χ^2 tests were used to compare the counts of receipt of age-appropriate preventive care of children with and without mental health diagnoses.

Discussion

This study establishes a framework for assessing healthcare use and receipt of age-appropriate preventive care among children with SCA who also have mental health diagnoses. In our study population, rates of receipt of antibiotic prophylaxis, hydroxyurea therapy, and TCD screenings remained suboptimal (despite their clinically proven, life-saving benefits) for all children in the study.[4] Although children with mental health diagnoses experienced greater rates of healthcare encounters, our results indicated that children with concurrent SCA and mental health diagnoses may be at greater risk for unmet needs for TCD screening as compared with children without mental health diagnoses.

Our findings regarding concurrent SCA and mental health diagnoses and receipt of age-appropriate preventive care are new contributions to the field. Our results suggest that all children with SCA, irrespective of having a mental health diagnosis, inadequately receive age-appropriate preventive care. This aligns with studies of children with other chronic conditions that require disease-modifying therapies to allay harmful disease effects, including pediatric asthma and epilepsy. Such studies indicate that the prescription receipt rate is suboptimal, no matter what measure is used to assess adherence.[29-33] However, our results indicate that adherence may be even lower among children with SCA. For example, Engelkes et al reported that children received inhaled corticosteroids covering 56% of the year, and Jacob et al found that two-thirds of children with epilepsy were adherent.[31,32] Comparatively, our study found among those eligible that 15.8% of person-years received at least 300 days of antibiotic prophylaxis, and 23.4% received 300 days of hydroxyurea therapy.

The low rates of receipt of age-appropriate preventive care are particularly pronounced for TCD screening in our study, where differences in rates were seen when a mental health diagnosis was present.[6,8,9,34] It is possible that having a mental health diagnosis and being enrolled in Medicaid may contribute to lower likelihood of receiving TCD screening. Socioeconomic status, indicated by income level and receipt of public insurance, has been demonstrated to place children with mental health diagnoses at greater risk of unmet needs for care coordination.[35] Medicaid plans also can limit access to specialized providers, such as hematologists.[36]

Furthermore, our findings regarding increased use of hydroxyurea therapy among children with a mental health diagnosis suggest that it is possible that mental health–related symptoms and SCA complications may be related.[10,37,38] For example, in a study of adults with SCA, it was found that depression and anxiety predicted more daily pain.[39] Although these findings indicate patterns before the release of the 2014 NHLBI guidelines, which recommend that hydroxyurea therapy be offered starting at 9 months of age regardless of disease severity, this should not have a differential effect on those with or without mental health diagnoses.[4]

In addition, comparable with previous studies, our study demonstrated that children with SCA and a mental health diagnosis are likely to use healthcare services more frequently, particularly acute care services.[10,12,13] These results suggest that increased healthcare use is a potential result of concurrent SCA and mental health diagnoses. This idea is supported by previous research that has indicated that children with mental health diagnoses tend to have greater and more frequent use of acute care rather than preventive care services.[35,40] Mental health–related behaviors and diagnoses may be associated with this healthcare use pattern.[10,37] However, it is also important to note that outpatient visits may have been greater among this group due to scheduled preventive care, such as hydroxyurea therapy, which requires regular monitoring. This is consistent with our findings that children with concurrent SCA and mental health diagnoses were more likely to receive hydroxyurea therapy.

Lastly, our findings could be partially explained by the impact of cerebrovascular disease on mental health diagnoses, healthcare use, and receipt of age-appropriate preventive care. First, the standard of care for children with history of stoke, silent infarct, or an abnormal TCD screening is monthly blood transfusions, which leads to more medical encounters. Second, children with cerebrovascular disease may not be considered for further TCD screenings and hydroxyurea

Table V. Multivariable models predicting mean counts of healthcare encounters and odds of receipt of age-appropriate preventive care by children aged 1-17 with SCA enrolled in Medicaid, 2005 to 2012, n = 22 242 person years

