SPECIAL ARTICLE

Opioids for chronic noncancer pain

A position paper of the American Academy of Neurology

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ABSTRACT

The Patient Safety Subcommittee requested a review of the science and policy issues regarding the rapidly emerging public health epidemic of prescription opioid-related morbidity and mortality in the United States. Over 100,000 persons have died, directly or indirectly, from prescribed opioids in the United States since policies changed in the late 1990s. In the highest-risk group (age 35–54 years), these deaths have exceeded mortality from both firearms and motor vehicle accidents. Whereas there is evidence for significant short-term pain relief, there is no substantial evidence for maintenance of pain relief or improved function over long periods of time without incurring serious risk of overdose, dependence, or addiction. The objectives of the article are to review the following: (1) the key initiating causes of the epidemic; (2) the evidence for safety and effectiveness of opioids for chronic pain; (3) federal and state policy responses; and (4) recommendations for neurologists in practice to increase use of best practices/universal precautions most likely to improve effective and safe use of opioids and to reduce the likelihood of severe adverse and overdose events. *Neurology*® 2014;83:1277–1284

GLOSSARY

AAN = American Academy of Neurology; **CNCP** = chronic noncancer pain; **COAT** = chronic opioid analgesic therapy; **FDA** = Food and Drug Administration; **MCID** = minimum clinically important difference; **MED** = morphine equivalent dose; **PDMP** = Prescription Drug Monitoring Programs; **RCT** = randomized controlled trials; **REMS** = Risk Evaluation and Mitigation Strategies; **VA** = Veterans Affairs.

Until the latter part of the 1990s, use of long-term opioid therapy for chronic noncancer pain (CNCP), or pain lasting beyond 3 months, was effectively prohibited in most states. An early case series study[1] suggested that patients with CNCP, if well-chosen, could take opioids long term safely and with fewer severe problems (e.g., abuse/addiction) than previously thought. The American Academy of Neurology (AAN) Ethics, Law, and Humanities Committee generally agreed: "there is consensus among pain specialists that opioid therapy is appropriate for selected patients with CNCP and can provide sustained benefit to such patients."[e1] Pain advocacy groups and groups of pain specialists successfully lobbied state Medical Boards and legislatures to change statutes and regulations to lift the relative prohibition on opioid use in the CNCP population.[e2] In at least 20 states, laws and regulations changed in the late 1990s, dramatically liberalizing use of opioids for CNCP based on "model" guidelines put forward by groups advocating for much more permissive use of opioids for CNCP.[2] However, the resulting model language, reflecting the prevailing thought at the time that there was no ceiling on dose, may have been too permissive (e.g., "No disciplinary action will be taken against a practitioner based solely on the quantity and/or frequency of opioids prescribed").[e3] Finally, the lobbying effort to liberalize opioid use was so successful that even the Joint Commission on Accreditation of Healthcare Organizations instituted screening for pain as the fifth vital sign.[3] Some of the organizations and individuals involved in the lobbying efforts have recently come under investigation both in the press[e4] and in the US Senate.[e5]

All of this activity emerged in the absence of any clear evidence from clinical trials that opioids could be safely and effectively used in patients with CNCP. Specific guidance on dosing of opioids for CNCP was not offered in any of the emerging statutes, regulations, or guidelines; the model pain acts passed by states often prohibited disciplinary action related to even extremely high doses, implying that there is no unsafe ceiling, and reflecting the axiom heralded by pain specialists that the way to treat tolerance was to continue to increase opioid dose. The emergence of increasing mortality from accidental poisoning, concomitant with dramatically increasing

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Approved by the Patient Safety Subcommittee on December 27, 2013; by the Practice Committee on January 13, 2014; and by the AAN Board of Directors on March 4, 2014. Following *Neurology*® peer review and approval, this document was resubmitted to the AAN Board of Directors and approved on June 24, 2014.

