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Abstract

According to the Center of Disease Control and Prevention (CDC) database the total number of deaths due to opioid overdose from 1999 through 2018 was 840,629. Given the alarming nature of these statistics, patients who requested prescription for opioids became targets of suspicion and possible accusation of maladaptive behavior. Patients with sickle cell disease (SCD) were often not exempt from such accusations and became guilty by association. In order to clarify the effect of opioids on the mortality of patients with SCD, the mortality rates for children and adults with SCD were investigated using the CDC Wide-ranging Online Data for Epidemiologic Research (WONDER) Multiple Cause of Death database which is based on all the death certificates issued in the United States from 1999-2018. The data showed 15,765 patients with SCD died from 1999-2018. Only 348 patients with SCD died due to opioids. The CDC database contains 27 categories of death based on ICD-10 codes in patients with SCD and opioids were the 19th ranking cause of death. Surprisingly the most common causes of death of patients with SCD included circulatory, infection, respiratory, genitourinary and vaso-occlusive crises/acute chest syndrome disorders in decreasing frequency. The mean age of death of females was 41.9 years and of males 39.3 years; $p < 0.0001$. Death due to SCD and death due to SCD and opioids were highest in the Southern Region of the United States.

Introduction

Sickle pain is unique [1]. It can be acute, chronic, intermittent, recurrent, remittent or persistent [1-5]. Physical sensation and emotion in sickle pain are intertwined in an unusually complex manner that is specific to each person and affects behavior differently in different patients and in different vaso-occlusive crisis (VOC). It is often described by some patients as: “a migraine headache that affects all your body; it controls you, you have no control over it;

toothache all over your body; it means pain and suffering, etc. etc." [6].

Up until the 1970s, sickle cell disease (SCD) was primarily a disease of children with relatively few adults affected. With time, however, the number of adults with SCD increased gradually and frequent visits to the emergency department (ED) and/or hospital admissions to treat severe pain due to VOCs became a status quo of the disease. Opioids were the best and the most common analgesics used to treat pain for the majority of patients. Issues associated with transition of care from pediatrics to adult care, race, education, insurance coverage and disparities conspired with the use of opioids to create a negative picture about adult patients with SCD. Descriptors about most patients with SCD as "frequent flyers," addicts, opioid abusers, maladaptive behavior, etc. emerged [6, 7].

The emergence of the opioid epidemic in the United States worsened the situation for patients with SCD who need opioids to alleviate their pain. The opioid epidemic was a justification for some providers to restrict the use of opioids to treat sickle cell pain and, possibly find alternatives to opioids. NSAIDS are often considered as an alternative but these are not as effective in adults as in children [6]. Moreover the systemic side effects of NSAIDS including renal failure, gastrointestinal bleeding, cardiovascular complications, etc. are worse than the systemic complications of opioids [6]. Cannabinoids and Kratom failed as replacements to opioids to date [8, 9]. Moreover, recent reports found that death due to opioids in SCD is much lower than in other conditions and the use of opioids by patients with SCD was constant over the years [10, 11]. The purpose of this study is to show that opioids are a minor cause of death in patients with SCD. The complications of SCD itself rather than the opioids are the major cause of death.

Methods

Data were collected using the Center of Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) Multiple Cause of Death database which is based on all the death certificates issued in the United states from 1999-2018 [12-14]. Causes of death are based on the ICD-10 codes indicated on the death certificate. In order to determine the number of deaths due to SCD and opioids, searches were conducted on the CDC's WONDER Multiple Cause of Death database using the ICD-10 codes for SCD and the same ICD-10 codes that the CDC uses at the end of every year to report the nationwide number of deaths due to opioids [12-14]. The CDC's WONDER Multiple Cause of Death database enables the user to run searches using multiple causes of death. The database allows the user to determine the number of deaths per year, by gender, census region and other various factors.

The codes used to determine death due to SCD were as follows:

D57.0 Sickle-cell anaemia with crisis
D57.1 Sickle-cell anaemia without crisis
D57.2 Double heterozygous sickling disorders
D57.8 Other sickle-cell disorders

The codes used to determine number of deaths due to opioids, as used by the CDC to determine nationwide rates, were the following:

T40.0 Opium
T40.1 Heroin
T40.2 Other opioids
T40.3 Methadone
T40.4 Other synthetic narcotics
T40.6 Other and unspecified narcotics
X40 Accidental poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics
X41 Accidental poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not classified elsewhere

