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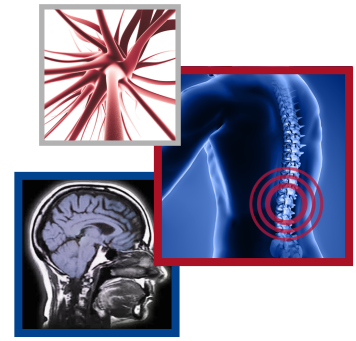
Pain Management



Management of chronic non-cancer pain: a framework

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Aim: Since publication of the CDC 2016 Guideline, opioid-related mortality in the USA has doubled and a crisis has developed among the 15–20 million Americans with chronic, moderate-to-severe, noncancer pain. Our aim was to develop a comprehensive alternative approach to management of chronic pain. **Methods:** Analytic review of the clinical literature. **Results:** Published science provides a solid framework for the management of chronic non-cancer pain, detailed here, even as it leaves many knowledge gaps, which we fill with insights from clinical experience. **Conclusion:** There is a sufficient basis in science and in clinical experience to achieve adequate control of chronic pain in nearly all patients in a way that adequately balances benefits and potential harms.

Plain language summary: Opioid-related mortality in the USA continues to increase rapidly despite the decline in opioid prescriptions achieved by the CDC 2016 Guideline. This Guideline has also created a crisis among the 15–20 million Americans with chronic, moderate-to-severe, noncancer pain. We offer a detailed framework for an alternative approach to management of chronic pain. We also offer some suggestions for solving the problem of illicit drug use, which now accounts for 84% of opioid-related deaths. To the extent possible, we have relied upon published science. However, we also identify many knowledge gaps that we address with insights from clinical experience and thousands of interactions with patients. These knowledge gaps will ultimately need to be addressed by further research.

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In 2016, the Centers for Disease Control and Prevention (CDC) published a guideline for management of chronic noncancer pain in adults [1]. It was ostensibly directed to primary care physicians but it rapidly became the *de facto* law of the land, constraining primary care physicians and pain specialists alike. The Guideline was premised on the concept that opioid deaths in America, which continue to spiral, are primarily caused by overprescribing by physicians [2]. There was some truth to this concept up to about 2012, the year by which most pill mills had been shut down. However, since then, opioid-associated deaths have been, to an ever-greater extent, propelled by the burgeoning use of illicit opioids, most particularly heroin laced with illicit fentanyl [2]. In 2019, there were 49,860 US opioid deaths, 13,501(27%) involving prescription opioids and 36,359 (73%) illicit opioids [3]. As of April, 2021, these numbers had risen to a total of 74,020 deaths, 84% from synthetic opioids (excluding methadone, i.e., illicit) and 18% from natural and semisynthetic opioids (i.e., prescription). The percentages sum to >100% because of the vicissitudes of data collection [4]. In the face of these facts, the CDC has continued its single-minded campaign to limit opioid prescribing for patients with chronic pain, even as robust science provides no support for its arguments [2]. In the process, the CDC has created a second crisis for the 15–20 million Americans who suffer with moderate to severe chronic pain [2].

Most seriously, the CDC, in its reporting practices over the years, has blurred the distinction between populations of people taking prescription opioids and populations using illicit opioids. This, coupled with misconceptions about

the difference between dependence and addiction [5], has fostered the widespread misconception that every clinic population is rife with addicted patients and that all patients prescribed opioids are at high risk for addiction – concepts strongly contradicted by scientific evidence [2,6,7]. Because it has proven very difficult to discern the very small percentage of clinic populations that is actually addicted, this has in turn led to extreme hesitance by clinicians to prescribe opioids for anyone, the more so since the issuance of the CDC Guideline. In fact, the two populations of opioid users – patients in pain receiving prescription drugs and people using illicit opioids and often addicted – appear to be, by and large, very different (see below: Opioids: dependence, tolerance and addiction). Indeed, serious risk of addiction is unlikely to be encountered by clinicians in clinical practice [2] – a phenomenon perhaps best demonstrated by the continued burgeoning of illicit opioid drug deaths despite draconian and quite effective efforts to reduce clinician prescribing of opioids. This reality has major implications for US public policies bearing on both pain management and addiction.

As the CDC argument has been revealed to lack scientific substance [2], the question arises as to what guideline should replace it. We here propose a framework for such a guideline. It is likely to be some years before the CDC relinquishes its regulation of the practice of medicine (the recently issued draft revision, currently in the public comment phase, is not fundamentally different from the 2016 Guideline). Until it does so, it will not be possible to put the entire framework we propose (and modifications thereof) fully into practice. However, we wish to delineate some fundamental principles and initiate a public conversation about what should constitute proper treatment of chronic noncancer pain. We also note that there is no principled reason to distinguish between cancer and noncancer pain but we will focus on the latter in our discussion of the science.

To the extent possible, we will rely on existing science. However, as robust as the science is, there are still many major knowledge and practice gaps. To fill these, we have had to rely on the 35-year experience of the first author in treating chronic pain and decades of experience by the second author as an advocate for chronic pain patients. In the process, we will delineate some domains in which further research is urgently needed and pose a number of hypotheses susceptible to empirical testing. This paper will not address interventional pain strategies such as epidural and facet joint steroid injections, ablative procedures such as medial branch blocks, spinal cord stimulators or intrathecal pumps.

The framework

Clinician–patient relationship

We propose that a relationship of mutual respect and trust between clinician and patient is foundational to optimal management of chronic pain. Patients derive enormous benefit from simply knowing that there will always be a clinician in their corner who will do their best to help them. Our experience suggests that, in a trusting relationship, patients are more likely be compliant with the necessarily disciplined medical regimens employed in management of chronic pain. On the other hand, the absence of trust may degrade healthcare [8,9].

This proposal runs strongly against the view that all patients taking opioids are drug seekers, if not addicts, who deserve no respect – a view that has animated the war on drugs, which began in earnest with the Harrison Act of 1914 [10,11]. Unfortunately, this view appears to be shared by many physicians, pharmacists and lawmakers today, a phenomenon that is likely of great harm to patients with chronic pain. Quite often family members seem share this view.

Estimates of the prevalence of opioid use disorder (OUD) among patients prescribed opioids vary enormously. The preponderance of evidence suggests that it is less than 3% [2]. How are these 3% to be identified? Despite considerable research, no adequate predictive criteria have emerged. We suggest three behaviors that might signal opioid abuse or opioid diversion in clinical practice: failure of progressively titrated dosage to provide any benefit in alleviating pain (although some patients may not achieve analgesia with certain opioids because of genetically mediated variations in metabolism); repeated running short on supply of opioids prescribed; and repeated 'accidents', for example, the pills were spilled in the toilet or were stolen. Everyone is entitled to an accident now and then and theft of opioids is commonplace, requiring some patients to purchase a safe and minimize the quantity of drug they hold in their possession [12,13]. In our clinical experience, evidence of abuse becomes apparent in the course of three to four patient visits, at which point a decision to taper and discontinue opioids but maintain other medications may be appropriate and eminently defensible to the patient provided they have been given adequate forewarning. Concern is often raised about the incidence of diversion of prescription opioids. The DEA is required by law to factor diversion estimates into its planned production quotas; recent estimates of diversion of hydrocodone, hydromorphone, and oxycodone are on the order of 0.07% of planned quotas [14].

Opioid contracts, urine drug screens (UDSs), and pill counts have become mandatory in many pain management clinics, often at the behest of provider organizations. However, there is no adequate scientific evidence that these measures are of any value in reducing the incidence of opioid abuse, even as they implicitly tell patients they are not trusted [15,16]. The CDC Guideline [1] conceded this lack of evidence. Commonly used UDSs (immunoassays) frequently yield false positive and false negative results [17]. Contracts and urine drug screens provide a commonly used fulcrum for terminating patient care; from our many-year observation of patients and clinical outcomes, these terminations are usually unjustified (see also [18]). We suggest that, given their potential for harm, these practices should be suspended pending the collection of scientific evidence that the potential harm is outweighed by benefit.

Prescription drug monitoring programs (PDMPs) can certainly be helpful in identifying the rare patients who doctor shop. However, it is important to clearly understand the role that PDMPs likely played in the licit opioid crisis driven by pill mills that existed until about 2013 and how this contrasts with the role they play today. There is a paucity of statistical data on pill mills precisely because, by design, they operated under the radar. In fact, one can only infer their prevalence and output from CDC state maps of prescriptions/100 persons [2,19]. Nonetheless, it appears that pill mills were responsible for flooding much of the country with large supplies of prescription opioids, likely starting in the late 1990s [2,20]. Because the use of drugs distributed by pill mills was not closely supervised medically, misuse, diversion, and addiction appear to have become prevalent, both in states with large pill mill distributions and in areas of the country that were most susceptible to the lure of opioids because of poverty, mental illness, hopelessness, and a complex of other factors [2,21–26]. Deaths from drugs prescribed by pill mills also likely made a substantial, albeit incalculable contribution to the rising mortality from prescription opioids between the late 1990's and 2012.

The pill mill crackdown, the introduction of abuse-resistant Oxycontin [27], and PDMPs brought the pill mill era to an end. Thirteen states, most importantly the State of Florida (arguably the pill mill epicenter), have enacted laws regulating pain management clinics that directly constrain pill mills, 12 by 2013 [28]. It is difficult to believe that this legislation by so few states was sufficient to put pill mills out of business. However, at the same time, individual states were establishing PDMPs, 27 by 2005, 43 by 2010, and presently, all states but Missouri [29]. It appears that the crucial part played by PDMPs was to shine a bright light on pill mills, rendering their activity so transparent that their business model became too risky (https://www.cato.org/events/patients-privacy-and-pdmps). After 2013, the legitimate role of PDMPs appears to have been reduced to one of discouraging the re-establishment of pill mills and their fueling of the illicit drug market. It is thus not surprising that in the post-pill mill era, the impact of PDMPs on the use of opioids to treat chronic pain in the clinic is unclear and controversial [30,31], dependent upon the details of PDMP laws [32], and may actually be negative [18,32,33].

