Special Article

Distributed Opioids in Morphine Equivalent: A Global Measure of Availability for Palliative Care

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Abstract

Context. Estimates of serious health-related suffering (SHS) demonstrate immense unmet need for palliative care, predominately in low- and middle-income countries (LMICs). Because opioids are essential medicines in palliative care (PC), measuring their availability can be used to evaluate the capacity of health systems to meet need.

Objectives. Present the methodology for calculating *Distributed Opioids in Morphine Equivalents (DOME)*— introduced in the Lancet Commission on Global Access to Palliative Care and Pain Relief report - and how it can be used as a simple indicator to quantify unmet pain relief and PC need.

Methods. Using International Narcotics Control Board (INCB) data, *DOME* applies relative potency estimates to convert the annualized quantities of clinically appropriate opioids procured by a country to oral morphine equivalent milligrams. To quantify unmet need, an expert group proposed health condition-specific estimates for opioid need and used available data on the burden of SHS to posit the annual opioid quantity required by country for symptomatic treatment of pain or breathlessness. Comparing this to DOME generates DOME%SHSNEED, the proportion of opioids needed for palliative care that can be fulfilled by the opioid procured by a country during a year.

Results. *DOME and DOME%SHSNEED* can be used to measure, over time, the capacity of countries to meet PC need, as a key component of universal health coverage. Identifying access gaps disproportionately impacting LMICs can promote better health system performance and guide countries and institutions in policy making.

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Conclusion. *DOME* and DOME%SHSNEED can be used to monitor health system progress to redress disparities and promote access to medically indicated opioid therapy in palliative care. J Pain Symptom Manage 2024;000:e1−e12.

Key Words

Opioids, palliative care, serious illness, pain management, health systems, global health, pain

Key Message

This article describes the methodology for calculating a measure of opioid accessibility— *Distributed Opioids in Morphine Equivalents* (*DOME*)—and discusses its use in estimating the unmet need for opioids in palliative care and monitoring progress in providing opioid access for palliative care.

Introduction

Resolving unmet need for palliative care (PC) and pain relief is a global health and equity priority.[1] The disparities in the burden of unrelieved suffering are reinforced by the paucity of policies and investments required to realize high-quality and sustained pain control and palliative care. Central to this is the dearth of access to opioid medications for palliative care that especially afflicts low and middle-income countries (LMICs). We draw on a robust body of literature, international legal frameworks, and human rights organizations that establish access to pain relief as fundamental to the right to life, to the highest possible standards of physical and mental health, and to ensure freedom from cruel and inhumane treatment.[2−4] They collectively highlight the unjustifiable burden that current opioid management policies place on LMICs, underscoring the imperative for a more equitable approach that respects the rights of all individuals to access necessary pain management and palliative care. For example, the Committee on Economic, Social, and Cultural Rights stated in 2000 that "…States are under the obligation to respect the right to health by, inter alia, refraining from denying or limiting equal access for all persons, including prisoners or detainees, minorities, asylum seekers and illegal immigrants, to preventive, curative and palliative health services…" and that the right to health of older patients includes "…attention and care for chronically and terminally ill persons, sparing them avoidable pain and enabling them to die with dignity".[4]

Large disparities in access to PC disproportionately impact resource-limited countries and are exemplified by the demonstrated disparities in opioid availability.[1,5] This lack of availability is further complicated by various structural, social, and historical factors that must be addressed to achieve equitable access. Progress in reducing global disparities has been very limited, despite multiple resolutions and political declarations urging governments to adopt rational drug policies that guarantee the safe accessibility of essential medicines such as morphine,[6−8] and nearly all governments' commitments to the 1961 Single Convention on Narcotic Drugs. As a result, lack of access to palliative care continues to constitute a major limitation in achieving Universal Health Coverage[9] and realizing Sustainable Development Goal (SDG) 3.[10]

A recent World Health Organization report suggests that limited opioid availability may be amplified by regulatory decisions within countries.[5] Hence data-informed policies and initiatives, both national and global, are needed to address the unmet clinical need for opioid medicines for PC, especially in resource-poor countries. In turn, national and global health authorities could use a measure of unmet need to monitor country-specific health care changes or benchmark a country's progress as these changes unfold. The development of measures to accurately calculate opioid accessibility and compare this to PC need are essential to support these efforts.