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average daily morphine equivalent doses of the most potent opioids, occurred quickly following the law changes. These opioid-related deaths have increased dramatically since the late 1990s, reaching 16,651 deaths in 2010, constituting a national epidemic and public health emergency.[4,5] The total number of opioid-related deaths in the United States (>100,000 between 1999 and 2010) far exceeds the number of US military casualties in the Vietnam War (58,000).

EVIDENCE FOR EFFICACY AND EFFECTIVENESS OF OPIOIDS FOR CNCP Recent systematic reviews of randomized controlled trials (RCT) have addressed the efficacy of opioids for CNCP generally,[6–8] in older adults,[9] for chronic low back pain,[10] and for neuropathic pain.[11] Opioids are not recommended for use in treating tension-type headaches,[12] and fewer than 20% of patients with refractory daily headache likely improve in sustained reduced pain and function.[e6] In addition, the AAN, in its Choosing Wisely campaign, recommends not using opioids or butalbital for treatment of migraine, except as a last resort.[13] Furlan et al.,[14] in a recent review of RCT of opioids for CNCP, concluded that the overall effectiveness of opioids for pain was modest, and that the effect on function was small. Most of the RCT were shorter than 4 weeks, and none was longer than a few months. Noble et al.,[8] in a Cochrane review of observational studies of cases on longer-duration treatment, concluded, "The findings of this systematic review suggest that proper management of a type of strong painkiller (opioids) in well-selected patients with no history of substance addiction or abuse can lead to long-term pain relief for some patients with a very small (though not zero) risk of developing addiction, abuse, or other serious side effects. However, the evidence supporting these conclusions is weak, and longer-term studies are needed to identify the patients who are most likely to benefit from treatment."

Thus, although there is evidence for significant pain relief in the short term (average duration of trials 5 weeks, range 1–16 weeks), there is no substantial evidence for maintenance of pain relief over longer periods of time, or significant evidence for improved physical function. Ballantyne and Shin[7] and Ballantyne[15] have expressed the opinion that possible mechanisms for loss of analgesic efficacy include development of pharmacologic tolerance or opioid-induced hyperalgesia. In addition, the premise that tolerance can be overcome by dose escalation is now seriously questioned.

Population-based epidemiologic studies provide additional data regarding effectiveness. In a large cross-sectional Danish survey conducted in 2000,[e7] persons in chronic pain on opioids reported decreased pain relief, functional capacity, and quality of life vs persons in chronic pain not on opioids, adjusting for severity. A recent prospective, population-based study on low back injured workers[16] revealed that although morphine equivalent dose (MED) increased significantly over 1 year, a minority of workers reported clinically meaningful improvement in pain and function.

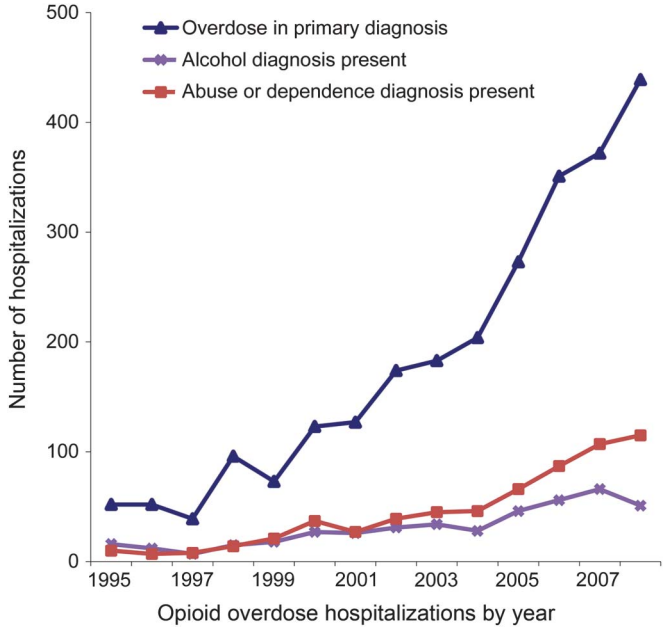
A recent randomized trial in the Veterans Affairs (VA) health system compared the effectiveness of a liberally escalating dosage strategy with a "hold the line" dosage strategy.[17] None of the primary pain and functional outcome variables was significantly improved in the escalating group; 27% of patients overall had to be discharged during the trial due to misuse/noncompliance.

