

Opioids as part of responsible pain management: a global crisis of extremes

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Abstract

The global landscape of opioid therapy presents a seemingly paradoxical duality: simultaneous over-use in high-income nations and under-access in low- and middle-income countries (LMICs). Despite decades of clinical experience and regulatory evolution, opioids remain among the most consequential, but controversial, drug classes in modern medicine. Responsible use requires an understanding of pharmacology, risk stratification, regulatory frameworks, and the sociocultural determinants that shape prescribing behavior across diverse international healthcare systems. This narrative review synthesizes peer-reviewed literature, World Health Organization (WHO) guidelines, Centers for Disease Control and Prevention (CDC) prescribing recommendations, and publicly available epidemiological data published through 2025. Sources were identified through PubMed, MEDLINE, and targeted reference searches. Evidence was evaluated with attention to clinical applicability across both resource-rich and resource-limited settings. Opioids, when prescribed judiciously for the right indication within a multimodal, comprehensive care framework, remain essential for the management of pain unresponsive to non-opioid therapies. The CDC Morphine Milligram Equivalent (MME) framework provides guideline thresholds for overdose risk stratification. At the same time, global opioid access disparities are severe: several billion people worldwide lack adequate pain relief, and less than 10% of global medical opioids reach the 80% of the world's population residing in LMICs. Multifaceted barriers – including opiophobia, regulatory complexity, shortcomings in governmental support systems, cross-border illicit fentanyl related deaths, and cultural factors – perpetuate both overuse in affluent nations, and under-use in LMICs. Opioid therapy in 2026 and beyond demands a nuanced, evidence-based approach that simultaneously addresses the risks of misuse and the moral imperative of adequate pain relief. Clinicians, health systems, policymakers, and professional societies should collaborate to build prescribing cultures grounded in the MME framework, multimodal care integration, and equitable global access. Ongoing education, regulatory modernization, and international collaboration are needed.

Key words: opioids; pain management; morphine milligram equivalents; WHO analgesic ladder; opioid access; global health; opioid use disorder; responsible prescribing.

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Introduction

Opioids occupy a singular and contested position in the pharmacotherapeutic armamentarium. No other class of analgesics approaches their efficacy – yet no other class has generated a more complex web of clinical, regulatory, public health, and ethical concerns.¹ As of 2026, the global opioid landscape is shaped by two simultaneous and seemingly contradictory crises that together define the central challenge of contemporary pain medicine. In high-income nations, particularly the United States, the legacy of well-meaning medical intent, but less well-meaning overly-aggressive opioid promotion in the late 1990s and early 2000s aided a public health crisis characterized by opioid use disorder (OUD), diversion, and overdose deaths.² Regulatory responses, including increasingly restrictive prescribing guidelines, prescription drug monitoring programs, and pharmacy dispensing limitations, have reshaped clinical practice – though they have also produced unintended consequences, including undertreatment of

legitimate pain and a shift to illicit synthetic opioids such as illicitly manufactured fentanyl (IMF).³ In stark contrast, low- and middle-income countries (LMICs) – which collectively account for more than 80% of the world's population – receive less than 10% of global medical opioid supplies.⁴ An estimated 5.5 billion people worldwide lack adequate access to pain relief, including patients with cancer, surgical conditions, trauma, and terminal illness who die in unmanaged pain.⁵ The barriers are systemic: overly restrictive regulations modeled on high-income nation frameworks without the accompanying prescribing infrastructure, inadequate prescriber training, bureaucratic procurement barriers, medication affordability challenges, and deeply ingrained cultural opiophobia among both providers and patients. This duality demands a globally informed, evidence-based response that simultaneously addresses the risks of overuse and the moral imperative of adequate pain relief. The purpose of this narrative review is to provide clinicians, pharmacists, policymakers, and educators with a current, comprehensive primer on opioid therapy

in 2026 and beyond – encompassing pharmacological classification, risk stratification using the Morphine Milligram Equivalent (MME) framework, the WHO Analgesic Ladder and its updates, practical prescribing strategies, and the barriers and opportunities for more equitable global access.⁶