In 2018, the Lancet Commission on Global Access to Palliative Care and Pain Relief (henceforth 'the Commission') report put forward novel methods and measures for both PC need and the capacity of countries to meet this need. The Commission outlined an Essential Package of Palliative Care and Pain Relief (the Essential Package), which could be used to estimate the gap between those treatments and services available through a health system and those that are essential to provide PC.[1] Access to one of the Essential Package's most important elements—opioid therapy for pain or dyspnea— has been used as a proxy for access to PC.[11] For this purpose, the measure of ***Distributed Opioid in Morphine Equivalents (DOME)*** can be used based on publicly reported data from the International Narcotics Control Board (INCB).[12] In this context, opioids are used as a tracer for country performance in PC access while acknowledging the measure's inherent limitation in not considering several fundamental pillars of PC that transcend controlled essential medicine access (e.g., health care professionals trained in palliative care). However, while access to opioids may not necessarily mean that people will have access to

comprehensive, interdisciplinary palliative care, the absence of opioids guarantees inadequate palliative care and unrelieved suffering.

The Commission also introduced a method to estimate ***serious health-related suffering (SHS)*** to quantify the populations experiencing physical and psychosocial symptoms associated with life-threatening and life-limiting conditions and as a novel measure of a country's need for PC services.[11] The SHS measure is uniquely suited to evaluate the global need for PC to alleviate suffering among both decedents and non-decedents.[13] The SHS burden is high, in part related to the prevalence of symptoms such as pain and dyspnea, and marked global disparities exist between HICs and LMICs. The Commission estimate of people experiencing SHS exceeded 60 million in 2015 — an immense global burden, with 80% of SHS in LMICs. Compared to high-income countries, LMICs have very limited opioid medicine availability, a disparity that has seen little change during the past decade.[14–16]

Comparing DOME to SHS is an initial approximation to understand how PC need is being fulfilled. According to these estimates, the poorest 10% of the world's population receives an average of 200 mg of morphine equivalents (DOME) per patient with SHS per year, not even enough for seven days of a typical starting dose of morphine, while the richest 10% receive an average of approximately 200,000 mg per patient with SHS per year.

In this paper we present details on how the indicator DOME is calculated and demonstrate its use in assessing national health system capacity to provide adequate opioid accessibility. We first provide details on the methods and the data used to calculate DOME. In the next section, we link DOME to PC need of patients with SHS. The final section considers the applications and limitations of these measures. No country data is provided as this is a methods paper that we hope will be used as reference to support other empirical work and provide necessary background to The Lancet Commission report.

The calculation of SHS that covered 20 health conditions is originally described in detail in the Appendix to the Commission report.[11,17] A published companion paper to this article outlines recent work to develop SHS 2.0, an improved methodology that includes 21 health conditions and uses the Global Burden of Disease data.[13] Longitudinal analysis of SHS, DOME and DOME compared to SHS is underway for the years 1990 to 2021 to test the validity of the measures and establish their usefulness as a tool for tracking changes in PC access over time.

Methods and Data for Calculating DOME

Definition of DOME

DOME is defined as the countries' reported quantity of clinically appropriate opioid medicines—expressed in terms of milligrams (mg) equivalent in analgesia to oral morphine—that has been supplied to any person or enterprise for retail distribution, medical use, or scientific research during a specified year.

Six opioids that are clinically accepted for the treatment of pain or dyspnea are included in the *DOME* measure: morphine, codeine, fentanyl, hydromorphone, oxycodone, and pethidine. To select these medicines, the Commission consulted the World Health Organization's current Model Lists of Essential Medicines.[18] *DOME* does not include methadone, given its prominent use in the treatment of opioid use disorder.[19] *DOME* does include two medicines no longer recommended for PC, pethidine (meperidine) and codeine, in recognition of the importance of each of these medicines in the 1990s and ongoing use in some countries. It is important to note that the database allows for disaggregation by specific medicine, which adds richness to the over-time analysis as countries shift their procurement patterns.

