Opioids May be Appropriate for Chronic Pain

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Chronic pain affects one third of Americans, accounting for an astounding 116 million people.[1] Moreover, eighty percent of the world population has little to no access to treatment for moderate to severe pain,[2] and evidence to date suggests that most chronic pain remains untreated, undertreated, and has become a significant public health problem.[3] Compared to the general population, those suffering from pain experience a substantial decrement in their quality of life and financial resources that quite naturally often lead to greater limitations in function, increased disability, depression, and anxiety.[4]

Beginning in the 1990s, physicians and other healthcare providers began expanding their use of opioids for chronic, non-cancer pain conditions. Most practitioners did so to improve the lives of the millions of patients suffering from poorly controlled pain. Research studies began highlighting the efficacy of opioids for conditions such as low back pain and neuropathic pain such as postherpetic neuralgia, certain pharmaceutical companies heavily marketed the benefits of opioids for non-cancerous pain conditions,[5] and the government as well as healthcare institutions promoted the importance of pain care in the hospital setting. As the medical community began liberalizing the use of opioids, the number of adverse effects from their application also grew; that is, there was an alarming increase in opioid-related overdose deaths, and an escalation in opioid use disorder.[6] Many politicians and government officials have since shared the devastating consequences of opioids on human life. For instance, The Centers for Disease Control (CDC) indicated in a landmark 2016 publication that a quadrupling of deaths had occurred from opioids during the last 15 years, citing failed efforts on the part of healthcare providers to consider the addictiveness potential of opioids, their low therapeutic ratio, and a dearth of data on their effectiveness.[7]

Though the number of deaths associated with opioids is intolerably high, the narrative must also include the risk of death related to uncontrolled chronic pain. For example, the risk of suicide nearly doubles for those living with chronic pain compared to those without the disease.[8] Patients feel demoralized because they have lost their ability to work, socialize, or exercise. In short, they frequently feel that those pursuits in life that make it worth living have been snatched

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away from them. For instance, patients with persistent pain will not infrequently say that, "life as I knew it is over," or "I'll never be the same." Sadly, chronic pain is associated with the worst quality of life compared to other chronic conditions such as chronic heart, lung, or kidney disease.[9]

In this context, patients living with chronic pain require appropriate access to opioid therapy along with improved access to pain care and additional therapeutic options. It's both medically reasonable and ethical to consider opioid therapy as a treatment option in the management of chronic, non-cancer pain for a subset of patients with severe pain that is unresponsive to other therapies (e.g., injections, other medications, integrative strategies), negatively impacts function or quality of life, and will likely outweigh the potential harms. Let's examine opioid therapy in the setting of the opioid epidemic, why critics feel that the CDC guideline has resulted in harsh consequences for patients and their physicians,[10] and the rationale for opioid therapy as a means of providing ethical and compassionate pain care.

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According to the U.S. Department of Health, a staggering 42,249 people died of an opioid-related overdose in 2016.[11] Yet, it seems that this figure may overestimate opioid mortality due to *prescription* opioids because the U.S. Department of Health has also recently indicated that at least 60% of the overdose epidemic is caused by illicit drugs rather than prescription opioids (U.S. Department of Health and Human Services (HHS)).[12] Furthermore, additional data suggest that the escalation in opioid-related deaths is primarily a consequence of illicit fentanyl use; therefore, the number of actual prescription opioid deaths probably reflects a smaller percentage of the overall opioid overdose statistics.[13] The distinction between mortality from illicit opioid use and prescription opioid use becomes critical when designing public health policies to address the problem. That is, fixating on prescription opioids as a substantial contributing factor to unintentional overdose may misallocate resources needed to correct the problem. It makes sense to implement efforts that curb the non-medical use of opioids and target those at high risk for illicit use by improving methods of drug storage and disposal, ensuring access to medications for addiction treatment — agonist therapy (e.g., methadone, buprenorphine/naloxone — suboxone), and making naloxone widely available, for example. Some have argued against a prescription opioid crisis in the United States and instead describe the existence of a polypharmacy overdose crisis. Either way, the overprescribing of opioids began in the 1990's, lead to rising numbers of overdose deaths beginning in 1999, and contributed to the opioid crisis of today.[14] Empirical data do show, however that more than 50% of deaths with an opioid positive toxicology include alcohol, and the average number of drugs identified in mortality toxicologies is 6.[15] Further, a 2017 examination of opioid-related deaths in New Hampshire uncovers that 72% of the deaths from oxycodone included alcohol, a benzodiazepine, kratom, methamphetamine, or another prescription opioid.[16] Even the CDC's Division of Unintentional Injury Prevention notes that, "multiple drugs were involved in almost half of the drug overdose deaths that mentioned at least one specific drug on the death certificate" in 2014.[17] Therefore, a deeper analysis of the opioid crisis indicates that a single prescription opioid may not be leading to an overdose death for a given patient; rather, it's the combination of licit and illicit drugs that seems to be precipitating death. Interestingly, the American Medical Association has noted a 20% decrease in opioid prescriptions between 2013-2017, and between the earlier years of 2010-2015, there was an 18% decrease in the number of opioids prescribed, according to the CDC.[18] Notwithstanding the controversy over the cause of the opioid-related deaths, the healthcare community has clearly engaged in possible solutions by reducing opioid supply, accessing prescription drug monitoring programs throughout the country (to prevent patients from obtaining prescription opioids from multiple sources), and educating themselves on opioid use disorder (addiction) and methods of treatment.

