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STATE OF THE ART REVIEW

Opioids for low back pain

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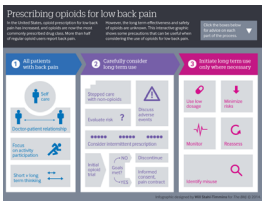
ABSTRACT

Back pain affects most adults, causes disability for some, and is a common reason for seeking healthcare. In the United States, opioid prescription for low back pain has increased, and opioids are now the most commonly prescribed drug class. More than half of regular opioid users report back pain. Rates of opioid prescribing in the US and Canada are two to three times higher than in most European countries. The analgesic efficacy of opioids for acute back pain is inferred from evidence in other acute pain conditions. Opioids do not seem to expedite return to work in injured workers or improve functional outcomes of acute back pain in primary care. For chronic back pain, systematic reviews find scant evidence of efficacy. Randomized controlled trials have high dropout rates, brief duration (four months or less), and highly selected patients. Opioids seem to have short term analgesic efficacy for chronic back pain, but benefits for function are less clear. The magnitude of pain relief across chronic non-cancer pain conditions is about 30%. Given the brevity of randomized controlled trials, the long term effectiveness and safety of opioids are unknown. Loss of long term efficacy could result from drug tolerance and emergence of hyperalgesia. Complications of opioid use include addiction and overdose related mortality, which have risen in parallel with prescription rates. Common short term side effects are constipation, nausea, sedation, and increased risk of falls and fractures. Longer term side effects may include depression and sexual dysfunction. Screening for high risk patients, treatment agreements, and urine testing have not reduced overall rates of opioid prescribing, misuse, or overdose. Newer strategies for reducing risks include more selective prescription of opioids and lower doses; use of prescription monitoring programs; avoidance of co-prescription with sedative hypnotics; and reformulations that make drugs more difficult to snort, smoke, or inject.



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Use our interactive graphic as a guide to prescribing opioids for low back pain. See www.bmj.com/content/350/bmj.g6380/infographic

Introduction

Back pain affects most adults, is a leading cause of activity limitation and work disability worldwide, and is among the most common reasons for seeking healthcare.[1-5] It has an enormous impact on individuals, healthcare systems, and national economies, and treatment approaches have important consequences for patients, clinicians, and society.

In the United States, the prescription of opioids for low back pain has increased.[5] Insurance claims data suggest that the opioids are the most commonly prescribed class of drug for back pain,[6] and more than half of regular opioid users report back pain.[7] Unfortunately, increased drug misuse, complications, and fatal overdoses have accompanied this rise in opioid use.[8] Clinicians must therefore weigh the possible analgesic benefits of opioid therapy against the risks.

The aims of this review are to examine trends and variations in the use of opioids for back pain; assess the evidence for opioid efficacy in acute and chronic back pain; summarize new data on the adverse effects of long term opioids; and make recommendations for judicious prescribing. The review is interspersed with commentary from a patient with back pain and extensive experience with opioid therapy.

Despite some evidence from randomized controlled trials (RCTs) on the efficacy of opioids in the short term treatment of low back pain, little evidence is available on long term efficacy and safety.[9] Because clinical trials in this area may not generalize well to routine care and provide no evidence on long term use, we also considered selected observational data.

Sources and selection criteria

We identified reviews of opioid efficacy for back pain published between 2000 and April 2014 in the PubMed database using the search terms low back pain and opioids, with a filter for systematic reviews. Because efficacy may differ for back pain relative to other pain conditions (such as neuropathic pain, headache, and fibromyalgia), we focused on reviews that separated back pain from other causes.

Patients with mood disorders or a history of substance misuse are often excluded from RCTs of opioids, but they are more likely to receive opioids in routine care.[10-12] No RCTs of opioids for back pain have lasted for more than four months,[9] although many patients receive treatment for longer. Thus, we also examined relevant cohort studies from primary care or employed populations.

Relevant RCTs have been too small, brief, and selective to adequately assess less common complications, those occurring with long term use, and those related to comorbid conditions or drug interactions. We therefore conducted a separate PubMed search for studies on the prevalence of

PATIENT INVOLVEMENT BOX

David Duhrkoop is a patient with chronic back pain who chairs a patient advisory committee for one of Dr Von Korff's research grants. He was recommended for this role by the director of the American Chronic Pain Association, a patient organization he has been involved with for many years. On a volunteer basis, Mr Duhrkoop has extensive experience in facilitating groups that help patients develop their abilities to effectively manage chronic pain. He reviewed and added to our initial outline of the manuscript and suggested topics on which he might comment. He offered novel ideas about our approach to developing the manuscript. He reviewed drafts of the manuscript as it evolved and offered his agreement with the content. He then prepared reactions and responses to the various components of the manuscript, offering personal experiences and those of other patients with whom he has worked. He reviewed and approved the final version of the paper for intellectual content.

opioid misuse in patients receiving long term prescriptions using the terms opioids, abuse, and prevalence, with a filter for systematic reviews. We considered systematic reviews published in 2007 and 2008, as well as articles published since 2007 that were based in primary care, observed patients for at least a year, and used standardized measures of opioid misuse or dependence.

We examined observational studies for other adverse events during long term treatment with opioids, using reference lists of other retrieved articles and our personal knowledge. We considered studies published since 2000 with comparators (opioids *v* no opioids, or high dose *v* low dose opioids).

Incidence and prevalence of low back pain

Prevalence of symptoms

The US national health interview survey reported that 28% of adults had experienced low back pain that lasted a whole day or more during the past three months.[13] About half of all adults experience some back pain over a one year period, with 20% reporting "frequent" back pain. The prognosis is good for acute back pain in primary care: within a month, pain and disability scores improve by an average of 58%,[14] but recurrence is common.[15] Only 10% of patients develop chronic pain (longer than three months), but these patients have higher healthcare and disability compensation costs.[2]