Data Sources for the DOME Calculation

DOME is calculated using data provided annually by all United Nations member states to the International Narcotics Control Board (INCB), an organization established by the international Single Convention on Narcotic Drugs of 1961, as amended by the 1972 protocol, as an independent, quasi-judicial expert body to monitor the global manufacture, consumption, imports, and exports of controlled substances. INCB's main function is to ensure adequate global supplies of controlled medicines for medical and scientific use and to support member states in their efforts to prevent diversion and illicit use. The INCB produces and provides an important global public good in the form of reports of each country's opioid amount available for retail distribution, medical use, or scientific research.[20] Quantities are expressed in kilograms (kg) or metric tons (1000 kg); data on quantities under 1 kg are not provided. INCB has been using SHS and comparing it to DOME in its annual reporting which is presented to countries and used to help propose and effect policy change.

Calculation of Morphine Equivalents

The quantities of the opioids included in the *DOME* measure were converted to a common metric—oral morphine equivalent milligrams (herein also designated morphine-equivalents). This conversion is necessary to account for the widely divergent potencies of the different opioids. Based on decades of research, these potency differences have been characterized in terms of analgesic potential, using morphine analgesia as a standard.[21] For example, studies have shown that the potency difference between oral morphine and oxycodone means that just 20.0–22.5 mg of oral

Table 1
Conversion Factors Used to Describe Quantities of the Opioid Medicines Included in the *DOME* Measure in Terms of Morphine Equivalent Milligrams

Medicine	Conversion Factor
Pethidine	0.25
Codeine	0.417
Morphine	1
Oxycodone	1.33
Hydromorphone	5
Fentanyl	83.33

oxycodone will provide analgesia equivalent to 30 milligrams (mg) of oral morphine in an opioid-naive patient with pain.[22]

Given these potency differences, the quantities of the different opioid medicines distributed within a country cannot be simply added to evaluate the capacity for clinical use. Meaningful interpretation requires that the quantity of each opioid other than morphine be adjusted to account for its potency relative to morphine. For the *DOME* measure, this adjustment was implemented by creating conversion factors (Table 1) based on the information in equianalgesic dose tables, which describe the doses of varied opioids that yield analgesia equivalent to a standard oral morphine dose. Although there are continuing controversies about the accuracy of some of the equianalgesic dose ratios,[23] the consistent use of an accepted equianalgesic dose table is a best practice during clinical care. It is therefore the tool used to calculate DOME.

Calculating Annual DOME

To calculate a country's *DOME* value for a given year, the quantities of each opioid included in the measure were averaged over the three prior years to generate a 3-year moving average. We undertook a sensitivity analysis before deciding on using the 3-year moving average. For example, the 2019 *DOME* value for country *i* is derived from the average opioid quantities in 2017, 2018, and 2019. Using this average mitigates concern about inaccurate or fluctuating year-to-year reports because of stockpiling. In other words, a country may hold previous stock and, therefore, import or produce less in a given year. Some member states even reported zero imports or production in some years. The sensitivity analysis evaluated moving averages longer or shorter than 3 years, but found the 3-year moving average most robust against these fluctuations.

The data base includes the 183 countries that reported DOME to the INCB for at least one of the three years required to construct the moving average. The countries that did not report any data and are excluded represent only 0.0134% of the global population. For countries that are missing data for a particular year, the moving average is constructed based on the reported years (e.g. if a country reported only 1988 and not 1989 or 1990, 1990 is equal to 1988; if 1989 and 1990, then 1990 is the average of 1989 and 1990).

The three-year average quantities of the six opioids included in the *DOME* measure were standardized into oral morphine equivalents by multiplying the quantities of the five opioids other than morphine by their respective conversion factors (Equation 1). Each medicine can be analyzed separately in morphine equivalent or summed and aggregated. The result ($DOME_i$ in Equation 1) may be converted to $DOME_i$ *per capita* by dividing the value by the total population of the country in the year of calculation. Alternatively, it may be converted to DOMEi per patient with SHS by using the SHS measure to determine the number of people with serious health-related suffering associated with the 21 clinical populations included in the SHS measure.[13]

Equation 1: Country-specific *DOME*

$$DOME_i, \text{ expressed in oral morphine} - \text{equivalents (mg)} = (\text{morphine}_i\text{mg}) + (\text{fentanyl}_i\text{mg X } 83.3) + (\text{hydromorphone}_i\text{mg X } 5) + (\text{oxycodone}_i\text{mgX } 1.33) + (\text{pethidine}_i\text{mg X } 0.25) + (\text{codeine}_i\text{mg X } 0.417),$$

where DOME is the Distributed Opioid in Morphine Equivalents during a specified year, and i is a country, and the conversion factor is used to convert each opioid into morphine equivalents; each quantity of a specific medicine is the average of the specified year, and the two prior years.