X42	Accidental poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere classified
X43	Accidental poisoning by and exposure to other drugs acting on the autonomic nervous system
X44	Accidental poisoning by and exposure to other and unspecified drugs, medicants and biological substances
X60	Intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics
X61	Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not classified elsewhere
X62	Intentional self-poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere classified
X63	Intentional self-poisoning by and exposure to other drugs acting on the autonomic nervous system
X64	Intentional self-poisoning by and exposure to other and unspecified drugs, medicants and biological substances
X85	Assault by drugs, medicaments and biological substances
Y10	Poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics, undetermined intent
Y11	Poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not classified elsewhere, undetermined intent
Y12	Poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere classified, undetermined intent
Y13	Poisoning by and exposure to other drugs acting on the autonomic nervous system, undetermined intent
Y14	Poisoning by and exposure to other and unspecified drugs, medicants and biological substances, undetermined intent

Many of the ICD-10 codes used by the CDC to determine the number of deaths due to opioids did not always include opioids. Reasons as to why these particular codes are used by the CDC were not of primary concern. The greater concern was to show that although the number of deaths due to opioids is quite high nationwide according to the CDC [12-14], that is not the case with patients with SCD. That is why searches pertaining to opioid deaths were conducted using the exact codes used by the CDC in addition to the ICD-10 codes for SCD.

Once the data were collected, basic statistics were calculated using Systat 13 to determine the mean and standard deviation. Figures indicating a scatter pattern reflect p values determined by regression analysis. P values indicated in the tables were calculated using the t score.

Results

According to the CDC WONDER Multiple Cause of Death database 840,629 patients in the general population died from 1999 through 2018 due to opioid overdose. However, only 348 patients with SCD died of opioid overdose during the same time ($p < 0.0001$) [14]. In addition, regression analysis of the data showed that the number of deaths of patients with SCD due to opioid overdose did not change significantly from 1999 through 2018 [11].

The CDC WONDER Multiple Cause of Death database contains 27 categories of death based on ICD-10 codes in patients with SCD arranged in decreasing order of frequency as shown in Table 1 with opioids ranking at number 19. These data indicate that the most common causes of death include the circulatory system followed by infection including sepsis, etc. Figure 1 is a bar diagram showing the five most common causes of death and includes death due to opioids for comparison.

The extensive CDC WONDER Multiple Cause of Death database allowed the exploration of the determinants of mortality of patients with SCD including sex, age, geographical location and etiology. The CDC data did not differentiate gender from sex. The relation between age/sex and mortality is summarized in Table 2. Specifically, during the 20 years of collected data by the CDC, the total number of women with SCD who died was greater than the total number of men: 8010 women v 7755 men ($p < 0.0001$). This difference seems to be primarily due to the difference in patients > 50 years old. On the other hand, the mean age of the

total number of deaths due to opioids is significantly lower than that for patients who died from other causes: 35.9 years v 40.7 years; $p < 0.0001$. The same is true for females and males (Table 2).

The number of death of patients with SCD due to opioid use is highest in the South and similar in the Northeast, Midwest and West regions of the United States. This pattern is similar to death due to opioids in non-SCD patients.

Discussion

The present study describes the age, gender, region and causes of death of patients with SCD using the CDC WONDER Multiple Cause of Death database as described in Methods above.

Life expectancy and risk factors for early death of patients with SCD have been an important subject that was addressed by several studies over the years. Most important among these is the study by Platt et al[15] indicating that 78% of deaths had pain, acute chest syndrome (ACS), or both and 22 percent had stroke. Opioids as a cause of death in that study were not mentioned since the opioid epidemic was not an issue at that time. Since then, the common causes of death of patients with SCD included infection, stroke, ACS, sudden death and organ failure [16-19]. Opioids were not mentioned in these studies as a cause of death. More recently, a comprehensive study by Lubeck et al [20] estimated life expectancy and income of patients with SCD but, opioids were not mentioned in that study as well. A recent report mentioned that patients with SCD are falsely accused of being part of the opioid epidemic [10]. In addition, opioid use by patients with SCD was stable over time both in the commercial and Medicaid cohorts [11].

It must be emphasized that this study is not an advocate for the use of high doses of opioids to treat sickle cell pain in general and pain associated with VOCs in particular. It is a recommendation for the adequate treatment of sickle cell pain that offers pain relief and better quality of life. This can be achieved by following the NIH guidelines for the treatment of sickle cell pain. These guidelines specifically state that the provider should determine the analgesic selection based on pain assessment, associated signs and symptoms, outpatient analgesic use and past experience with side effects [21, 22]. This almost always includes the use of the most appropriate opioid and its dose for the patient in question. In addition, a written treatment plan signed by the patient and the provider must be established. The plan should include the performance of random urine drug screening.