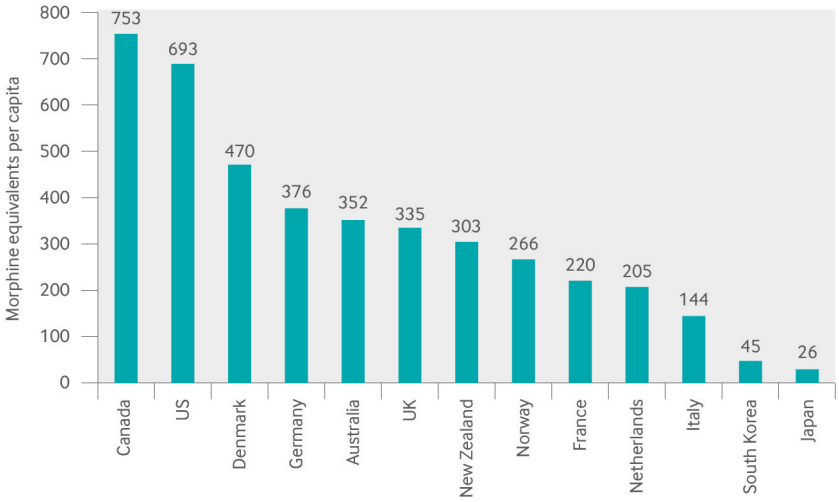

Fig 1 | International use of six powerful opioids—fentanyl, hydromorphone, methadone, morphine, oxycodone, and pethidine (meperidine)—during 2010 (www.painpolicy.wisc.edu)

Prevalence of pathophysiologic changes

The differential diagnosis of back pain is broad, including degenerative conditions in the intervertebral discs and vertebrae and musculoligamentous conditions. However, degenerative radiologic findings are common in pain-free individuals, so the cause of pain is often unclear.[16] Degenerative conditions often coexist, increasing uncertainty. Chronic pain itself can induce structural and functional changes in the central nervous system, perpetuating the perception of pain.[17-19] Mood disorders and workplace factors often influence the evolution of, and the adaptation to, chronic back pain.[10-12] Thus, a biopsychosocial model of back pain is widely accepted, and a meaningful anatomical diagnosis remains uncertain for many patients.

Serious systemic diseases such as metastatic cancer, spinal infections, and inflammatory spondylopathies each account for less than 1% of patients with back pain in primary care.[20] Therefore, we focused on opioid treatment of back pain without underlying serious systemic disease.

Trends in opioid prescribing

Opioid prescribing has increased worldwide, with US opioid sales quadrupling between 1999 and 2010.[21] This was in part a response to undertreatment of patients receiving cancer care, palliative care, or treatment for acute pain. However, opioid therapy for chronic musculoskeletal pain, including back pain, also grew substantially and disproportionately.[7 22] As US opioid sales quadrupled, admissions to substance misuse treatment programs and opioid related overdose deaths also increased fourfold.[8 21] Similarly, deaths in England and Wales involving methadone or codeine doubled between 2005 and 2009.[23]

US national survey data showed a 660% increase in expenditure on opioids for spine problems from 1997 to 2006 owing to increasing prices and increasing use.[24] From 1999 to 2010, the proportion of visits to ambulatory physician practices for back and neck pain that resulted in prescription of an opioid increased from 19% to 29%.[25] In a per person analysis of privately insured employed people, 42% of patients received a prescription within a year of index diagnosis.[6]

Opioids are mostly prescribed for chronic pain. In one US health plan, 87% of all morphine equivalents for pain were dispensed to patients receiving long term opioids.[26] Patients with back pain seem to be more likely than patients with other common pain diagnoses to receive high doses.[27]

Substantial geographic variations in opioid prescribing may reflect limited professional consensus on appropriate use. Per capita use of potent opioids is higher in North America than in other developed countries: twice the rate seen in the United Kingdom; three times that in the Netherlands; and 26 times that in Japan (fig 1). Even within the US, per capita opioid prescription varied 23-fold among state run low income insurance programs.[28]

Several factors account for North America's increased use of opioids. In the 1980s, on the basis of a small case series

and an inpatient sample, pain experts argued that opioids were underused and that the risks of misuse were minimal.[29 30] Starting in the mid-1990s, drug industry marketing assumed an important role, with extensive sponsorship of pain specialty societies, continuing medical education programs, and guidelines.[23 31-33] The prescription of potent opioids quickly increased (fig 2),[34] However, some marketing was misleading: The manufacturer of OxyContin (oxycodone hydrochloride) and its three top executives pleaded guilty to criminal charges for misbranding the drug with claims of lower risk of misuse than for other opioids.[23 31]

The growth in opioid prescribing for back pain belies a paucity of evidence for efficacy, safety, and optimal prescribing. For example, US pain society guidelines for chronic non-cancer pain summarized data from short term opioid RCTs, but of 25 recommendations, 21 were based on "low quality evidence."[35]

PATIENT COMMENTARY

"Why do people seek opioids? By the time pain becomes chronic, most patients have tried less potent drugs and they seek relief from a stronger prescribed source. We're a society of bad backs, and people don't want their backs to hurt. So they're looking to their doctors for a silver bullet."

Efficacy and effectiveness of opioids for low back pain

Acute low back pain

The analgesic efficacy of opioids for acute pain is well established, but there is a paucity of data on back pain in particular. A systematic review by the American Pain Society and the American College of Physicians found no RCTs comparing opioids with placebo for acute low back pain. Instead, they reported "fair" evidence based on trials for other acute pain conditions.[36] However, it is uncertain how opioids compare with non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, or other alternatives. It is also unclear whether opioid prescribing for acute back pain hastens recovery or return to work and how often it leads to long term use.

In a state-wide observational study of patients with acute work related back injuries (n=1843), a third of patients received an opioid prescription within six weeks, most at the first medical visit. After adjusting for pain, injury, and functional severity, patients who received more than seven days of opioids were twice as likely to remain work disabled at one year.[37] A national study found that opioid prescribing within 15 days of injury was associated with longer work disability, even after adjusting for the severity of injury, demographic characteristics, and job tenure. Longer work disability was also associated with higher doses of opioid.[38] It may be that opioids worsen outcomes—for example, by promoting physical deactivation and apathetic mood. Alternatively, patients prescribed opioids may simply be at higher risk of poor outcomes independent of medication. Regardless, these studies do not suggest that opioids expedite the return to work.

In a UK study of 715 primary care patients with low back pain, two thirds had acute pain and one third received opioids. Those receiving opioids had worse pain, functioning, self efficacy, catastrophizing, fear of movement, and depression. Even after adjusting for these and other baseline variables, patients who received opioids had worse functioning after six months than those who did not—an association not found among patients who received NSAIDs.[39] As with the return to work studies, the causal pathways are uncertain, but opioid prescribing at baseline was not linked to improved functional outcomes.