Unfortunately, the triumph achieved by PDMP contributions to eliminating pill mills has likely come at great cost as these databases were instituted as a law enforcement tool and not for purposes of enhancing public health. As a result, they are highly susceptible to misuse by national (e.g., DEA) and state law enforcement agencies to take action against clinicians who are 'high prescribers' simply by virtue of the nature of the patients they treat [18] or the high overdose risk scores generated for their patients on the basis of the NarxCare© algorithm (currently nested in the PDMP platform of most states). NarxCare© overdose risk scores are calculated on the basis of an opaque proprietary algorithm, the scientific basis for which is unknown (and notwithstanding the absence, to our knowledge, of any scientific studies of causes of overdoses – see below). Overdose risk scores are translated into odds ratios of unintentional overdose death (over what time interval is not stated). In the State of Florida, a score of 0–200 is assigned an odds ratio of 1. A score of 901–990 is associated with an odds ratio of 329, an instrinsically alarming number. However, it is worth considering that, if the risk of overdose death with a score of 0–200 were 0.001%, then the risk with a score of 901–990 would be 0.329%. Because of the NarxCare© algorithm, PDMPs may artificially inflate risk scores for women, racial minorities with complex, pain-related conditions, the poor, the uninsured and under-insured, rural patients, and patients with multiple comorbid diseases, including mental health disorders [18].

The CDC 2022 draft guideline concedes that 'there is no validated', reliable way to predict which patients will suffer serious harm from opioid therapy and no reliable way to predict which patients will benefit from opioid therapy [34]. We suspect that, in the extraordinarily complex and dynamic process of providing individualized treatment of patients in chronic pain, the problem of calculating risks and benefits at the start of treatment is sufficiently complex to not be susceptible to any formulaic approach. Even an artificial intelligence approach would require collection of a large amount of scientifically valid data on a large population of patients and their clinicians and it would require additional data collection over the longitudinal extent of treatment as that treatment, the

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patient, and the clinician change over time. In the meantime, clinicians can only deal with the problem through thorough patient evaluation, judicious care, and very cautious introduction and titration of treatment.

The mere possibility of state action, as well as high computed overdose risk scores, seems likely to discourage prescription *per se* or prescription of adequate doses, which in turn might lead some patients to seek medication in the illicit market [18,32]. In sum, using PDMPs to avoid duplication of prescriptions appears to be prudent; however, use of the PDMP overdose risk score may be associated with harm.

Therapeutic targets

Complete alleviation of pain is not a realistic target for any pain management program. Rather, the objective should be minimizing suffering and maximizing functionality. Minimizing suffering and maximizing functionality are multidimensional goals, achievement of which requires taking a broad-spectrum approach to pain management, particularly including successful treatment of depression (see below).

It is our impression from clinical observations that maximizing functionality, whether it be in home activities and social life or actually returning to work, can be analgesic. Unfortunately, we were able to find only a single study bearing on this issue: in a prospective cohort study of 557 employees with back injury, return to work within 7 days was associated with a reduction of pain at 3 months, controlling for baseline pain (measured on a visual analog scale [VAS]34) and a large number of variables previously shown to be predictive of return to work [35]. Given the many limitations of this study, these results can be viewed as no more than suggestive.

The customary target of pain treatment in both research and clinical practice is score on a VAS in various forms [36] or numerical rating scales (NRSs). While this type of measurement may be of some value in both fields, it also has serious weaknesses [2]. In research, VASs and NRSs may be, like subjective measures in general, susceptible to anchor point drift over time [37]. VASs also correlate poorly with more objective, laboratory-based measures of pain and with the McGill Pain Questionnaire [38].

In clinical practice, VASs/NRSs do not provide the clinician a firm fulcrum for decision making. For example, in our experience, it is very common for patients, when asked about their pain, to say that it is terrible. However, when asked how well they are controlling their pain with their current medical regimen, they often respond that they are doing fine and do not want to change a thing. Thus, whether or not pain is *adequately controlled* constitutes a measure that reflects the sufficiency of the current medical regimen and provides a logistical guide to clinical decision making. If control is adequate, even if not perfect, then nothing needs to be changed. If control is inadequate as reported by the patient, then something needs to be changed (although often not opioid dosage). Research studies of treatment of chronic pain could also benefit from use of a logistic outcome measure, either loss of pain control or sufficient participant unhappiness with the regimen (because of lack of benefit or presence of intolerable side effects) that they drop out of the study [2,39]. The use of exit interviews could further illuminate the reasons for trial drop out.

Usually, whether or not pain control is adequate can be discerned from a directed discussion with the patient. However, it may only emerge through the course of the visit as a Gestalt impression that the patient is not doing well or that their status has declined since the last visit. The 3-item PEG scale (average pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G)) does not provide a logistic end point and is susceptible to the weaknesses of analogue self-report scales in general. However, it may nevertheless be helpful to the practitioner to the extent that it informs the discussion. The PEG scale is extremely brief and it is well validated [36].

Individualization of treatment

Because of the complexity of patients with chronic pain, variability in severity of pain and its impact on the patient's life, enormous differences in drug metabolism and sensitivity and a high prevalence of idiosyncratic side effects [2], individualized treatment is essential.

Treatment constraint

Treatment of chronic pain often requires the use of multiple drugs with limited therapeutic windows. This is particularly the case with opioids. Not just dosage but timing of dosing may be important. Maximizing precision in defining and constraining the daily medical regimen and assuring tight compliance becomes essential. Full knowledge of all CNS-active drugs a patient is taking is paramount. State PDMPs can be helpful with prescribed controlled substances. However, consumption of one CNS-active drug – alcohol – is difficult to quantify and

may be denied by patients, even as its addition to pain regimens may be dangerous as it too is a CNS depressant. Furthermore, consumption of alcohol in conjunction with some long-acting opioid formulations can markedly accelerate release of the opioid [40]. Alcohol is involved in 20% of emergency department visits, as well as deaths involving opioids [41].

Unfortunately, presently available statistics do not adequately define alcohol use in patients prescribed opioids for management of chronic pain, as opposed to patients using illicit drugs, in whom polysubstance abuse is the rule [42,43]. Furthermore, no studies have been conducted that seek to quantify the incremental risk of death posed by co-consumption of alcohol, as has been done with benzodiazepines (see below). Notwithstanding the absence of precise data, it would seem that alcohol consumption should be either completely proscribed or be extremely limited in patients under treatment for chronic pain.

'Borrowing' medication from a friend or family member may be another contributor to lack of therapeutic control.

Depression

As Braden *et al.* [44] put it, "It is possible that opioids prescribed to depressed persons may be treating an undifferentiated state of mental and physical pain." If depression can be viewed as an amplifier of suffering related to pain, then successful treatment of depression might be expected to reduce chronic pain and reduce the needed opioid dosage [2]. Our experience has been that definitive treatment of depression may be the single most important approach to the patient with chronic pain, routinely making a major contribution to control of suffering related to pain and often obviating the need for opioid dosage escalation. Unfortunately, because of limitations in opioid treatment clinical trial design (see below), this hypothesis has not been formally tested.

Between 30 and 54% of people with chronic pain also have major depressive disorder (MDD) [45]. Patients with moderate to severe pain have a more than twofold increase in the risk of developing a mood or anxiety disorder [46]. General practitioners detect on average 50% of cases of depression [47]. Rates of depression reported in large opioid database studies range from 12.9% to 32% [48,49]. Our clinical experience is that the figure commonly seen in pain management practice may be greater than 90%. This suggests that depression is also commonly missed in patients being treated for chronic pain [2]. Diagnosed depression is often untreated or under-treated [50]. Many studies suggest that aggressive treatment of depression has salutary effects on pain management and might mitigate many of the most troublesome issues associated with treatment of chronic pain in patients with comorbid depression [2].

A recent study demonstrated that the Patient Health Questionnaire-9 [51] achieved high sensitivity (85%) and specificity (85%) for a diagnosis of depression (using a score of $\geq$10 as the criterion) relative to a gold standard semi-structured diagnostic interview (e.g., Structured Clinical Interview for Diagnostic and Statistical Manual) [52]. The brevity of the PHQ-9 instrument renders it readily usable in office practice.

Depression can usually be successfully treated. However, to accomplish this, it may be necessary to pursue well-titrated pharmacologic regimens. Combinations of antidepressants, e.g., selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs), bupropion, and mood stabilizing anticonvulsants, e.g., carbamazepine, valproate, or lamotrigine (even in patients without a history of bipolar disorder) may be useful. Psychological therapies may be of additional benefit for some patients. Interpersonal psychotherapy, behavioral activation, cognitive behavioral, problem solving, and psychodynamic therapies, social skills training, and supportive counseling have been shown to be equally effective with effect sizes in the 0.6–0.9 range [53]. Unfortunately, there do not appear to have been any studies of patient characteristics that predict better response to these therapies. The extent to which such therapies are readily available, the extent to which health insurance will cover their costs, and the ability of patients to participate have not received adequate attention.

Sleep disorders

Sleep disturbances occur in 50%–70% of patients with chronic pain [54,55]. It is a matter of common sense that daytime exhaustion because of poor sleep is unlikely to be conducive to successful pain management. It also seems likely that enduring pain during long sleepless nights is associated with inordinate suffering. Assuring good sleep by non-narcotic means might also help to prevent the development of tolerance, to the extent that this is ever a concern (see below), by providing an overnight opioid holiday. Assuring good sleep on a regular schedule might also help to achieve the precise timing of daytime medications, including opioids, that is needed to achieve adequate pain control and minimize risks.

