

AN ANALYSIS OF DRUG THERAPY TAPERING GUIDELINES

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INTRODUCTION

Chronic pain, the kind of pain a person wakes up with every morning and goes to sleep with every night, has a standard of care that is often incomplete and sometimes inaccurate. Chronic pain treatment often revolves around drug therapy and managing side effects without addressing non-drug therapies or holistic lifestyle changes needed to resolve the source of pain.

Equally as often, the drug therapies selected create more issues than they solve. This affects quality of life, functional level and continued pain. Iatrogenic pain, described as pain resulting from the treatment itself (drugs, surgeries, hospital readmissions, etc.), makes identification and proper treatment of pain even more complicated. When the decision is made to reduce dosages, remove drugs and address coping skills to restore function and quality of life, the process of tapering drug therapy becomes further confounded by poor documentation, few clinical studies and undereducated prescribers.

The confluence of drug treatment complexities, combined with lack of guideline clarity, can undermine the goal of restoring function because the tapering process is often deferred indefinitely or handled incorrectly. In order to bring clarity to this important healthcare issue, we conducted a quantitative assessment of the available recommendations on the tapering process as articulated in chronic pain guidelines and identified gaps in information that need to be addressed.

THE SCOPE OF THE PROBLEM

Treating chronic pain is a challenge for healthcare providers regardless of geographical location or payer. A 2008 World Health Organization survey measuring the pervasiveness of chronic pain determined 37.3 percent of the population in developed countries and 41.1 percent in developing countries lived with some degree of chronic pain.¹ To put these numbers in perspective, in 2008 the prevalence of cardiovascular disease in the United States was reported to be 37.1 percent.² This means that just as many people live with chronic pain as with cardiovascular disease. In terms of healthcare costs and productivity lost, chronic pain is estimated to cost up to \$635 billion dollars a year, which is more than heart disease, diabetes or cancer.³

Table 1 Costs of Common Healthcare Conditions

Condition	Direct Costs*	Indirect Costs*	Total Costs*
Chronic Pain ¹	\$261-\$300	\$299-\$334	\$560-\$635
Diabetes ²	\$176	\$69	\$245
Cardiovascular Disease ³	\$273	\$172	\$444
Cancer ⁴	\$87	\$130	\$217

*Approximate Cost in Billions

1) Darrell J. Gaskin, Patrick Richard. The Economic Costs of Pain in the United States. The Journal of Pain. Volume 13, issue 8. 2012. Page 715.

2) Economic costs of diabetes in the U.S. in 2012. American Diabetes Association Diabetes Care. Volume 36, issue 4. April 2013. Pages 1033-46. <http://www.ncbi.nlm.nih.gov/pubmed/23468086>.

3) Forecasting the Future of Cardiovascular Disease in the United States. AHA Policy Statement. Circulation. Volume 123. 2011. Pages 933-944. <http://circ.ahajournals.org/content/123/8/933.long>.

4) The National Institutes of Health (NIH) estimated the 2009 overall annual costs of cancer. <http://www.cancer.org/cancer/cancerbasics/economic-impact-of-cancer>.

Chronic pain and loss of functionality has a profound impact on a person’s quality of life. Untreated or poorly treated chronic pain can cause real physical harm to patients. Untreated pain alters hormone function and metabolism, promoting bodily deterioration. Pain also contributes to suicide, depression, cardiovascular stress, suppression of the immune system, gastrointestinal problems and disability. **Most importantly, untreated or poorly treated acute pain increases the chances that a patient will develop chronic pain in the future.**⁴

While the need for and importance of good pain management is well established in medical literature, the number of studies looking at the various aspects of treatment, as well as the quality of these studies, varies widely. As with any other chronic health condition, the approach to treatment should begin with a clear outcome goal, well-studied tools and measures for objective assessment of progress. Each of these criterion should be based upon the best available evidence from medical literature.

However, for practitioners faced with the challenge of addressing chronic pain, the three phases of drug therapy – initiation, maintenance and tapering – are not as fully or evenly studied as other disease treatments. While there is clear guidance to prescribers for the initiation and maintenance of therapy, there is very limited actionable guidance on tapering therapy when the drugs are no longer effective or the risks outweigh the benefits.

To illustrate the disproportional emphasis on initiation and maintenance of information available to prescribers, Appendix 1 analyzes the information provided to physicians within the FDA Approved Package Insert, one of the most commonly used sources of prescribing information.

The limited scope of clinical standards of care for tapering drug therapy only adds to the issue of undereducation of prescribers on management of chronic pain. A 2011 study of 117 U.S. and Canadian medical schools found 17 of 104 schools offered a designated pain elective and only eight of those offered more than one elective course in pain education. Of the 104 U.S. medical schools included in the study, only four schools required a course in pain management. A majority of those electives were administered by anesthesiology departments from which the sub-specialty in chronic pain management is derived. A large number of U.S. medical schools offer no course on pain management and an equally large number devote less than five hours of coursework.⁵

If physicians are not trained in or have limited expertise on the subject of pain, how can they be expected to understand the best methods for managing pain?

In a June 2011 interview with PBS Newshour, Dr. David Kloth, a pain management physician and spokesman for the American Society of Interventional Pain Physicians, stated, "In most cases, doctors contribute innocently because they haven't been trained properly on how to prescribe in a responsible way, how to identify a drug addict and help them." Dr. Kloth went on to say, "In fact, 80 to 90 percent of physicians in the United States have absolutely no training or education in the use of controlled substances."⁶ Physicians often rely on input from peers, pharmaceutical sales representatives or clinical articles and content from medical education organizations. Unfortunately, there is substantial research to show that these sources can be biased in favor of new and expensive drug therapies over many tried and true non-drug options.^{7,8,9}

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Dr. David Kloth

The lack of understanding, education and limited focus on the bio-psychosocial model of treating the entire person further limits the chances of treatment success. Biological interventions such as surgery, injections or prescription drugs are easier to define and measure and therefore it becomes easy for the medical community to default to "medicalization" of symptom treatment. However, psychological makeup (e.g., catastrophic thinking, perceived injustice, fear, avoidance or childhood abuse) and social environment (e.g., family life, socioeconomic circumstances, ethnic or cultural differences) of the patient are equally as important to the treatment of the

patient's chronic pain. The addition of other co-morbidities such as diabetes, hypertension, smoking or obesity further complicates the healing as well as the pain management process. Failure to address the psychosocial component of a patient's care can hinder functional progress.^{10,11}