Mean counts of healthcare encounters				
	IRR (95% CI)*			
Healthcare use and age-appropriate preventive care	Inpatient	Outpatient	ED	Well-child
Presence of a mental health diagnosis	1.46 (1.36-1.56)†	1.27 (1.21-1.34)†	1.39 (1.30-1.48)†	1.19 (1.11-1.29)†
Age	1.01 (1.01-1.02)†	0.99 (0.98-0.99)†	1.01 (1.01-1.01)†	0.88 (0.88-0.89)†
Sex (female)	1.03 (0.99-1.08)	1.02 (0.99-1.06)	1.05 (1.00-1.09)†	1.02 (0.99-1.07)
Sex (male)	Ref	Ref	Ref	Ref
Odds of receipt of age-appropriate preventive care				
	OR (95% CI)*			
	Antibiotics	Hydroxyurea	TCD screening	
Presence of a mental health diagnosis	1.56 (0.70-1.90)	1.17 (1.03-1.33)†	0.79 (0.68-0.93)†	
Age	0.88 (0.85-0.91)†	1.13, (1.12-1.14)†	0.93 (0.92-0.94)†	
Sex (female)	0.89 (0.76-1.04)	0.89 (0.80-1.00)	1.09 (1.01-1.19)†	
Sex (male)	Ref	Ref	Ref	

*All models were also adjusted for geographic residence (Florida, Illinois, Louisiana, Missouri, South Carolina, or Texas) and calendar year enrolled (2005-2012).
†Statistically significant at alpha equals less than 0.05.

therapy in many sickle cell centers. Also, a moderately strong association exists between ADHD or loss of executive function and cerebrovascular disease among children with SCA.[41-44] This suggests that the connection between our study outcomes, mental health diagnoses, and cerebrovascular disease warrants further investigation.

Limitations in this study exist as this study relies on the completeness and accuracy of administrative claims data. Our study includes children with a history of using care related to their SCA diagnosis. As such, children with SCA who do not use SCA-related care will not be included in our denominator population. However, given the accuracy of the case definition as compared with the gold standard of newborn screening records, we anticipate this proportion will be small.[15] Future studies could consider using data from a registry, such as the sickle cell disease registries in California and Georgia, to address this limitation.[15,45] We were unable to ascertain whether the children had any acute clinical indications that eliminated the necessity or eligibility for TCD screening or hydroxyurea therapy, such as a previous high-velocity reading, previous stroke, a recent blood transfusion, transient marrow suppression, or pregnancy.[4,8,46] However, given previous research, we anticipate the impact of these exclusions on our results would be minimal.[8,47] Having used an administrative claims database, we were unable to assess child and parent characteristics and health behaviors that may influence a child's use of well-child visits; these unmeasured factors may explain the discrepancy in the direction of the relationship between mental health diagnoses and number of well child visits found in bivariate compared with multivariate analyses.[48]

The observed prevalence of mental health diagnoses among children with SCA may be lower than the true prevalence of mental health diagnoses among this group. First, our study indicated a lower prevalence than the general pediatric population.[10,12,13,18,19,49] Further, other studies have suggested that the administrative claims contained within the MAX dataset may underestimate the true prevalence of mental health and that black children in general are less likely to use healthcare services relating to a mental health diagnosis or be diagnosed with a mental health diagnosis.[50,51] In addition, mental health diagnoses for children with SCA may be less documented than for children without SCA. As SCA may play a role in each visit, a visit may be coded exclusively for SCA, resulting in a missed opportunity for documenting a mental health diagnosis. With this potentially understated prevalence of mental health diagnoses, we took a conservative approach to defining mental health diagnoses. As such, it is likely that our estimates of healthcare use and receipt of age-appropriate preventive care are attenuated. This emphasizes the overall importance of the associations revealed by this study. Lastly, we provide a cross-sectional rather than a longitudinal perspective on the relationships evaluated by this study.

In conclusion, our study found that among children with SCA, those with mental health diagnoses are more likely to use healthcare services and receive hydroxyurea therapy, while being less likely to receive TCD screenings than children without mental health diagnoses. Overall, our main findings support the importance of developing and implementing mental health screening guidelines for all children with SCA to improve comprehensive care. As mental health symptoms may be related to SCA complications and resultant healthcare use, coordinating mental health and SCA services throughout the life course may help to ensure receipt of age-appropriate preventive care and potentially decrease reliance on acute care, which tend to include high-cost health encounters.[52] This suggestion has grounding in the literature; a study in young children with sickle cell disease indicates that developmental screenings, which include aspects assessing attention and behavior, may help predict cerebrovascular complications.[53] Future research should investigate how such pediatric behavioral health interventions could be modeled to decrease acute care use and increase receipt of age-appropriate preventive care among all children with SCA. ■

We thank Dr Ella August (Department of Epidemiology, University of Michigan, Ann Arbor, Michigan) for her review of the manuscript.

Submitted for publication Dec 8, 2019; last revision received May 10, 2020; accepted May 14, 2020.

