BACKGROUND

Sickle cell disease (SCD) is a term used to describe a group of genetic red blood cell disorders affecting hemoglobin. Hemoglobin is a protein in red blood cells that carries oxygen through the body. Red blood cells are normally disc shaped allowing them to be flexible and move freely through blood vessels delivering oxygen. In individuals with SCD, abnormal hemoglobin strands cause red blood cells to become an irregular, sickle shape. These sickle-shaped red blood cells are not flexible and can cause blockages slowing the flow of blood.

Sickle cell disease affects approximately 100,000 Americans.\(^1\) It is primarily found in individuals of African, Mediterranean and Asian descents.\(^2\) Although SCD is associated with high morbidity, currently 90 percent of children diagnosed with SCD survive into adulthood.\(^3\) Pain and acute chest syndrome (ACS) are common complications associated with SCD. Pain, the most common symptom of SCD, can be characterized as acute or chronic.

As there is no cure for SCD, proactive management of SCD complications is a mainstay of therapy. For over 20 years, hydroxyurea has been the primary pharmacotherapeutic agent available for preventing SCD complications. Hydroxyurea increases fetal hemoglobin, reduces “sickling” of red blood cells, and improves blood flow.\(^4\) In 2014 the Expert Panel Report on Evidenced-Based Management of Sickle Cell Disease recommended a treatment protocol for the utilization of hydroxyurea.\(^5\) With each recommendation, the panel listed strength of recommendation and quality of evidence based on:

- protocols used in published clinical trials and observational studies,
- indirect evidence derived from basic science and pharmacokinetics of hydroxyurea, and
- a consensus process

The Expert Panel’s recommended treatment protocol is summarized in Figure 1.

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In July 2017, the U.S. Food and Drug Administration (FDA) approved L-glutamine (Endari®), the first new therapeutic agent for treating SCD in over two decades. Endari is approved for use in patients ≥ 5 years to reduce acute complications of sickle cell disease. Preliminary data suggests Endari can reduce painful events, acute chest syndrome events, and hospitalizations. In the clinical trials, most patients studied

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were also receiving hydroxyurea. Endari was approved through the orphan drug designation and is distributed through specialty pharmacies.

MS-DUR conducted an analysis of the treatment of Mississippi Medicaid beneficiaries with SCD. The primary objectives were to examine hydroxyurea utilization and any Endari claim approvals through March 2018. This analysis, along with clinical trial data and expert panel recommendations, will serve as references in the development of recommendations in the treatment of SCD in Mississippi Medicaid beneficiaries.

**METHODS**

MS-DUR identified all Mississippi Medicaid beneficiaries with a diagnosis of SCD (ICD-10 D57 – excluding D57.4 sickle cell trait) present on a medical claim paid anytime between July 2016 and March 2018. Pharmacy claims for hydroxyurea or Endari paid between January 2017 and March 2018 were extracted for these beneficiaries.

**RESULTS**

Table 1 shows the characteristics of beneficiaries identified with SCD through medical claims. Almost half (54%) of the SCD patients were adults (ages 21 and above) and over a fourth (28%) were children ages ≤6 years.

Hydroxyurea, Endari and narcotics can be used for treatment of pain associated with SCD. Only one (1) prescription claim for Endari had been paid at the time of this analysis. Over half of the beneficiaries with SCD had not received a prescription for hydroxyurea or narcotics during the last year. Of those that had received prescriptions that could have been for pain, most were being treated with narcotics only.

Although the ages of beneficiaries with SCD varied amongst the fee-for-service (FFS) and the coordinated care plans (CCOs), the treatment patterns for SCD did not meaningfully vary across pharmacy programs.

<table>
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<tr>
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<td>538</td>
<td>608</td>
<td>1,555</td>
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</table>

TABLE 1: Characteristics of Medicaid Beneficiaries With Sickle Cell Disease* (January 2017 - March 2018)

* At least one medical claim had a diagnosis code of D57 Sickle Cell Diseases — excluding D57.4 Sickle Cell Trait.
Table 2 illustrates use of hydroxyurea by beneficiary age for those beneficiaries continuously enrolled in the last four months included in the analysis. There are just over 4,000 beneficiaries currently enrolled that have SCD. The currently enrolled beneficiaries represent 82% of all beneficiaries with SCD that have been enrolled in Medicaid for any length of time during the last year. This indicates that the SCD population in Medicaid is fairly stable and many of these patients will remain enrolled; thus managing progression of the disease is critical.

Although younger children were somewhat less likely to be treated with hydroxyurea, use of the product was very low for all ages. Overall, 88% of beneficiaries with SCD were not treated with hydroxyurea between January 2017 and March 2018.

Table 3 shows the number claims for hydroxyurea and narcotics for beneficiaries with SCD who were continuously enrolled during the last four months of the analysis. Overall, 37% of SCD patients were treated with narcotics while receiving no prescriptions for hydroxyurea. It should be noted that 13% of all beneficiaries receiving narcotics received 6 or more prescriptions for narcotics in this timeframe. Thus these beneficiaries can be classified as being chronically treated with narcotics.
CONCLUSIONS AND RECOMMENDATIONS

Endari should provide a new treatment alternative for pain associated with SCD. However, Endari is recommended as (a) adjunctive therapy with hydroxyurea when treatment with hydroxyurea alone is not adequate or (b) as monotherapy when a patient cannot tolerate hydroxyurea. Two major conclusions from this analysis are:

- Hydroxyurea appears to have limited utilization in the SCD population.
- Narcotics are being over-utilized to treat pain associated with SCD and appear to be used instead of hydroxyurea rather than in conjunction with hydroxyurea.

Recommendations:

1. MS-DUR should implement an educational initiative encouraging the utilization of hydroxyurea, as referenced in Figure 1, for the proactive management of sickle cell complications such as pain and ACS while discouraging the inappropriate use of narcotics. The educational initiative should also address the role of Endari in the management of SCD.

2. Endari should be prescribed for use in addition to hydroxyurea unless intolerance or contraindication of hydroxyurea has been documented.

3. DOM Office of Pharmacy should implement manual PA criteria for Endari use.