In chronic pain management, **polypharmacy**, which is defined as the use of too many or redundant drugs, is a common complication. Multiple drug therapy itself is not an issue provided the number of drugs to achieve the treatment goal is kept at the minimum necessary. Polypharmacy becomes problematic when multiple drug therapy begins to generate bad outcomes for the patient. It can result in unnecessary and/or inappropriate prescribing, increase the chance of drug interactions, make it hard for patients to adhere to drug treatment, and increase overall drug costs.^{12,13}

For example, side effects from chronic use of opioids include constipation, sleep disorder, cognitive impairment, somnolence, atrophy, dry mouth, depression and/or anxiety, and many others. Drugs used to treat these symptoms would include stool softeners, sleep aids, stimulants, muscle relaxants, anti-depressants and tranquilizers. Therefore the introduction of a single drug, like oxycodone, can turn into a regimen of multiple drugs that primarily address the symptoms that arise from side effects and not the remaining pain. Thus, polypharmacy tremendously complicates the drug regimen and reduces the patient's function level, as well as dramatically increases the complexity of the taper process.

Limited clinical guidance, poor pain management education, "medicalization" of treatment and polypharmacy all work against improved function, quality of life and make successful tapering difficult, if not impossible.

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PURPOSE AND METHODS

In 2003, an international group of medical researchers and guideline developers published a tool to evaluate medical guideline quality. The Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument, which was developed to address the variability in guideline quality, defined quality of medical guidelines as, “The confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid, and are feasible for practice.”¹⁴ The AGREE Instrument outlines several attributes of high quality guidelines, including the use of a comprehensive literature search for evidence and the review and rating of the quality of evidence used to create the guideline.¹⁵

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The purpose of our analysis was to conduct a quantitative assessment of relevant information present, comparing chronic pain guidelines based on the information provided to guide physicians tapering patients off opioid medications. Assessment criteria focused upon whether the guidance was clear and actionable to the reader. A second review to compare the quality of taper information is planned for a subsequent white paper.

Using the keywords “opioids,” “chronic pain,” “guideline” and “recommendation,” an online search was conducted of the National Library of Medicine (NLM) and the Agency for Healthcare Research and Quality’s National Guidelines Clearinghouse™ (NGC) to find chronic pain guidelines that met certain criteria. Guidelines appear in the NGC provided they have met NGC development criteria and qualify per their standards. Between the two databases, 257 documents were identified by the keyword search. Of the 22 documents meeting our criteria for selection, four documents were later disqualified by the review group for failing to meet the selection criteria. Ultimately, 18 guidelines (see Appendix 2) met the inclusion criteria in Table 2 and were used in the final analysis.

Table 2 **Chronic Pain Guideline Criteria**

Inclusion Criteria	Exclusion Criteria
Documents meeting the definition of a “guideline” according to the Institute of Medicine: <i>“Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.”¹⁶</i>	Guidelines for acute pain only, pain treatment for cancer pain, end of life or hospice care, pain treatment for labor and delivery and pain management in the hospital setting.
Guidelines published, reviewed or updated between 1/1/2009 and 2/1/2014.	Guidelines for specific diseases or conditions where pain management is not the primary purpose of the guideline.
Guideline objectives are chronic pain management focused.	Pain guidelines for specific diseases or conditions where opioid treatment is not effective or dangerous.
Guidelines include information on self-administered drug treatments and include opioid drug treatments.	Any guideline last published, reviewed or updated before 1/1/2009.
Guidelines created by using a systematic review of the medical literature and rating system to evaluate the quality of the information.	Guidelines that do not include self-administered drug treatment options.
Guidelines must be available in English.	Guidelines that do not use a systematic literature review and quality rating system to aid in developing recommendations.

The Substance Abuse and Mental Health Services Administration (SAMHSA) guideline, “Managing Chronic Pain in Adults with or in Recovery From Substance Use Disorders,” did not meet selection criteria because documentation of the development did not speak to the use of a quality rating for the evidence used to create the guideline. However, given the broad use of the SAMHSA guideline as a treatment reference, they were assessed and included in the evaluation table for display only, but not included in the analysis.

The review group formulated assessment questions along with definitions of “Yes” to quantify the presence of information in specific areas of treatment, including drug tapering. Any guideline determined by reviewers not to meet the definition of “Yes” was documented as “No.” The information evaluated, questions used and definitions of “Yes” are provided in Appendix 3.

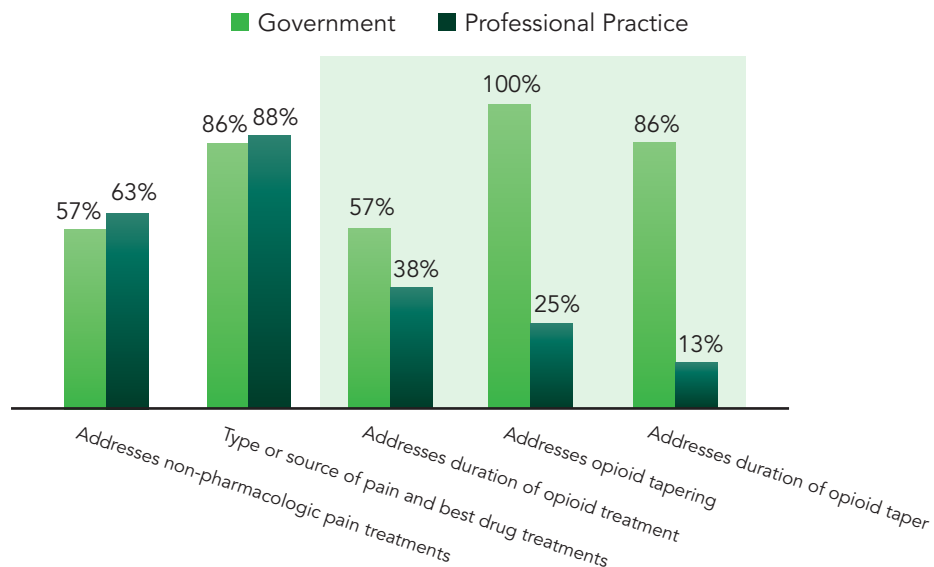
ANALYSIS AND RESULTS

Of the guidelines that met the criteria for review, 14 were developed by U.S. health entities and four by health entities outside the United States. The majority of guidelines (83 percent) in the analysis were developed by professional practice (eight) or government organizations (seven).