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Statistical associations between sleep disruption and chronic pain have been documented but the direction of causality has not been established [56–58]. A recent secondary analysis of an RCT of opioid treatment found that greater sleep disturbances at baseline predicted less improvement in pain in both treatment groups [59]. There have been no adequate RCTs to address this question (but see pilot studies [60]).

Restless legs syndrome/periodic limb movements of sleep (RLS/PLMS) has a prevalence of 5–13% in North American and European populations, with or without pain [61]. Prevalence is higher in patients with renal failure, iron deficiency, and pregnancy. There is an association with a host of other factors, including use of a number of major drug classes, a large spectrum of neurological disorders, rheumatologic disease, hypoxic conditions (e.g., chronic obstructive pulmonary disease, COPD), hypertension, obesity, and diabetes [61]. The disorder can be extremely distressing and markedly reduce sleep hours and quality of life [61]. In our experience, it can lead to daytime impairment in concentration, if not frank hypersomnolence. The syndrome is readily treated with dopaminergic agents or with calcium channel α2δ receptor ligands (gabapentin or pregabalin) [61].

In most of the remainder of patients with insomnia, the disorder is idiopathic. The vast treatment literature has recently been captured in an overview of systematic reviews [62]. Insomnia may be mitigated in some patients with improvements in sleep hygiene and with cognitive behavioral therapy (CBT), assuming it is available, covered by insurance, the patient can accommodate the time commitment, and compliance is good. CBT is the first line non-pharmacologic therapy recommended by the American College of Physicians and the American Academy of Sleep Medicine [63,64]. CBT has demonstrated effect sizes as high as 0.8 for some sleep outcome measures but data on the long-term durability of the effect are lacking [64]. It may also be effective in only 30–40% of patients [63]. Rosenberg *et al.* [63] suggest that this may reflect the effects of time commitments, the work involved to change sleep habits and schedules, and highly ingrained maladaptive beliefs about sleep. There is a great need for treatments of insomnia that work quickly and are immediately available to all patients.

Beyond these measures, clinical experience suggests that prolonged sleep latency can usually be readily treated with a titrated second-generation benzodiazepine. We are aware of the large number of publications and guidance documents by professional associations strongly recommending against their use. However, adequate quality scientific evidence for these recommendations appears to be lacking (see below). In our experience, poorly sustained sleep/terminal insomnia can almost always be treated with titrated trazodone. This impression receives support from clinical trials [65], although these can be criticized for their generally small numbers of participants, limited titration range, and short duration [62]. A small percentage of patients treated with trazodone develop severe imbalance and a feeling of mental cloudiness; the drug is absolutely contraindicated in such patients. Orexin receptor antagonists (e.g., suvorexant) have demonstrated effectiveness and have recently received a lot of attention, but we lack comparative effectiveness studies [63]. Diphenhydramine, the hypnotic constituent of nearly all over the counter sleep medications, is contraindicated because of its potent anticholinergic effects and their potential impact on memory acquisition and consolidation (reviewed in [66]).

Specific drugs for specific types of pain

Different types of pain call for different treatment approaches.

Somatic pain

The overwhelming preponderance of pain encountered in medical practice is somatic/nociceptive and is of musculoskeletal origin [67]. This pain may be variously characterized as aching, hard, or sharp but steady. Nonsteroidal anti-inflammatory drugs (NSAIDS) are viewed as the drug of choice and a large number of RCTs have demonstrated their efficacy and relative safety [68,69]. However, although the effect sizes reported have often been in the moderate range (~0.5), the absolute effects have been limited: 14–16 mm on a 100 mm VAS [68]. Potential hazards from long-term high-dose therapy with NSAIDS are well established and should prompt judicious monitoring of side effects.

From our clinical experience, the mainstay of treatment for somatic pain, at least when it is moderate to severe, is likely to be opioids. There are over 100 RCTs of opioids [2]. Unfortunately, they have substantially failed in a number of ways [2,39]. They have not provided sufficiently compelling evidence of the efficacy and safety of opioids in the treatment of chronic pain. They do not emulate good clinical practice (e.g., given their short duration, they fail to achieve the very gradual upward and often extended titration needed to assure safety, minimize side effects, and achieve optimal pain control and successful treatment of important comorbidities). They have not accommodated the enormous range of opioid metabolism and dosing requirements or the prevalence of idiosyncratic side effects

of opioids. By virtue of the limitations of their designs, in most studies, dosage has been limited, thereby limiting generalizability of results to patients with moderate to severe pain, and side effects have been magnified. They have not provided an adequate platform for comparative effectiveness studies (e.g., with NSAIDS or nonpharmacological treatments) or studies of the influence of important co-morbidities. And finally, they have not enabled the extended testing of opioid treatment needed to answer questions bearing on long-term opioid use [2,39]. We have proposed a clinical trial design, the enriched enrollment, randomized gradual withdrawal (EERGW) design, that might serve to address these problems [39].

Topical diclofenac gel may provide some benefit for joint pain [68]. Clinical experience suggests that topical lidocaine, diclofenac gel and muscle relaxants such as benzodiazepines (discussed more extensively below), carisoprodol, methocarbamol, metaxalone, baclofen, cyclobenzaprine, and tizanidine (even if prescribed only at bedtime because of associated sleepiness) may provide some relief of chronic neck or low back pain but clinical trial data bearing on these treatments is almost non-existent [70,71]. In our experience, most of these pharmaceuticals are niche drugs – helpful in some patients and of no value in others. Given this anecdotal clinical evidence that they are niche drugs, it will be important for clinical trials to assess outcomes in terms of responders and non-responders. Such trials might also benefit from enriched enrollment designs. The potential adverse effects of these commonly used drugs also need to be assessed.

Strategic use of soft-cervical collars for neck pain (e.g., during long stints at a computer or during long drives) may be beneficial but there is no clinical trial evidence bearing on this application. Gabapentin and pregabalin ('gabapentinoids') have come into widespread use for treatment of musculoskeletal pain but RCTs have demonstrated no efficacy in this application [72] and both drugs are associated with a substantial incidence of side effects, at times severe enough to warrant drug discontinuation [69].

Neuropathic pain

Neuropathic pain is characterized as burning, searing or stinging and it is often associated with allodynia, whether the cause is central or peripheral. By far the most common settings are diabetic polyneuropathy and post-herpetic neuralgia but neuropathic pain may also occur after traumatic or surgical neural injury and it may be associated with idiopathic small fiber neuropathy, complex regional pain syndrome and paroxysmal extreme pain syndrome.

RCTs of gabapentinoids support their use for neuropathic pain [69,73,74]. The effect size in participants with painful diabetic polyneuropathy has been moderate (0.44) [75].

Multiple RCTs support the use of SNRIs (e.g., duloxetine) for treatment of neuropathic pain [75,76]; the effect size for diabetic polyneuropathy has been 0.47 [75]. A number of studies also support the use of SNRIs for treatment of somatic pain [77,78]. For neither type of pain is it clear whether the drug effect is achieved via impact on descending serotonergic and noradrenergic pathways or on comorbid depression [79].

Amitriptyline, a tricyclic antidepressant, has shown an effect size of 0.95 for painful diabetic polyneuropathy [75]. However, the side effects of this drug and its potent anticholinergic effects present strong contraindications to its use.

Moderate effect sizes have been demonstrated for voltage sensitive sodium channel agents (e.g., lamotrigine, lacosamide, carbamazepine, oxcarbazepine and valproate) in treatment of painful diabetic neuropathy [75]. One RCT [80] and a network meta-analysis have shown topical lidocaine to be as effective as pregabalin for neuropathic pain and to be associated with fewer side effects [81].

A meta-analysis of 16 controlled studies concluded that, notwithstanding limitations related to trial design, opioids do provide substantial relief for neuropathic pain [82]. Our experience is that neuropathic pain is often very difficult to treat adequately and often, multiple drugs must be tested and multi-drug regimens used. Unfortunately, retrospective cohort studies have shown that concurrent use of gabapentin and opioids is associated with an odds ratio of drug-related hospital utilization of 1.64 [83] and of opioid-associated death of 1.5 [84]. Notably, the study by Peckham *et al.* controlled for pre-treatment event rate, thereby suggesting that the increase they documented was predominantly related to the drug combination and not to underlying co-morbidities. However, neither study entertained the possibility that gabapentin use is associated with encephalopathy in a modest subset of all patients (~10% in our experience), a subset in whom we would consider the drug to be contraindicated. Neither study examined respiratory side effects *per se*. There do not appear to have been any adequate clinic studies of respiratory depression by gabapentinoids alone.

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Neuralgic pain

Neuralgic pain is classically characterized by repetitive intense, lightning-bolt like pain, trigeminal neuralgia being the prototype [85,86]. In our experience, this type of pain may occur in the extremities of some patients, most often in the wake of orthopedic or vascular surgery, and it may occur after amputation (often in association with neuroma development), in which case there may be a phantom limb component. It may also occur with central nervous system lesions, as in multiple sclerosis [87].

Mechanisms underlying pain following neural injury are complex and not well understood, different mechanisms may be operative in different patients, and pain is characterizable as true neuralgia in only some cases. At times, even in the case of trigeminal neuralgia, the pain is not lightning in nature but rather aching, hard, or burning in quality, it may be variable in duration (up to hours), and its distinguishing characteristic is very rapid onset and offset [85]. The true neuralgias are associated with myelin injury and, in the face of such injury, affected axons insert extra voltage-sensitive sodium channels in the axonal membrane, thereby enhancing the probability of successful action potential propagation but at the risk of causing ectopic generation of action potentials, ephaptic transmission, and paroxysms of high frequency discharges. For this reason, the treatment of choice would logically be drugs that prolong the closed state of voltage sensitive sodium channels.