With respect to classifying deaths from opioids in death certificate data, there seem to be multiple confounders as well. For example, toxicology data from death certificates do not distinguish among drugs that are pharmaceutically manufactured, pharmaceutically manufactured but diverted (not prescribed to the patient), illicitly manufactured, or prescribed by

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a healthcare practitioner.[19] Furthermore, out of the 42,249 opioid-involved deaths in 2016, the term "opioids" included prescription opioids such as oxycodone or morphine, illicit opioids such as illicitly manufactured fentanyl or heroin, or a combination of both prescription and illicit opioids. In recent years, illicitly manufactured fentanyl has become a major driver of opioid overdose deaths in multiple states, according to the CDC Morbidly and Mortality Weekly Report,[20] and illicitly manufactured fentanyl cannot be readily distinguished from prescription fentanyl in death certificate data either.[21] Identifying the actual cause of these deaths, therefore becomes complicated because multiple types of opioids are frequently involved and a growing number of synthetically manufactured, illicit opioids such as fentanyl cannot be detected in toxicologic testing. Fortunately, the CDC has allocated more funding to enhance the ability of toxicologic testing of opioid overdose deaths to identify a broader array of fentanyl analogs such as carfentanil and acetylfentanyl.[22]

Researchers from the CDC Division of Unintentional Injury Prevention point out that CDC statistics have included many deaths from illicit opioids such as heroin and fentanyl in their estimates of prescription opioid-related deaths.[23] Moreover, if these deaths include illicitly manufactured fentanyl and other synthetic opioids, both of which are contributing more significantly to overdose deaths, then perhaps the estimates of prescription opioid deaths are overinflated. If true, then public health measures such as the CDC guideline that target opioid prescribers and pain patients in an effort to restrict opioids, cap opioid doses, limit duration of opioid therapy, or mandate the use of prescription drug monitoring programs are misdirected. Determining an accurate count of the true heath burden of opioids, and distinguishing between prescription and illicit opioid–associated deaths are critical in implementing effective public health efforts as well as ensuring access to opioids for those who need them. There is no question that even one death from an opioid is too many, but if we examine a revised estimate of the death toll from *prescription* opioids that excludes synthetic opioids (tramadol, fentanyl) other than methadone in 2016, there were 17,087 deaths compared to the official number of 32,445 prescription opioid deaths, a 50% decrease.[24] This revised estimate removes synthetic opioid deaths other than methadone, "because of the high proportion of deaths that likely involve illicitly manufactured fentanyl," according to the CDC Unintentional Injury Prevention Division. Similarly, less than half of the opioid overdose deaths in 2015 (33,000) involved a prescription opioid (15,000).[25] Although the data indicate substantially fewer prescription opioid deaths during each one of these years, the total number of deaths remained high and demonstrated an acceleration of mortality from one year to the other.

The opioid crackdown has taken a toll of pain care. For instance, greater numbers of clinicians across the country, including oncologists/hematologists as well as the American Medical Association report that payers have applied the CDC guideline in a way that denies opioids, and requires extensive prior authorizations for patients with pain from cancer treatment, end-of-life care, and other non-cancer pain conditions such as sickle cell disease.[26] This is occurring despite the intent of the guideline aimed at primary care clinicians prescribing opioids for patients with chronic pain who are not engaged in active cancer treatment, palliative care, or end of life care. Drug enforcement policies have led to involuntary opioid tapers, patient abandonment, and practitioner flight, namely due to a fear of institutional, state, or federal government sanctions.[27] Some clinicians are deciding against the use of opioids for pain because they fear litigation by patients claiming iatrogenic addiction, or litigation by states or payers. The CDC guideline was not developed for pain specialists who treat complex pain patients and not intended to deny patients suffering from chronic pain the option of opioid therapy; however, the guideline has resulted in an arbitrary adoption by regulators and health care organizations. Consequently, there has been a reduction in opioid supply without an expansion of other resources for pain care, and this reduction has led some patients to the illicit opioid market with greater harm. [28] Indeed, the authors of the guideline admit that misapplication of the recommendations have led to harm due to abrupt opioid discontinuation and patient dismissal from clinical practices.[29] Moreover, they write that, "policies should allow clinicians to account for each patient's unique circumstances in making clinical decisions" which certainly adheres to more reasonable and ethical decision making.