Methods

This narrative review was developed by an interdisciplinary author group with recognized expertise in clinical pharmacology, pain medicine, anesthesiology, pharmaceutical regulation and compliance, addiction medicine, epidemiology, and public health. The methodological approach was designed to ensure a rigorous, transparent, and reproducible narrative synthesis while preserving the interpretative flexibility that characterizes high-quality narrative reviews. The preparation and reporting of the manuscript were therefore informed by the principles of the Scale for the Assessment of Narrative Review Articles (SANRA), which provides a structured framework for methodological transparency, literature justification, scientific reasoning, and balanced interpretation in narrative reviews.

A structured literature search was conducted in the electronic databases PubMed/MEDLINE to identify relevant publications addressing opioid prescribing practices, opioid misuse, opioid-related harms, and contemporary approaches to safe and individualized pain management. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords using Boolean operators. The principal search terms included: “opioid analgesics,” “opioid prescribing,” “opioid misuse,” “opioid use disorder,” “opioid stewardship,” “morphine milligram equivalents,” “opioid prescribing guidelines,” “WHO analgesic ladder,” “pain management,” “multimodal analgesia,” “opioid-induced hyperalgesia,” “opioid risk stratification,” “prescription drug monitoring programs,” “global opioid access,” “opioid epidemic,” and “opiophobia.” Additional searches were performed using combinations of these terms to improve sensitivity and identify emerging themes not adequately indexed within MeSH terminology. The search strategy prioritized peer-reviewed publications written in English and focused primarily on studies, reviews, consensus statements, and policy documents published within the last 10 years, while allowing inclusion of older landmark studies and historically relevant publications considered foundational to the understanding of opioid pharmacology, cancer pain management, and the evolution of opioid stewardship concepts. Particular attention was devoted to high-quality evidence sources, including randomized controlled trials, large observational studies, systematic reviews, meta-analyses, expert consensus statements, and evidence-based clinical practice guidelines. To enhance methodological robustness and minimize selection bias, the review process followed a staged narrative synthesis approach. Initially, titles and abstracts identified through database searching were independently screened by members of the author group according to relevance to the predefined thematic domains of the manuscript. These domains included: i) epidemiology of opioid prescribing and misuse; ii) disparities in global opioid access; iii) opioid pharmacology and dose standardization; iv) morphine milligram equivalent limitations and controversies; v) opioid-related adverse events and misuse risk factors; vi) opioid stewardship strategies; vii) multimodal and opioid-sparing analgesia; and viii) public health implications and future policy directions. Full-text assessment was subsequently performed for studies

considered highly relevant to the conceptual framework of the review.

Given the narrative nature of the manuscript, formal quantitative meta-analysis and statistical pooling were not performed. Similarly, no formal risk-of-bias scoring tool was systematically applied, as the primary objective of the review was interpretative synthesis rather than quantitative evidence aggregation. Nevertheless, the authors critically appraised the methodological quality, scientific credibility, and contextual relevance of the included literature during manuscript development. Greater interpretative weight was assigned to studies with robust methodology, adequate sample size, multicenter design, validated outcome measures, and strong external validity. International guideline documents and regulatory recommendations were retrieved from authoritative institutional sources, including the World Health Organization, the Centers for Disease Control and Prevention, the Food and Drug Administration, the International Association for the Study of Pain, and other relevant professional societies involved in pain management and addiction medicine. Epidemiological and surveillance data were derived from publicly available national and international databases and institutional reports addressing opioid consumption trends, overdose mortality, prescribing practices, and healthcare utilization.