This hypothesis has only been tested in patients with trigeminal neuralgia, for which anticonvulsants such as carbamazepine and oxcarbazepine have been the standard of therapy for decades, despite the absence of adequately powered RCTs [85,86,88]. Alternatives include other voltage sensitive sodium channel agents such as lamotrigine [88], lacosamide [89], eslicarbazepine, and phenytoin [86,88], as well as a number of other agents including baclofen, gabapentinoids and botulinum toxin type A [86,88]. Often dosage of voltage sensitive sodium channel agents needs to be titrated to very high in the therapeutic range. Our limited experience in treating true peripheral neuralgia suggests that these drugs can be quite effective. However, research on treatment of neuralgia affecting nerves in the extremities has not been sufficient to validate our hypothesis. In most studies, the precise nature of the pain is not adequately specified and the term neuropathic pain has come to represent all pain thought to be of neural origin, regardless of its characteristics (e.g., [90]).

Migraine

Medications now available for abortive treatment of acute migraines, most notably triptans and gepants (ubrogepant, rimegepant and atogepant) have markedly improved the level of control of individual headaches achievable by migraineurs [91,92]. Nonsteroidal anti-inflammatory agents (NSAIDs) may also have adjuvant value in the abortive treatment of migraine [92]. Older prophylactic drugs, e.g., β-blockers, tricyclic antidepressants, SSRIs, SNRIs, calcium channel blockers, NSAIDS and anticonvulsants (valproate, topiramate), while supported by RCTs, have largely failed to translate into clinic practice. Perhaps the best evidence of this is the small percentage of patients still taking these drugs a year later (as low as 17% [93–95]). However, newer approaches, most importantly monoclonal antibodies to the calcitonin gene related peptide (CGRP) or its receptor (erenumab, galcanezumab, eptinezumab and fremanezumab) substantially reduce migraine frequency or severity in many patients [96]. Botulinum toxin treatment may be of modest benefit in some patients [97].

Even with recent advances in abortive and prophylactic therapy of migraine, there remain many patients who are either disabled, miss much work, or experience poor quality of life despite optimal treatment. There are two circumstances in which opioids might play a role: as adjuvants to abortive treatment of migraine and as palliative treatment for headache that is constantly present or for which sufficient abortive control cannot be achieved. Several preclinical studies [98–100] have demonstrated opioid receptors on trigeminal endings that plausibly could mediate an opioid abortive effect in parallel to the triptan effect. In a recent comparative effectiveness review of acute treatment of migraine [91], none of the 15 RCTs of opioids used them for abortive treatment of migraine (i.e., at the instant of migraine onset, with or without a triptan or gepant, and not for analgesia). Our clinical experience is that the effect can be quite large and side effects absent or acceptable. Constant headache or slowly waxing and waning headache can often be treated adequately with butalbital-acetaminophen ±caffeine compounds, despite the major onus surrounding these drugs as a potential cause of medication overuse headache and the paucity of studies testing their efficacy [101]. When pain is more severe and not sufficiently controlled with these drugs, an opioid regimen may be necessary to enhance analgesia (see below).

Specific treatments: opioids

Two classes of drugs – opioids and benzodiazepines – both valuable in the treatment of patients in chronic pain, have come under fire. For this reason, we have devoted special sections to the discussion of these two drug classes.

Opioid benefits & risks

Practitioners have a solid grasp of the efficacy of opioids in chronic non-cancer pain. However, the over 100 RCTs of opioids for chronic pain have suggested only modest effects and no trials have been definitive [2]. Unfortunately, absence of evidence is all too often construed as evidence of absence. The discrepancy between conclusions drawn from clinical practice and conclusions drawn from the RCTs is readily explained by inadequate RCT design. Opioids are not like atorvastatin: they require considerably more ingenious trial designs to test drug efficacy and to bring participant experience in clinical trials into close alignment with patient experience in clinical practice (see above). We have elsewhere suggested a trial design (EERGW) to meet this challenge [39].

Much has been made in the CDC guideline and by many other authors of the alleged harms associated with opioid treatment of chronic pain. The estimated annual opioid-associated case fatality rate with prescriptions of <20 milligrams morphine equivalent/day (MMED) is 0.035%; 20-<50 MMED 0.066%; 50-<100 MMED 0.16%; >100 MMED 0.25% [102] and >400 MMED 0.5% [103]. These data define a more or less linear increase in estimated opioid-associated case fatality rate with increasing dosage, without any inflection points. Therefore, the data do not support the use of any particular doses as definitive points that should guide opioid prescribing, e.g., 50 MMED or 90 MMED, as the CDC has done [1]. The CDC itself [1] conceded: "a single dosage threshold for safe opioid use could not be identified." We also do not know to what extent these mortality figures reflect the effects of opioids *per se*, and to what extent they reflect the effects of inadequate control of pain and associated comorbidities, e.g., depression. Finally, we do not know what percentage of these deaths reflect use of illicit opioids by patients managed in clinics [104,105], which, since the introduction of fentanyl, have become deadly. Occasional or consistent use of illicit opioids by only one in 400 clinic patients could generate the 0.25% opioid-associated mortality rate. One is led to ask, to what extent does undertreatment of pain incentivize patients to seek recourse in the illicit drug market?

The case fatality figures we have cited argue for clinical discretion in weighing benefits against risks. Furthermore, the risks and benefits of opioid treatment appear to be comparable to those associated with treatments in other domains of medicine [2]. For example, the case-fatality rates associated with >100 MMED and >400 MMED opioid therapy are comparable to the risks of fatal bleeding associated with use of rivaroxaban (0.2%/year) and warfarin (0.5%/year) in the prophylaxis of stroke due to atrial fibrillation [106]. This might be considered an inapt comparison. However, systemic anticoagulation for atrial fibrillation is recommended for CHA_2DS_2-VASc scores of ≥2 [107], which correspond to an annual stroke risk of ≥2.2% [108]. The 5-year likelihood of being stroke free in a patient with the 2.2% annual stroke risk is 89.5%, making long-term discounting of expected disvalue a significant factor. On the other hand, the patient with moderate to severe chronic pain experiences suffering and disability from the outset [2], in which case there is no expected disvalue discounting. In our experience, patients in moderate to severe chronic pain are often amazed that we even bring up mortality risks on the order of 0.25%/year, as if this might dissuade them from using opioids to treat a condition that dominates their lives and is associated with great suffering. And finally, it can be argued that, from an ethical perspective, the acceptable risk of death should be a matter for the patient to decide, not her physician or august government institutions.

Prescription opioid use may be associated with harms short of death (see review, [109]). These include androgen deficiency, hypogonadism or erectile dysfunction in men [110,111], altered menstruation and menopause in women [112], osteoporosis, risk of falls [113–115], accidental self-injury (fractures, ligamentous tears and head trauma) [113,114,116,117], peptic ulcer disease or gastrointestinal bleeding [113], iron-deficiency anemia [113], prolonged QT interval (especially with methadone) and myocardial infarction [118–120]. It has not been determined to what extent these harms are a consequence of opioids *per se*, chronic pain and its comorbidities or some combination of the two.

All opioids (including buprenorphine) have a dose-related depressive effect on all respiratory parameters, including respiratory rate, tidal volume, minute ventilation and sensitivity to hypoxia and hypercapnia [121]. These effects can be magnified by co-administration of benzodiazepines (see below). Opioids also induce central apnea and worsen obstructive sleep apnea. The impact of opioids on respiratory function is even greater in patients with sleep disordered breathing (SDB; number of apneic and hypopneic episodes/hour (AHI)) and the impact may be further

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increased in patients with SDB and COPD [121]. In both rapid eye movement sleep (REM) sleep and non-REM (NREM) sleep, ventilatory responses to CO_2 are blunted but responses to hypoxia are better maintained.

In a large retrospective cohort study (n = 130,979) of patients 66 years and older with COPD employing propensity score matching, the introduction of opioids was associated with significant increases in emergency room visits for COPD or pneumonia (hazard ratio [HR]: 1.14); COPD or pneumonia-related mortality (HR: 2.16); and all-cause mortality (HR: 1.76) [122]. Risks associated with use of pure opioids were even higher but results bearing on relationship to dosage were contradictory. Unfortunately, the analysis was not controlled for the incidence of outcome events in the period *before* initiation of opioids; therefore, we cannot know to what extent the results reflect the impact of pain and its comorbidities, opioids or some combination of the two. Nadpara *et al.* [123] employed a retrospective nested case control design to determine risk factors for life threatening respiratory or CNS depression among 18,365,497 patients in the IMS PharMetrics Plus database. The most prominent factors associated with elevated risk were substance use disorder (odds ratio [OR]: 10.20), depression (OR: 3.12) and bipolar disorder (OR: 2.18) (see [2] for extended discussion of the challenges associated with operationalization of the diagnosis of substance use disorder). COPD and sleep apnea were associated with lesser (albeit statistically significant) risk (ORs of 1.47 and 1.11, respectively). A comparable study of Veterans Health Administration patients [124] published four years earlier found the OR of an adverse outcome associated with COPD to be 1.5 and with sleep apnea 1.4.

We have little data bearing on practical approaches to the challenges posed by potential respiratory insufficiency in patients with SDB or COPD treated with opioids. Clearance of CO_2 is a more sensitive measure of ventilatory adequacy than O_2 levels [125] and serum bicarbonate would provide a ready measure of chronic CO_2 retention. Because oxygen drive becomes more important during sleep in patients treated with opioids [121], treatment with oxygen is contraindicated. In patients with SDB, it is not clear whether severity of individual hypoxic events or the cumulative impact of multiple hypoxic events is more important [121]. In either event, overnight oximetry might provide a useful basis for informed decision making. It is clear enough that clinicians need to be vigilant for SDB, including nocturnal snoring and observed apneic events and daytime hypersomnolence, fatigue and impaired concentration. The threshold for referral to a sleep specialist or pulmonologist should probably be low.

