The current state of the global opioid crisis.

AS OPIOID MISUSE BECOMES A GLOBAL EPIDEMIC, REAL-WORLD EVIDENCE MAY HELP TO INFORM TREATMENT GUIDELINES SO AS TO ACHIEVE SAFER AND MORE EFFECTIVE PRESCRIBING BEHAVIORS, ESPECIALLY IN CHRONIC PAIN SUFFERERS.

By Michele Cleary

INTRODUCTION

The pernicious opioid crisis is rapidly spreading worldwide. As stakeholders are taking bold steps to contain this epidemic, approximately 27 million people globally are suffering from opioid use disorders.[1] Paradoxically, efforts designed to stem the epidemic's growth may now be fueling its spread. Chronic pain sufferers, faced with firm prescription limits, are finding relief with illicit opioids, while regulations are pushing opioid manufacturers into previously under- supplied markets in developing nations.

Between the overuse of prescription opioids and the worsening spread of illicit opioids, we are facing a global health crisis. As policy makers, clinicians, and other stakeholders initiate new treatment guidelines, laws, and regulations, health economics and outcomes research (HEOR) professionals must consider how we can contribute to the search for solutions to ensure ethical pain management for those in need.

OPIOIDS AS PROACTIVE PAIN MANAGEMENT

The opioid crisis began in the 1990s, stemming from a legitimate concern that many patients were living with unacceptable levels of pain. In the United States, The Joint Commission—formerly The Joint Commission on the Accreditation of Healthcare Organizations or JCAHO—characterized pain as the "fifth vital sign." Medical and patient associations advocated for a more proactive approach to pain management, encouraging broader use of opioids for pain management to address the epidemic of untreated pain.[2]

These changes in the perception of pain management coincided with the release and intensive promotion of OxyContin (oxycodone). Equipped with only minimal pain management training, many providers began prescribing opioids beyond palliative care to patients with chronic, nonmalignant pain, despite a lack of supporting evidence of their effectiveness.[3] ›

These conditions fostered a flurry of opioid prescribing. Between 1991 and 2009, the number of opioid prescriptions filled in the United States tripled, reaching prescribing levels sufficient to medicate every citizen continuously for a month. In 2014, opioids became the most frequently prescribed medications in the United States, making the country the global leader in prescription opioid use, consuming 80% of the global supply of opioids, despite accounting for less than 5% of the world's population.[4]

THE SHORT PATH FROM PRESCRIPTION OPIOID USE TO MISUSE AND ABUSE

As has been well documented, rampant prescription opioid use often leads to opioid misuse and abuse of prescription—and sometimes illicit—opioids. Up to a quarter of long-term prescription opioid users treated for chronic nonmalignant pain battle opioid addiction, often leading to future illicit opioid use and overdose.[5]

This descent into illicit drug use is often based in misguided attempts to manage pain. In a 2014 survey of people undergoing treatment for opioid addiction, 94% of respondents said they turned to heroin because prescription opioids were more expensive and harder to obtain.[6]

THE STAGGERING HUMAN COSTS OF THE OPIOID CRISIS IN THE UNITED STATES

The costs of opioid misuse and abuse have been staggering. Since 2000, more than 600,000 Americans have died from opioid-related drug overdoses, eclipsing the total number who died in World Wars I and II combined. In 2016 alone, 42,000 Americans—an average of 116 every day—died from opioid overdose.[7] Roughly half of these deaths involved a prescription opioid. Yet as staggering as these totals are, opioid-related overdose deaths may be dramatically undercounted. Some have suggested that the actual number of opioid-related deaths may be 24% higher than previously reported.[8]

Even with possible undercounting, "opioid overdose" has become the leading cause of accidental death in the United States, contributing to a drop in life expectancy for the third year in a row. This marks the first time that this country has witnessed a three-year continuous drop in life expectancy since the early 20th century when the nation was in the throes of World War I and the Spanish Flu epidemic of 1918.[9]

Beyond the pain and suffering stemming from opioid misuse, the economic costs have been monumental. The White House Council of Economic Advisers places the economic burden of opioid misuse at more than $500 billion, roughly 2.8% of gross domestic product.[10]

THE EPIDEMIC SPREADS

Rampant opioid misuse is now plaguing Canada, Australia, and parts of Europe.