To improve completeness and contextual integration, the reference lists of all selected articles and guidelines were manually screened for additional relevant publications not captured during the primary electronic search. Citation tracking and targeted searches were additionally employed for controversial or evolving topics, including opioid dose thresholds, opioid tapering strategies, opioid-induced hyperalgesia, and the balance between opioid accessibility and misuse prevention. The final manuscript was developed through iterative interdisciplinary discussion among all authors, with emphasis on maintaining scientific balance, minimizing ideological bias, and integrating clinical, pharmacological, ethical, and public health perspectives. The authors specifically sought to contextualize opioid misuse within the broader framework of appropriate pain management, recognizing the coexistence of two major global challenges: opioid-related harm in regions characterized by excessive prescribing and inadequate access to essential analgesics and related harm in many low- and middle-income countries.

Opioid pharmacology and classification

Opioids are most commonly classified by their origin: natural, semi-synthetic, or synthetic. Natural opioids such as morphine and codeine (‘opiates’) are derived directly from the latex of the opium poppy (*Papaver somniferum*). Morphine, first isolated in 1804, remains the reference standard against which other opioids are measured, and is designated as an essential medicine by the WHO.⁷ Codeine, a mainly prodrug requiring CYP2D6-mediated conversion to morphine, has variable analgesic efficacy and significant safety concerns in CYP2D6 ultra-fast metabolizers.

Semi-synthetic opioids such as hydrocodone, hydromorphone, oxycodone, and oxymorphone are produced by chemical modification of natural opioid precursors, typically morphine or thebaine, and thus have similar chemical structures to morphine. This class was much of the ‘first wave’ opioid epidemic in the United States.⁸ Buprenorphine, a partial agonist with high mu-receptor affinity and a ceiling effect on respiratory depression, occupies a unique

position as both an analgesic and a cornerstone of OUD treatment pharmacotherapy.

Synthetic opioids such as methadone, meperidine, tramadol, tapentadol, and fentanyl are fully synthesized without natural plant-derived precursors. Fentanyl, approximately 100 times more potent than morphine, has legitimate medical applications in anesthesia and cancer pain, but has become the dominant agent in illicit overdose deaths. Illicitly manufactured fentanyl (IMF) and its analogs (e.g., acetylfentanyl, carfentanyl) now account for the majority of opioid overdose fatalities in the United States.³ Methadone's complex and non-linear pharmacokinetics, including a highly variable half-life and the potential for QTc prolongation, require specialist expertise for safe use in pain management.

Opioids are further classified by their affinity and intrinsic activity (efficacy) at opioid receptors, of which three primary subtypes have been characterized: μ (mu, MOR, MOP), δ (delta, DOR, DOP), and κ (kappa, KOR, KOP).^{7,9} Full agonists such as morphine, hydromorphone, oxycodone, methadone, and fentanyl maximally activate μ -opioid receptors at less than full receptor occupancy, but lack a ceiling on respiratory depression risk. Partial agonists such as buprenorphine have less intrinsic activity at μ -receptors, but have a desirable ceiling effect on respiratory depression, conferring a more favorable safety profile. Mixed agonist-antagonists such as butorphanol, nalbuphine, and pentazocine have a more complex receptor binding and efficacy profile.¹⁰

The role of opioids

The clinical evidence supporting opioid therapy for specific pain conditions remains robust, even as the landscape of appropriate use has been substantially refined. For moderate to severe acute pain such as postoperative pain, trauma pain, and cancer pain, opioids provide effective analgesia when non-opioid therapies are insufficient. In palliative care and end-of-life settings, opioids are irreplaceable for achieving adequate comfort and maintaining dignity.¹¹ For cancer-related pain, the evidence base is extensive, and the WHO essential medicines list includes oral morphine as the cornerstone of Step 3 analgesia. The role of opioids in chronic non-cancer pain (CNCP) is more nuanced and contested. Systematic reviews have demonstrated that opioids provide modest short-term reductions in pain intensity for CNCP, but long-term benefit on functional outcomes remains less well established.¹² The 2022 CDC Clinical Practice Guideline for Prescribing Opioids reflects this evidence base, recommending that clinicians carefully weigh the benefits and risks, maximize non-opioid therapies, and when opioids are used, prescribe the lowest effective dose for the shortest appropriate duration.¹³ Contemporary evidence and opinion strongly prefer the integration of opioids within a multimodal analgesic framework rather than as monotherapy. Combining opioids with non-opioid analgesics such as acetaminophen (paracetamol), NSAIDs, and gabapentinoids produces additive or synergistic analgesic effects, allowing lower opioid doses and reduced side-effect burden.¹⁴ Physical therapy, cognitive-behavioral therapy (CBT), mindfulness-based interventions, and procedural approaches (nerve blocks, spinal cord stimulation) each address pain through distinct mechanisms and contribute to durable functional improvement. This approach is reflected in the 2018 WHO Guidelines, which explicitly foreground non-pharmacologic options and emphasize multimodal therapy integration.⁶