Prescription of opioids for acute pain may inadvertently lead to long term use if prescribers provide a large supply or simply continue to refill the prescription. This can lead to drug dependence and long term use.[40]

Chronic low back pain

Opioids versus placebo

Most RCTs of opioids for back pain have assessed chronic pain. Even here the evidence is meager and inconclusive. No trials lasted beyond four months,[9 41] and all had high dropout rates (>20%), mostly because of adverse effects or inefficacy.[9]

To reduce dropouts some opioid RCTs used an "enriched enrollment randomized withdrawal design," excluding patients who did not respond to treatment or had unacceptable adverse effects. Potential participants received the study drug before randomization and were included only if they benefited and tolerated side effects. Participants were then randomized to opioid withdrawal or continued treatment. This design underestimates adverse effects and risks overestimating efficacy.[42]

Many RCTs excluded patients with a history of substance misuse or mental disorders. Clinical guidelines typically caution against long term opioid prescribing for such patients. However, in routine care these patients are most likely to receive and sustain opioid use, a phenomenon called "adverse selection."[10-12 43] They are also more likely to receive higher doses and concurrent treatment with a sedative hypnotic drug.[10] Thus, safety data from clinical trials may generalize poorly to routine care.

Systematic reviews largely agree that opioids have greater short term analgesic efficacy than placebo, but that benefits for function are less clear.[9 36 41 44-47] They also agree that the evidence is sparse and of low quality. The mean magnitude

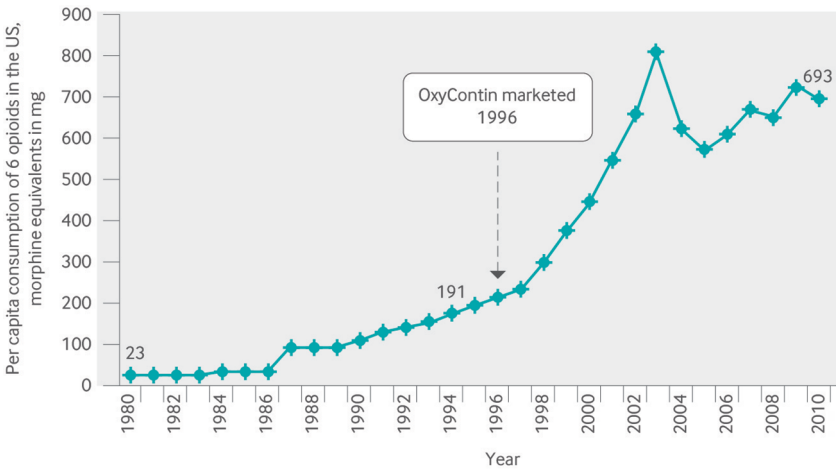

Fig 2| Per capita consumption of fentanyl, hydromorphone, methadone, morphine, oxycodone, pethidine (meperidine) in the United States. This figure does not include all opioids, and hydrocodone, in particular, is not included. Data from the US Centers for Disease Control indicate that total opioid sales in the US continued to rise consistently at least through 2010[21]

Trial	Patient sample	Treatment groups	"Enriched enrollment"	Industry sponsor	Duration, FU rate	Results by group; P value
Chu (2012)[56]	**N=139** LBP ≥6 months; low dose opioids okay *Exclusions*: History of substance misuse, psychiatric disease, pain outside low back	Group 1: Long acting morphine Group 2: Placebo	🔴	🔴	1 month 74% FU	Average pain improvement: Group 1: 44% Group 2: 23% P<0.001
Hale (2010)[61]	**N=268** LBP≥6 months; already receiving ≥60 MEQ daily opioid; titrated on hydromorphone before randomization *Exclusions*: Depression, other pain conditions	Group 1: Hydromorphone ER Group 2: Placebo (hydromorphone discontinued)	🟢	🟢	12 weeks Overall: 41.4% FU Group 1: 49.6% FU Group 2: 33.1% FU	Worsening on 11 point scale: Group 1: 0.2 units Group 2: 1.6 units P<0.001
Buynak (2010)[55]	**N=981** Chronic LBP ≥3 months; must be taking analgesics for ≥3 months *Exclusions:* Psychiatric diseases	Group 1: Tapentadol ER Group 2: Oxycodone controlled release Group 3: Placebo	🔴	🟢	Titration phase +12 weeks Group 1: 47.6% FU Group 2: 52.2% FU Group 3: 40.5% FU	≥30% improvement in pain: Group 1: 39.7% Group 2: 30.4% Group 3: 27.0% Group 1 *v*3: P=0.016
Khoromi (2007)[57]	**N=55** Lumbar radiculopathy ≥3 months *Exclusions*: Substance misuse, depression, unwilling to taper off opioids for 2 weeks	Group 1: Long acting morphine + inert placebo Group 2: Nortriptyline + inert placebo Group 3: Both active drugs Group 4: Active placebo*	🔴	🔴†	1 month on each regimen (crossover) 51% FU	≥30% improvement in pain: Group 1: 42% Group 2: 40% Group 3: 67% 4) 37% Only group 3 significantly better than placebo
Hale (2007)[58]	**N=143** LBP ≥3 months; already receiving ≥60 MEQ daily opioid *Exclusions*: Radiculopathy	Group 1: Oxymorphone ER Group 2: Placebo (oxymorphone discontinued)	🟢	🟢	12 weeks Group 1: 70% FU Group 2: 25% FU	Worsening on VAS pain score: Group 1: 8.7 mm Group 2: 31.6 mm P<0.0001
Katz (2007)[59]	**N=205** LBP ≥3 months; titrated on oxymorphone before randomization *Exclusions*: Radiculopathy	Group 1: Oxymorphone ER Group 2: Placebo (oxymorphone discontinued)	🟢	🟢	12 weeks Group 1: 68% FU Group 2: 47% FU	Worsening on VAS pain score: Group 1: 10.0 mm Group 2: 26.9 mm P<0.0001
Webster (2006)[60]	**N=719** LBP ≥6 months; any opioids discontinued *Exclusions*: History of substance misuse, litigation	Group 1: Placebo Group 2: Oxycodone four times daily Group 3: Oxycodone + naltrexone 1 µg four times daily Group 4: Combination twice daily	🔴	🟢	Titration phase + 12 weeks 46% FU (2/3 of dropouts during titration phase)	% improvement in pain score: Group 1: 32% Group 2: 46% Group 3: 41% Group 4: 42% Groups 2-4 better than placebo, P<0.05

🟢 = yes, 🔴 = no

*The "active placebo" group received benztropine, which has no known effect on neuropathic pain but causes side effects that mimic those of morphine and nortriptyline, with the intent of producing more effective blinding than inert placebo. † No industry sponsorship, but MS Contin placebo tablets were a gift from Purdue Pharma.