There is an emerging sense that our ethics of pain care have diverged from compassionate, rational use of opioids to a swift restriction of access for patients genuinely needing them. Some have even questioned whether we are violating the "human right" to pain management.[30] For instance, many international bodies embrace the idea of a human right of access to pain management and argue that by limiting access to opioids, we deny a "right to access." Moreover, statements from United Nations human rights officials further assert that, "the failure to ensure access to controlled medicines for the relief of pain and suffering threatens the protection of persons from cruel, inhuman,

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and degrading treatment."[31] Clearly, the government is responsible for protecting its citizens from the potential harm related to opioid therapy which reflects the tenor of the CDC guideline: written in response to rising opioid overdose deaths, ensuring that physicians and patients consider non-opioid therapies, and mitigating against the risk of developing opioid use disorder (addiction). Unfortunately, the interpretation of the guideline has resulted in a strictly regulated environment that Brennan et al. argue, "…is an arbitrary restriction of access to opioids to patients who genuinely require them, which may constitute a violation of human rights."[32] Other commentators feel as though that claim may be too strong, noting that a right to managing pain may or may not include opioid therapy. One solution may be to ensure that patients with chronic non-cancer pain continue to have access to the World Health Organization's (WHO's) Essential Medication List (e.g., opioids, NSAIDS, muscle relaxants, antidepressants) while realizing that a right to pain relief does not imply a right to opioid therapy. For example, patients are not at liberty to say, "I have the right to opioids for managing my pain." Rather, they do have the right to a quality assessment of their pain, and the formulation of a treatment plan based on the best available evidence in concert with the clinician's experience and judgement.

Since the publication of the CDC guideline, there have been some unintended, adverse consequences. For example, pain specialists and oncologists/hematologists have noted that patients with chronic, non-cancer pain such as those with sickle cell disease or past cancer may be denied pain relief from opioid therapy.[33] Chronic pain can occur from multiple sources in sickle cell disease: recurrent, acute painful episodes of unclear etiology; avascular necrosis of the hips or shoulders; ischemia to nerves of the extremities or spinal cord inducing neuropathic pain; or episodes of breakthrough pain lasting seconds up to hours. Many patients will report that opioid therapy is needed to ease their pain and make life livable. Non-opioid therapies are simply inadequate. Further, if we examine the number of deaths from opioids compared to all-cause mortality in sickle cell patients from 1999-2013, we see that there were 95 deaths over a 14 year period.[34] That represents a 0.77% death rate. Although any death is one too many, sickle cell patients would probably argue against withholding opioid therapy from them based on 95 deaths spanning a 14 year period. This number of deaths is comparatively very small against the backdrop of the CDC's estimate of 47,600 opioid-related deaths in 2017. The quest to avoid the use of opioids in sickle cell patients unwittingly led to the death of a young mother in Las Vegas when she was given excessive doses of the non-steroidal anti-inflammatory drug (NSAID) ketorolac (Toradol) in the hospital to control her painful crisis.[35] The jury awarded her husband and daughter approximately $43 million in damages.

Restricting the appropriate use of opioids has the potential to hurt not only sickle cell patients, but patients with painful debilitating diseases. Patients with multiple sclerosis, Parkinson's disease, spinal cord injury, and amyotrophic lateral sclerosis (ALS) can experience substantial, enduring pain for which opioids serve as an important ally in managing a life without suffering. This also applies to a growing number of patients who are surviving HIV, cancer, and cardiovascular disease, but find themselves in continual pain from the disease itself, nerve damage from the disease, or interventions needed to treat the disease such as surgery, chemotherapy, or radiation therapy.[36] In contrast to one of the recommendations put forth by the CDC guideline,[37] physicians treating patients with these chronic, non-cancer pain conditions cannot expect functional improvement to occur as a requisite of continual opioid therapy. It may be a reasonable expectation for subsets of these patients, but not for all of them.