Comparing only professional practice and government guidelines, the chart below shows that government guidelines addressed duration of opioid treatment, opioid tapering and duration of taper far more often than professional practice guidelines (81 percent vs. 25 percent).

Chart 1

Government vs. Professional Practice Guidelines



PSYCHOSOCIAL CONSIDERATIONS

Considering the psychosocial aspects of treating chronic pain, 13 guidelines (72 percent) addressed at least one of the three cognitive or behavioral considerations of treatment as defined on page 21. Five guidelines (28 percent) did not address cognitive or behavioral considerations at all, while eight (44 percent) addressed all three.

When examined by organization type, government organization guidelines were far more likely to address cognitive or behavioral considerations of treatment with four of the seven government guidelines (57 percent) providing guidance in all three areas, as opposed to two of the eight (25 percent) professional practice guidelines. Though only two independent health/quality organization guidelines were represented in our analysis, both addressed all three cognitive or behavioral considerations.

DRUG-RELATED CONSIDERATIONS

Drug therapy management is a dynamic process in which treating physicians must consider a multitude of patient, disease and drug characteristics in order to select the best drug therapy for a patient. In addition to assessments of patient and disease factors, physicians must monitor and adjust therapy regularly to reach treatment targets. To support best practices in chronic pain management, physicians should have access to guidance that addresses the three phases of drug therapy treatment – initiation, maintenance and tapering. Our analysis examined the information provided in chronic pain management guidelines with regard to drug-related aspects of treatment and tapering, such as:

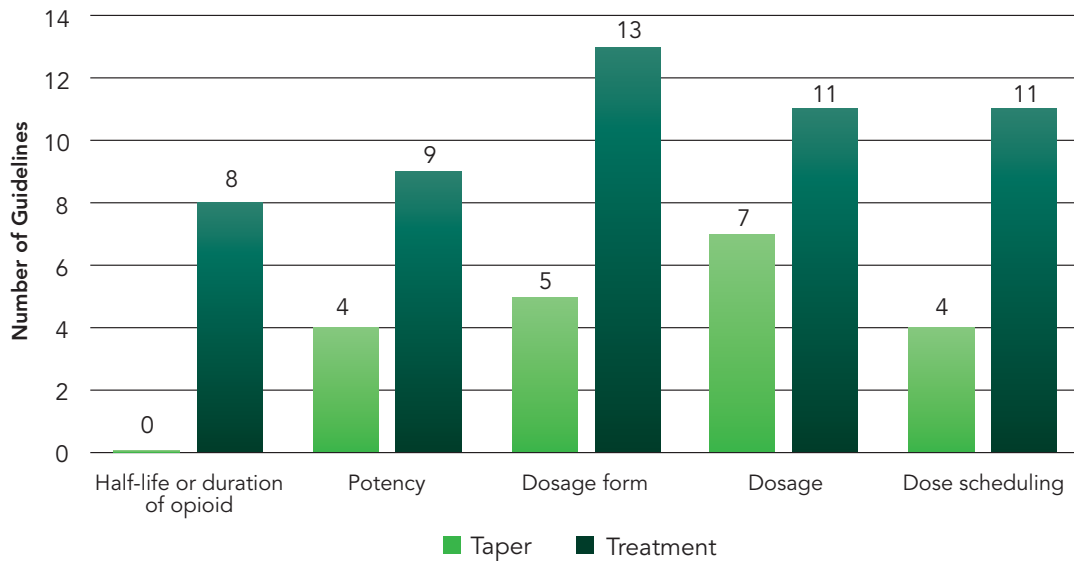
- Duration of an opioid’s action in the body
- Potency of an opioid compared to other opioids
- Dosages to begin therapy and treat pain
- Dosage forms available or circumstances in which a particular dosage form is preferred
- Dose schedules to manage pain symptoms

Of the 18 guidelines included in our analysis, 78 percent addressed at least one of the pharmacologic and pharmacokinetic considerations of opioid treatment. However, only five (28 percent) of the guidelines addressed all five pharmacologic and pharmacokinetic considerations. Of these five, three guidelines were from government organizations, one was from a healthcare institution and one was from a professional practice organization.

Looking at information on pharmacologic and pharmacokinetic considerations of opioid taper, 11 guidelines (61 percent) did not address tapering at all. At least one of the five pharmacologic and pharmacokinetic considerations was addressed by 39 percent of the guides. However of these seven guidelines, none addressed duration of action and only three guidelines addressed the remaining four pharmacologic and pharmacokinetic considerations.

Chart 2

Comparison of Taper vs. Treatment
Pharmacologic & Pharmacokinetic Considerations



When examining pharmacologic and pharmacokinetic considerations by organization type, the disproportionality between treatment and taper information provided is most striking. Of the seven government organization guidelines included in the analysis, five guidelines (71 percent) addressed at least one of the pharmacologic and pharmacokinetic considerations of tapering. In contrast, none of the eight professional practice guidelines addressed the pharmacologic and pharmacokinetic considerations of tapering.