Fig 3| Randomized trials of strong opioids versus placebo for chronic low back pain or sciatica included in a systematic review.[20] ER=extended release; FU=follow-up; LBP=lower back pain; MEQ=morphine equivalents; VAS=visual analogue scale

of pain relief across a variety of chronic non-cancer pain conditions is about 30%.[47] Given the short duration of available studies, the reviews conclude that the effectiveness and safety of long term opioid use is unknown.

Of 15 RCTs in the most recent systematic review,[9] five examined the weak opioid agonist tramadol.[48-52] The reviewers found "low quality evidence" that tramadol was better than placebo at reducing pain, and "moderate quality evidence" that it was better at improving functional outcomes.

Two studies in this review assessed transdermal buprenorphine.[53 54] The reviewers found "very low quality evidence" that this drug was better than placebo for pain or functional outcomes.[9]

Seven RCTs compared long acting strong opioids (tapentadol, morphine, oxymorphone, hydromorphone, and oxycodone) with placebo (fig 3).[55-61] Five were industry sponsored, and three tested withdrawal of the drugs using the "enriched enrollment" design. The review found "moderate quality" evidence that these drugs are better than placebo in reducing pain and improving function, again in the short term.[9]

Opioids versus other drugs

For regulatory purposes, industry sponsored trials generally compare analgesics with placebo.[9 41] However, trials comparing opioids with alternatives are more relevant for clinicians and patients. Unfortunately, few RCTs have compared opioids with alternatives such as NSAIDs, antidepressants, or muscle relaxants.

One small RCT (n=55) for lumbar radiculopathy compared morphine, the tricyclic antidepressant nortriptyline, or a combination of both of these drugs with placebo (fig 3).[57] By the end of this crossover trial with four study groups almost 50% of participants had dropped out. Morphine and nortriptyline had similar analgesic effects and only the combination of the two drugs worked significantly better than placebo.

Two identical RCTs (total n=1598) compared a fixed dose of celecoxib with a fixed dose of tramadol.[62] At six weeks, significantly more patients achieved 30% pain relief with celecoxib than with tramadol (63% *v* 50% in study 1; 64% *v* 55% in study 2).

One small RCT compared the strong opioid oxycodone (or a combination of oxycodone plus morphine) with naproxen.[63] Both opioid groups had greater analgesia than the naproxen group, but no differences were seen in patient activity levels.

Together, these trials provide only weak evidence but suggest that NSAIDs may have analgesic efficacy intermediate between tramadol and stronger opioids, with similar effects on functioning.

Observational studies for chronic back pain

Given the short duration of available RCTs, observational studies provide the only evidence on the long term efficacy of opioids for back pain. In a study of work related back injuries, 38% of patients received an opioid at an early medical visit (n=694), but only 16% of them (n=111) received opioids for four calendar quarters. Among these long term users, a quarter experienced a 30% improvement in pain, but only 16% had improvement in function.[64] Average opioid doses increased each calendar quarter, except among the few patients with functional improvement.

A Danish population survey found that people taking long term opioids for non-cancer pain reported worse pain and quality of life than those with chronic pain who were not taking opioids.[65] People taking opioids may have had worse initial pain, but the drug did not achieve pain relief or quality of life comparable even to others with chronic pain. Thus, despite modest short term efficacy for chronic pain, it is unclear whether long term opioid therapy has meaningful therapeutic benefits.

Reasons for potential loss of efficacy

It has been proposed that loss of efficacy with long term use of opioids may be the result of tolerance and hyperalgesia (increased pain sensitivity).[66] Opioid tolerance—a need for increasing doses to achieve a desired effect—is seen in experimental pain (artificially induced pain, often with heat or cold) and after one month of oral morphine in patients with back pain.[56 67] Tolerance is seen in animal studies and in routine care when higher than usual doses are needed for acute pain in patients receiving long term opioids.[66] Tolerance may account for the common need to increase the dose with longer term use of opioids.[64 68]

Hyperalgesia is a common feature of opioid withdrawal that also occurs with experimental pain when opioids are stopped.[69] However, hyperalgesia may occur during opioid therapy, with both animal models and experimental pain models suggesting this effect.[66 70] Thus, repeated opioid use may spur both the development of tolerance (desensitization to opioids) and a pro-nociceptive process (sensitization to pain).

Responses to opioid tapering

The phenomena of tolerance and hyperalgesia raise the possibility that many patients receiving long term opioids would fare as well or better without them. This possibility has been tested in multidisciplinary pain treatment programs that include opioid cessation, which have reported success among participants who taper the dose over three weeks.[71-73] On average, these patients reported less pain after completing the program. The degree of improvement was similar whether or not participants were receiving opioids when they started. Mean depression scores and physical functioning improved substantially over the three week treatment period—for patients with back pain, in particular, and among those with or without previous spine surgery.[73 74] It is uncertain how these results generalize to patients who declined participation or did not complete the program. Nonetheless, these results suggest that many patients with persistent back pain can achieve favorable pain and function outcomes after stopping opioids in a multidisciplinary intervention.

PATIENT COMMENTARY

"Once patients start using opioids long term they are likely to continue, even if the doctor suspects it's not doing them much good—because patients expect it and feel it's important to their quality of life. Too often doctor and patient do not discuss whether opioids are improving the patient's overall quality of life, and patients often report that they do not understand the risks of continued opioid use."