Comparing the age at death of this study to previous studies raises several questions. Overall, the mean age at death of this study is 40.7 years with 41.9 for females and 39.3 for males (Table 2). Similarly, Lanzkron et al reported the mean age at death of females was 36.9 years and 33.4 years for males [19]. For patients older than 50 years the age at death for females was 61.1 years and 59.8 years for males (Table 2).

Of concern, is the mean age at death of patients who died due to opioids is younger than the mean age at death due to other causes than opioids: 35.9 vs 40.7 ($p < 0.0001$) This is also true for both females an males (Table 2). Whether this is due to opioids or complications of SCD is unknown.

The clinical manifestations and the causes of death in patients with SCD have changed over the years. As mentioned above, the major cause of death in the 1990s was VOCs and ACS. Currently, VOCs and ACS rank number 5 after circulatory, infection, respiratory and genitourinary complications (Figure 1). Similarly, infection was the most common cause of death

of patients with SCD in Rio de Janeiro, Brazil [23]. Nevertheless, VOCs continue to be the major cause of admissions to the ED and hospital. Thus, figuratively speaking, the VOC seems to be the tip of the iceberg of the complicated hidden pathophysiologic events of the disease. The silent mediators of inflammation originate from activated leukocytes, mast cells, macrophages, platelets and endothelial cells that release histamine, serotonin, prostaglandins, leukotrienes, chemokines, cytokines, platelet activating factor and reactive oxygen species among others. As the concentration of these mediators increase gradually, a point is reached where they cause further tissue damage leading to the precipitation of a new VOC or reactivating a previously resolving VOC. Accordingly, a vicious cycle of recurring VOCs is created and associated with gradual increase in inflammation and organ damage.

The current study has some limitations. The first pertains to the fact the data were based on information included in the death certificates. This may be inaccurate and is usually based on what happened during the 24 hours before death. The second limitation is that the data were not categorized according to the type of SCD. The CDC data lumped all types of SCD together. Individuals with sickle cell trait were excluded. Patients with hemoglobin (Hb) SC disease are known to have better survival than patients with sickle cell anemia (SSA). In the study by Platt et al [15] the median survival of males with Hb SC was 60 years and for females was 68 years. In this study, the mean survival of males with all types of SCD excluding sickle cell trait was 39.3 years and for females was 41.9 as shown in Table 2. On the other hand, in this study, the mean age of survival for males who died due to opioids was 36.0 years and for females was 35.8 years (Table 2). Given that patients with Hb SC have better survival, the survival of patients with SSA in this study would be less than shown in Table 2. In addition, a recent study from Brazil reviewed survival data of patients with SCD from 2000 to 2018 and found the median survival of

9812 patients to be 29.5 years with the median survival of 4782 males equals 27.5 years and of 5030 females equals 31.0 years [24]. Similarly, another Brazilian study from a single institution showed that among 1676 patients with SSA the median age at death was 28.98 years for men and 34.02 years for women [23].

Thus, it seems there has been no improvement in the survival of patients with SSA in both males and females with and without opioid use in the present study compared with Platt's et al study [15]. Hopefully, the recent advent of disease modifying therapies including L-glutamine, crizanlizumab and voxelotor as well as advances in stem cell transplantation and gene therapy will improve survival of patients with SCD in the near future.

In summary, this study shows that survival of patients with SCD is gender, age and region dependent. Opioids were not a major cause of death. The overall mean age of death of females and males was less than that reported by Platt et al in 1994 [15]. Females who died due to SCD live longer than males in the > 50 years age group but not in patients with SCD who died due to opioids in the same > 50 years age group. Mortality of patients with SCD was highest in the southern region of the US. The most common cause of death was not VOC/ACS but the circulatory and infection/sepsis complications. More prospective studies are needed to characterize the changing clinical landscape of SCD.

Legend to the Figures:

Figure 1: Number of Causes of Deaths of Patients with Sickle Cell Disease from 1999-2018. Centers for Disease Control and Prevention. CDC WONDER Multiple Cause of Death database, 1999-2018. 2020.

Declarations

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Conflict of interest: The author has served on the speakers' bureau for Novartis Pharmaceuticals Corporation and has received honoraria from Novartis Pharmaceuticals Corporation.

Ethical approval

This article does not contain any studies with human participants or animals performed by the author.

Availability of data and material: Data are available upon request from the corresponding author.