THE MINIMUM CLINICALLY IMPORTANT DIFFERENCE IN OUTCOME Most randomized trials of efficacy of opioids and other therapies and interventions for CNCP rely primarily on pain relief measured across groups without a predetermined degree of pain relief or physical function specified. Recently, the concept of a minimum clinically important difference (MCID) in pain and function has been used, including patient-reported "minimum acceptable" degrees of relief of pain and improvement in function.[18,19] For drug approval trials, the Food and Drug Administration (FDA) requires only that pain be a primary outcome, whereas other critical outcomes (function, quality of life) are secondary outcomes. The ideal approach would be to prespecify an MCID in both pain and functional outcome on the order of a 20%–30% improvement, and perhaps to use a composite measure including both measures.[e8]

THE POOR SAFETY PROFILE OF OPIOIDS: EMERGENCE OF A NATIONAL EPIDEMIC OF MORBIDITY AND MORTALITY Adverse events most commonly reported in randomized trials include constipation, nausea and vomiting, dizziness, and drowsiness.[6,9,11] Much more serious long-term consequences of opioids have only been more clearly identified from observational and epidemiologic investigations, and include inhibition of endogenous sex hormone production, hypogonadism, and infertility[e9]; immunosuppression[e10]; falls and fractures in older adults[e11]; neonatal abstinence syndrome[e12]; cardiac issues, including QT prolongation, related to methadone[e13]; sleep-disordered breathing[20]; opioid-induced hyperalgesia[15]; nonfatal overdose hospitalizations[21]; emergency department visits[22]; and death from unintentional poisoning.[23] Figure 1 demonstrates the dramatic rise in Washington State hospitalizations associated with opioid overdose between 1995 and 2008.

A rise in deaths related to unintentional poisoning from prescription opioids was first reported from a state workers' compensation system beginning within 2 years of change in the law.[24] Other studies further documented the emerging national epidemic of unintentional poisoning deaths associated with prescription opioids,[e14,e15] and the strong relationship between mortality and sales of

Figure 1 Hospitalizations from opioid overdose (Washington State, 1987–2008)



specific prescription opioids (oxycodone, methadone), a surrogate measure of prescription opioid volume and dose.[4] Nationally, by 2005, these deaths exceeded deaths from both firearms and motor vehicle accidents in persons aged 35–54 years. Throughout the period 1999–2006, people aged 35–54 years had higher poisoning death rates involving opioid analgesics as compared with those in other age groups.[25] By 2006, unintentional poisoning deaths accounted for 20% of years of potential life lost before age 65.[e16] Thus, preventing these deaths would have a large impact on reducing years of preventable life lost.

The true incidence of physical dependence and addiction in this population is unknown; however, it is likely that many more patients than previously reported develop these serious complications of treatment.[26] Fifty percent of patients taking opioids for at least 3 months are still on opioids 5 years later.[e17] Most problematic is the lack of a useful case definition for any of these dependent states,[15] making it challenging for an uninitiated prescribing provider to identify and intervene appropriately. In addition to refractory dependence, data from a large, population-based prospective study of workers with low back injuries reported a twofold increased likelihood, after adjusting for injury severity, of developing long-term disability after receiving prescription opioids soon after injury.[27]

OPIOID DOSING AND MORTALITY In the sentinel case series that suggested opioids could be used safely in persons with CNCP,[1] the vast majority of patients were taking <40 mg/day MED/d. The average dosage range reported in a recent large population-based observational study was 55 mg/d MED.[e18] However, among injured workers taking long-acting Schedule II opioids, the average daily MED increased substantially between 1996 and 2002, from 80 mg/d MED to 140 mg/d MED.[24] Thus, there is a large "tail" of prescribed dosage.