Morphine milligram equivalents: risk stratification in practice

Morphine milligram equivalents (MME) provide a standardized metric for converting doses of different opioid medications to a common morphine-equivalent value, enabling consistent assessment of total opioid exposure and overdose risk across formulations and agents. The CDC defines MME as: Strength per Unit $\times$ Number of Units per Day $\times$ MME conversion factor.¹⁵ Morphine serves as the reference standard (conversion factor = 1.0), and all other opioids are expressed relative to it.¹³ The clinical utility of MME extends beyond individual dose comparisons. It enables monitoring of total opioid burden in patients receiving multiple opioid medications, facilitates communication among prescribers and pharmacists, supports prescription drug monitoring program analytics, and provides a defensible standard of care benchmark in medicolegal contexts. The MME framework has been incorporated into state prescription monitoring programs, clinical decision support tools, and quality metrics across health systems in the United States. The 2022 CDC Clinical Practice Guideline establishes three clinically significant MME thresholds that define escalating 'risk zones' for overdose:¹³

- Lower risk zone (<20 MME/day): consistent with baseline overdose risk. Appropriate for initial opioid therapy and most acute pain scenarios, with emphasis on non-opioid alternatives when feasible.
- Caution zone (20-50 MME/day): overdose risk increases beyond baseline. The guideline recommends careful benefit-risk reassessment, consideration of dose reduction strategies, and enhanced patient education regarding overdose risk and naloxone availability.
- High risk zone (≥ 50 MME/day): overdose risk is at least double that of doses below 20 MME/day. Prescribers should avoid this threshold unless risk-benefit analysis strongly favors continuation, and must implement enhanced monitoring that includes frequent follow-up visits, naloxone co-prescription, and urine drug screening.
- Extreme risk zone (≥ 90 MME/day): the CDC recommends avoiding this dose range except in exceptional situations such as cancer pain, and palliative and end-of-life care, where specialist consultation is recommended.

Clinically useful conversion factors include: morphine (1.0), codeine (0.15), hydrocodone (1.0), oxycodone (1.5), hydromorphone (4.0), oxymorphone (3.0), transdermal fentanyl (2.4 MME per mcg/hr), tramadol (0.1), and buprenorphine sublingual (30.0 per mg, per CDC 2022 guidance). Methadone presents unique challenges due to its non-linear dose-dependent conversion factor (approximately 3.0-8.0 at lower doses, increasing substantially at higher doses), necessitating specialist guidance for MME calculation and dose conversion.¹³ The clinical and legal significance of MME thresholds was starkly illustrated in a case drawn from VHA national data, in which a patient chronically prescribed between 400 and 1,000+ MME per day – multiples of the extreme risk threshold – died of opioid overdose two days after the final prescription was dispensed. More broadly, VHA surveillance data demonstrate that overdose decedents averaged 98 MME/day versus 48 MME/day among survivors, providing a compelling pharmacoepidemiological basis for adherence to CDC guidance.¹⁶