Opioid dosing

It is well established from RCTs that there is a roughly 13-fold variability in opioid dose requirements [2,126,127]. These results are congruent with those of multiple studies of management of post-surgical pain in opioid-naive patients, which have revealed an approximately 15-fold variability in opioid dose requirements [128–131]. This experience with opioid-naive patients suggests that dose-variability is a phenotypic phenomenon and not simply related to tolerance [2]. Severity of pain, genetically related differences in metabolism of prodrug and drug, and differences in CNS sensitivity are likely responsible for this enormous variability [2]. Thus, it is very clear that, contrary to the CDC Guideline, there is no scientific basis for a one dose fits all recommendation, much less the assertion that dosage above some arbitrary level, e.g., 90 MMED, is associated with sufficient risk to warrant dosage limitation [2]. Failure to recognize the high variability in opioid dosing requirements has also powerfully fueled the notion that requests for higher doses to treat uncontrolled pain constitute evidence of addiction when, in reality, pseudo-addiction is almost certainly the better term [6,132] and further dose titration would provide a solution.

In recognition of this dosage variability, we suggest that clinical practice should incorporate opioid titration to efficacy in *control* of chronic pain or just short of cognitive or neurological side effects, most particularly reduced alertness (or worse, sleepiness), slurring of speech and imbalance. It is well established that opioids are associated with a high incidence of idiosyncratic side effects [133,134]. These include dysphoria, euphoria, nausea, dizziness and itching (at times extreme). What is not well recognized is that these side effects are often associated with particular opioids and, in our experience, may be avoided by switching to a different opioid. Most patients treated with opioids experience constipation. In nearly all, this can be satisfactorily treated with docusate, titrated polyethylene glycol, or senna, and failing this, bowel opioid receptor antagonists such as naloxegol or naldemedine, or titrated linaclotide.

There is no evidence that different opioids vary in their efficacy in treatment of pain when differences in potency and individual metabolism are taken into account. However, the potential for drug–drug interaction effects might ultimately be relevant to choice of drug [40]; further research is needed. We have found that side effects are presently the major limiting factor in managing pain with opioid analgesics. If side effects become intolerable before adequate pain control is achieved, a switch to a different opioid may solve the problem. Some patients cannot tolerate adequate doses of any opioid available. Average dose equivalents (MMED) for alternative opioids are listed in Table 1. These

Table 1. Approximate dose equivalence of opioids in widespread use[§].

Drug (immediate or sustained release)	Morphine equivalent conversion factor/mg of opioid[†,‡]
Morphine	1.0
Buprenorphine transdermal	2.4
Codeine	0.15
Fentanyl transdermal	2.4
Hydrocodone	1.0
Hydromorphone	4.0
Meperidine	0.1
Methadone	3.0
Oxycodone	1.5
Oxymorphone	3.0
Tramadol	0.10

[†]Examples: 30 mg of codeine is equivalent to 4.5 mg of morphine/day; 30 mg of methadone is equivalent to 90 mg of morphine/day; a 10 mcg/h buprenorphine patch is equivalent to 24 mg morphine/day; and a 100 mcg/hour fentanyl patch is equivalent to 240 mg morphine/day.
[‡]Equivalencies are based on average data and may vary substantially from patient to patient. Therefore, when converting from one opioid to another, one should err on the side of substantial underdosing. For example, if converting from morphine 90 mg/day to oxycodone; the starting dose of oxycodone should be 30–45 mg/day.
[§]Adapted from [135]. (See also dose calculator: https://www.oregonpainguidance.org/opioidmedcalculator/).

figures do not reflect individual differences in opioid pro-drug or drug metabolism, which vary from drug to drug. Unfortunately, because MMED can serve only as a very rough guideline to clinicians switching opioids, an MMED guided approach does not appear to meet the standards required of a metric for acceptable opioid dosing, CDC recommendations notwithstanding [1].

There is limited clinical trial evidence, deriving from those few RCTs in which full titration was enabled, bearing on the range of opioid dosage likely to be required in clinical practice. Katz *et al.* [127] reported the results of an enriched enrollment, randomized withdrawal trial (a design that enables full dosage titration): 53% of participants had been titrated to ≤90 mg morphine equivalent/day (MMED), 81% to ≤150 MMED, and 93% to ≤240 MMED. Maximum dosage in the trial was 420 MMED (see also Rauck *et al.* [136]). There are anecdotal reports of some patients successfully managed with dosage >1000 MMED [137].

The clinical trial designs used to test the value and disvalue of opioid treatment have not been adequate to assessing the value of particular opioid regimens. Therefore, we rely solely on logic and clinical experience in the following suggestions. It is clear enough from clinical practice that dosing needs to be individualized. For many patients, a short-acting opioid prescribed 1–3 times daily as needed will suffice. Others with moderate to severe pain will benefit from a 'base' of a titrated long-acting opioid scheduled twice a day, optimally on waking and 8 h later. It seems to be widely accepted that sustained release opioids (e.g., morphine sulfate ER and Oxycontin) and long-acting opioids (e.g., methadone) provide 12-h pain relief. However, in practice, a better estimate would seem to be 8-hour duration of action – an observation supported by data on pharmacokinetics [40]. Supplementation of these regimens with two to three doses of a short acting opioid can often be very beneficial.

From clinical experience, it appears that proactive dosing of both short and long-acting preparations is preferable – slowing or stopping the build-up of pain rather than treating pain that has already become severe. A typical regimen might consist of morphine sustained release 30 mg on awaking and 8 h later, plus two doses/day of immediate release morphine 15–30 mg, one taken on awaking because pain is often severe then, the other taken as needed. Usually, adequate sleep can be achieved with hypnotics without use of a third dose of opioid in the evening, thereby allowing opioid levels to reach a trough overnight. This theoretically might mitigate respiratory depression during sleep and it may be of value in preventing development of tolerance. However, the need to take any measures to deal with SDB or the development of tolerance remains to be determined by controlled clinical trials. On the face of current evidence, risk of tolerance in clinic populations appears to be extremely low (see below).

The low estimated annual case fatality rate associated with opioids should not be construed as evidence that they are perfectly safe. As we have noted, tight control of opioid regimens in each patient is essential. We also suggest uniformly starting at the lowest possible dose and very gradually titrating until adequate control of pain is achieved (short of cognitive or neurological side effects). It may take many months to achieve optimal dosage and to effectively treat common but important comorbidities such as depression.

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The CDC Guideline [1] reviewed the evidence bearing on the pros and cons of long-acting versus short acting opioids. Even though this evidence was conflicting and yielded no consensus, the Guideline recommended the use of short acting opioids over long-acting opioids. In many patients, particularly those with mild to moderate pain, short-acting opioids will suffice and there is no need to use long-acting opioids. We suggest on the basis of clinical practice that actually, use of long-acting opioids might be safer [137] (see also [40]). However, comparative effectiveness studies are clearly needed. Long-acting opioids need to be scheduled: doses are stipulated to be taken at specific times of the day. Thus, there is, in principle, much less chance for inadvertent overdosing related to taking these doses at excessively short intervals [138]. Long-acting opioids also help to provide constant analgesic effect over the entire day. However, because of the extended time required to achieve steady-state levels using such preparations, titration must be made at long intervals, e.g., >2 weeks (longer with methadone – see below). Short acting opioids are the ideal approach to breakthrough pain.

Factors associated with overdoses of prescribed opioids have not received adequate scientific attention [139]. We define overdose as inadvertent or deliberate ingestion of excessive doses, not encephalopathy associated with use of prescribed medications as directed, recognizing that for patients receiving opioids titrated to just short of cognitive or neurological side effects, the likelihood is higher that an inadvertent overdose will have serious consequences. Factors associated with overdoses likely include excessively rapid dosage titration by physicians, inadvertent double dosing by patients, insufficiently close clinical monitoring and patient-initiated dosage escalation outside the context of clinic visits [2]. Clinical warning signs, including reports by family members of altered mentation, and observation of cognitive or neurological impairment by clinicians, should lead to immediate measures to improve discipline in opioid dosing or reduction in total dosage [2]. With short-acting opioids, there is a particular risk that a patient may take a dose and then, an hour later, take another dose, forgetting that the first dose had been taken – effectively double dosing [2]. This is the most common reason for serious opioid-related alteration of consciousness that we have been able to discern, though, to our knowledge, no systematic studies have validated this impression. In our experience, the problem may be effectively circumvented by having patients keep a notebook beside the opioid supply, documenting the exact time they took the dose.

The CDC Guideline recommended making naloxone available to all patients prescribed opioids, despite explicitly conceding that there were no data bearing on its value [1]. Naloxone is almost certain to be of value for users of illicit drugs, who, since the advent of admixed heroin and fentanyl (and its various, even more potent derivatives), face enormous risks of overdose death. However, an RCT did not show naloxone prescription to be of benefit in clinic populations [140].

Methadone and fentanyl patches are special cases. The appeal of methadone is that it is a highly effective analgesic, generally well tolerated, and very inexpensive. However, it prolongs QT interval. Therefore, electrocardiographic monitoring is indicated. With sustained dosing, the elimination half-life increases to as much as 120 h because of tissue deposition, hence a need for particularly slow dose titration. Fentanyl patches are intended to be worn around the clock, thus theoretically posing risk of development of tolerance.

Buprenorphine is yet another special case. It was first synthesized in 1966 and since 2013, it has been used as a pharmacological adjuvant in the treatment of addiction [141]. However, over time, its value as an analgesic has been increasingly appreciated and, since CDC 2016, the drug, often in combination with low dose naloxone, has come into widespread use in the treatment of chronic pain. Buprenorphine is a high affinity partial agonist at the μ-opioid receptor, an inverse agonist at the κ-receptor, and an antagonist at the δ-receptor. A recent Bayesian network meta-analysis of 23 RCTs involving many different opioids suggested that oxymorphone was 5.1-times as likely to achieve 50% relief of pain relative to placebo, buprenorphine 2.38-times, and tramadol+acetaminophen 2.10-times [142]. Median time in randomization phase was 11 weeks (interquartile interval 2–13 weeks). Drop-out rate in the drug and placebo groups was similar, suggesting that participants were experiencing mild to moderate pain at baseline.