A recent study in a large health maintenance organization was the first to report a relationship between prescribed opioid dose and overdose events, with a ninefold increased risk of overdose at doses exceeding 100 mg/d MED compared to doses below 20 mg/d MED in patients with CNCP.[28] For each fatal overdose in the study, more than 7 nonfatal overdoses were observed. Two additional high-quality studies, in the VA health system and in Canada, have corroborated substantially increased risk associated with doses at or above 100–120 mg/d MED.[29,30] Thus the evidence in high-quality epidemiologic studies, across 3 very different health care systems, is consistent: increasing opioid doses are strongly related to large increases in risk of overdose morbidity and mortality. Risk was substantial even at lower dose levels, with a 3.7- to 4.6-fold increased risk at doses between 50 and 100 mg/d MED compared to doses less than 20 mg/d MED.[28,30]

The majority of opioid overdose deaths occur in the home, and a minority appear to be intentional. Recent observational studies suggest that disordered breathing during non-REM sleep increases with dose.[20] The potent effect of opioids in depressing central respirations in both animals and humans is well-documented. It is also likely that tolerance to analgesic effects of opioids occurs prior to tolerance for respiratory depression.[e19] Thus, it is possible that a seemingly normally functioning patient on 200 mg/d MED opioids could die during sleep, particularly if opioids were being used in combination with other CNS depressants, which is commonplace.

The exact proportionate contribution to mortality of overprescribing per se, misuse of prescribed opioids, or diversion is unknown. In one population-based study in Ontario, Canada, of all deaths attributable to opioids during 2006–2008, 7% of patients had died from opioids diverted from friends or family, and 19% had inappropriately self-administered (e.g., inhaled, injected).[e20] A greater proportion of deaths may be associated with diversion in rural states.[e21]

POLICY RESPONSES TO AN URGENT PUBLIC HEALTH PROBLEM In response to the epidemic of severe morbidity and mortality, Washington State public agencies, in collaboration with academic and practicing pain clinicians, promulgated an opioid dosing guideline in 2007. The core of this Guideline is a recommendation for a prescribing provider to seek consultation if a patient reaches 120 mg/d MED and if pain and function have

not substantially improved. This "yellow flag" dosage recommendation has now been included in a new Centers for Disease Control and Prevention issue brief,[e22] and other states are pursuing similar policies. The Washington Opioid Dosing Guideline has been updated[31] to include brief, publicly available tools to allow prescribing providers to conduct best practices when prescribing opioids to patients with CNCP, including (1) a brief tool to track pain and function; (2) tools to screen for past and current substance abuse, alcohol abuse, and significant depression; (3) prudent advice in conducting targeted urine drug testing; and (4) a Web-based application that allows calculation of daily MED in real time. Table 1 contains examples of conversions of commonly used opioids referenced to morphine in MED; an online calculator and app allows calculation of MED from all sources of opioids[32] (methadone is not included in table 1 because of its complex pharmacokinetics).

The Washington legislature passed landmark legislation in March 2010 to address the urgent public health problem, mandating that the Boards and Commissions representing prescribing providers in Washington repeal all prior rules related to the prescription of opioids for CNCP and create new rules by June 2011.[e23] The bill, which received substantial bipartisan support, mandated that the new rules include dosing criteria, guidance on when to seek consultation, and guidance on tracking clinical progress by using assessment tools focusing on pain, physical function, and overall risk for poor outcome. The majority of best practices reflected in the Washington statute and dosing guideline emulate widely agreed-upon best practices in other recent evidence-based guidelines.[e24–e26] They can be thought of as universal precautions aimed at increasing the effectiveness, and reducing the potential for harm, from the use of opioids for CNCP. The yellow flag dose of 120 mg/d MED reflected in the Washington guideline is strongly supported by high-quality evidence that was not available at the time evidence reviews were conducted for the other guidelines.[28–30] Other states are actively engaged in the adoption of similar guidelines, policies, or regulations.[e27–e29] Most recently, the State Medical Board of Ohio issued new guidelines with an 80 mg/d MED "trigger point."[e30]