While the CDC guideline appropriately raised awareness of opioid-related risks, in practice, some healthcare systems interpret-

ed the recommendations more rigidly than intended. In some cases, this led to rapid tapering, undertreatment of legitimate pain, and possibly contributed to an unintended shift among certain patients toward illicit opioid use.¹⁷

The WHO analgesic ladder: historical perspective and modern evolution

Introduced by the WHO in 1986 in the context of cancer pain management, the ‘Analgesic Ladder’ provided a stepwise, evidence-based framework for escalating analgesic therapy matched to pain severity. The original three-step model progressed from Step 1 – ‘mild’ pain (non-opioid analgesics); Step 2 – ‘moderate’ pain (‘weak opioids’), to Step 3 – ‘severe’ pain (‘strong opioids’), with adjuvant medications at each step if needed. Although no longer the prevailing philosophy of the best approach to pain treatment, the simplicity and scalability of this framework enabled broad global adoption, including in resource-limited settings where access to specialist pain services was unavailable.¹⁴ Some fundamental principles embedded in the original analgesics ladder remain clinically sound: individualized treatment tailored to the individual patient; titration to effect rather than adherence to arbitrary dose ceilings; proactive side-effect management; and bidirectional movement – including de-escalation when pain diminishes.

The 2018 WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents substantially updated the original ladder, reflecting four decades of clinical evidence and shifting paradigms in pain medicine.¹⁵ Key modifications include the explicit elevation of non-pharmacologic approaches such as physiotherapy, CBT, and mindfulness from adjunctive status to co-equal treatment modalities. The updated guidelines also take a more conservative stance on opioid use for non-cancer chronic pain, reflecting accumulating evidence of modest long-term efficacy and significant potential harms in this population. The updated framework additionally acknowledges limitations of the original three-step model: it can oversimplify complex pain conditions, particularly neuropathic pain, which often responds poorly to opioids and requires specialized adjuvant approaches (e.g., anticonvulsants, SNRIs, TCAs). Individual patient factors such as comorbidities, polypharmacy, substance use history, renal and hepatic function require personalization beyond what a stepwise framework can adequately capture. However, ‘ladders’ are overly simplistic and ignore the utility of interventions that can obviate or greatly reduce the need for analgesics. Contemporary practice includes a more mechanistic and holistic approaches.

Evidence-based prescribing: practical strategies

When non-opioid therapies and non-pharmacologic approaches are insufficient, and the decision to initiate opioid therapy is supported by a thorough benefit-risk assessment, several evidence-based principles should guide prescribing. Morphine remains the preferred strong opioid in many clinical contexts, particularly in resource-limited settings, owing to its established efficacy, multiple available formulations (e.g., oral immediate-release, oral sustained-release, and injectable), cost-effectiveness, and inclusion on the WHO essential medicines list.⁷ For opioid-naïve patients, initiating at the lowest effective dose (typically at or below the <20 MME/day threshold)

and titrating based on individual response minimizes early adverse effects and supports dose-finding. For persistent pain, scheduled around-the-clock dosing using sustained-release or long-acting formulations, supplemented with short-acting preparations for breakthrough pain, produces more consistent analgesia than as-needed dosing alone. Clear treatment goals – defined in terms of functional improvement rather than pain score reduction alone – should be established at the outset and reassessed at regular intervals. Documentation of the rationale for opioid prescribing, including prior therapeutic trials, risk-benefit discussion with the patient, and the MME calculation, is sound for both clinical practice and medicolegal protection. Comprehensive opioid risk assessment includes evaluation of personal and family history of substance use disorder, psychiatric comorbidities, concurrent CNS depressant use (e.g., benzodiazepines, muscle relaxants, alcohol), pain etiology, and functional status. Validated screening tools, including the Opioid Risk Tool (ORT) and the DIRE (Diagnosis, Intractability, Risk, Efficacy) instrument, provide structured risk stratification to guide monitoring intensity. Urine drug screening at baseline and at regular intervals provides objective verification of adherence and identification of non-prescribed substances. Naloxone co-prescription for patients at elevated overdose risk, and education of patients and household contacts on recognition and response to opioid overdose, are standard-of-care in 2026.