Canada is now the world's second largest per capita consumer of prescription opioids. The number of prescriptions written for oxycodone increased in Canada by 850% between 1991 and 2007. And as with the United States, the aggressive prescribing of opioids has led to skyrocketing rates of opioid misuse and abuse. In 2017, nearly 4000 Canadians died as a result of opioids, a 34% increase over the year prior.[11]

Data from Safescript show that in Europe, roughly three-quarters of the continent's 1.3 million high-risk opioid users reside in 1 of 5 countries: Germany, Spain, France, Italy, and the United Kingdom.[12] Prescription rates in Germany have risen to nearly the Canadian level, while the number of opioids prescribed in the United Kingdom doubled between 2006 and 2016. And in Australia, the number of OxyContin prescriptions nearly quintupled between 2001 and 2013.[12]

REINING IN AN EPIDEMIC

Stakeholders worldwide are scrambling to control this health crisis. From the United Nations Office on Drugs and Crime (UNODC) and the European Union Drug Strategy to the US Food and Drug Administration's (FDA) Opioid Policy Steering Committee and the Canadian Drugs and Substances Strategy, regulatory bodies worldwide have all introduced multipronged initiatives to combat the opioid crisis, including strategies designed to prevent new addictions, treat opioid use disorder, develop new pain therapies, and improve drug enforcement.

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Other strategies include the Lancet Commission, which recommended closer monitoring of opioid marketing and restrictions on direct marketing of opioid medications to healthcare providers by pharmaceutical companies. And both the FDA and the European Medicines Agency have approved antideterrent formulations.

GROWING CONTROVERSY SURROUNDING OPIOID PRESCRIBING LIMITS

Many physicians have reported feeling that their pain management training has been insufficient to manage pain effectively.[14] In 2016, the US Centers for Disease Control (CDC) released their Guideline for Prescribing Opioids for Chronic Pain to help practitioners deliver ethical and effective pain management for their chronic pain patients.[15] These guidelines joined the World Health Organization (WHO) Cancer Pain Ladder in recommending nonopioids as first-line therapy for patients suffering from chronic pain; both recommended strong opioids only as other nonopioids failed to control pain.

Yet across the United States, state and federal governing bodies have incorporated these pain management guidelines into more concrete prescription limits, taking more aggressive action to minimize patient exposure to opioids and flag possible over-prescribers. Laws in more than half of US states limit acute pain sufferers to only 3 to 7 days of prescription opioids, regardless of the severity of their surgery or injury. Some payers, pharmacy benefit managers (PBMs), and major pharmacy chains also have adopted mandatory restrictions on the opioid prescriptions they will fill, often requiring prior authorizations before filling opioid prescriptions. And on January 1st of this year, Centers for Medicare and Medicaid Services initiated new prior authorization

rules for Medicare that trigger reviews for prescriptions over 200 mg MME (morphine milligram equivalents).

These limits may have contributed to reductions in opioid prescribing rates, which in the United States have fallen to their lowest rates in a decade. However, this trend appears to be due to fewer acute pain prescriptions being filled, as the average number of days supplied increased from 13.3 in 2006 to 17.7 in 2015.[15]

ARE OPIOID PRESCRIBING POLICIES ABANDONING CHRONIC PAIN PATIENTS?

But formalizing opioid prescribing guidelines into strict dosing limits may be jeopardizing the well-being of patients most in need—those in the grips of chronic pain. In the United States alone, approximately 18 million chronic pain sufferers are currently prescribed opioids. While some chronic pain sufferers may be treated effectively within current limits or by using nonopioid therapies, others find that their pain requires more aggressive treatment beyond what many prescription limits allow.

More flexible prescribing limits are needed, as well as better guidance regarding opioid tapering and opioid avoidance. Ideally, guidelines would also address the psychological reluctance felt by patients and providers to accepting opioid reductions.

MEANWHILE, ILLICIT MARKETS GROW

These rigorous dosing limits often treat chronic opioid users as opioid abusers, stigmatizing those patients for whom prescription opioids are both necessary and medically appropriate. Many chronic pain sufferers—even those suffering from malignant pain—fear that opioid prescription limits will lead to the resurgence of uncontrolled pain.[16]

Facing increasingly restricted access to their opioid prescriptions, some chronic pain sufferers are turning to illicit opioids, such as heroin. The illicit market is booming, filled by the rapid proliferation of highly potent, inexpensive synthetic opioids, such as fentanyl or its analogs. Between 2010 and 2016, the United States observed a 546% increase in overdose deaths from synthetic opioids (mostly fentanyl).[18] Meanwhile, fentanyl-related deaths are becoming increasingly common in Canada and across Europe.[11,13]

The fact that in 2018, so many people lack access to the medicines they need while in other parts of the world, the oversupply, aggressive marketing, and excessive prescription practices has led to a fatal opioid overdose crisis is one of the major paradoxes we face. We must find ways of doing better.