Table 1 Opioid equianalgesic doses[a]

Opioid	Approximate equianalgesic dose (oral and transdermal)[a]
Morphine (reference)	30 mg
Codeine	200 mg
Fentanyl transdermal	12.5 μg/h
Hydrocodone	30 mg
Hydromorphone	7.5 mg
Oxycodone	20 mg
Oxymorphone	10 mg

[a] This table should only be used for calculating daily morphine equivalent dose from all sources of opioids, not for conversion from one opioid to another.[32]

A new Washington guideline, specific to workers compensation and implemented July 1, 2013, addresses a number of issues not adequately dealt with in earlier guideline efforts: a tapering algorithm for patients on high doses who have not demonstrated meaningful improvement in function, recommendations for perioperative opioid use in patients on chronic opioid analgesic therapy (COAT) in whom elective surgery is planned, a definition of meaningful improvement in pain and function, and specific guidance on use of opioids during the acute/subacute pain period.[33] This guideline recognized that careful assessment during this period, linked to gains in pain and function, would be crucial to the decision to embark on chronic opioid analgesic therapy. In addition, a stronger statement recommending against use of opioids for mild to moderate pain conditions, such as chronic musculoskeletal conditions, headache, and fibromyalgia, is included.

Through authority granted in 2007, the FDA has implemented Risk Evaluation and Mitigation Strategies (REMS) for extended-release and long-acting Schedule II opioids.[e31] The principal REMS strategy relies on manufacturer-delivered prescriber education, with guidance from an FDA-developed blueprint.[e32] The FDA has recently moved to (1) upschedule hydrocodone products to Schedule II[e33] and (2) change labeling on extended-release/long-acting opioids to reserve their use for patients with more severe pain requiring around-the-clock dosing.[e34]

The Drug Enforcement Administration promulgated new rules, effective June 1, 2010, regarding electronic prescribing of controlled substances, including opioids.[e35] The new rules require the same e-prescribing standards for Schedule III–V opioids as for Schedule II opioids and represent a significant step toward defining prescribing standards for electronic medical record systems for controlled substances.

The White House Office of National Drug Control Policy provided additional national guidance related to the opioid epidemic, emphasizing prescriber education and enhanced capacity of state-based Prescription Drug Monitoring Programs (PDMP).[e36] Forty-eight states have or will soon have available PDMPs that allow prescribers to check on dispensed sources of all controlled substances in near real time.[34] These programs will likely become a standard part of best practice related to chronic opioid prescribing, but they are currently underfunded, underutilized, and not interoperable across state lines or health care systems (e.g., with the VA Health System). At this time, 4 states (New York, Kentucky, New Mexico, Tennessee) have some form of mandatory use of the

Figure 2 Risk/benefit of opioids for chronic noncancer pain

PDMP. However, in many states, PDMP programs are underutilized, perhaps due to inadequate guidance as to the most effective/efficient use of these programs, and a perception that accessing the program is burdensome to the physician.

WHEN AND HOW SHOULD PRESCRIBERS USE COAT? Figure 2 is a theoretical schematic showing an imbalanced risk–benefit equation for the use of opioids for CNCP. The severity of the imbalance is largely contributed to by (1) an underappreciated longer-term physical dependence risk associated with long-term disability and (2) underuse of best practices/universal precautions. Most pain specialists believe that some of their patients benefit from COAT, but who these patients are has not been adequately addressed in high-quality scientific studies, and consensus on this is under active reassessment. It seems likely that, in the long run, the use of opioids chronically for most routine conditions, such as chronic low back pain, chronic headaches, or fibromyalgia, will not prove to be worth the risk. However, even for more severe conditions, such as destructive rheumatoid arthritis, sickle-cell disease, severe collagen disease, or severe neuropathic pain, prescribers need specific guidance on dosing, publicly available brief tools to effectively screen patients for risk, and guidance on how to monitor patients for early signs of severe adverse events, misuse, or opioid use disorder.