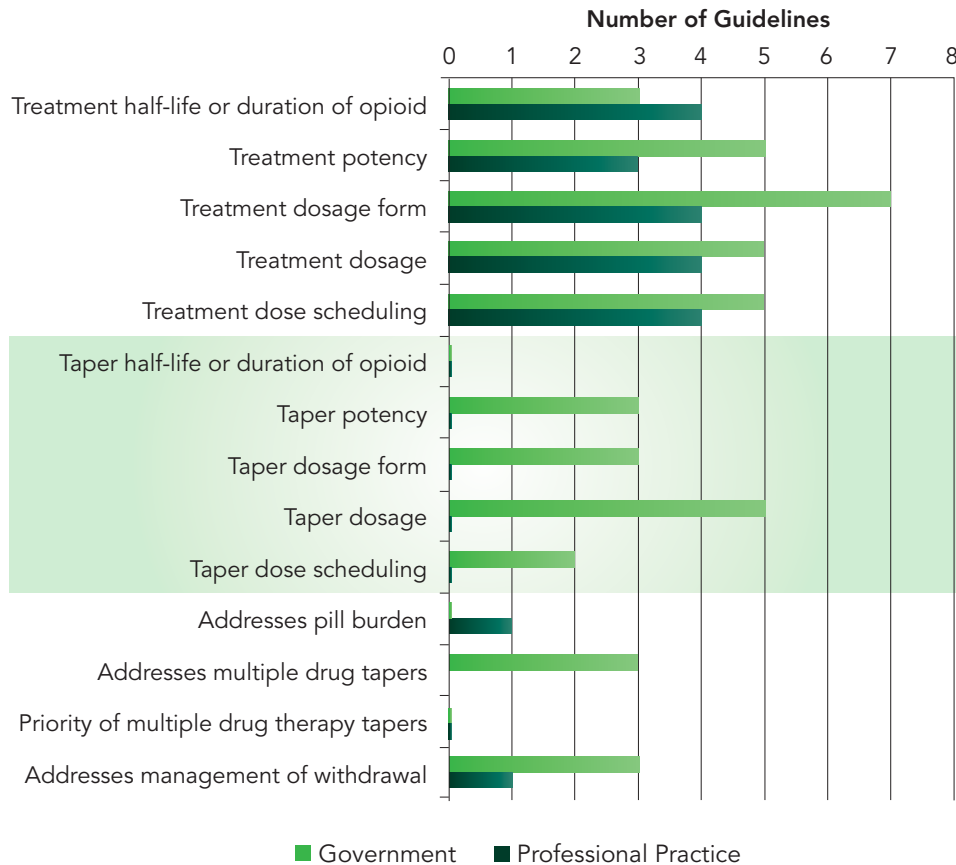
PATIENT-RELATED CONSIDERATIONS

The analysis also examined the information provided on patient-related considerations that might impact treatment success, influencers of patient adherence through regimen complexity or adverse effects, such as:

- Patient pill burden, which is defined as the number of pills a patient regularly takes in a day
- Managing multiple drug tapers
- Determining the priority order of multiple drug tapers
- Managing opioid withdrawal symptoms

The chart below shows that 50 percent of the guidelines addressed patient-related considerations of opioid treatment or tapering. Out of the nine, five (56 percent) were from government organization guidelines. Professional practice guidelines were far less likely to address patient-related considerations that might influence the success of an opioid taper. Of the eight professional practice guidelines analyzed, two addressed at least one of the four patient-related considerations, only one addressed pill burden and another addressed only withdrawal symptoms.

Chart 3 Comparison of Government vs. Professional Practice Guidelines Drug Management & Taper Information



WITHDRAWAL INFORMATION

Physical withdrawal symptoms have a potent psychological impact on a patient's behavior, often driving a pathologic need to resolve the withdrawal symptoms.¹⁷ Chart 3 on the previous page shows that out of the 18 guidelines included in the analysis, five (28 percent) provided information on withdrawal management and all five addressed at least one of the pharmacologic and pharmacokinetic considerations for both treatment and tapering. Again, government organization guidelines were dominant, making up three of the five guidelines, with the fourth and fifth coming from professional practice and independent health/quality organizations.

DISCUSSION

Chronic pain patients often have other diseases or conditions that come with their own treatments and influences. The art of medicine entails navigating the complexities of physical symptoms, patient attitudes, patient knowledge and cultural perceptions of illness to develop an actionable plan for treatment. Drug therapy selection is likewise an art in the respect that physicians must consider all the same complexities and patient tolerances to select the drug therapy of greatest benefit and the least amount of harm.

Many medications share similar side effects (SEs) and adverse effects (ADRs), sometimes causing effects that mimic the disease being treated. Manifestations of poorly controlled pain can produce symptoms such as rapid heartbeat, sweating, stomach discomfort, constipation, nausea, vomiting, nervousness, hormonal dysfunction, depression, anxiety, sleep disturbances and even suicide.¹⁸ Many drug therapies used in the treatment of chronic pain share these same symptoms as side effects of treatment.

When opioids are included in the pain treatment regimen, symptoms of withdrawal must also be considered in the circumstance of abrupt interruption of treatment. Withdrawal symptoms such as runny nose, abdominal cramping, rapid heart rate, diarrhea, sweating, nervousness and difficulty sleeping are shared symptoms of pain as well as manifestations of drug therapy SEs and ADRs. Consider Chart 4, which demonstrates the significant overlap in SEs and ADRs for

The art of medicine entails navigating the complexities of physical symptoms, patient attitudes, patient knowledge and cultural perceptions of illness to develop an actionable plan for treatment.

the different drug classes used to treat chronic pain. Chart 5 illustrates how SEs and ADRs for chronic pain treatments overlap symptoms of withdrawal or untreated pain.

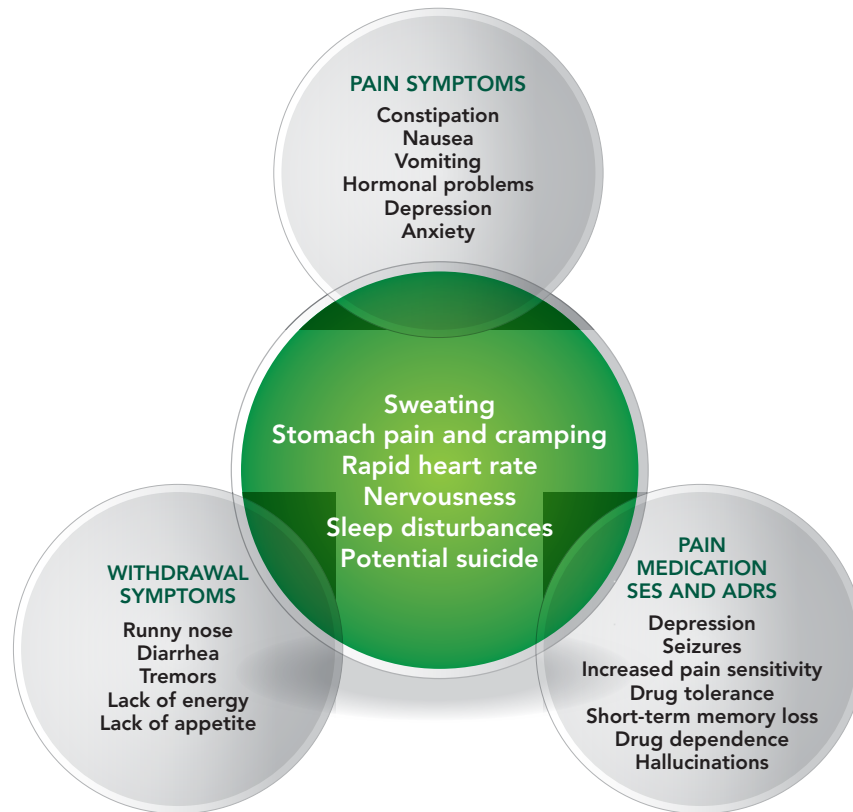
So how does a physician properly determine if symptoms are directly associated with or a combination of the original type or source of pain, SEs, ARs or withdrawal? Charts 4 and 5 show the complexity facing a physician trying to manage chronic pain and the need for guidelines to help disentangle the symptoms.

