Comparative Effectiveness of Alternative Strategies for Decreasing Initiation of Opioids for Managing Chronic Pain Workgroup: Topic Brief

March 7, 2016

High-Level Research Question

What is the comparative effectiveness of alternative strategies for decreasing the initiation of opioids for managing chronic noncancer pain in primary care while improving patient outcomes (e.g., functioning, quality of life, reducing pain) and reducing patient harms (e.g., opioid misuse, abuse, overdose)?

The focus of this workshop is on the comparative effectiveness of different strategies to reduce the initiation of opioids among primary care providers for patients with chronic noncancer pain outside of palliative or end-of-life care. The patient population of interest includes those who are potentially new or repeat users of opioids.

Assignment for Workgroup Participants

- Based on your perspective (patient, clinician, payer, etc.), what are two of the most relevant comparative effectiveness research questions focusing on decreasing the initiation of opioids and improving patient outcomes that warrant further research to address current gaps in knowledge?

- Submitted questions will be used to structure an agenda for the meeting.

"This document was prepared for informational purposes only and should not be construed as medical advice or used for clinical decision making."

Research Prioritization Topic Brief:
Comparative Effectiveness of Alternative Strategies for Decreasing Initiation of Opioids for Managing Chronic Pain

PCORI Scientific Program Area:
Improving Healthcare Systems

Executive Summary

Overall Comparative Research Question: What is the comparative effectiveness of alternative strategies for decreasing the initiation of opioids for managing chronic noncancer pain in primary care while improving patient outcomes (e.g., functioning, quality of life, reducing pain) and reducing patient harms (e.g., opioid misuse, abuse, overdose)?

Brief overview of the topic: Chronic pain is a common issue in the United States, causing significant suffering and disability. The use of opioids to treat chronic pain has dramatically increased during the past 20 years, promoted by pain clinical guidelines that have encouraged the use of opioids, although this is starting to change. These increases in opioid use have caused significant harms to patients and society, including misuse, addiction, and overdose deaths. Since chronic pain often initially presents as acute pain and opioid use for acute pain often evolves into chronic use, strategies to decrease initiation of opioids for chronic pain must address acute opioid use as well. These may include strategies such as provider reminder systems or protocols, audit and feedback to providers from insurers or health systems, provider education and behavior change, patient or community education, organizational change such as investment in alternative pain management strategy programs, regulatory or legislative initiatives, or some combination of these strategies.

Patient-centeredness: Initiatives should include use of alternative treatments to improve chronic pain patients' functioning and quality of life. Initiatives focused on reducing opioid prescribing must provide alternative avenues for helping patients with chronic pain; account for the needs of patients currently on chronic opioids; and not adversely affect the care of persons who require opioids for end-of-life care.

Impact on Health and Populations: Chronic pain is estimated to affect tens of millions of Americans. The costs of pain treatment, lost productivity, and disability are estimated at up to

$635 billion each year in the United States.[1] Opioid use also has significant negative impacts: in 2014, more than 18,000 Americans died from overdoses related to prescription opioids, a four-fold increase since 1999.[2] Opioid abuse is costly for society; a recent systematic review of economic studies estimated annual US overall societal costs at $55.7 billion, including $23.7 billion in healthcare costs.[3]

Assessment of Current Options: Little evidence currently exists on strategies for effectively decreasing initiation of opioids specifically; most research focuses on patients maintained on opioids for chronic pain. A systematic review conducted for the American Pain Society-American Academy of Pain Medicine (APS-AAPM) Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain through October 2008[4] found no systematic reviews, randomized trials, or controlled observational studies addressing the three questions relevant to this topic brief: (1) In patients being considered for opioids for chronic noncancer pain, how effective is risk assessment for improving clinical outcomes? (2) What are the benefits associated with behavioral therapy, multidisciplinary rehabilitation, and/or functional restoration/work hardening in addition to or instead of opioids for chronic noncancer pain? (3) What are the effects of opioid prescribing policies on clinical outcomes?

Likelihood of Implementation of Research Results in Practice: At the macro level, insurers, health systems, providers, and government agencies have high interest in reducing the burden of prescription opioid use. However, changing provider behavior and public attitudes about pain management is difficult, and alternatives to opioids, such as multimodal chronic pain management programs, are often not available or easily accessible. Additionally, the range of settings, providers, and types of patients involved in initiating opioids is vast and therefore interventions need to be widely disseminated. At the micro level, prescribing an opioid is often much easier for providers than referring to alternative programs. Clinicians may discount the potential likelihood of addiction or other adverse events associated with opioid use. Limited time is available in primary care, the emergency department, or on hospital discharge for alternative approaches to pain management. Identifying incident pain cases for targeted interventions is challenging.