Adverse effects of opioid treatment for low back pain

Opioid dependency, misuse, and addiction

Dependency

Most patients prescribed opioids continue to take them for days or weeks only. Acute pain may subside, many patients experience side effects, and others find the drugs unhelpful. However, insurance data show that more than half of patients who continue to take opioids for at least three months are still taking them years later.[75]

With prolonged use of these drugs many patients develop opioid dependence, meaning that cessation causes an unpleasant withdrawal syndrome (such as agitation, insomnia, diarrhea, rhinorrhea, piloerection, and hyperalgesia). Physical dependence results from compensatory adaptations in parts of the brain that control somatic functions, especially in the locus coeruleus. Psychological dependence refers to unpleasant emotional effects on withdrawal, including anhedonia, dysphoria, and the motivational effect of craving opioids.[66] Experimentally, withdrawal symptoms can be reliably induced with even a single parenteral dose of morphine or hydromorphone, followed by the opioid antagonist naloxone.[76]

Clinically important opioid dependence—as opposed to experimentally induced dependence—may emerge at different times in different patients. Evidence from a clinical trial for back pain suggests that dependence can emerge with just one to three months of daily use.[60] In this trial, patients underwent an opioid washout period before randomization. One study arm then received oxycodone, titrated to achieve pain relief. Patients who took the drug for at least four weeks before stopping completed the short opiate withdrawal scale, which measures the severity of 10 withdrawal symptoms (mostly physical symptoms), producing a score of 0-30. The day after stopping, 24% of patients in the oxycodone group scored over 5 and 12% scored over 10, whereas only 3.5% of the placebo group had scores over 5 and no scores over 10.

Although physical dependence is distinct from addiction, it can still be problematic for patients wishing to end long term treatment with opioids. For patients who continue to take opioids, dependence can cause withdrawal symptoms if they are unable to obtain a refill.

Problem use of prescription opioids

Problem use of prescription opioids ranges from overuse (occasionally using more than prescribed), to misuse (use that is potentially harmful or dangerous), to opioid use disorder (or addiction). Addiction is characterized by repeated

Table 1 | Prevalence of opioid "dependency," "abuse," or "misuse" among patients receiving prescription opioids

Patients	Type of dependency, misuse, or abuse; criteria	Prevalence
Opioid dependence or abuse		
n=801; primary care practices of 235 physicians[81]	Current (30 day) dependence or abuse, DSM-4 and ICD-10 criteria*	3.7%
n=705; 9 primary care and 3 specialty clinics[80]	Current dependence, DSM-4 criteria	26%
Heterogeneous studies that excluded previous substance abuse[83]	Variable criteria	0.19%
Studies that did not exclude previous substance abuse[83]	Variable criteria	5.0%
Opioid misuse		
Primary care[81]	Purposeful oversedation	24%
	Requested early refills	45%
	Increased dose on own	37%
	Medication lost or stolen	30%
	Obtained extra opioids from other doctors	8%
	Used opioids for purposes other than pain	16%
	Drank alcohol to relieve pain	20%
n=100; primary care[82]	Abusive behaviors: lost or stolen medications, documented use of other sources of medications, requests for 2 or more early refills	24-31%
Heterogeneous studies that did not exclude previous substance abuse[83]	"Adverse drug related behaviors"	11.2%
Urine drug screens		
Heterogeneous studies[83]	Non-prescribed opioid in urine or no opioid in urine	20.4%
Primary care[81]	Any illicit drug (mostly marijuana)	24.0%

*DSM-4=*Statistical Manual of Mental Disorders*, fourth edition; ICD-10=*International Statistical Classification of Diseases and Related Health Problems*, tenth revision. Both sets of criteria for "dependence" incorporate features commonly associated with addiction.

compulsive drug seeking (psychological dependence) and continued use despite adverse social, psychological, or physical consequences. Physical dependence can occur in patients receiving long term opioids with or without an opioid use disorder.

Although conceptually distinct, these terms may be part of a continuum of "opioid use disorder." This is how they are used in the American Psychiatric Association's new *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5).[77] However, in DSM-5, tolerance and dependence are removed as criteria for opioid use disorder when considering prescribed opioids, because they are expected iatrogenic consequences of regular opioid use. In the earlier DSM-4, criteria for dependence and opioid misuse were distinct, although the criteria for "dependence" included many features typically associated with addiction.[78]

These terms are used variably, often with implicit criteria, and often without uniform application to a study population. Furthermore, DSM-4, DSM-5, and ICD-10 (international classification of diseases, 10th revision) do not use the term "addiction."[79] However, many clinicians and researchers use the term for what these manuals label "substance use disorder" or "dependence." Confusion regarding these concepts has made it difficult to reliably determine the prevalence of opioid use disorder from existing research.

Prevalence of problem use

The reported prevalence of opioid addiction among long term opioid users in routine care varies widely. Few studies have used formal diagnostic criteria. One study in primary care used a diagnostic interview to assess DSM-4 criteria for opioid "dependence" (similar to addiction). Among those who received four or more opioid prescriptions in a year (n=705), 26% met criteria for "dependence" (table 1).[80] However, another primary care study using similar methods reported only a 3.7% prevalence of opioid "dependence" or "abuse" among patients receiving daily opioids for at least three months (with 96% using for more than a year) (table 1).[81] Serious opioid misuse was substantially more common (table 1), and 9.7% met criteria for dependence or abuse of any substance. Similarly, another study reported misuse (lost or stolen medications, use of multiple sources of medication, multiple early refill requests) in 24-31% of patients receiving long term opioids for non-cancer pain.[82]

Studies of urine drug screens have reported aberrant findings, including no opioid in the urine (possibly indicating diversion of prescribed opioids for non-medical use, such as sale on the street), a non-prescribed opioid, or an illicit drug (table 1). Rates of unexpected findings are typically greater than 20%, which is substantially higher than patient self reports.[81 83] However, accurate interpretation requires more clinical information.

Despite guideline cautions, patients with a history of substance misuse or mood disorders are among those most likely to receive long term opioids in routine care.[10-12] These disorders are risk factors for opioid misuse, prompting the term "adverse selection."[43] By contrast, patients with a history of substance misuse or mood disorders are usually excluded from opioid RCTs for ethical, efficacy, and safety reasons. As a result, evidence from RCTs probably underestimates the rate of misuse in community practice.

A systematic review of heterogeneous studies with variable diagnostic criteria supported this concern. The lowest rates of substance misuse came from studies in which patients with previous alcohol or illicit drug use were excluded, resulting in typical misuse rates of 0.19%. Among studies without such exclusions, rates averaged more than an order of magnitude higher (5.0%).[83] Informal evidence of misuse, in turn, appears several-fold greater (table 1).

The increase in admissions to addiction treatment programs highlights the risk of addiction with prescribed opioids. As opioid prescribing quadrupled in the US, so did addiction therapy, with prescription opioids as a reason for admission second only to marijuana.[8]

PATIENT COMMENTARY

"What I've learned from working with patients with chronic pain is that many don't decide to become long term opioid users, they slide into it instead. There's a significant habitual side to it.