Chart 4 Shared Side Effects & Adverse Reactions of Medications Used to Treat Pain



Chart 5

**Overlapping Symptoms & Side Effects of Pain,
Pain Medication and Withdrawal**



SUMMARY

Our analysis demonstrates that chronic pain guidelines emphasize information on opioid initiation and treatment, but do not consistently address drug-related or patient-related aspects of opioid taper. Important patient-related considerations are the least likely to be addressed by guidelines, thereby missing key opportunities to address patient controlled treatment challenges such as pill burden, recognition of drug interactions, multi-drug tapers and withdrawal symptom management. Results also demonstrate that government organization guidelines address the management challenges of all three phases of treatment (initiation of drug therapy, maintenance of drug therapy and tapering of drug therapy) more consistently than other organizational guidelines.

These findings, combined with the relative undereducation of physicians in chronic pain management and drug therapies, highlight the information void in which physicians are expected to successfully manage chronic pain and opioid tapering. The current gap, characterized by limited guidance and understanding of the tapering process by treating physicians, must be filled with actionable and understandable information.

APPLICATION

Treatment success is dependent upon the ability to properly educate prescribers and patients. Consolidation of best practices into a single, actionable and individualized roadmap clarifies the ambiguities that limit positive outcomes of opioid tapering. The following is an example of a typical polypharmacy drug regimen:

- 1 Sustained release oxycodone for long-acting analgesia
- 2 Hydrocodone/acetaminophen combination for short-acting analgesia
- 3 Lidocaine topical patch for localized neuropathic pain
- 4 Docusate for constipation
- 5 Carisoprodol for muscle spasticity, atrophy
- 6 Zolpidem for sleep disorders
- 7 Modafinil for over-somnolence
- 8 Duloxetine for depression and anxiety
- 9 Alprazolam for anxiety

In addition, there may be other drugs involved to deal with co-morbid conditions like cardiovascular disease, diabetes, obesity, smoking cessation or contraception for females. The age and overall health of the patient complicates not only the drug therapy (only a portion of which may be related to pain management), as well as the tapering methodology and psychosocial contributors.

While some of the guidelines evaluated address the taper process for individual drug classes, **none** provide prescribers a recommendation to which drugs and/or dosage should be

discontinued first, which could be discontinued concurrently, and which should be saved for last. There are certain clinical specialties (e.g., addictionology, pain management, medication therapy management) that have formal training and active practice experience in discontinuing these “cocktails.” However, the majority of chronic pain patients are in fact managed by primary care prescribers who are often the least prepared to navigate the complexities of tapering chronic pain medications. Therefore it is the primary care prescriber that is most in need of a resource to tie together scattered resources into a single tactical plan that is customized for the individual patient’s drug regimen.

Precise pacing of a taper cannot be outlined as there are too many patient-dependent variables that determine when a patient is ready for the next downward step. However, there should be a focus on tapering milestones. For example, at what point in an opioid taper is it acceptable to begin a muscle relaxant taper? Or, when in the taper process is it acceptable to increase the dosing interval?

While some of the guidelines evaluated address the taper process for individual drug classes, none provide prescribers a recommendation to which drugs and/or dosage should be discontinued first, which could be discontinued together and which should be saved for last.

The question becomes do providers have enough evidence-based directed guidance available to help them effectively taper drug therapy in chronic pain cases? The answer is a resounding “No.” For tapering to be successful, the provider needs a customized, actionable plan that is based on the best collective evidence. Our research shows that information is either inadequate or unavailable, therefore requiring the prescriber to create tapering strategies based on their own level of understanding. Starting a drug regimen is relatively easy and reducing or removing a drug regimen is significantly difficult. This information gap is the ultimate challenge in healthcare today.

Contact PRIUM today to learn more about TaperRx, an evidence-based, individualized approach to tapering drug therapy that takes into consideration the entire drug regimen.