REGULATORY PRESSURE PUSHING OPIOIDS INTO NEW MARKETS

The increasingly regulated market for prescription opioids has pushed some opioid producers to other global markets, such as Latin America, Asia, or North Africa—regions that have historically suffered from insufficient access to pain therapies.[19] The global gap in effective pain management and access to prescription opioids has long been an area of concern. Per capita medicinal opioid consumption in many of these regions is far below the International Narcotics Control Board's minimum global standard to meet citizens' palliative care needs (of 200 daily doses per million inhabitants per day). This dearth of effective pain management has led to calls by the United Nations to increase access to opioids for pain management in certain low- and middle-income countries.[19]

In the face of such minimal access to effective pain treatments, pain sufferers throughout these new markets have been highly receptive to new prescription opioids. Prescription opioid sales in Brazil increased 465% between 2009 and 2015. Even China, despite a long, bitter history with opium, is seeing a rapid rise in the number of prescriptions for opioids to treat pain.

RESISTANCE TO THE USE OF GUIDELINES GROWS

This past fall, members of the American Medical Association (AMA) House of Delegates approved a resolution advocating against inappropriate use of the CDC opioid prescribing guidelines for chronic pain. Delegates noted the dangerous impact of some opioid regulations.

The 2017 AMA Prior Authorization Physician Survey found over 90% of doctors believed that limits on prescription days/dosages and prior authorizations negatively impacted patient outcomes. Since the release of the CDC guidelines, chronic pain sufferers are reporting increasing difficulty filling their opioid prescriptions due to these mandated restrictions. Some patients have reported being abandoned by their treating physicians who fear regulatory reprisal for prescribing opioids.

The resolution formally pushes back against the misapplication of the CDC's guideline by regulatory bodies, state medical boards, pharmacists, PBMs, insurers, and others. The resolution argues that the dosage guidance should not be used as a rigid dosage limit or mandate. Some patients require doses higher than those recommended by the CDC guidelines. Furthermore, the resolution asserts that flagging physicians for suspect prescribing—subjecting these providers to potential sanctions—does a tremendous disservice to many chronic pain sufferers by disincentivizing these providers from caring for these patients.

In November 2018, a letter published in *Pain Medicine* expands upon the AMA resolution by suggesting that the risks associated with forced tapering of opioids may do more harm than good.[23] Members of the International Stakeholder Community of Pain Experts and Leaders noted that rapid forced tapering off opioids can destabilize patients, leading to worsening of pain, severe loss of function, and crippling withdrawal symptoms. In the letter, the authors strongly petition for more realistic treatment guidelines that avoid "aggressive and unrealistic" dosing goals.

NEXT STEPS

With persistently high rates of opioid prescribing worldwide, rising nonmedical prescription opioid use, and global opioid market diversification (including the emergence of high-potent, synthetic opioids), a pressing need exists for well-informed policies to prevent further expansion of this opioid epidemic. This will require a thoughtful and coordinated approach focused

not only on evidence-based supply reduction strategies (eg, safer prescribing, curtailment of prescription industry influence), but also on the need for dramatic efforts to implement and scale up public health and addiction treatment interventions globally.

More opioid prescribing guidelines are on the horizon. In October 2018, President Trump signed the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment Act into law, providing additional support to the FDA's current efforts to promote the development of evidence-based opioid prescribing guidelines for treating acute pain resulting from specific conditions or procedures. The FDA enlisted the support of the National Academies of Sciences, Engineering, and Medicine to develop these guidelines by reviewing existing opioid analgesic prescribing guidelines, identifying potential gaps in evidence that informed those guidelines, and specifying any additional research needed to fill these gaps in evidence gaps.

HEOR research will be critical to ensuring that North America's opioid emergency does not foreshadow a global crisis. Real-world evidence (RWE) combined with sound public health policy research can help us learn from past mistakes while informing future steps. Evidence-based guidelines can lead to more appropriate opioid prescribing behavior. Equipped with sound RWE research, stakeholders can develop evidence-based policies to ensure pain patients receive the treatment best suited to their needs—be it an opioid or a non-opioid alternative.

Much rests on these new approaches. As Dr. Viroj Sumyai, president of the United Nations International Narcotics Control Board, reiterated during the Commission on Narcotic Drugs meeting in November 2018:

The fact that in 2018, so many people lack access to the medicines they need while in other parts of the world, the oversupply, aggressive marketing, and excessive prescription practices has led to a fatal opioid overdose crisis is one of the major paradoxes we face. We must find ways of doing better.

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