Interpreting the DOME Measure and Estimating Unmet PC Need for Opioid Medicines

Although the DOME value cannot be interpreted in terms of opioid milligrams consumed by patients (with or without SHS) or even as having reached the points where patients can access (hospitals, dispensaries, etc.), it may be considered a proxy for the opioid quantity that could "potentially" be made available to meet SHS need. In other words, if DOME is not available in a country, there is no chance that it can be accessed by patients in need or by providers of PC. Further, in comparing DOME to SHS, the outcome measure reflects the minimum unmet need because it also assumes that all DOME is allocated to PC, whereas there are multiple scenarios (such as surgery) in the health care sector that require DOME. The benchmarking exercise

described below provides one way of controlling for this source of bias.

For cross-country or over-time comparisons, the DOME value may be normalized by population (per capita DOME) or, more precisely, by an estimate of the clinical requirements of a country aligned with their epidemiological profile. In the case of PC need, DOME is compared to the number of people with SHS using estimates of average opioid medicine requirements per patient for each SHS health condition.[13] The calculation quantifies the extent to which a country's opioid medicine procurement is potentially sufficient to manage the pain or dyspnea experienced by its population with SHS in a specific period (a year).

Estimating Condition- and Country-Specific Opioid Need

The efforts to determine the total amount of morphine required to alleviate pain and dyspnea experienced by decedents and non-decedents with SHS over the course of one year came from various approaches across the life span of the Lancet Commission on Global Access to Palliative Care and Pain Relief, its follow-up implementation body, and the Research Hub on Global Access to Palliative Care and Pain Relief between 2015 and 2021. The amount of morphine required to alleviate pain and dyspnea for the decedents of the initial 20 conditions and the non-decedents for hemorrhagic fever, TB, HIV, malignant neoplasms (except leukemia), dementia, inflammatory disease of the CNS, degenerative disease of the CNS, cerebrovascular disease, congenital malformation, injuries, and musculoskeletal disorders came from the literature review and expert groups convened by the Lancet Commission.[11,13] These estimates were applied to all age groups. The details of the expert group can be found in the recent publication describing the methods of generating SHS.[13] After publication of the Commission report, work continued with the International Children's Palliative Care Network to refine the estimates for children. It was through a literature review, a two-round Delphi process with a pediatric palliative care expert panel, and continuous discussion in semi-structured focus group discussions and email exchanges that we finalized the total amount of morphine required to alleviate pain and dyspnea for children with type 1 diabetes mellitus, thalassemia, and sickle cell disorders. This review also suggested the need to add the non-decedent categories to four other conditions, namely, leukemia, diseases of the liver, renal failure, and low birth weight and birth trauma. For these conditions, the amount of morphine required for children's age groups was calculated from the round-two results of the online Delphi process and reviewed and agreed upon in focus group discussions later.

Next the research group convened another smaller expert team of palliative care clinicians and researchers, which agreed that except for type 1 diabetes, thalassemia, and low birth weight and birth trauma, adults also suffer from those conditions that were added by the pediatric expert group, namely, nondecedents of leukemia, disease of the liver, renal failure, and both decedents and nondecedents of sickle cell disorders. This expert group then discussed the total amount of morphine those patients would require annually and reached a consensus with the support of the literature review. More details of those approaches, for example, the composition of the expert groups, can be found in our previous publication.[13]

For each SHS condition, group members posited the total number of oral morphine equivalent milligrams required to manage pain or dyspnea during a one-year period. These estimates of opioid need, expressed in terms of oral morphine equivalents, were developed separately for patients who were alive and experienced SHS during a specified year (nondecedents) and those who died with SHS during that year (decedents). Disagreements within the group were resolved by discussion, and consensus emerged on an average for the total opioid need during a year for decedent and non-decedent patients with SHS (Table 2). One clear limitation discussed further below is that country-specific and over-time differences in needs for opioid medicines were not considered in the groups. In other words, the groups produced one estimate that is applied in all years and across all countries as a standard.

The expert group's consensus-derived estimates for the average total opioid need experienced by decedent and nondecedent patients with SHS. Each of the 21 conditions yielded a country-specific estimate of opioid need during a year (Equation 2). The sum of these estimates across all SHS conditions provides an estimate of a country's total opioid need (TON_i) for the management of pain or dyspnea associated with SHS.