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REFERENCES

1. A. Tsang, M. Von Korff, S. Lee, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J. Pain*. Volume 9, Issue 10. 2001. Pages 883–891.
2. Statistics Committee and Stroke Statistics Subcommittee. AHA Statistical Update: Heart Disease and Stroke Statistics—2008 Update. A Report from the American Heart Association. *Circulation*. Volume 117. 2008. e25-e146. Referenced March 2014: <https://circ.ahajournals.org/content/117/4/e25/T3.expansion.html>.
3. D. Gaskin, P. Richard. The Economic Costs of Pain in the United States. *The Journal of Pain*. Volume 13, Issue 8. 2012. Page 715.
4. N. Wells, C. Pasero, M. McCaffery. Chapter 17. Improving the Quality of Care through Pain Assessment and Management. *AHRQ Patient Safety and Quality: An Evidence-based Handbook for Nurses*. Referenced March 2014: http://www.ahrq.gov/professionals/clinicians-providers/resources/nursing/resources/nurseshdbk/WellsN_SMTEP.pdf.
5. L. Mezei, B. Murinson, Johns Hopkins Pain Curriculum Development Team Pain Education in North American Medical Schools. *Journal of Pain*. Volume 12, Issue 12. December 2011. Pages 1199-1208.
6. Public Broadcasting Service Newshour. Referenced March 2014: <http://www.pbs.org/newshour/rundown/doctors-tell-congress-how-to-rein-in-prescription-drug-abuse/>.
7. Drug and Medical Device Companies Have Outsized Influence on FDA. Union of Concerned Scientists. Referenced March 2014: http://www.ucsusa.org/scientific_integrity/solutions/agency-specific_solutions/drug-companies-influence-FDA.html.
8. S. Rothman, PhD, K. Brudney, MD, W. Adair, BA, D. Rothman, PhD. Medical Communication Companies and Industry Grants. *JAMA*. Volume 310, Issue 23. 2013. Pages 2554-2558. doi:10.1001/jama.2013.281638.
9. G. Spurling, P. Mansfield, B. Montgomery, J. Lexchin, J. Doust, N. Othman, A. Vitry. Information from Pharmaceutical Companies and the Quality, Quantity, and Cost of Physicians' Prescribing: A Systematic Review. *PLOS Medicine*. October 2010.
10. W. Hooten, R. Timming, M. Belgrade, J. Gaul, M. Goertz, B. Haake, C. Myers, M. Noonan, J. Owens, L. Saeger, K. Schweim, G. Shteyman, N. Walker. Institute for Clinical Systems Improvement. Assessment and Management of Chronic Pain. November 2013.
11. Colorado Division of Workers' Compensation. Chronic pain disorder medical treatment guidelines. Denver (CO): Colorado Division of Workers' Compensation. December 2011.
12. E. Hajjar, A. Cafiero, J. Hanlon. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother*. Volume 5, Issue 4. 2007. Pages 345-351.
13. J. Vande Griend, PharmD, BCPS. Common Polypharmacy Pitfalls. *Pharmacy Times*. January 2009. Referenced March 2014: <http://www.pharmacytimes.com/publications/issue/2009/2009-01/2009-01-9968#sthash.R5sAahj3.dpuf>.
14. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care*. Volume 12, Issue 1. February 2003. Pages 18-23.
15. Appraisal of Guidelines for Research & Evaluation II Instrument: The AGREE Next Steps Consortium. May 2009.
16. Institute of Medicine. Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, editor(s). *Clinical practice guidelines we can trust*. Washington (DC): National Academies Press. 2011. Page 2. Referenced March 2014: <http://www.iom.edu/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust/Standards.aspx>.
17. Sadock, B. J, & Sadock, V. A. Kaplan & Sadock's comprehensive textbook of psychiatry. 8th Edition Copyright. Lippincott Williams & Wilkins. 2008.
18. N. Wells, C. Pasero, M. McCaffery. Chapter 17. Improving the Quality of Care through Pain Assessment and Management. *AHRQ Patient Safety and Quality: An Evidence-based Handbook for Nurses*. Referenced March 2014: http://www.ahrq.gov/professionals/clinicians-providers/resources/nursing/resources/nurseshdbk/WellsN_SMTEP.pdf.

APPENDIX 1

Drug	Initiation
OxyContin ¹	<p>2.1 INITIAL DOSING</p> <p>Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with OxyContin [see Warnings and Precautions (5.2)].</p> <p>Consider the following factors when selecting an initial dose of OxyContin:</p> <ul style="list-style-type: none"> • Total daily dose, potency, and any prior opioid the patient has been taking previously. • Reliability of the relative potency estimate used to calculate the equivalent dose of oxycodone needed (Note: potency estimates may vary with the route of administration). • Patient's degree of opioid experience and opioid tolerance. • General condition and medical status of the patient. • Concurrent medication. • Type and severity of the patient's pain. <p>Use of OxyContin as the First Opioid Analgesic:</p> <ul style="list-style-type: none"> • Initiate therapy with 10 mg every 12 hours. • Conversion from other oral oxycodone formulations to OxyContin. • Patients receiving other oral oxycodone formulations may be converted to OxyContin by administering one-half of the patient's total daily oral oxycodone dose as OxyContin every 12 hours. <p>Conversion from other Opioids to OxyContin:</p> <ul style="list-style-type: none"> • While there are useful tables of oral and parenteral equivalents, there is substantial inter-patient variation in the relative potency of different opioid drugs and formulations. Specific recommendations are not available because of a lack of systematic evidence for these types of analgesic substitutions. As such, it is safer to underestimate a patient's 24-hour oral oxycodone requirement and provide rescue medication (e.g., immediate-release oxycodone) than to overestimate and precipitate an adverse reaction. In general, begin with half of the estimated daily oxycodone requirement as the initial daily OxyContin estimate, then divide into two doses taken 12 hours apart, and manage inadequate analgesia by supplementation with immediate-release oxycodone. • Published relative potency data are available and may be referred to in clinical practice guidelines such as those published by authorities in the field of pain medicine, but such ratios are approximations. Consider contacting your specific state medical or pharmacy professional societies for further information on how to safely convert patients from one opioid to another. <p>Conversion from Transdermal Fentanyl to OxyContin:</p> <ul style="list-style-type: none"> • 18 hours following the removal of the transdermal fentanyl patch, OxyContin treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg every 12 hours of OxyContin, should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OxyContin, as there is limited documented experience with this conversion.
Dilaudid ²	<p>DOSAGE AND ADMINISTRATION</p> <p>Dilaudid Tablets</p> <p>The usual starting dose for Dilaudid tablets is two mg to four mg, orally, every four to six hours. Appropriate use of the Dilaudid tablets must be decided by careful evaluation of each clinical situation.</p> <p>A gradual increase in dose may be required if analgesia is inadequate, as tolerance develops or if pain severity increases. The first sign of tolerance is usually a reduced duration of effect. Patients with hepatic and renal impairment should be started on a lower starting dose (See CLINICAL PHARMACOLOGY - Pharmacokinetics and Metabolism).</p>
Lortab ³	<p>DOSAGE AND ADMINISTRATION</p> <p>Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.</p> <p>The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage for adults should not exceed 8 tablets.</p>
Percocet ⁴	<p>DOSAGE AND ADMINISTRATION</p> <p>Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of opioids. If pain is constant, the opioid analgesic should be given at regular intervals on an around-the-clock schedule. Percocet tablets are given orally.</p> <p>Percocet 2.5 mg/325 mg: The usual adult dosage is one or 2 tablets every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed four grams.</p> <p>Percocet 5 mg/325 mg; Percocet 7.5 mg/325 mg; Percocet 10 mg/325 mg: The usual adult dosage is one tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed four grams.</p>