Primary care physicians are the principal prescribers in practice, and they are more likely to use opioids with confidence in environments that support use of best practice tools to assist with these often complex and difficult patients.[e37] Table 2 summarizes the types of best practices and brief, publicly available tools[32] that are virtually universally agreed upon if one is to safely and effectively use opioids for CNCP. The most crucial best practices would be as follows:

1. Track pain and function at every visit using a brief, validated instrument, so that the practitioner is aware of the effectiveness of opioids at every step
2. Document the daily MED in mg/d from all sources of opioids at every visit
3. Access the state PDMP data (a) at the time of a first prescription for opioids, particularly if that visit is to an emergency department; (b) at the time of a decision as to whether to institute COAT; and (c) periodically during monitoring of COAT, with a frequency according to risk of abuse
4. Screen for past and current substance abuse and for severe depression, anxiety, and posttraumatic stress disorder prior to initiation of COAT
5. Use random urine drug screening prior to initiation of COAT and periodically during monitoring of COAT, with a frequency according to risk
6. Use a patient treatment agreement, signed by both the patient and prescriber, that adequately addresses the risks of COAT and the responsibilities of the patient, at the initiation of COAT and annually
7. Avoid escalating doses above 80–120 mg/d MED unless sustained meaningful improvement in pain and function is attained, and not without consultation with a pain management specialist

Patients who are discovered to be misusing opioids, obtaining opioids from multiple prescribers or emergency departments, or otherwise placing themselves at risk by not fulfilling their responsibilities as outlined in the signed treatment agreement may be discharged from practice. Some practices have implemented additional, practical policies, such as having a single prescriber, and no prescribing for COAT patients at night or on weekends.

Table 2 What prescribers can do to safely and effectively use opioids for CNCP[a]

Opioid treatment agreement
Screen for prior or current substance abuse/misuse (alcohol, illicit drugs, heavy tobacco use)
Screen for depression
Prudent use of random urine drug screening (diversion, nonprescribed drugs)
Do not use concomitant sedative-hypnotics or benzodiazepines
Track pain and function to recognize tolerance and track effectiveness
Track daily MED using an online dosing calculator
Seek help if MED reaches 80–120 mg and pain and function have not substantially improved
Use the state Prescription Drug Monitoring Program to monitor all sources of controlled substances

Abbreviations: CNCP = chronic noncancer pain; MED = morphine equivalent dose.
[a] All the brief, publicly available tools necessary to utilize best practices tools can be found online at http://www.lni.wa.gov/claimsins/providers/treatingpatients/ByCondition/Opioids/default.asp.[32]

Integration of guidelines into electronic health records, use of pharmacist comanagement,[35] regular use of state prescription drug monitoring programs, and more widespread use of specialty consultation via video linkage to academic medical centers[36] are currently expanding areas of innovation. In addition, payers need to offer adequate payment incentives for treatment alternatives to the opioid prescription for acute, subacute, and chronic pain. Cognitive–behavioral therapy, structured exercise, spinal manipulation, and interdisciplinary rehabilitation, although proven to be moderately effective in treating subacute and chronic low back pain, are often either not available or not adequately funded.[37] A collaborative care model for the care of patients with chronic pain, not unlike similar models aimed at chronic disease management of diabetes and other conditions,[38] should be a crucial element in the evolving health care reform environment.

In considering opioid policies, it is reasonable to address "legacy" COAT patients who have been on high doses (e.g., over 120 mg/d MED for at least 90 days) as a separate class. There are hundreds of thousands of such patients in state Medicaid and workers compensation programs, so policy responses should reasonably address these patients. One possible approach is to implement a tapering trial if any of the following is present: (1) the patient has experienced a severe adverse or any overdose event; (2) the patient has evidence of aberrant behavior; or (3) the patient requests a taper. Prudent tapering policies should also be implemented following hospitalization, particularly in patients who were on COAT at the time of hospital admission.[33] A plan to address posthospital transitions back to outpatient care, including a tapering plan, should be addressed preoperatively in nonurgent cases.