Equation 2: Total opioid need to manage pain and dyspnea associated with SHS per year

$$\mathrm{TON_{ij,}\ expressed\ in\ morphine\ equivalent\ mg} = \left(\mathrm{ME_{jd}} * \mathrm{TP_{ijd}}\right) + \left(\mathrm{ME_{jn}} * \mathrm{TP_{ijn}}\right)$$

Where TON_{ij} is the total opioid need for condition j (one of 21 conditions in the SHS measure) in country i; ME_{jd} is the expert consensus on the total annual need for opioids in morphine equivalent milligrams for one patient with condition j dying in that year (decedent), ME_{jn} is the expert consensus on the total annual need for opioids in morphine equivalent milligrams for one patient with condition j alive throughout that year (non-decedent), TP_{jd} is the total number of decedents with condition j in country i and TP_{jn} is the total number of non-decedents with condition j in country i.

Table 2

Morphine Equivalents Requirements in mg for SHS by Condition and Age Group According to Estimated Intensity and Duration of Symptoms

ICD 10	Conditions	Decedents				Non-Decedents			
		All ages	Under 5	5- 19	+20	All ages	Under 5	5- 19	+20
A96,98,99	Hemorrhagic fevers	80				80			
A15-19	TB deaths from M/XDR TB	264				90			
A15-19	TB deaths from regular TB	42							
B20-24	HIV disease	675				150			
C00-97 (except C91-95)	Malignant neoplasms	9000				480			
C91-95	Leukemia	990					1393	4162	480
F00-04	Dementia	270				10			
G00-09	Inflammatory disease of the central nervous system	160				160 (TN)			
G20-26; G30-32; G35-37; G40-41; G80-83	Degenerative disease of central nervous system	288				30 (PD); 80 (MS)			
I60-69	Cerebrovascular disease	180				10			
I05-09; I25; I42 & I50	Chronic rheumatic heart disease; cardiomyopathy & heart failure	480							
I25	Chronic ischemic heart disease	540							
J40-47; J60-70; J80-84; J95-99	Lung disease	540							
K70-77	Diseases of liver	270					744	2218	2190
N17-19	Renal failure	270					706	2143	1460
P07; P10-15	Low birth weight & prematurity; Birth trauma	42					553 (PT) 2514(BT)	6668 (BT)	
Q00-99	Congenital malformations	84				24			
S00-99; T00-98; V01-Y98	Injury, poisoning, external causes	400				400			
I70	Atherosclerosis	1980							
M00-97:	Musculoskeletal disorders	396				396			
E40-46	Protein-Energy Malnutrition	4							
D50-89, E00-89	Endocrine, Metabolic, Blood and Immune Disorders		504 (DM); 668 (T); 1823 (SC)	1391 (DM); 6536 (T); 10365 (SC)	2520 (SC)		351 (T); 972 (SC)	1651 (T); 4651 (SC)	2520 (SC)

TN: Tetanus; PD = Parkinson's disease; MS = multiple sclerosis; PT = preterm birth; BT = birth asphyxia and birth trauma complications; DM = Diabetes Mellitus; T = Thalassemias; SC = Sickle cell disorders.

Estimating Country-Specific Capacity to Meet SHS Need for Opioids

The capacity of a national health system to meet the need for opioid medicines for patients with SHS who experienced pain or dyspnea during a one-year period is described by the extent to which a country's $DOME_i$ value meets or exceeds its TON_i value during the same period. The $DOME_i$ value can be depicted as a percentage of TON_i (Equation 3).

Equation 3: Proportion of total need for SHS-associated opioid therapy that can be potentially met by *DOME* per year

$$\mathrm{DOME\%SHSNEED} = \mathrm{DOME_i} / \mathrm{TON_i} \times 100\%$$

Where DOME%SHSNEED is a percentage indicating the extent to which the quantity of clinically appropriate opioid medicines procured by country i is less than, equal to, or more than that required to meet the total need for opioid medicines to manage pain and dyspnea associated with 21 SHS conditions during a one-year period. $DOME_i$ is the estimated total quantity of clinically appropriate opioids, in morphine equivalent milligrams, procured by country i during one-year period and TNO_i is the total estimated need in the same country to manage moderate or severe pain or dyspnea associated with SHS conditions during the same period.