Opiophobia – the disproportionate and clinically unsupported fear of prescribing opioids – remains a significant barrier to adequate pain management in both high- and low-income settings. In high-income nations, the post-epidemic regulatory and cultural backlash has produced well-documented undertreated pain in patients with cancer, sickle cell disease, postoperative pain, and terminal illness. In LMICs, opiophobia operates through prescriber education deficits, regulatory restrictions that treat any opioid prescribing as high-risk, and cultural frameworks in which pain acceptance and endurance is normalized. The antidote to opiophobia is education (e.g., clear, evidence-based instruction on the distinction between physical dependence and tolerance (predictable pharmacological phenomena occurring in any patient on chronic opioid therapy) and SUD (a complex disorder including compulsive use despite harm). Structured training programs that build prescriber confidence in applying MME thresholds, risk stratification tools, and monitoring protocols provide a pathway from opiophobia to informed, appropriate prescribing.

Prescription Drug Monitoring programs (PDMP’s) are state-run electronic databases that can be used to track the prescribing and dispensing of controlled substances, primarily to prevent drug diversion, abuse, and ‘doctor shopping’.¹⁸ The value of PDMP’s is in screening for questionable orders, duplicative therapies, possible diversion, *etc.* If they were properly used, they would go a long way in establishing credible pain management and curbing illicit use; but they are underutilized.

Global disparities in opioid access

The international access deficit in opioid availability and prescribing constitutes one of the most under-addressed crises in global health. According to the International Narcotics Control Board (INCB), approximately 5.5 billion people (predominantly in Africa, Asia, and Latin America) lack adequate access to controlled medicines for pain relief.¹⁹ High-income countries, which represent less than about 20% of the global population, consume more than 90%

of the world's morphine supply.²⁰ Only 8% of global medical opioids reach the 83% of the population residing in LMICs, where the majority of patients with cancer, AIDS-related pain, trauma, and surgical conditions may die without provision of pain relief. The barriers to opioid access in LMICs are multifactorial and deeply entrenched. Regulatory barriers are among the most significant: many countries have adopted highly restrictive scheduling and procurement frameworks modeled on US or European regulations without the corresponding prescribing infrastructure, physician training, or dispensing capacity to implement them effectively. Complex multi-step authorization processes, quantity limits, and requirements for specialist prescribing effectively prevent most patients from accessing opioids even when they are nominally available.²¹ Healthcare system limitations, including inadequate palliative care infrastructure, severe specialist scarcity, geographic access disparities, and resource allocation pressures, compound regulatory barriers. Provider education deficits, including suboptimal training in pain assessment and opioid prescribing, are pervasive in LMIC healthcare systems. Cultural factors, including family decision-making dynamics, religious frameworks that valorize suffering, and deeply held beliefs among providers and patients that opioids inevitably cause addiction, create additional layers of resistance.

Addressing the global access crisis requires coordinated action at multiple levels. At the policy level, regulatory frameworks should be modernized to balance legitimate diversion prevention with the imperative of adequate pain relief – the ‘dual obligation’ articulated by the INCB. The WHO's Access to Controlled Medicines Programme provides technical assistance for regulatory reform and procurement simplification. International collaborations, including academic partnerships, exchange programs, and shared training curricula, accelerate the diffusion of evidence-based prescribing practices. Technology, including telemedicine consultation networks and online education platforms, enables specialist expertise to reach underserved settings.

Advocacy, systems change, and the role of healthcare professionals

Sustainable improvement in pain management, whether addressing overuse in high-income nations or under-access in LMICs, needs engagement at every level of the healthcare system. Healthcare administrators and institutional leaders should champion pain management as a quality metric, allocate resources for palliative care development, and set organizational standards for opioid risk monitoring. Regulatory bodies face the complex challenge of simultaneously streamlining legitimate access and preventing diversion, challenges that require evidence-based policymaking, ongoing data analysis, and willingness to revise regulations in response to outcomes evidence.