Polypharmacy is also important to consider, particularly with regard to continuous ongoing use of benzodiazepines and sedative–hypnotics. Guidelines suggest not using these drug classes concurrently with COAT.

RESEARCH GAPS Research gaps related to opioid efficacy and management have recently been identified in a systematic review, including a lack of effectiveness studies on long-term benefits and harms of opioids for CNCP.[39] Further research on the effectiveness of prescription drug monitoring programs is also indicated. In addition, comparative effectiveness research should be conducted in each of the following areas: (1) effective treatments to prevent the transition from acute/subacute pain to chronic pain; (2) effective treatment of chronic pain, including the place of less intensive but potentially effective methods of improving patient self-efficacy, such as cognitive behavioral therapy and activity coaching[37,40]; and (3) effective tapering regimens that permit clinicians to add an exit strategy to their armamentarium for patients on COAT who are at risk or for whom there has been no meaningful improvement in function.

Other emerging issues will require critical original research to determine effectiveness and appropriateness of use: (1) extent, intensity, and quality of urine drug testing; (2) genotyping to determine whether response to opioid therapy can/should be more individualized; and (3) how to identify patients who benefit from chronic opioid use but are not adversely affected by long-term side effects.

POLICY LESSONS MOVING FORWARD Most health care delivery, including policies related to who may prescribe opioids and potential limits on such prescribing, is regulated at the state level. This is why, more than a decade ago, advocates for more liberalized use of opioids for CNCP focused on changing state laws.[e2] The language in these laws implying no ceiling on dose, or placing no limits on dispensing controlled substances from prescriber offices, should be revisited in the context of the benefits, morbidity, and mortality as referenced in this review. However, reversing current opioid overdose epidemic trends will not be easily accomplished by informal or even mandatory education alone. A number of states have had mandatory education for many years, and this has not reversed the overdose trends. Public agencies whose patients are likely overrepresented in the morbidity and mortality statistics (state Medicaid programs, state workers' compensation funds, agencies caring for those with serious mental health disorders) should be actively collaborating with state Departments of Health, gubernatorial office executive staff, and appropriate state professional societies to urgently develop a strategic path forward. These types of collaborative efforts have been effective in Washington,[31] Ohio,[e30] Utah,[e36] and some smaller state areas (e.g., southern Oregon).[e38] State Departments of Health are particularly important because of their capacity to track overdose hospitalization (figure 1) and mortality statistics. The public agencies that are also payers can use administrative billing data to track opioid dosing patterns, including clustering associated with "pill mills" or individual prescribers, and can track patients receiving high doses or receiving opioids from multiple prescribers or emergency departments.

DISCUSSION Current opioid prescribing practices have been associated with substantial morbidity and mortality of epidemic proportions. The determination of functional benefit of any pain management intervention or treatment is important in the management of patients with chronic pain conditions. Patients on chronic opioid therapy should be managed according to best practices and universal precautions as outlined in table 2. If daily dosing exceeds 80–120 mg/d MED, consultation with a pain management specialist is recommended, particularly if pain and function have

not substantially improved. Opioid therapy should be only part of a multifaceted approach to pain management. The risks for chronic opioid therapy for some chronic conditions such as headache, fibromyalgia, and chronic low back pain likely outweigh the benefits. Ongoing research and data collection regarding opioid efficacy and management are needed, as well as revision in state and federal laws and policy to assure patient safety.

AUTHOR CONTRIBUTIONS

Dr. Franklin: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and final approval, study supervision.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The author reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received March 12, 2014. Accepted in final form June 13, 2014.

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Neurology 2014;83;1277-1284
DOI 10.1212/WNL.0000000000000839