Given the multiple clinical and nonclinical (scientific) uses for opioid medicines, DOME%SHSNEED can range in value from 0 to thousands of percent and has no specific upper value. Countries with opioid availability sufficient to meet SHS need for moderate or severe pain or dyspnea would have *DOME%SHSNEED* values that exceed 100%. Countries with high rates of opioid use for chronic pain or dyspnea unrelated to serious illness or high rates of prescription opioid abuse would be expected to have *DOME%SHSNEED* values that substantially exceed 100%. Further, a value of or close to 100% should be interpreted as having sufficient opioid medicines in the country to potentially meet all PC need if and only if those medicines are used for no other clinical or scientific purpose and there is no wastage or stockpiling at the retail level.

Western European Countries as Opioid Benchmarks

Cross-country comparisons of the DOME and DOME%SHSNEED may be enhanced by the ability to benchmark a country's data against a group of countries that meet criteria for good performance—defined as opioid distribution from national authorities sufficient to provide opioid treatment for pain or dyspnea associated with serious illness while managing the risks associated with broader access to these medicines. In effect, this produces a benchmark that necessarily higher than SHSNEED, as it also includes opioid use for nonpalliative care indications.

We selected a set of Western European countries—Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and United Kingdom—to explore meaningful benchmarks. The risks associated with relatively high levels of opioid availability—risks related to opioid use disorder and overdose—have had relatively less societal impact in those countries than in the USA, Canada or Australia.[29] As a result, this set of the Western European countries was selected as the performance benchmark for good practice in meeting total clinical and scientific need for opioid medicines. The application of this benchmarking technique however, requires adjustments for differences in the epidemiological profiles of the benchmark country compared to the country of interest using GBD data.[30]

In 2019, the average DOME per patient with SHS value among the Western European countries was 16,529.90 morphine equivalent milligrams (range 1,192.60 mg to 44.257.89 mg) and the average TNO per patient with SHS was 2,013.25 morphine equivalent milligrams (range 1,861.52 mg−2,355.70 mg). The average DOME%SHSNEED was 821.05% (range 58.71%−2,173.33%). (Table 3).

The following equation was used to calculate DOME as a benchmark per year:

Equation 4: Calculation of opioid medicines required by a country anchored in Western European DOME as a benchmark per year

$$\mathrm{MEbenchmarki} = \mathrm{TNOi} * (16,529.90/2,013.25)$$

where [Equation] is the adjusted total opioid need, in morphine-equivalents, of country i based on the benchmark model for morphine use in Western Europe; TNOi is the total estimated need in the same country to manage moderate or severe pain or dyspnea associated with SHS during the same period; and 2,013.25 and 16,529.90 are the 2019 TNOi per SHS patient and DOME per SHS patient of the benchmark countries.

Discussion

Overview and Advantages of the DOME and SHS Framework

The *DOME* measure describes a country's reported quantity of clinically necessary opioids available for consumption, with the quantities of six medicines standardized as oral morphine equivalents. The measure allows for analysis by country, over time, and for each medicine individually in morphine equivalent. When linked to SHS, the framework allows for monitoring a country's unmet need for opioid medicines for PC.

Table 3
Characteristics of Western European Countries Proposed for the Benchmarking of Country-Specific Opioid Availability Data

Country	*DOME* (kilograms)	*TNO per patient with SHS (morphine equivalents in miligrams)*	*DOME per patient with SHS (morphine equivalents in miligrams)*	DOME%SHSNEED per patient with SHS (%)
Austria	4,543.56	2036.41	44,257.89	2,173.33
Belgium	3,051.12	2,033.92	21,253.67	1,044.96
Denmark	1,561.32	2,355.70	22,583.46	958.67
Finland	704.45	1,928.59	10,284.67	533.27
France	9,611.72	2,049.24	10,985.69	536.09
Germany	29,250.40	1,965.19	23,763.93	1,209.24
Greece	1,338.40	2,061.23	8,719.55	423.03
Iceland	112.79	2,070.44	36,452.12	1,760.60
Ireland	681.91	2,120.80	15,754.23	742.84
Italy	5,993.92	1,892.33	6,564.11	346.88
Luxembourg	81.22	2,175.14	14,135.47	649.86
Malta	5.33	2,031.29	1,192.60	58.71
Netherlands	4,801.84	2,105.40	22,349.92	1,061.55
Norway	1,222.26	2,127.83	22,670.62	1,065.43
Portugal	1,363.96	1,861.52	8,842.06	474.99
Spain	12,033.79	1,897.12	20,276.25	1,068.79
Sweden	1,970.14	2,071.60	16,943.07	817.87
Switzerland	2,430.24	1,905.68	25,661.84	1,346.60
United Kingdom	12,115.11	2,233.55	15,569.22	697.06
Average (19 countries)	92,873.85	2013.25	16529.90	821.05