The results of meta-analyses have been substantially congruent [143,144]. In none of these studies was there any basis for assessing drug titration effects – a crucial omission given the 15-fold variability in opioid response. A 12-week Phase III enriched enrollment trial in 662 patients with moderate-to-severe low back pain (APS≥5) tested the value of transdermal buprenorphine 5 mcg/h (BTDS 5) and 20 mcg/h (BTDS 20) against oxycodone 40 mg/day [145]. Buprenorphine 5 mcg/h served as the placebo. The enrichment period served to eliminate people who could not tolerate the medications, not to titrate dosage. For the BTDS 5, BTDS 20, and the oxycodone 40 mg/day treatment groups, respective mean pain scores were 6.36, 6.46 and 6.46 at screening and 4.02, 3.35 and 3.26 at week 12. The pain scores indicate that these were predominantly patients with moderate pain. Nonetheless,

completion rates for the BTDS 5, BTDS 20, and the oxycodone 40 mg/day treatment groups were 58, 67 and 72%; rates of discontinuation due to lack of efficacy were 24, 11 and 7%, that is, substantial drop-out in the placebo group. This study demonstrated modest efficacy for BTSD 20 and oxycodone but it is impossible to put these results in context because of the absence of dosage titration and the limited duration of the study. A very small 10-day study suggested that higher doses of buprenorphine, up to 70 mcg/h, might be beneficial in patients with severe pain (>8/10) but at the cost of considerable side effects [146].

Opioids: dependence, tolerance & addiction

Dependence – the propensity for development of withdrawal symptoms with opioid cessation – is likely to develop in all patients on chronic opioid regimens [5]. However, dependence is typically much milder than the syndromes depicted by Hollywood; it is generally safe except in vulnerable populations (e.g., those with coronary artery disease or severe uncontrolled anxiety disorder), and it is easily avoided simply through gradual tapering. Of course, even in the absence of withdrawal effects, opioid tapering will be associated with redevelopment of uncontrolled pain.

The risk of developing tolerance – the need for constantly increasing opioid dosage to maintain effect – is uncertain. It is further uncertain whether all patients are susceptible to developing tolerance. Several studies, non-randomized, involving large numbers of patients treated with either transdermal fentanyl or oxycodone continuous release, have demonstrated the ability to achieve sustained relief of pain for years without dose increments [2,147–150]. It is also unknown whether regimens designed to mitigate development of tolerance, e.g., dosing with a long-acting opioid first thing in the morning and 8 h later, succeed in avoiding development of tolerance without seriously degrading pain control. Because of the seriousness of the development of tolerance, which destabilizes opioid regimens, adequately designed clinical trials are urgently needed to determine risk.

Addiction is a complex phenomenon, thought to be difficult to even define [151]. However, the problem becomes less opaque when all of the relevant variables are taken into consideration. Direct effects of drugs on the brain undoubtedly make some contribution, albeit a rather small one [10]: witness the important but very modest effect of nicotine replacement therapy on smoking cessation (16% compared with 10% for placebo) [152]. Nicotine is widely regarded as the single most addictive substance in common use.

In reality, a complex array of factors contributes to addiction, many of them psycho-social and economic [11,24,153,154]. Even in studies of rodents, animals housed in isolation consume far more morphine solution that do animals housed in complex colonies or even in pairs [155,156]. However, controversy remains as to what extent these results reflect effects of the opioid on stress wrought of isolation of these very social animals and to what extent avoidance of morphine is related to drug-induced social dysfunctionality in a group environment.

There is no good evidence that addiction is prevalent in clinic populations. However, the term opioid use disorder (OUD) has gained wide currency. There is strong reason to believe that OUD, in almost all cases, actually represents pseudo-addiction – the seeking of higher doses of drug because of inadequately controlled pain [6,132]. The diagnosis is made because a patient with inadequately controlled pain requests an increase in dosage, or because patients who undergo surgery request opioids long after all post-surgical pain is supposed to have resolved. It is noteworthy than even DSM5 criteria for OUD are likely to substantially conflate behavior associated with efforts to gain pain relief with efforts to achieve opioid-associated euphoria [2]. Absent an accurate quantitative measure of OUD, it is impossible to determine its incidence in clinical populations with any degree of confidence.

Opioid-induced hyperalgesia

Opioid-induced hyperalgesia has been well documented in preclinical studies; however, its mechanisms have proven to be extraordinarily complex and the phenomenon is still poorly understood [157,158]. The conclusion of the authors of a recent systematic review of 20 clinical studies accurately summarizes the current state of the science: "There is consistent type 3 and 4 study evidence that opioid tapering in [patients with chronic pain] reduces pain or maintains the same level of pain. However, these studies represented lower levels of evidence . . . , with the evidence being marginal in quality with large amounts of missing data" [159] (see also [160]). The prevalence of missing values is of particular concern because patients who could not tolerate the taper would be more likely to drop out. The existence of clinically significant opioid-induced hyperalgesia and its quantification could readily be determined using the EERGW RCT design that we have recently proposed [39].

Efforts to reduce opioid dosage, including those by the CDC, have effectively reduced opioid prescribing quite dramatically [2]. However, results of surveys, consistent with abundant publications in the gray literature, have suggested that this dosage reduction has been achieved at major cost, including worsening of pain, level of function,

mental health, ability to work and interpersonal relationships [161]. Two studies suggested increased risk of suicide, overdose deaths, heroin overdoses and opioid-related adverse events [162,163]. Other clinical trial data suggest that such adverse effects might be mitigated by comprehensive pain management programs but the quality of these studies has been insufficient to enable confident conclusions [164,165]. Given the fact that 18 million Americans have moderate to severe chronic pain [166], the limited availability of such programs needs to be taken into account. Thus, we need both better data on the harms associated with forced opioid tapering and a robust empirical demonstration of the clinical relevance of opioid-induced hyperalgesia before drawing any firm conclusions.

Specific treatments: benzodiazepines

Although benzodiazepines are not analgesic, they might provide a powerful pharmacological tool for dealing with some of the many problems that can arise in the management of chronic pain. They appear to be highly effective drugs for treatment of anxiety [167] and they are effective hypnotics [62,168]. However, the duration of benzodiazepine trials has been far too short to enable adequate individualization of treatment or to support inferences about the effects of long-term use. Benzodiazepines might enable relaxation of neck and back muscles, enabling better control of pain without increasing opioid dosage or perhaps avoiding opioids entirely. Unfortunately, there are no adequate studies of this application.

There exist several major impediments to use of benzodiazepines [169]. Benzodiazepine use, particularly in elderly patients, has long been guided by the Beers criteria [169,170]. The Beers criteria are based on an expert consensus developed through an extensive literature review with a bibliography and questionnaire evaluated by nationally recognized experts in geriatric care, clinical pharmacology, and psychopharmacology using a modified Delphi technique to reach consensus. Our impression is that the Beers criteria have been widely taken as an absolute contraindication to use of any dose of a benzodiazepine in the elderly and to strongly question the benefit/risk ratio in all patients [169]. However, the specific recommendation of the 2003 version of the Beers criteria on benzodiazepines is the following: Potentially inappropriate use: "short-acting benzodiazepines: doses greater than lorazepam, 3 mg; oxazepam, 60 mg; alprazolam, 2 mg; temazepam, 15 mg; and triazolam, 0.25 mg"; concern: "Because of increased sensitivity to benzodiazepines in elderly patients, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the suggested maximums" [170].

The 2019 update of the Beers criteria [171] is less specific and simply lists benzodiazepines as "potentially inappropriate . . . in elderly patients." Even now, 19 years after the Fick *et al.* report [170], we find little to disagree with. Nevertheless, we felt it worth reconsidering the benzodiazepine literature, if for no other reason than to emphasize the need for further studies.

Most of the case against benzodiazepines derives from cohort or case control studies [169,172]. In such studies, patients in the drug group are assumed to differ from those in the control group only in that they are taking the drug [169]. Quite obviously, patients in the drug group differ in another important respect: they suffered symptoms that led physicians to prescribe the drug, symptoms that might be having a major detrimental impact on the patient's life and that might be associated with intrinsic hazard, as well as additional comorbidities. Cohort studies can only establish statistical association. However, all too often, causality is inferred. It is unlikely that prescribing rationale for benzodiazepines can be adequately captured in retrospective studies by using propensity score matching [169].

By the very nature of cohort studies, risk is reported as relative risk. A relative risk of 3 might sound impressive until one is told that the baseline risk of the adverse effect in question is .01%/year. Clinical decision making is based upon the weighing of absolute likelihood of benefit against absolute risk of harm [173]. It might be perfectly appropriate to incur a certain risk of harm to achieve an important benefit (as we do, for example, in the use of antipsychotic medications and in the use of anticoagulants to mitigate stroke risk in patients with atrial fibrillation).

Absolute drug dosage may be a poor guide because optimal dosage, probably influenced in part by genetics, likely varies substantially between different patients [2,169]. The possibility that certain side effects may be associated predominantly with certain risk factors, e.g., falling/fear of falling resulting from imbalance (which is associated with heightened anxiety [174–176]), or idiosyncratic in nature (likely also because of genetic variants) is seldom considered. When guidelines proscribe the use of certain drugs, the absence of suitable alternatives is seldom considered [169].