Still, most patients have no idea they're becoming dependent on opioids—until for some reason they run out or can't get more. Then the withdrawal symptoms begin, and that's very painful.

I went through some times when I was taking too much and running out early. You can't go to your doctor and say you've been taking four pills a day instead of two. So you end up lying to your doctor. I found myself in that position many times, and I've heard similar stories from dozens of patients over the years.

It took a shock to realize that what I was doing was affecting my family. I didn't notice because I was high. I used to take my family for a drive after taking my meds. Then one day I was holding my granddaughter on the beach, and I realized I might not ever hold her again. I knew I was taking too much medicine and feared that sooner or later I'd fall asleep and not wake up. My wife and two daughters confronted me that weekend. They said that I'd become a completely different person and that they missed the old me. My wife told me she wanted her husband back. I realized I had to change or I wasn't going to be around to enjoy the many things I had. That was my turning point. I decided to go to rehab to get myself back."

Overdose and mortality risks

By 2010, deaths related to prescription opioid overdose had reached 16 651 a year in the US, far exceeding deaths from cocaine or heroin.[84 85] Deaths from prescription opioids have also increased in the UK.[23] Respiratory depression is the usual cause.

It was traditionally thought that there is no upper limit to opioid dosing for patients in pain, as long as increases are gradual. However, recent large studies suggest that opioid overdose and mortality risks increase in a dose related manner.[86-88] Compared with patients receiving 20 mg or less of morphine equivalents per day, the risk of serious or fatal overdose increased 1.9-3.7-fold in those receiving 50-100 mg per day. In those receiving more than 100-200 mg per day the risk increased 2.9-8.9-fold.

Opioid overdoses often involve multiple drugs, and certain combinations pose particular risks. For example, one study reported a threefold increase in serious overdoses in patients receiving concurrent opioids and benzodiazepines.[87] Surprisingly, these coprescriptions occur more often with increasing dose and duration of opioid therapy.[68 89 90]

Many patients continue long term opioid treatment even after spinal surgery.[91 92] In a cohort study of patients who had lumbar fusion operations, opioid related overdose was the most common cause of death in the three years after surgery.[93]

Although patients receiving daily opioids have the highest risk of overdose, they accounted for only a quarter of overdoses in an insured population. More patients receive less than daily opioids and they accounted for a larger proportion of overdoses.[68] Similarly, in a workers' compensation system, most opioid overdoses occurred in patients who were not receiving high dose or long term opioids.[94] Thus, efforts to reduce overdose risks may need to extend to all patients receiving prescription opioids.

Some guidelines have recommended opioids as a safer choice than NSAIDs for pain in older people (mainly those aged 75 years or more), given the gastrointestinal, renal, and cardiovascular risks associated with NSAIDs.[95] However, a cohort study found higher all cause mortality among older people using opioids for arthritis than among those using NSAIDs.[96] Rates of heart disease, fractures, and bowel obstruction were particularly high among opioid users. Thus, comparative safety remains uncertain.

Table 2 | Common short term side effects of opioids compared with placebo in short term trials[47]

Side effect	Trials (n)	Occurring with opioid (%)*	Occurring with placebo (%)*	Relative risk (95% CI)	NNH†
Constipation	8	41	11	3.6 (2.7 to 4.7)	3.4
Nausea	8	32	12	2.7 (2.1 to 3.6)	5.0
Sedation	7	29	10	3.3 (2.4 to 4.5)	5.3
Vomiting	7	15	3	6.1 (3.3 to 11)	8.1
Dizziness	8	20	7	2.8 (2.0 to 4.0)	8.2
Itching	6	15	7	2.2 (1.4 to 3.3)	13
Dry mouth	7	13	9	1.5 (1.0 to 2.1)	Not calculated
Discontinued treatment because of a side effect	8	24	15	1.4 (1.1 to 1.9)	12
Any adverse event	4	80	56	1.4 (1.3 to 1.6)	4.2

*Total number of patients experiencing the symptom divided by total number receiving treatment summed across studies.
†NNH=number needed to harm

Other adverse effects

The common short term side effects often make opioids unappealing to patients (table 2).[47] Most cause no permanent harm and some improve with time. Constipation is an exception and often requires long term management. In short term trials, the number needed to harm, considering all the side effects in table 2, was 4.2.[47]

Sedation and dizziness

Sedation and dizziness seem to contribute to dose related increases in falls and fractures, especially in older people.[97-101] Sedation may also contribute to a possible increased risk of motor vehicle crashes in drivers using prescription opioids, with a relative increase of 20-50%.[102 103] Studies conflict, however, and pain, other drugs, or comorbid conditions may also contribute.[104 105] Nonetheless, patients receiving long term opioids (median dose, 60 mg morphine equivalents) for pain showed reduced reaction time, attention, and psychomotor speed in laboratory testing.[106]

Depression

Depression may be another important central nervous system side effect of opioids. Causality is difficult to assess, however, because patients with depression are more likely to use opioids than those without depression. Cross sectional studies report more depression with increasing dose and duration of opioid therapy.[89] Furthermore, a cohort study of patients without a diagnosis of depression who started treatment with opioids suggested an increased likelihood of depression during treatment and greater risk with a longer duration of treatment.[107]

Endocrine effects

Long term opioid treatment is linked to important endocrine side effects, with hypogonadism being recognized in

the 1970s among men on methadone maintenance.[108 109] More recent studies detected hypogonadism in patients receiving oral opioids for chronic pain.[110-112] The mechanism is suppression of gonadotropin releasing hormone secretion by the hypothalamus.[113 114] This suppresses pituitary gonadotropins, which fall acutely with opioid ingestion. This in turn reduces sex steroid synthesis in the testes and ovaries.

Decreased testosterone levels have been reported in men receiving long acting opioid analgesics or opioids for at least a year.[110 112] Amenorrhea or oligomenorrhea can occur in premenopausal women receiving such treatment; both testosterone and estradiol are reduced.[111 112] Estimates of the prevalence of hypogonadism with opioid treatment range from 0% (small, short term randomized trials) to almost 90% (self selected patients on long acting opioids).[111 112]

Although erectile dysfunction in men with back pain may have multiple causes, the use of drugs for the condition is associated with both the dose and duration of opioid treatment.[115] Among men with back pain taking long term opioids at a daily dose of at least 120 morphine equivalents, 19% used drugs for erectile dysfunction or testosterone replacement. Among those with back pain but no opioid use, 7% used such drugs, with an adjusted odds ratio of 1.45 for long term opioid use. Symptoms of sexual dysfunction may have a gradual onset, and neither patient nor clinician may consider medication as a cause. Furthermore, patients are often reluctant to report sexual problems, so they may go unrecognized and untreated.