DOME: Distributed Opioids in Morphine Equivalents procured by a country for retail distribution, medical use, or scientific research; TNO: estimated Total Opioid Need for pain and dyspnea related to SHS; DOME%SHSNEED: percent indicating the extent to which the opioid quantity expressed by DOME is less than, equal to, or more than the TNO; per patient with SHS: values normalized by population with SHS, as determined by the SHS measure.

DOME builds on prior work, which started with a metric developed by the INCB known as "Defined Daily Doses" (DDD), subsequently changed to "Defined Daily Doses for Statistical Purposes" (S-DDD). This metric, which depicts opioid dose per million inhabitants per day, has been used to compare opioid consumption across countries and over time.[31] The INCB posited that opioid consumption would be inadequate, below a level of 200 S-DDDs per million inhabitants per day.[32]

To improve the empirical basis of estimates of unmet need for opioid medicines, Seya et al.[25] created an "Adequacy of Consumption Measure" (ACM). This morbidity-adjusted measure describes the per capita opioid amount that would be sufficient to treat the pain related to cancer, acquired immunodeficiency disease, and injuries. This measure was updated[33] and later modified by Scholten et al. to become the "Adequacy of Opioid Consumption" (AOC) index, which does not require mortality data and includes a larger group of opioids than the ACM.[34] An AOC index score consistent with adequate opioid availability was calculated using the top 20 countries in the Human Development Index as a gold standard, and the 200 S-DDD threshold used by the INCB was shown to be at only 3% of this score.[34] Both the ACM and the AOC revealed large disparities in availability, disproportionately affecting LMICs.

The *DOME* measure improves upon these earlier approaches in several respects. First, it includes only those opioids used clinically to manage pain and dyspnea associated with serious illness, as suggested in the World Health Organization's Model Lists of Essential Medicines.[18] Instead of the 18 opioid compounds used to calculate the ACM, *DOME* measures six that are or have historically been widely used clinically for PC. Second, three years of data are averaged to create an annual *DOME* value, increasing the stability of the value in the event of time-restricted changes in opioid distribution and stockpiling. Third, like prior measures, the quantities of the opioids included in the *DOME* measure are converted to morphine equivalent milligrams to account for the variation in potency across opioid medicines; this is accomplished through a simple calculation involving conversion factors based on accepted equianalgesic dose tables. Finally, *DOME* data can be normalized by the burden of serious health-related suffering in a country (*DOME per patient with SHS*),[13] enabling comparison to PC needs. Indeed, *DOME%SHSNEED* allows for monitoring a country's unmet need for opioid medicines in tandem with *DOME* to compare progress over time or across geographic regions, for example.

A set of 19 Western European countries was selected as opioid benchmarks. While benchmarking using countries with the highest Human Development Index has been attempted,[24,25] this is a sub-optimal strategy because several countries in this group—in particular the United States, Canada and Australia—are large and have relatively high levels of opioid use in populations with chronic non-malignant pain unrelated to serious illness and struggle with problems associated with opioid excess.[26–28] Including these countries would generate large upward bias for TOTNEED values, which suggest the need for an alternate group for benchmarking purposes.

Limitations and Future Work

Opioid availability is an important tracer for tracking how countries are likely to perform in improving access to PC. We argue, despite the limitations discussed below, that DOME can be meaningfully applied to monitor change over time in specific countries or compare opioid availability for PC across countries. It is crucial to note that despite ample research and advocacy to improve PC access globally, there are many other structural, social, cultural, and historical factors that impact availability. While providing data on DOME and SHS will support policy makers with the empirical rationale to improve PC infrastructure and capacity building, generating the political will to implement sustained and measurable improvements in PC access will require additional multisector partnerships and advocacy efforts.