Compared to other medications used for pain control, opioids may be a safer option. For example, there can be multiple adverse effects of NSAIDS; namely, nephrotoxicity, gastrointestinal bleeding, cardiotoxicity, and coagulation abnormalities. In fact, the American Geriatrics Society Panel (AGS) on the pharmacological management of persistent pain in older persons only recommends NSAIDs, "with extreme caution", due to the physiological changes associated with aging that predispose older adults to an elevated risk of NSAID side effects.[39] Furthermore, many non-selective NSAIDs (e.g, ibuprofen, naproxen, meloxicam) appear on the American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults along with many other non-opioid medications often prescribed for pain including the tricyclic antidepressants, serotonin-norepinephrine reuptakes inhibitors, and muscle relaxants.[40] Other than recommending to minimize the number of central nervous system drugs when using opioid analgesics, the only opioids the AGS suggests avoiding include meperidine and pentazocine, or tramadol with patients with varying levels of kidney dysfunction.[41] Citing low quality evidence with a strong recommendation, the AGS Panel does say that all patients with moderate to severe pain, functional impairment, or reduced quality of life should be considered for opioid therapy.[42] Similar to the AGS Panel, the British Geriatric Society indicates that,

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"opioids may be considered for patients with moderate to severe pain, particularly if the pain is causing functional impairment or is reducing their quality of life" in their guidance document on the management of pain in older people.[43] They add that this therapy must be customized and carefully monitored. Older adults need meaningful and safe pharmacological and non-pharmacological therapy, especially since pain is highly common, costly, and frequently disabling for this population. Specifically, hospitalization, chronic diseases, and surgery all occur at higher rates in older adults, which elevate their risk for developing pain.[44] As a matter of fact, 20% of the population will reach or exceed age 65 by 2030,[45] making pain management in older adults an emerging public health concern.

Diminishing the large burden of suffering from pain while containing the harm associated with opioid medications remain a challenge for regulatory agencies. Understanding the breadth and depth of the chronic pain problem is at the forefront of formulating effective solutions, however. As clinical awareness intensifies on the appropriate and more specific use of opioids for pain, the medical community has curtailed the proliferation of these medications as a first line therapy. Furthermore, patients and healthcare provides alike are better understanding the benefits of non-opioid medications, procedural interventions, and integrative treatments in the management of chronic pain.[46] Some authors are providing countering perspectives on the risks of opioid therapy, hoping to persuade regulators and clinicians that opioids should remain an option for pain care.[47] For example, in contrast to the idea that a large percentage of patients who are prescribed opioids die of an overdose, there are data demonstrating that the rate of opioid-related deaths in patients prescribed opioids is as low as 0.02%.[48] Moreover, prescription opioid use disorder (OUD) has been linked to extended-release opioids, prompting insurers to require prior authorization or triggering a complete denial. One study however supports a longer held clinical belief that most patients with OUD prefer immediate-release rather than extended-release opioids.[49] It's clear, nonetheless that concurrent use of opioids with benzodiazepines substantially elevates the risk of overdose, even at lower doses,[50] and data from the American Association of Poison Control Centers demonstrate that the use of multiple substances leads to most opioid-related overdoses.

A number of studies conclude that opioids offer few benefits and pose a substantial risk of abuse, diversion, or OUD, i.e, addiction. Consequently, the natural action in response to the opioid crisis has been to limit prescribing. There is evidence to counter the assumption that opioids are leading chronic pain patients to addiction and overdose deaths, however. For instance, Fishbain et al. reviewed 67 studies on addiction and opioid use and found a 3.27% risk of addiction among chronic pain patients while a Cochrane review reported an incidence of 0.5% of de novo addiction with a prevalence of 4.5%.[51] Further, the director of the National Institute of Drug Abuse, Dr. Nora Volkow has stated that, "addiction occurs in a small percentage of people exposed to opioids — even with pre-existing vulnerabilities."[52] Interestingly, a recent study demonstrated a low risk of OUD by prescreening patients prescribed opioids in a primary care setting.[53] Although these published rates of addiction are low, other studies indicate that over 20% of patients using opioids for chronic pain meet DSM 5 criteria for OUD.[54] Despite the conflicting data, no patient is at zero risk for abuse or OUD; therefore, clinicians should continue to implement risk mitigation strategies such as opioid questionnaires, history taking, prescription drug monitoring programs, and urine or oral fluid drug monitoring.