Interference with other treatments

Interference with other treatments is a growing concern. Success rates of lumbar facet denervation for back pain were lower in patients receiving opioids.[116] After multidisciplinary rehabilitation for back pain, opioid dependent patients were less likely to return to work and more likely to seek new sources of care.[117] It is unclear whether these problems result from the pharmacologic effects of opioids, characteristics of patients most likely to receive them, or some combination.

PATIENT COMMENTARY

"I have had low back pain for over 22 years. I have had eight low back operations and two cervical fusions. I have taken opioids in several forms for over 20 years. My experience led me to become a patient advocate and to join the American Chronic Pain Association, where I've led dozens of patient groups and helped people in seeking hospital or emergency room care. It's alarming how many patients don't ask anything about the meds or the side effects. They don't take the time to find out about the risks—like overdose and addiction. A common perspective among patients with chronic pain is that they just want to rely on their doctors for decisions and information. But most doctors don't have a lot of time to inform patients of the up and down sides of these meds."

Reducing risks of opioid therapy

Screening

Efforts to maximize the safety of opioids have centered on screening patients for a high risk of misuse; use of "pain contracts" to specify expectations and limits on prescribing; and use of routine urine drug screening. However, a systematic review found only weak evidence to support the effectiveness of opioid treatment agreements and urine testing for reducing opioid misuse in patients with chronic pain.[118]

Other systematic reviews used structured interviews, observation, and self report questionnaires to identify high risk patients. They concluded that the psychometric properties of risk screening tools are weak and that study samples were small and unrepresentative.[119 120] Personal history of alcohol or drug misuse was the strongest predictor of risk; pain severity was not a predictor. No single method can reliably identify patients who are unsuitable for opioid treatment or who require closer monitoring.[120] The screening of patients may stigmatize them or leave them feeling abandoned if opioids are withheld.[121]

Opioid prescription, misuse, and overdose have all increased despite guidelines that recommend screening tools, treatment agreements, and urine testing. It is unclear whether this is because the recommendations are difficult to implement and inconsistently used or because they are ineffective.[118 122] The acknowledgment that these measures seem insufficient may shift attention from trying to identify "risky patients" to broader awareness of inherent drug risks.[121]

Newer safety strategies

Many argue that alternative treatments for back pain should be more readily available and affordable,[123] with easier access and better insurance coverage. Systematic reviews suggest that services such as exercise therapy and cognitive behavioral therapy benefit patients with back pain. Exercise seems to reduce pain, risk of recurrence, and work disability.[124-126] Cognitive behavioral therapy seems to improve pain scores and enhance the effects of exercise.[127-129] Both approaches support long term self care strategies. Systematic reviews also suggest that spinal manipulation, acupuncture, and massage may be at least as effective as conventional primary care, with advantages in safety.[130-133]

Prescription drug monitoring programs

Such programs are emerging in North America. Most are web based databases to which all pharmacies in a state report prescriptions filled for controlled substances. Clinicians can access these data to identify patients with overlapping opioid prescriptions, prescriptions from multiple clinicians or pharmacies, or risky coprescriptions. The information may influence prescribing decisions or referrals for addiction treatment and occasionally results in law enforcement actions for illegal prescribing or drug diversion. Limited data from these programs suggest that they may reduce the risk of overdose.[134 135]

Evidence on dose related overdose risk has prompted recommendations for maximum opioid dosing. For example, in 2007 Washington state public insurance agencies (Medicaid, workers' compensation, public employees, prison health) developed prescribing guidelines that warned against doses exceeding 120 mg per day of morphine equivalents and advised consultation with a pain

Practical principles in prescribing opioids for low back pain[145]

For all patients with back pain

- Emphasize that self care is the foundation of effective back care and that it is usually more important to remain physically active and continue rewarding activities rather than rely on medical prescriptions
- An empathetic supportive doctor-patient relationship can encourage effective self care
- Rather than monitoring progress by changes in reported pain alone, it may be more effective to guide care towards participation in activities
- Differentiate goals of short term pain relief from those of long term effectiveness. For long term use, opioids have unproven benefits and substantial risks

For patients in whom long term opioid use is considered

- Use stepped care with non-opioid drugs before considering a trial of opioids for long term use. This may include non-steroidal anti-inflammatory drugs, tricyclic antidepressants, and topical analgesics
- Put safety first, placing patient and clinician on common ground. Adverse effects, including addiction, overdose, dependence, depression, cognitive impairment, sexual dysfunction, chronic constipation, motor vehicle accidents, and fractures due to falls, should all be discussed
- Systematically evaluate risk but do not overestimate your ability to identify high risk patients. Minimize "adverse selection" by using extra caution in patients with a history of substance misuse (opioids or others) or mood disorders such as depression or anxiety. If a prescription drug monitoring program is available, it should be checked before prescribing
- Consider intermittent opioid prescription, with clear expectations for short duration of use. Prescription of a few days to a week of short acting opioids may reduce risks of tolerance, dependence, and dose related adverse effects
- Avoid long term opioid use without decisive benefits. Place a one month time limit on an initial opioid trial. Involve the patient in choosing functional goals for the trial. If goals are not met, discontinue opioids and try alternative approaches. If opioids are continued, obtain informed consent regarding known risks and uncertain benefits. A pain contract can help establish expectations: a single prescriber, one designated pharmacy, regular monitoring, and precautions to prevent diversion

For patients in whom long term use is initiated

- Keep the opioid dose as low as possible. When the dose reaches 50-100 mg morphine equivalents per day, re-evaluate treatment and consider specialist consultation. Higher doses have unproven benefits and increased risks, and make discontinuation more difficult
- Because of the risk of overdose, avoid concurrent opioids, sedative-hypnotic drugs, and alcohol
- Closely monitor use, inquiring about misuse and adverse behavioral or medical effects. Check urine drug screens and prescription drug monitoring program data regularly
- Regularly reassess whether the opioid dose can be reduced or discontinued. High risk misuse or drug diversion requires discontinuation; non-fatal overdose requires reduction or tapering off
- Identify and treat opioid misuse: misuse or addiction should be treated rather than result in discharge from care. Addiction referral options should be identified

specialist before prescribing higher doses. The guideline included a web based calculator to determine daily morphine equivalents for any opioid drug (http://agencymeddirectors.wa.gov/mobile.html). The number of opioid prescriptions and the mean daily dose in the workers' compensation system plateaued, then fell in 2009 and 2010. Opioid related deaths rose through 2009, then fell sharply in 2010.[136]