Author contributions: SKB performed the literature search and extracted data from selected studies. He also assessed the quality of the included studies and performed a cross-check for data accuracy and wrote the manuscript.

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Table 1

Causes of Death of Patients with Sickle Cell Disease Arranged in Decreasing Order of Frequency 1999-2018

	Cause of Death	Number of Deaths	Gender	% of Total Deaths
1	Circulatory system (including PAH and HF)	8643	4439 (F) 4204 (M)	54.8
2	Infection (including Sepsis and Pneumonia)	3585	1875 (F) 1710 (M)	22.7
3	Respiratory conditions (excluding Pneumonia)	2935	1520 (F) 1415 (M)	18.6
4	Genitourinary system (including CKD)	2836	1416 (F) 1420 (M)	18.0
5	Infection (including Sepsis)	2756	1452 (F) 1304 (M)	17.5
6	Symptoms, signs and abnormal clinical and laboratory findings not classified	2519	1316 (F) 1203 (M)	16.0
7	Acute Chest Syndrome/Vaso-occlusive crises	2448	1210 (F) 1238 (M)	15.5
8	Digestive system diseases	2038	993 (F) 1105 (M)	12.9
9	Endocrine, nutritional and metabolic diseases	1778	972 (F) 806 (M)	11.3
10	Heart Failure	1211	649 (F) 562 (M)	7.7
11	Pulmonary Hypertension	1034	623 (F) 411 (M)	6.6
12	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	978	522 (F) 456 (M)	6.2
13	Injury, poisoning and certain other consequences of external causes	886	400 (F) 486 (M)	5.6
14	Mental and behavioral disorders	838	363 (F) 475 (M)	5.3
15	Pneumonia	829	423 (F) 406 (M)	5.3
16	Nervous system diseases	666	350 (F) 316 (M)	4.2
17	Other external causes of morbidity and mortality	371	189 (F) 182 (M)	2.4

18	Musculoskeletal system (including Osteoporosis and osteopenia)	369	222 (F) 147 (M)	2.3
19	Opioids	348	147 (F) 201 (M)	2.2
20	All Accidents	280	126 (F) 154 (M)	1.8
21	Skin and subcutaneous tissue diseases	115	67 (F) 48 (M)	0.7
22	Congenital malformations, deformations and chromosomal abnormalities	92	42 (F) 50 (M)	0.6
23	Conditions originating in the perinatal period	24	9 (F) 15 (M)	0.2
24	Pregnancy, childbirth and the puerperium	17	17 (F) 0 (M)	0.1
25	Eye and adnexa diseases	14	6 (F) 8 (M)	0.1
26	Suicide	12	3 (F) 9 (M)	0.1
27	Ear and mastoid process diseases	10	6 (F) 4 (M)	0.1

CKD = Chronic kidney disease; HF = Heart failure; PAH = Pulmonary arterial hypertension; SCD = Sickle cell disease

Reference: Centers for Disease Control and Prevention. CDC WONDER Multiple cause of Death database, 1999-2018.