The CDC guideline pointed out that the evidence base for chronic opioid therapy is poor. For example, the duration of most randomized controlled trials (RCTs) is often 6 weeks or less, there is no comparative, long-term data on opioids compared to other treatments for pain, function, or quality of life, and several studies conclude that opioids may worsen pain and function. Actually, there are very few, if any RCTs greater than 12 weeks. Even a large meta analysis on the effectiveness and side effects of opioids that included 41 randomized trials and over 6,000 patients with chronic, non-cancer pain had an average trial duration of just 5 weeks, with a range of 1-16 weeks.[55] Weak opioids (e.g, codeine, tramadol) and strong opioids (e.g, morphine, oxycodone) were studied in patients with nociceptive pain (e.g, osteoarthritis, rheumatoid arthritis, low back pain), neuropathic pain (e.g, postherpetic neuralgia, diabetic peripheral neuropathy, phantom limb pain), fibromyalgia, and mixed pain. The authors did determine that, "opioids were more effective than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain, or fibromyalgia." The average trial duration is short which makes both estimates of long-term efficacy difficult as well as the potential for adverse effects. However, critics argue that the FDA doesn't require a study duration of more than 12 weeks due to high placebo dropout rates, and that several 52 week open label studies of extended release/long acting opioids do show benefit and safety.[56] Of note, the pharmaceutical industry funded the majority of the studies included in this meta-analysis, raising the question of possible publication bias. When delving into the evidence base for

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the pharmacological treatment of neuropathic pain specifically, a systematic review and meta-analysis of 229 studies found a lower NNT for strong opioids and tramadol among other medications compared to gabapentinoids and SNRIs, but both opioids and tramadol received a weak recommendation as a second and third line agent respectively after considering the risk of abuse, and increases in prescription opioid-related deaths, diversion, and misuse.[57] However, one RCT comparing controlled release morphine to nortriptyline and placebo in patients with postherpetic neuralgia, a neuropathic pain condition found more effective pain reduction, a trend toward a lower NNT, and stronger patient preference for the opioid medication.[58] Taken together, the evidence reminds practitioners to consider opioid therapy when necessary in select patients, at the lowest effective dose, and to assess regularly for possible harms.

Pain touches all of us at some point during our lives. It may affect us as infants or children, but more likely as adults. If we have escaped its influence during those phases of life, then it may weigh us down as older adults, from cancer, or at the end of life. Opioids can help reduce human suffering for those with legitimate need. These certainly include patients with cancer pain or in palliative care settings, and equally important are patients enduring chronic, non-cancer pain that is severe, inadequately responsive to other therapies (e.g., injection therapies, other medications, neuromodulation, integrative treatments), or adversely affects their function or quality of life.It is reasonable to consider opioids when pain cannot be controlled otherwise, and when their benefits will likely outweigh any potential harms. Physicians and other healthcare providers must be aware of the hazards of high dose prescribing, polypharmacy, the risk of OUD, and the array of existing traditional, innovative, and integrative treatments when considering an opioid for managing pain.

It appears that the opioid crisis is shifting from a preponderance of overdose deaths due to prescription opioids, then heroin, and now to illicitly manufactured fentanyl. For instance, the CDC reports that the quantity of prescribed opioids have consistently decreased since 2010 while opioid overdose deaths have risen.[59] Furthermore, illicit opioid use is projected to escalate by 61% between 2015-2025,[60] prompting a dire need for the mobilization of public health interventions to address the epidemic. The provision of naloxone to reverse opioid overdoses, and the broader availability of agonist treatments such as buprenorphine, buprenorphine and naloxone (suboxone), and methadone reflect important strategies for combatting illicit and prescription opioid abuse alike. Additional, multifaceted measures must be implemented, though in order to alter the course of the crisis. For example, reducing the supply of prescription opioids is projected to have a modest effect on opioid overdose deaths based on the findings of two recent studies,[61] although Pitt et al. predict that gradually reducing prescription opioid use will yield health benefits such as lowering mortality in the long term.[62] In the short term, interventions geared toward lowering prescription opioid misuse are projected to decrease overdose deaths by only 3.0% – 5.3%.[63]

Multiple efforts to stem the opioid crisis are underway. They range from preventing exposure to prescription opioids by curbing the supply to mitigating possible harm from the drug itself by introducing abuse-deterrent formulations (ADF), expanding access to naloxone, and broadening the availability of agonist treatments. Economic modeling data suggest that ADF offer the potential to substantially reduce the incidence of abuse (IV or intranasal) in chronic pain patients, but at a significantly higher cost.[64] Further research is required to support the beneficial heath and economic impact of ADF on the opioid crisis at this time, although some states now require insurers to provide coverage for a least one ADF.[65] The Opioid Crisis Response Act proposes multidimensional approaches to the crisis by changing opioid packaging to limit overprescribing, encouraging safe disposal systems to prevent diversion, expedit-

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ing FDA approval for novel non-opioid therapies, and increasing NIH flexibility for approving cutting-edge research addressing the opioid crisis.[66]

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Note

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