Drug	Maintenance
OxyContin ¹	<p>2.2 Titration and Maintenance of Therapy</p> <p>Individually titrate OxyContin to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OxyContin to assess the maintenance of pain control and the relative incidence of adverse reactions. During chronic therapy, especially for non-cancer-related pain (or other pain associated with terminal illnesses), periodically reassess the continued need for the use of opioid analgesics.</p> <p>If the level of pain increases, attempt to identify the source of increased pain, while adjusting the OxyContin dose to decrease the level of pain. Because steady-state plasma concentrations are approximated in one day, OxyContin dosage adjustments may be done every one to two days. Patients who experience breakthrough pain may require dosage adjustment or rescue medication with an appropriate dose of an immediate-release opioid and non-opioid medication.</p> <p>If signs of excessive opioid-related adverse reactions are observed, the next dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.</p> <p>There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose, each time an increase is clinically indicated.</p>
Dilaudid ²	<p>INDIVIDUALIZATION OF DOSAGE</p> <p>The dosage of opioid analgesics like hydromorphone hydrochloride should be individualized for any given patient, since adverse events can occur at doses that may not provide complete freedom from pain.</p> <p>Safe and effective administration of opioid analgesics to patients with acute or chronic pain depends upon a comprehensive assessment of the patient. The nature of the pain (severity, frequency, etiology, and pathophysiology) as well as the concurrent medical status of the patient will affect selection of the starting dosage.</p> <p>In non-opioid-tolerant patients, therapy with hydromorphone is typically initiated at an oral dose of 2-4 mg every four hours, but elderly patients may require lower doses (see PRECAUTIONS - Geriatric Use).</p> <p>In patients receiving opioids, both the dose and duration of analgesia will vary substantially depending on the patient's opioid tolerance. The dose should be selected and adjusted so that at least 3-4 hours of pain relief may be achieved. In patients taking opioid analgesics, the starting dose of Dilaudid should be based on prior opioid usage. This should be done by converting the total daily usage of the previous opioid to an equivalent total daily dosage of oral Dilaudid using an equianalgesic table (see below). For opioids not in the table, first estimate the equivalent total daily usage of oral morphine, then use the table to find the equivalent total daily dosage of Dilaudid.</p> <p>Once the total daily dosage of Dilaudid has been estimated, it should be divided into the desired number of doses. Since there is individual variation in response to different opioid drugs, only 1/2 to 2/3 of the estimated dose of Dilaudid calculated from equivalence tables should be given for the first few doses, then increased as needed according to the patient's response.</p> <p>Since the pharmacokinetics of hydromorphone are affected in hepatic and renal impairment with a consequent increase in exposure, patients with hepatic and renal impairment should be started on a lower starting dose (See CLINICAL PHARMACOLOGY - Pharmacokinetics and Metabolism).</p> <p>In chronic pain, doses should be administered around-the-clock. A supplemental dose of 5-15% of the total daily usage may be administered every two hours on an "as-needed" basis.</p> <p>Periodic reassessment after the initial dosing is always required. If pain management is not satisfactory and in the absence of significant opioid-induced adverse events, the hydromorphone dose may be increased gradually. If excessive opioid side effects are observed early in the dosing interval, the hydromorphone dose should be reduced. If this results in breakthrough pain at the end of the dosing interval, the dosing interval may need to be shortened. Dose titration should be guided more by the need for analgesia than the absolute dose of opioid employed.</p>
Lortab ³	No information provided.
Percocet ⁴	No information provided.
Drug	Discontinuation
OxyContin ¹	<p>2.4 Discontinuation of OxyContin</p> <p>When the patient no longer requires therapy with OxyContin tablets, use a gradual downward titration of the dose to prevent signs and symptoms of withdrawal in the physically dependent patient. Do not abruptly discontinue OxyContin.</p>
Dilaudid ²	<p>Information for Patients/Caregivers</p> <p>Patients should be advised that if they have been receiving treatment with Dilaudid for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the Dilaudid dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.</p>
Lortab ³	No information provided.
Percocet ⁴	<p>Cessation of Therapy</p> <p>In patients treated with PERCOCET tablets for more than a few weeks who no longer require therapy, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.</p>

1) <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=bfdf235-d717-4855-a3c8-a13d26dadede#section-2.4>. Accessed: 2/28/14
 2) <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=3afae8b9-bb24-447a-bc7f-041c8326a438#n1m34068-7>. Accessed: 2/28/14
 3) <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=1fb18a80-8ef0-4bce-bb0d-9a86851c5206#n1m34068-7>. Accessed: 2/28/14
 4) <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=4dd36c5-8f73-404a-8b1d-3bd53bd90c25#n1m34068-7>. Accessed: 2/28/14