Reformulation

Another strategy for reducing misuse and diversion is to reformulate long acting opioids to prevent them being crushed or dissolved, making them more difficult to snort, smoke, or inject. After extended release oxycodone was reformulated in 2010, surveillance suggested a reduction in misuse and diversion.[137 138]

PATIENT COMMENTARY

"Once I decided to start cutting back and talked with my doctor about it, I came to the conclusion that opioids had little to do with pain and more to do with habit. Opioids took control over my life because the habit of taking them was the most important thing. Now I take only what is prescribed—not more or less. I've learned to follow the rules. I know now that even when the physical cause of pain is clear, the feeling of pain is subjective. It is related to anxiety, stress, work, family, relationships—all these can cause a person to have more pain, and it becomes an Achilles heel.

I've observed that many people who take opioids don't see this reality or take responsibility for their meds. They don't like taking these drugs, but they're afraid not to. Some realize it's bad for them, but they underestimate the power they have to beat this problem. When patients realize that they're responsible for how they use these meds—that's when I've seen them change their lives."

Emerging treatments

There is a growing sense that the management of back pain should focus on return to normal activities more than pain relief because a reduction in pain often follows improved function. For example, the Subgroups for Targeted Treatment (STarT Back) trial offered the highest risk patients a program of psychologically informed physical therapy, which resulted in improved outcomes and reduced cost.[139] High risk for prolonged pain was identified and treated by non-drug based management—a distinctly different approach from adverse selection of high risk patients into long term opioid therapy. The generalizability of this approach is being tested in diverse settings and countries.

Guidelines

Although guidelines from the UK National Institute for Health and Care Excellence (NICE) and joint guidelines from the American College of Physicians and the American Pain Society (ACP/APS) recommend paracetamol (acetaminophen) as the first line drug,[140 141] a recent study did not support its efficacy for back pain.[142] The NICE guideline then recommends either NSAIDs or weak opioids such as codeine. Strong opioids are recommended only as short term treatment for severe pain. Specialist assessment is recommended when considering long term use of strong opioids.

The ACP-APS guideline is similar, recommending opioids or tramadol as an option after a trial of NSAIDs and advocating careful consideration of benefits and potential harms. If a patient does not respond to a time limited course of opioids, alternative treatments or specialist referral should be considered. Both guidelines recommend tricyclic antidepressants, exercise, cognitive behavioral therapy, spinal manipulation, acupuncture, and massage as treatment options.

Several guidelines have assessed opioid therapy for chronic pain in general, and a systematic review of 13 guidelines is available.[143] Only two were judged to be of high quality: one from the American Pain Society and the American Academy of Pain Medicine,[35] and another from a Canadian national opioid use guideline group.[144] Most guidelines recommend avoiding doses greater than

FUTURE RESEARCH QUESTIONS

Relative to alternatives, how safe and effective are opioids for long term management of back pain?

Can a subset of patients with chronic back pain in whom long term opioid use is safe and effective be accurately identified?

How common are serious adverse effects of long term opioid use, including addiction, drug induced mood disorders, behavioral deactivation, hyperalgesia, sexual dysfunction, fractures, and motor vehicle injuries?

Are there mitigation strategies that appreciably reduce the risks of adverse events in patients using long term opioids, such as frequent monitoring visits; rotation of opioid preparations; or use of low or intermittent dosing regimens?

90-200 mg of morphine equivalents per day. Despite weak evidence, most recommend the use of opioid risk assessment tools, written treatment agreements, and urine drug testing. Ten of the guidelines note that opioids and benzodiazepines are a high risk combination. Ten also name a history of substance misuse or mental health disorders as the leading risk factors for overdose or misuse.

Conclusion

Clinicians must treat back pain as effectively as possible while minimizing the associated risks, and the box outlines the practical principles in prescribing opioids for low back pain (box).[145] As clinicians' perceptions of the effectiveness and safety of opioids shifted over the past two decades, prescribing increased dramatically. However, the effectiveness of long term opioid therapy for back pain remains unclear, and surveillance data have shown markedly increased rates of opioid overdose and addiction. Patients at the highest risk of these major adverse outcomes are the most likely to receive long term opioids. Other long term complications of opioid treatment include falls, fractures, motor vehicle crashes, and other injuries; cognitive and mood effects; and hypogonadism and sexual dysfunction.

There is no evidence that opioids improve return to work or reduce the use of other treatments. They may even limit the effectiveness of other treatments. Clinicians may want to monitor treatment success on the basis of functional ability, in addition to self reported pain severity.

Short term opioid use has analgesic benefits, but it may be necessary to avoid the adverse selection of patients with past substance misuse or mood disorders and to set limits on the duration of prescription to avoid inadvertently initiating long term use. An effective strategy for reducing misuse, diversion, and overdose would be to limit patients' exposure to opioids. Canadian and American researchers have argued that "many physicans and patients have had unreasonable expectations of opioids and have seriously underestimated their risks. It is time to collectively lower expectations and prescribe these drugs less readily, to fewer patients, at lower doses, and for shorter periods."[146]

In current practice, patients at highest risk of adverse effects are most likely to receive opioids. Thus, support for alternative treatments should be strengthened. One promising approach is to improve access to psychologically informed interventions that support return to meaningful life activities, with more intensive intervention for patients at the highest prognostic risk.

PATIENT COMMENTARY

"I have good days and bad days, like everyone else. What's different now is that I'm not seeking an answer out of a medicine bottle. I start by analyzing my situation, what's causing my stress, what's making me want to take more meds today. What I have to do is understand that this is a normal process, and that I must take responsibility for it. Then I find a way to manage the stress rather than take something to mask it. Now I have 12 years of experience working with patients in chronic pain groups. I've learned that, with the support of others, there's a better way to live—even with chronic pain. Taking more meds than prescribed isn't a solution, it's just the beginning of a disastrous cycle. I've learned to accept my pain because I know it's my reality and that I can still be productive and enjoy life."

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