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50 Years Ago in *The Journal of Pediatrics*

L-Asparaginase Therapy in Pediatric Acute Lymphoblastic Leukemia: Optimizing Efficacy and Minimizing Toxicity

Pratt CB, Simone JV, Zee P, Aur RJ, Johnson WW. Comparison of daily vs weekly L-asparaginase for the treatment of childhood acute leukemia. J Pediatr 1970;77:474-83.

L-asparaginase is a chemotherapeutic agent that was discovered in the 1950s and first administered to patients in the 1960s. By 1970, several studies had shown that L-asparaginase therapy could induce temporary bone marrow remission in patients with leukemia; however, its toxicity was underappreciated. For example, a study from 1969 reported the efficacy of L-asparaginase therapy and asserted that it was "relatively nontoxic…" and that "it does not possess the toxicity associated with conventional treatment."[1] Nevertheless, some oncologists at the time were beginning to observe substantial and unique toxicities with L-asparaginase therapy as it became more frequently administered.[2]

In this study, Pratt et al sought to more fully characterize L-asparaginase toxicity and to evaluate whether an alteration in its dosing regimen could ameliorate the toxicity while preserving its efficacy. The investigators treated 19 children with relapsed acute leukemia, 16 with acute lymphoblastic leukemia (ALL) and 3 with acute myelogenous leukemia. Patients were randomized to either conventional daily dosing or weekly dosing of L-asparaginase for 2 weeks as monotherapy. The authors performed extensive laboratory, clinical, and postmortem examinations to assess toxicity. L-asparaginase therapy was found to alter liver function studies and coagulation measures, as well as to cause nausea, vomiting, and weight loss in the majority of patients. The authors observed single instances of severe pancreatitis, hemorrhage, and hypersensitivity, all of which are now well-characterized toxicities with L-asparaginase therapy. Notably, thrombosis is an important toxicity that was not observed in this study. The authors found a trend toward diminished L-asparaginase toxicity in the weekly dosing group and similar efficacy in inducing bone marrow remission in the daily and weekly dosing groups.

This study is an early instance of a paradigm in designing treatment protocols for pediatric ALL: striving to optimize outcomes while minimizing toxicity from treatment. In 2020, L-asparaginase therapy is an integral part of all pediatric ALL treatment protocols both in the US and internationally. Numerous studies have demonstrated the important contribution of L-asparaginase therapy to the improved outcomes in pediatric ALL seen over the last 50 years, with regards to both its initial inclusion in treatment protocols and further upon intensification of treatment (an excellent review has been provided by Pieters et al[3]). Other advances in L-asparaginase therapy, and in some instances continuing areas of investigation, include using different formulations of L-asparaginase as well as altering the dosage, timing, and duration of L-asparaginase therapy.

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Table I. Claims-based definitions of mental health diagnosis variables