APPENDIX 2

Guideline Type	Domestic or Foreign	Included Guidelines	Attribute Areas							Total
			Non-pharmacologic treatment	Pain type/source & best drug treatments	Drug-related attributes of opioid treatment & tapering	Behavioral, psychosocial & social support considerations	Polypharmacy & pill burden	Withdrawal symptoms treatment		
			Out of 1 Question	Out of 1 Question	Out of 10 Questions	Out of 3 Questions	Out of 3 Questions	Out of 1 Question	Out of 19 Questions	
			Number of "Yes" answers to the Quantitative Assessment Questions in each Attribute Area							
Government	Canadian	Institute of Health Economics and the Alberta Ministry of Health. Toward Optimized Practice. Guideline for the evidence-informed primary care management of low back pain. Edmonton (AB): Toward Optimized Practice. November 2011. p. 37.	1/1	1/1	8/10	3/3	1/3	0/1	14/19	
Government	Canadian	National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic non-cancer pain. Part B: recommendations for practice. Hamilton (Ontario): National Opioid Use Guideline Group. April 2010. p. 126.	0/1	1/1	8/10	3/3	1/3	0/1	13/19	
Healthcare institution	U.S.	University of Michigan Health System. Managing chronic non-terminal pain in adults including prescribing controlled substances. Ann Arbor (MI): University of Michigan Health System. January 2011. p. 36.	1/1	1/1	9/10	1/3	1/3	0/1	13/19	
Independent health or quality organization	U.S.	Work Loss Data Institute. Pain Chapter. Encinitas (CA): Work Loss Data Institute. 2011.	1/1	1/1	6/10	3/3	1/3	1/1	13/19	
Government	U.S.	Washington State Agency Medical Directors' Group. Interagency guideline on opioid dosing for chronic non-cancer pain: an educational aid to improve care and safety with opioid treatment. Olympia (WA): Washington State Department of Labor and Industries. 2010. p. 55.	0/1	0/1	8/10	0/3	1/3	1/1	12/19	
Professional practice	U.S.	American Medical Directors Association. Pain management in the long term care setting. Columbia (MD): American Medical Directors Association. 2012. p. 60.	1/1	1/1	5/10	3/3	1/3	0/1	11/19	
Government	U.S.	Utah Department of Health. Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain.	1/1	1/1	6/10	2/3	0/3	1/1	11/19	
Professional practice	England	Guidance on the management of pain in older people. Age Ageing (2013)42 (suppl 1): i1-i57.	1/1	1/1	3/10	3/3	0/3	1/1	9/19	
Government	U.S.	Management of Opioid Therapy for Chronic Pain Working Group. VA/DoD clinical practice guideline for management of opioid therapy for chronic pain. Washington (DC): Department of Veterans Affairs, Department of Defense. May 2010. p. 159.	0/1	1/1	6/10	1/3	0/3	1/1	9/19	
Government	U.S.	Substance Abuse and Mental Health Services Administration. Managing Chronic Pain in Adults with or in Recovery From Substance Use Disorders. HHS publication no. (SMA) 12-4671. Rockville (MD): Substance Abuse and Mental Health Services Administration. 2011. p. 114 (Treatment improvement protocol (TIP) series; no. 54).	1/1	1/1	4/10	1/3	0/3	1/1	8/19	
Professional practice	U.S.	American Geriatrics Society Pharmacological Management of Persistent Pain in Older Persons. JAGS. Vol. 57, no. 8. August 2009.	1/1	1/1	4/10	1/3	0/3	0/1	7/19	
Professional practice	U.S.	American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: part 2 - guidance. Pain Physician. July 2012.15(3 Suppl):S67-S116.	0/1	1/1	4/10	0/3	0/3	1/1	6/19	
Government	U.S.	Colorado Division of Workers' Compensation. Chronic pain disorder medical treatment guidelines. Denver (CO): Colorado Division of Workers' Compensation. December 2011.	1/1	1/1	1/10	3/3	0/3	0/1	6/19	
Government	U.S.	Colorado Division of Workers' Compensation. Complex regional pain syndrome/reflex sympathetic dystrophy medical treatment guidelines. December 2011.	1/1	1/1	1/10	3/3	0/3	0/1	6/19	
Professional practice	U.S.	American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. Feb 2009.;10(2);p. 113-30.	0/1	1/1	3/10	1/3	0/3	0/1	5/19	
Independent health or quality organization	U.S.	Institute for Clinical Systems Improvement. Assessment and Management of Chronic Pain. Updated November 2013.	1/1	1/1	0/10	3/3	0/3	0/1	5/19	
Professional practice	U.S.	American Society of Anesthesiologists Task Force on Chronic Pain Management, American Society of Regional Anesthesia and Pain Medicine. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. April 2010. 112(4):810-33.	1/1	1/1	0/10	0/3	0/3	0/1	2/19	
Professional practice	U.S.	American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). April 2012. 64(4): p. 465-74.	1/1	0/1	0/10	0/3	0/3	0/1	1/19	
Professional practice	Netherlands	General treatment of chronic pelvic pain. In: Engeler D, Baranowski AP, Elneil S, Hughes J, Messelink EJ, Oliveira P, van Ophoven A, de C. Williams AC. Guidelines on chronic pelvic pain. Arnhem (The Netherlands): European Association of Urology. February 2012. p. 122-30.	0/1	1/1	0/10	0/3	0/3	0/1	1/19	

■ Not included in analysis

APPENDIX 3

<p>NON-PHARMACOLOGIC TREATMENTS</p> <p>Does the guideline address non-pharmacologic pain treatment? Yes = Provides information, tools or resources on non-pharmacologic pain treatments</p>
<p>TYPE OR SOURCE OF PAIN AND BEST DRUG TREATMENT</p> <p>Does the guideline address type or source of pain symptom addressed by the drug therapy? (Type of pain best addressed by a given drug treatment) Yes = Presence of treatment information specific to type of pain (neuropathic, musculoskeletal, mechanical...)</p>
<p>DRUG-RELATED ATTRIBUTES OF OPIOID TREATMENT AND TAPERING</p> <p>Does the guideline address duration of opioid treatment? Yes = Provides context to duration of opioid use in relation to successful achievement of therapeutic goals that must be of sufficient detail to provide definitive measurement of therapeutic goal</p> <p>Does the guideline address opioid taper? Yes = Provides sufficient details on methods, strategies, tools or resources for a physician to initiate a taper process</p> <p>Does the guideline address duration of opioid taper? Yes = Provides sufficient detail, resources or references for a physician to assess length of time needed to complete an opioid taper</p> <p>Does the guideline address any of the 5 pharmacologic & pharmacokinetic considerations of treatment: Half-life/duration of opioid? Potency? Dosage form? Dosage? Dose scheduling? Yes = Provides a sufficient level of detail such that a physician can select specific therapy based upon pharmacologic or pharmacokinetic characteristics of individual drugs, forms, formulations</p> <p>Does the guideline address any of the 5 pharmacologic & pharmacokinetic considerations of tapering: Half-life/duration of opioid? Potency? Dosage form? Dosage? Dose scheduling? Yes = Provides a sufficient level of detail such that a physician can initiate taper based upon pharmacologic or pharmacokinetic characteristics of individual drugs, forms, formulations</p>
<p>BEHAVIORAL/PSYCHOSOCIAL OR FAMILY/SOCIAL SUPPORT CONSIDERATIONS</p> <p>Does the guideline address any of the following psychological considerations, tools or resources?</p> <ul style="list-style-type: none"> • Behavioral/Cognitive? Yes = Provides information on cognitive/behavioral therapies, tools or resources such as biofeedback, relaxation techniques, meditation, hypnosis, restructuring and pain problem solving techniques • Psychosocial functioning? Yes = Provides sufficient detail, tools or resources to assess for concurrent depression, dysphoria, frustration or pain-related anxiety, psychological attitudes of physical functioning • Family/Social support factors? Yes = Provides sufficient information, tools or resources to assess family and/or social support
<p>CONTRIBUTIONS OF POLYPHARMACY AND PILL BURDEN</p> <p>Does the guideline address complexity of the patient's total drug therapy (pill burden)? Yes = Provides information, tools or resources on polypharmacy management strategies</p> <p>Does the guideline address concurrent or sequential drug tapers (polydrug or multi-drug tapering)? Yes = provides information, tools or resources for tapering multiple pain management medications</p> <p>Does the guideline address the priority order of multiple drug therapy tapers? Yes = Provides information on prioritizing taper of multiple pain medication therapies</p>
<p>TREATMENT OF WITHDRAWAL SYMPTOMS</p> <p>Does the guideline address management of withdrawal symptoms? Yes = Provides information, tools or resources to identify and manage opioid withdrawal symptoms</p>