Table 2

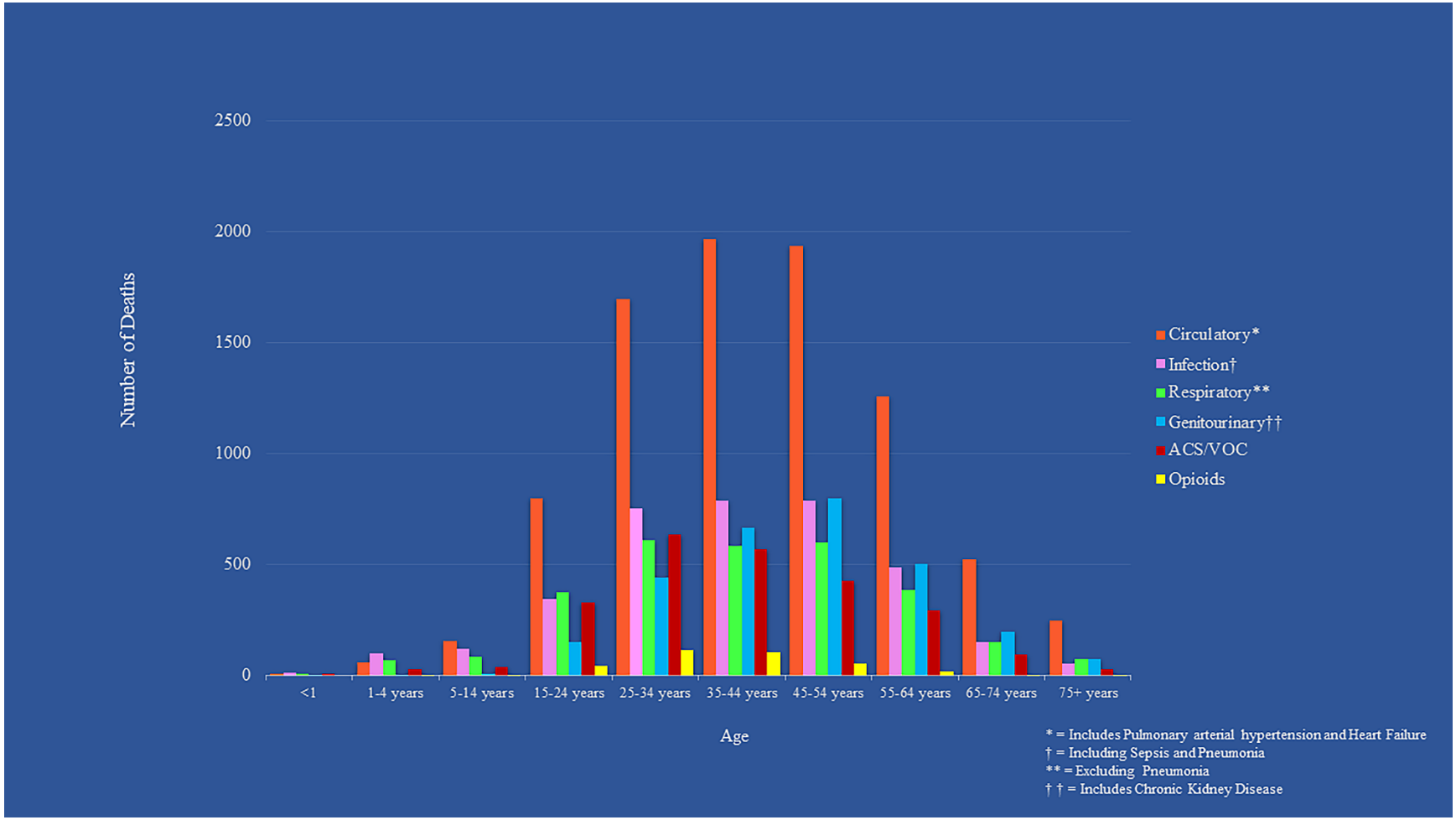
Mean Age of Death of Patients with SCD and of Patients with SCD Who Died Due to Opioids

Number of Deaths of Patients with SCD				Number of Deaths of Patients with SCD Who Died Due to Opioids		
Age Group	(n) Mean Age Total (yrs)	(n) Mean Age Females (yrs)	(n) Mean Age Males (yrs)	(n) Mean Age Total (yrs)	(n) Mean Age Females (yrs)	(n) Mean Age Males (yrs)
0-18	(1136) 9.4*	(524) 9.5*	(612) 9.3*	(12) 12.2*	(4)12.0*	(8) 12.3*
19-35	(4912) 27.9[a]	(2322) 28.1*	(2590) 27.7[b]	(167) 28.5[a]	(68) 27.5*	(99) 29.3[b]
36-50	(5400) 43.0*	(2736) 43.1*	(2664) 42.8[b]	(137) 42.0*	(62) 42.1*	(75) 42.0[b]
> 50	(4317) 60.5[c]	(2428) 61.1[c]	(1889) 59.8 [c]	(32) 57.6 [c]	(13) 56.6 [c]	(19) 58.3 [c]
0-100	(15765) 40.7 [d]	(8010) 41.9 [d]	(7755) 39.3 [d]	(348) 35.9 [d]	(147) 35.8 [d]	(201) 36.0 [d]

n = Number of patients; SCD = Sickle cell disease; yrs = Years

* Not significant; a = $p < 0.01$; b = $p < 0.05$; c = $p < 0.0001$; d = $p < 0.0001$

Reference: Centers for Disease Control and Prevention. CDC WONDER Multiple cause of Death database, 1999-2018.


2500
2000
1500
1000
500
0
Number of Deaths
<1
1-4 years
5-14 years
15-24 years
25-34 years
35-44 years
45-54 years
55-64 years
65-74 years
75+ years
Age
Circulatory*
Infection†
Respiratory**
Genitourinary††
ACS/VOC
Opioids
* = Includes Pulmonary arterial hypertension and Heart Failure
† = Including Sepsis and Pneumonia
** = Excluding Pneumonia
† † = Includes Chronic Kidney Disease