Diagnosis	Code	Description
Depression	293.83	Organic Affective Syndrome
	296.2	Depressive Affective Disorders—Unspecified
	296.21	Depressive Affective Disorder—Mild
	296.22	Depressive Affective Disorder—Moderate
	296.23	Depressive Affective Disorder—Severe Without Psychotic Behavior
	296.24	Depressive Affective Disorder—Severe With Psychotic Behavior
	296.25	Depressive Affective Disorder—Partial Remission
	296.26	Depressive Affective Disorder—Full Remission
	296.3	Recurrent Depressive Disorder—Unspecified
	296.31	Recurrent Depressive Disorder—Mild
	296.32	Recurrent Depressive Disorder—Moderate
	296.33	Recurrent Depressive Disorder—Severe
	296.34	Recurrent Depressive Disorder—Severe With Psychotic Behavior
	296.35	Recurrent Depressive Disorder—Partial Remission
	296.36	Recurrent Depressive Disorder—Full Remission
	311	Depressive Disorder Not Elsewhere Classified
	300.4	Dysthymic Disorder
Anxiety	300	Anxiety State—Unspecified
	300.01	Panic Disorder—No Agoraphobia
	300.02	Generalized Anxiety Disorder
	300.09	Other Anxiety States
	300.1	Hysteria—Unspecified
	300.11	Conversion Disorder
	300.12	Dissociative Amnesia
	300.13	Dissociative Fugue
	300.14	Dissociative Identity Disorder
	300.15	Dissociative Disorder or Reaction—Unspecified
	300.2	Phobia—Unspecified
	300.21	Agoraphobia With Panic
	300.22	Agoraphobia Without Mention of Panic Attacks
	300.23	Social Phobia
	300.29	Other Isolated or Specific Phobias
	300.3	Obsessive Compulsive Disorder
	309.81	Posttraumatic Stress Disorder
Bipolar disorder	296	Bipolar I Disorder, Single Manic Episode, Unspecified
	296.01	Bipolar I Disorder, Single Manic Episode, Mild
	296.02	Bipolar I Disorder, Single Manic Episode, Moderate
	296.03	Bipolar I Disorder, Single Manic Episode, Severe, Without Mention of Psychotic Behavior
	296.04	Bipolar I Disorder, Single manic Episode, Severe, Specified as With Psychotic Behavior
	296.05	Bipolar I Disorder, Single manic Episode, in Partial or Unspecified Remission
	296.06	Bipolar I Disorder, Single manic Episode, in Full Remission
	296.1	Manic Affective Disorder, Recurrent Episode, Unspecified
	296.11	Manic Affective Disorder, Recurrent Episode, Mild
	296.12	Manic Affective Disorder, Recurrent Episode, Moderate
	296.13	Manic Affective Disorder, Recurrent Episode, Severe, Without Mention of Psychotic Behavior
	296.14	Manic Affective Disorder, Recurrent Episode, Severe, Specified as With Psychotic Behavior
	296.15	Manic Affective Disorder, Recurrent Episode, in Partial or Unspecified Remission
	296.16	Manic Affective Disorder, Recurrent Episode, in Full Remission
	296.4	Bipolar I Disorder, Most Recent Episode (or Current) Manic, Unspecified
	296.41	Bipolar I Disorder, Most Recent Episode (or Current) Manic, Mild
	296.42	Bipolar I Disorder, Most Recent Episode (or Current) Manic, Moderate
	296.43	Bipolar I Disorder, Most Recent Episode (or Current) Manic, Severe, Without Mention of Psychotic Behavior
	296.44	Bipolar I Disorder, Most Recent Episode (or Current) Manic, Severe, Specified as With Psychotic Behavior
	296.45	Bipolar I Disorder, Most Recent Episode (or Current) Manic, in Partial or Unspecified Remission
	296.46	Bipolar I Disorder, Most Recent Episode (or Current) Manic, in Full Remission
	296.5	Bipolar I Disorder, Most Recent Episode (or Current) Depressed, Unspecified
	296.51	Bipolar I Disorder, Most Recent Episode (or Current) Depressed, Mild
	296.52	Bipolar I Disorder, Most Recent Episode (or Current) Depressed, Moderate
	296.53	Bipolar I Disorder, Most Recent Episode (or Current) Depressed, Severe, Without Mention of Psychotic Behavior
	296.54	Bipolar I Disorder, Most Recent Episode (or Current) Depressed, Severe, Specified as With Psychotic Behavior
	296.55	Bipolar I Disorder, Most Recent Episode (or Current) Depressed, in Partial or Unspecified Remission
	296.56	Bipolar I Disorder, Most Recent Episode (or Current) Depressed, in Full Remission
	296.6	Bipolar I Disorder, Most Recent Episode (or Current) Mixed, Unspecified
	296.61	Bipolar I Disorder, Most Recent Episode (or Current) Mixed, Mild
	296.62	Bipolar I Disorder, Most Recent Episode (or Current) Mixed, Moderate
	296.63	Bipolar I Disorder, Most Recent Episode (or Current) Mixed, Severe, Without Mention of Psychotic Behavior
	296.64	Bipolar I Disorder, Most Recent Episode (or Current) Mixed, Severe, Specified as With Psychotic Behavior
	296.65	Bipolar I Disorder, Most Recent Episode (or Current) Mixed, in Partial or Unspecified Remission
	296.66	Bipolar I Disorder, Most Recent Episode (or Current) Mixed, in Full Remission
	296.7	Bipolar I Disorder, Most Recent Episode (or Current) Unspecified

(*continued*)

Table I. Continued

Diagnosis	Code	Description
	296.8	Bipolar Disorder, Unspecified
	296.81	Atypical Manic Disorder
	296.82	Atypical Depressive Disorder
	296.89	Other Bipolar Disorders
	296.9	Unspecified Episodic Mood Disorder
	296.99	Other Specified Episodic Mood Disorder
	314	Attention Deficit Disorder Without Mention of Hyperactivity
Attention deficit disorder of childhood	314.01	Attention Deficit Disorder With Hyperactivity
	312.4	Mixed Disorder Conduct/Emotion
Conduct disorder	312.81	Conduct Disorder Childhood Onset
	312.82	Conduct Disorder Childhood Onset
	312.89	Other Conduct Disorder
	312.9	Conduct Disturbance NOS
	312.4	Mixed Disorder Conduct/Emotion
Oppositional defiant disorder	313.81	Oppositional Defiant Disorder

NOS, not otherwise specified.