Well-designed RCTs can address many, albeit not all, of the problems that plague cohort and case-control studies [169]. Testing the effects of drugs that require titration constitutes a particular challenge for RCT design [169]. There have been no RCTs of benzodiazepines that have been sufficiently long to enable individualized titration and a true test of benefit, or lack thereof, for chronic neck and back pain.

A number of other factors have been influential in arguments against benzodiazepines (see [177] for history and summary of the case against benzodiazepines). Foremost among these is the concept that the development of physical dependence with extended use constitutes an absolute contraindication to long-term benzodiazepine prescription [167]. Nearly any drug acting on the central nervous system is likely to alter receptor numbers or dynamics such that sudden withdrawal will have untoward effects. Avoidance of such effects becomes merely a matter of assuring that the medication is not suddenly interrupted and that cautious tapering is used when a decision is made to stop the drug.

Second, it is not widely recognized that symptoms that emerge after benzodiazepine withdrawal may reflect re-emergence or rebound of the symptoms for which the drug was originally prescribed, new symptom emergence, a withdrawal syndrome, or symptom over-interpretation [178,179].

Third, the idea that benzodiazepines are susceptible to abuse appears to have arisen in no small part from the fact that they are commonly used by illicit drug users, typically as a component of poly-substance abuse, often to mitigate undesirable side effects of drugs such as cocaine. However, abuse is actually rare in clinic populations [178].

Fourth, the co-prescription of opioids and benzodiazepines was strongly proscribed in the CDC Guideline [1]. The combination is associated with an approximate doubling of risk of opioid overdose death, which, for patients receiving >100 MMED, has been estimated to be 0.25%/year (see above). However, it is unknown to what extent this doubling of risk reflects the effect of the drug combination or the excess mortality associated with the underlying comorbidities (e.g., inadequately treated pain, insomnia, and anxiety) [180,181]. The incidence of ostensible drug-associated encephalopathy appears to decline steadily over the first year after concurrent drug initiation, even by the end of the first 90 days [182]. This raises the possibility that excessive starting dose or over-rapid titration may be contributory factors. In any event, the accumulated data we now have on the absolute risk associated with the combination of opioids and benzodiazepines now enable a well-informed dialogue with the patient in which benefits and risks are carefully weighed and the patient is able to provide informed consent. Our clinical experience is that, given the dire condition of many patients in moderate to severe chronic pain, nearly all easily accept the added risk.

Clearly, any use of benzodiazepines (even in the absence of opioids) is contraindicated in patients with serious pulmonary dysfunction, whether pulmonary or neuromuscular in origin. However, the CDC 2016 recommendation against co-prescription of opioids and benzodiazepines has led to widespread use of such alternatives as anti-histamines (e.g., hydroxyzine and diphenhydramine, the active ingredient in most over the counter hypnotics) with their anticholinergic effects and associated impairment in memory acquisition and consolidation, as well as constipation, and quetiapine, which, in common with other neuroleptics, may be associated with a doubling of risk of death [183].

SSRIs and SNRIs have for some time been recommended as the preferred treatment for anxiety disorders. However, in a recent meta-analysis [167], benzodiazepines, SSRIs and SNRIs showed equally large effect sizes (in the 2.15 range). One must ask if the effectiveness of SSRIs and SNRIs is related to the fact that anxiety and depression are frequently co-morbid. In one of the most commonly used anxiety scales, the Hamilton Anxiety Scale, 5 out of the 14 items plausibly probe for depression. To our knowledge, benzodiazepines and antidepressants have not been tested for their efficacy in treating anxiety in the absence of depression, nor have they apparently been tested in patients who have disabling anxiety in the context of effectively treated depression.

Finally, and perhaps most seriously, these various factors have inhibited clinical research on benzodiazepines, leaving us with a substantial knowledge gap. Use of benzodiazepines has been discouraged for 40 years (see [177]), in part for lack of scientific support – support that is lacking because it was long ago concluded that further research was not justified because the drugs often led to physical dependence, which is still often confused with addiction.

Non-invasive non-pharmacological therapies

There is a substantial literature on these approaches [184–186]. While the clinical trials, by and large, are characterized by serious methodological weaknesses, there are enough data to suggest that some of these approaches may have some value, particularly in patients with mild to moderate pain. However, it seems unlikely that they will be of sufficient value to supplant opiates in patients with moderate to severe pain. What is needed is comparative effectiveness studies in which the potential of non-opioid therapies for reducing opioid dosage is scientifically tested. Unfortunately, this is one more instance in which the limitations of opioid trial design have stood in the way of such studies. The EEGRW trial design we have suggested could solve most of the problems extent in published

RCTs [39]. Also not considered by the CDC [1] are the ubiquitous problems with availability and insurance coverage for nonpharmacologic therapies.

Training

Almost certainly, quality of care for chronic pain could be improved and prescription opioid case fatality rates, however modest, further reduced by better training of physicians [187]. However, mandatory lectures and seminars are unlikely to be adequate. Rather, more extensive programs integrated into medical school and residency programs, or delivered through apprenticeships or workshops, will likely be necessary. Any program of mandatory education must be linked to a standard of practice under which medical professionals may safely operate with confidence that they will not have their clinical privileges terminated or be persecuted or sanctioned by law enforcement authorities, state medical boards, or the Drug Enforcement Administration. At present, no accepted consensus standard exists.

Reimbursement

Management of chronic pain is complex, labor intensive, stressful, requires considerable investment of time and healthcare resources, and entails significant risk to the practitioner. These factors all serve as major disincentives to clinicians to manage chronic pain. The average duration of primary care visits in the USA is 9.02–21.07 minutes (26 studies) [188]. Major improvements in healthcare infrastructure and re-imbursement policies are needed to optimize care, minimize risk, and incentivize clinicians to care for patients in pain. Expansion of the clinician population that is qualified to treat pain will almost certainly be necessary.

Translation of the framework to clinical practice

The CDC 2016 guideline has had profound ramifications for the practice of pain medicine, realized through its impact on the actions of care provider organizations, insurance companies, state medical boards, pharmacy practice, the DEA, state legislatures, public and professional perceptions of opioid risk, and ultimately, practitioners willing to provide care for patients in chronic pain. It will almost certainly take years for these trends – all of which harm patients and none of which have contributed to the solution of the opioid crisis – to be reversed. Given the enormous influence of the CDC that has become manifest since 2016, it appears that the single most essential step to bringing science to the care of patients with chronic pain must consist of reversing the trends that the CDC has set in motion and advancing both the care of patients in pain and the treatment of people using illicit drugs, who presently account for 85% of opioid overdose deaths. We suggest that this reversal requires, at the least, a comprehensive revision of the CDC Guideline. One could even ask whether the CDC has any remit to regulate clinical practice, even as the rapidly escalating disaster ongoing in the illicit drug use population would seem to fall squarely within the CDC's mission. It is hoped that our framework may offer at least a beginning toward a more evidence-based and patient-centric consensus of care.

Conclusion

Epidemiologic studies suggest that 22% of US adults (55 million) experience chronic pain and 7% (18 million) moderate to severe chronic pain [166]. In 2011, the Institute of Medicine estimated that the annual cost to American society of chronic pain, including post-operative pain, was $560–635 billion [189], including estimated healthcare expenditures and costs of lost productivity.

In 2016, the CDC compounded this problem, at untold human cost, by the issuance of a Guideline that has severely degraded pain management for this population. In this paper, we have sought to show that current science is adequate to support judicious pain management, the many knowledge gaps notwithstanding. This management involves the careful balancing by individual clinicians of the benefits and risks unique to each patient – just as in medical practice in general. We believe this is a matter for the well-trained clinician.

The science bearing on chronic pain management is consistent with our clinical experience. Nevertheless, clinical experience cannot substitute for well-controlled scientific studies. Our frequent mention of conclusions drawn from clinical experience has highlighted knowledge gaps and, in many instances, provided hypotheses to drive clinical trials.

It is now quite clear that there exist two major populations in this country for whom opioids are an issue [2]. One is the chronic pain population – the focus of this paper. The other is the population of people who rely primarily on illicit drugs, sometimes diverted but more often, illegally imported street heroin and fentanyl. There is substantial evidence that, at worst, there is only minimal overlap between these two populations, a fact that should provide great

Table 2. Demographics of opioid associated mortality[†].

Age group (years)	2012 mortality (per 100,000)	2017 mortality (per 100,000)
15–24	8	18
25–34	7.7	16.8
35–44	9	15
45–54	5.3	10.8
55–64	1.2	2.2
65–74	0.6	0.8
75–84	0.5	0.7

[†]Data taken from [191].

assurance to clinicians in their professional relationships with patients in chronic pain and substantially alter our approaches to dealing with the opioid crisis. The incidence of OUD in populations of patients prescribed opioids is almost certainly less than 3% [2]. The false notion that everyone prescribed opioids is at grave risk of developing addiction has been laid to rest [2]. There are also dramatic demographic differences in opioid overdose mortality between clinic populations and populations of people using illicit drugs (Table 2). The age groups most likely to be prescribed opioids for chronic pain, seniors over age 55 [2,190], and that likely benefited the most from the liberalized opioid prescription policies of the 1990s and early 2000's, experienced low opioid-associated mortality rates and a small absolute increase in opioid-overdose related mortality over the years, whereas mortality was high and rose rapidly among younger people who are infrequently prescribed opioids for longer than a few days [2].

The population of illicit drug users, now accounting for 85% of all opioid-related deaths, has now been fairly well characterized. A variety of studies suggest that most of these people are succinctly characterized as suffering a disease of desperation rather than the consequences of pharmaceutical opioid exposure [10,153]. They are preponderantly male, white, young, less than high school educated, single, without children, have an income below twice the federal poverty level, and are unemployed; they often report fair or poor health, disability, and impairment in mental health [153]. The factors conducive to opioid abuse include poverty, lack of opportunity, substandard living and working conditions (and the contribution of job-related injury to pain and downward mobility), unstable housing, imprisonment for drug-related offences, childhood adverse experiences, poor physical and mental health, social isolation, and the development of hopelessness and despair [10,11,24]. These are rarely the characteristics of clinic patients.