There are several limitations in the data and application of the DOME and DOME%SHSNEED . First, the *DOME* value includes not only the opioid quantity that should be consumed for SHS through PC, but also other quantities used for clinical or nonclinical purposes or stockpile, and the proportion devoted to PC presumably varies across countries and time. Moreover, the *DOME* value does not include tramadol, a drug that is used clinically in many countries, and methadone, which is used for pain in some. Future work should consider how to incorporate these medicines without bias toward their application to opioid use disorder.

The INCB reports have not been entirely consistent for all countries over time, and especially for historical data, there is missing information that can affect the accuracy of cross-country comparisons. Further, there may be inaccuracies in the data reported to the INCB, and one comparative study of seven European countries reported significant discrepancies between national data and the INCB report.[35] Dome calculation included only oral conversion ratios between opioids, and parenteral application of morphine, hydromorphine, or pethidine would require different conversion ratios. However, it was assumed that the reported quantities would be used for oral application, as this is the most common form in LMIC. Future studies should explore whether there is systematic bias in the INCB reports that should be addressed when they are used to calculate DOME.

The average DOME per patient with SHS among the 19 Western European countries used for benchmarking was eight times higher than the total need of opioids for SHS. This is likely to be related to the widespread need and use of opioids included in DOME for other indications outside of palliative care, such as trauma, emergency, or intensive care. It could also be related to an underestimation of the opioid needs for relief of SHS in Western Europe. Further analysis using detailed data on the distribution of opioid medicines in each country is required. In addition, the benchmarking exercise that was undertaken does not control for differences in need for opioid medicines across countries associated with the disease profile beyond SHS and palliative care need. The next step in this research will be to incorporate data on opioid needs for other non-SHS conditions and for health system platforms such as trauma.

It is important to note that the measurement relies on the estimates of a relatively small group of clinical experts and a literature review that has not been further validated due to a lack of resources. Future surveys of clinical practitioners are needed to validate the estimates and clarify the impact of multimorbidity on opioid need, and this should be a priority for research funding. However, even with these limitations, calculating unmet need for opioid medicines should be a valuable approach to monitor changes over time and benchmark the progress that individual countries realize through policies and initiatives intended to improve access to PC.

The present work focuses on a single class of medicines (opioids) for two SHS symptoms (pain and dyspnea). It should be considered one step in an effort toward achieving a larger objective: the development of measures that characterize and monitor a country's access to a larger array of PC interventions relative to the clinical needs for mitigating SHS. The Commission's Essential Package includes a variety of safe, effective, and inexpensive medicines and equipment, social support for patients in extreme poverty, and training and staffing recommendations to provide PC. Thus, DOME%SHSNEED is only an approximate measure of met and unmet PC need, and better measures are needed. This research is underway in a project that includes global expert data collection, in-depth work in El Salvador, Colombia, and Mexico, and cross-country analysis of the dimensions of suffering and the value placed by patients and loved ones on its alleviation.[36–38]

Conclusions

The development of a global, population-level measure of opioid access to describe unmet clinical needs for PC could advance outcome monitoring within and across countries and promote the development of policies and initiatives intended to redress deficiencies and disparities in care. In this sense, the *DOME* and *DOME%SHSNEED* measures can be used by individual countries and the global health community to effect change. Improved measurement of opioid availability in countries around the world and an approach to connecting this value to measurement of the clinical need for opioid therapy are necessary steps in providing evidence that can be used to develop data-informed policies and initiatives that improve care and redress

disparities and permit the monitoring and benchmarking of outcomes as national and international efforts unfold. The DOME measurement is only a tracer for palliative care, and adequate opioid availability does not mean that other dimensions of palliative care are covered adequately. However, access to opioids is a fundamental prerequisite of adequate palliative care. Although the DOME measurement approach has limitations, they can be addressed through future research and, alongside SHS, represent a novel contribution that can now be used in the global effort to address the preventable suffering of populations and the unmet need for palliative care.

Improving the management of pain and dyspnea for the millions of people living and dying with SHS is a global health and equity imperative. It will require international and national reforms that culminate in safe opioid access sufficient to address medical needs in much of the world and redress the large disparities that unjustifiably burden LMICs. It is equally important to recognize that addressing the lack of availability of opioid medicines, especially in LMICs, involves complex structural, social, and historical factors beyond just political will. The *DOME* and SHS measures can provide actionable and ongoing data to inform policy and advance these reforms.

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