Professional societies, including those dedicated to pain medicine, oncology, palliative care, and pharmacy, can play an indispensable role in developing and disseminating clinical guidelines, providing continuing education, and advocating for evidence-based policy. The collective credibility of organized medicine and pharmacy is a powerful lever for regulatory change. Patient advocacy organizations contribute the moral authority of lived experience, effectively communicating the human cost of both undertreated pain, and OUD, to policymakers and the public.

Individual clinicians are at the forefront for translating evidence into practice: applying the MME framework, conducting compre-

hensive risk assessments, integrating multimodal approaches, prescribing naloxone to at-risk patients, and engaging in the difficult conversations about goals of care that underpin sound opioid therapy. Continuous learning, through CME activities, peer consultation, and engagement with the emerging literature, is not merely a professional goal, but a clinical advantage in a rapidly evolving field.

Discussion

The opioid landscape in 2026 defies simple narratives. The public health discourse in high-income nations has been dominated by the devastation of the opioid epidemic, a crisis that has claimed hundreds of thousands of lives and demands ongoing, multifaceted responses. But an exclusive focus on restricting opioid access risks institutionalizing a different moral failure: the systematic undertreatment of pain in patients who have a legitimate clinical need and a right to adequate relief of pain.

Global disparities in opioid access represent an ongoing humanitarian crisis that must be positioned alongside the epidemic of overuse as a co-equal priority in international pain medicine policy. The suffering of billions of people dying without adequate pain relief is not a consequence of inevitable scarcity, it is a consequence of policy choices that can be changed. The evidence base for safe, effective opioid prescribing in appropriate clinical contexts is robust; the barriers are regulatory, educational, and cultural, not pharmacological.

The WHO Analgesic Ladder, though nearly four decades old, continues to provide a scalable framework for pain management that is accessible across resource environments. Its 2018 evolution appropriately reflects the evidence on non-pharmacologic approaches and the more complex picture of opioid efficacy in chronic non-cancer pain. The ladder's enduring strength is its principle-based simplicity: individualize, titrate, reassess, and treat the whole patient.

The MME framework represents one of the most significant advances in operationalizing opioid risk management in clinical practice. By providing evidence-based, quantitative thresholds linked to overdose risk, the CDC's 2022 guideline transforms opioid prescribing from an art relying on clinical intuition to a discipline grounded in measurable pharmacoepidemiological risk. The case for universal MME tracking across prescribers, dispensers, and health systems is compelling, both for patient safety and for medicolegal accountability.

Of course there are limitations of a narrative review, including reliance on published literature that disproportionately reflects high-income nation perspectives, the inherent heterogeneity of a narrative (versus systematic) methodology, and the rapidly evolving regulatory and epidemiological context that may alter specific data points presented. Future research priorities include prospective studies of MME-guided prescribing outcomes, effectiveness trials of opioid access interventions in LMIC settings, and implementation science research on provider education programs targeting opioidphobia.

Conclusions

Opioids in 2026 remain clinically essential, pharmacologically complex, globally inequitably distributed, and improperly often overused or underused depending on geography and context. The path forward is neither unconstrained prescribing nor the reflexive restriction that produces undertreated pain – it is the evidence-based, risk-stratified, multimodal, and patient-centered approach that the

WHO Analgesic Ladder, CDC MME framework, and decades of clinical experience together support.

The four suggestions for clinicians, health systems, and policy-makers are clear: consider the MME framework as an initial guide for standard of care; integrate opioid therapy within comprehensive multimodal frameworks; address opiophobia through education rather than restriction; and work toward equitable global access to pain relief as a fundamental dimension of the right to health. The suffering caused by both extremes – undertreated pain due to opioid under-use, and harm of opioid excess use – is preventable. The tools and knowledge exist. What remains is to apply them.

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