The better understanding we now have of the population of illicit drug users not only provides a basis for constructive solutions – it demonstrates that the neurobiologic model of addiction constitutes a vast oversimplification. The euphoria associated with opioid abuse, which provides a temporary escape from desperation, is certainly very real, hence the value of methadone and buprenorphine in treating addiction. However, these drugs do not remotely cure addiction and real solutions lie in addressing the much larger psycho-social and economic issues noted above. On the other hand, while there have been few systematic studies, there is mounting evidence that the problem of addiction is substantially soluble [10].

From the studies reviewed here, we conclude that true solutions to today's opioid crisis, which combines serious undertreatment of patients with chronic pain with an overdose crisis almost entirely confined to users of illicit drugs, need to start with comprehensive revision of the 2016 CDC Guideline, if not complete withdrawal by CDC from the business of regulating clinical care.

Future perspective

Preclinical research on mechanisms of nociception has demonstrated an extraordinarily complex system [192,193]. Studies on the transition from acute pain perception to the experience of chronic pain have revealed additional perverse neuroplastic processes that eventually implicate further highly complex mechanisms, including many that involve the cerebrum [194,195]. Altogether, this complexity provides enormous opportunities for therapeutic intervention. By far the most promising line of research at present is focused on the $Na_V1.7$ voltage sensitive sodium channel, which is located on the terminals of dorsal root ganglion cells [196]. It appears to play a key role in regulation of nociceptive signaling. Over-function mutations of the SCN9a gene that codes this channel have been implicated in several very painful human conditions and nonfunction mutations have been associated with insensitivity to pain. Developing drugs sufficiently specific for the $Na_V1.7$ channel to avoid serious side effects has

proven to be a major challenge, as has been the identification of mechanisms for manipulating extremely complex $Na_V1.7$ interactome [196]. Nevertheless, multiple pharmaceutical companies are presently engaged in early phase clinical trials.

The future for clinical science, while potentially bright, is seriously clouded. A great deal of outstanding work has been published, much reviewed here and in our companion papers [2,39]. However, across the field, there has been a widespread failure of scientific responsibility. Echoing René Descartes [197], Carl Sagan, one of the leading philosophers of science of our age, put it this way: "The scientific way of thinking . . . urges on us a delicate balance between no-holds-barred openness to new ideas, however heretical, and the most rigorous skeptical scrutiny of everything – new ideas and established wisdom." [198]. As a field, we have very seriously failed in the rigor of our skepticism. Worse: we have allowed our conclusions to be steered by the notion that the harms of opioids exceed the benefits under any and all circumstances – in complete contradiction to vast clinical experience. The relative absence of practicing pain clinicians from such key groups as the CDC 2016 advisory committee has been a major factor in allowing this outcome. The details of methods and results of scientific studies have not been sufficiently scrutinized. Statistical association has all too often been interpreted as evidence of causation. Absence of evidence has all too often been construed as evidence of absence. Conclusions have not been consistently held to what is solidly supported by the data presented.

Unsupported or simply false conclusions have been so widely and repeatedly reported as fact that they have become generally accepted as scientific truth by scientists, politicians and the general public. Among the more flagrant mythologies:

- There is no evidence that opioids are of benefit for chronic pain;
- The dangers of opioids are too high for these drugs to be used in the routine practice of medicine;
- One dose fits all (and the sanctification of MMED);
- There exist many safer and better alternatives to opioids in the treatment of chronic pain;
- There is a very high probability that someone who take opioids for however short a time will develop opioid use disorder;
- Most heroin addicts started their lives of illicit opioid use with prescription opioids;
- The opioid crisis, since 2012 related almost exclusively to the use of illicit opioids that today account for 84% of opioid-associated mortality, can be addressed solely by constraining the use of prescription opioids.

These outcomes reflect substantial ignorance of the history of the opioid crisis and the crucial roles in its creation played by the triumvirate of pill mills, drug distribution companies, and the Drug Enforcement Agency (DEA), ignorance that appears to persist to this day. There also appears to be substantial unawareness of the subsequent role of state governments that, with the best of intentions, transformed the pill mill crisis into the illicit opioid crisis in the 2011–2013 period.

We have also lost more than a little compassion – in the consignment of millions of patients in chronic pain to suffering, in the patient blaming implicit in the diagnosis of opioid use disorder (and despite its deeply flawed operational definition [2]), and most recently, focusing our research on our success in reducing opioid prescribing rather than on improving the health and welfare of patients [199]. The incomprehensible CDC 2016 targeting of prescription opioids has also assured that the people who have experienced the most deaths from the opioid crisis, users of illicit opioids, have remained largely neglected.

Scientists have played a major role in creating the crises in which we now find ourselves. They are capable of turning around the crisis in care of patients with chronic pain. They are also capable of informing constructive policies to deal with the challenges posed by illicit drug users, even though illicit drug use constitutes a largely psychosocial and economic problem.

However, we must all be cognizant of the momentum created by CDC 2016, now realized in a pervasive web of DEA policies, state laws, insurance company policies and pharmacy practices. Even if the CDC fundamentally changed its position vis a vis opioids today, it would take years to undo this web. However, this period might be substantially shortened were the CDC to publicly acknowledge its errors and fully repudiate its 2016 Guideline, rather than tweaking it as detailed in the draft update currently under review.

Executive summary

- Since publication of the CDC Guideline for prescribing opioids for chronic pain in 2016, annual opioid-associated deaths have doubled (to 74,000); 84% occur in people using illicit drugs. The Guideline has also created a crisis in the care of the 15–20 million Americans with moderate to severe chronic pain.
- We provide an alternative framework for the management of chronic pain. To the extent possible, we have relied upon published science. However, we also identify many knowledge gaps, which we fill with insights from decades of clinical experience and person to person patient contacts. Ultimately, these gaps will need to be addressed by further research.
- We suggest that mutual respect and trust between clinician and patient is foundational to optimal management of chronic pain. Opioid contracts and urine drug screens undermine trust but serve no scientifically proven purpose.
- Prescription drug monitoring plans (PDMPs) can aid clinicians by revealing duplications in prescriptions. PDMPs and legislation have served to largely eliminate pill mills, the chief contributor to the opioid crisis. However, PDMPs pose significant risk of harm to patients and clinicians by virtue of the opioid overdose risk calculator embedded in them.
- We suggest that the target of pain management should be achieving adequate *control* of pain rather than elimination of pain. Treatment must be highly individualized.
- Depression is nearly ubiquitous in patients with chronic pain, though often undetected and undertreated. Effective treatment may be the single most important constituent of pain management programs.
- Sleep disturbances occur in 50–70% of patients with chronic pain. Effective treatment can improve quality of life for patients and is important to maintaining tightly controlled drug regimens.
- Different types of pain call for different treatment approaches.
  - Somatic pain (aching, hard or sharp but steady), is usually of musculoskeletal origin and accounts for the vast majority of pain. Nonsteroidal anti-inflammatory drugs are of proven benefit but have limited efficacy. We suggest that opioids constitute the mainstay of treatment of more severe pain. Unfortunately, because of inadequate study design, neither the efficacy nor the safety of opioids have been adequately tested in the over 100 randomized controlled trials that have been published. We have separately proposed a novel and potentially more successful trial design.
  - Neuropathic pain (burning, searing, or stinging), is caused by neural damage, central or peripheral. Common causes are diabetic polyneuropathy and shingles. Gabapentin and pregabalin are the first line therapies, followed by antidepressants. Opioids have been shown to be beneficial in some patients.
  - Neuralgic pain (repetitive intense, lightning-bolt like pain, trigeminal neuralgia being the prototype), is best treated with voltage sensitive sodium channel anticonvulsants.
- Opioids:
  - Estimated annual opioid-associated mortality is 0.25% for dosage >100 mg morphine equivalents/day (MMED) and rises to approximately 0.5% with dosage >400 MMED. This risk is comparable to that of other drugs commonly used in medical practice.
  - Opioid treatment has been associated with a number of other potential harms. However, no studies have determined to what extent risk is related to the underlying disorder (chronic pain) or to the drug itself.
  - Opioids cause respiratory depression via a number of well-defined mechanisms.
  - We suggest that the best approach to opioid treatment is to start at very low doses and very gradually titrate over months until satisfactory pain control is achieved and without significant impact on cognitive or neurological function. This also provides ample opportunity to treat important co-morbidities, such as depression. Treatment must contend with prevalent drug-specific idiosyncratic side effects and a well-established 13-15-fold variability in opioid dose requirements.
  - Opioid dependence and tolerance reflect pharmacodynamic effects of the drugs. Dependence has no relationship to addiction and it is readily dealt with. Addiction is a complex psychosocial and economic phenomenon to which the euphoric effects of opioids make a modest but crucial contribution. Risk of addiction (opioid use disorder) in clinic populations is likely less than 3%.
- Benzodiazepines
  - Benzodiazepines potentially play useful roles in pain management through their beneficial effects on anxiety, insomnia and muscle tightness.
  - The co-prescription of benzodiazepines and opioids has been strongly proscribed by the CDC because it is associated with an approximate doubling or mortality. However, it is unclear to what extent this excess mortality is related to the drug combination or to underlying comorbidities.
- Care of patients with chronic pain could undoubtedly be improved and risks reduced by better clinician training.
- Current re-imbursement structures do not remotely compensate for the complex, labor intensive and stressful work that is essential to treatment of chronic pain.
- The single most essential step to bringing science to the care of patients with chronic pain will be achievement of transformative change in the CDC Guidelines or withdrawal of CDC from regulation of medical care. This step can set the stage for advancing both the care of patients in pain and resolution of the illicit drug problem.

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