Durability of Information: There is limited ongoing research specifically related to new strategies for decreasing initiation of opioids. Information from comparative effectiveness research would therefore have a high likelihood of remaining current.

Comparative Effectiveness of Alternative Strategies for Decreasing Initiation of Opioids for Managing Chronic Pain

Overall Comparative Research Question:
What is the *comparative effectiveness of alternative strategies for decreasing the initiation of opioids for managing chronic noncancer pain in primary care* while improving patient outcomes (e.g., functioning, quality of life, reducing pain) and reducing patient harms (e.g., opioid misuse, abuse, overdose)?

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2. Introduction:

Chronic pain is a major public health problem, estimated to affect tens of millions of Americans and causing significant suffering and disability.[5] Chronic pain is generally defined as pain lasting more than three months.[5] Common causes of chronic pain include acute conditions, such as low back pain, other musculoskeletal conditions or injuries that can develop into chronic pain conditions, as well as chronic issues such as headaches, fibromyalgia, and neuropathy.[5] Many chronic illnesses, such as diabetes and cancer, and their treatments can also result in chronic pain. Chronic pain is a complex biopsychosocial condition, requiring treatment of physical pain but also more holistic care addressing physical functioning and psychosocial issues, such as coping.[5]

Treatment options for pain include over-the-counter and prescription nonopioid analgesics, medications for specific conditions such as neuropathy, and nonpharmacologic options such as physical therapy and cognitive behavioral therapy. In recent decades, use of opioids has become a more accepted treatment for chronic pain as well, and their use has increased substantially. National US data on opioid use does not differentiate between acute and chronic pain or prevalent and incident use of opioids. By 2011-2012, 6.9 percent of adults aged 20 and over reported using a prescribed opioid in the past month, an increase from 5 percent in 1999-2002.[6] Data on sales and distribution of opioids show an increase from 96 mg of morphine equivalents per person in 1997 to 710 mg in 2010, equivalent to a supply of 5 mg of hydrocodone every six hours for 45 days per American.[7] In 2012, 259 million prescriptions were written for opioids in the United States.[8] One study of new ambulatory care visits for musculoskeletal pain found that opioid prescribing increased 62 percent, from 15 percent of visits in 2000 to 24

percent in 2010.[9] However, evidence does not support improvement in the US burden of chronic pain.[5,9]

Use of opioids for acute conditions is common and is an important predictor of chronic opioid use, although limited evidence is available on how often this occurs. One study using 2011-2012 data found that 43 percent of opioid-naïve patients seen in one emergency department for acute pain conditions were prescribed an opioid. Those who filled an opioid prescription were at high risk for recurrent prescription opioid use at one year after the visit (12 percent of patients).[10] Strategies to decrease the initiation of opioids for chronic pain must therefore address both provider prescribing behavior for acute conditions that may become chronic, as well as for chronic conditions. Key issues include preventing acute pain from becoming chronic; use of (and availability of) alternatives to opioids; reducing opioid prescribing in all settings; and preventing acute opioid use from becoming long-term use.

A 2015 systematic review on the effectiveness and risks of long-term opioid therapy for chronic pain for a National Institutes of Health Pathways to Prevention Workshop[11] found no observational studies or randomized trials comparing opioid to non-opioid strategies addressing long-term (>1 year) benefits, opioid abuse, or addiction. The review did identify a limited number of shorter-term observational studies (mostly uncontrolled or retrospective) on significant rates of adverse events in patients taking chronic opioids, such as risk for dependence (3 percent to 26 percent), abuse (0.6 percent to 8 percent), and aberrant behavior (6 percent to 37 percent). Controlled observational studies comparing opioid to non-opioid users found an increased risk for overdose [adjusted hazard ratios (HR) ranging from 1.4 to 8.9], myocardial infarction [adjusted odds ratio (OR) 1.3 to 2.7], sexual dysfunction (adjusted OR 1.5), and motor vehicle accidents (adjusted OR 1.2 to 1.4). These studies were rated as good and fair quality. Opioids may also increase the risk of disability:[12] for example, one study of workers with low back injuries reported twice the rate of long-term disability when opioids were prescribed for the injury than when opioids were not prescribed.[13]

Despite this lack of evidence, during the 1990s and 2000s, many chronic pain guidelines recommended the use of opioids for chronic pain, even as first-line therapy for some populations. Recommendations have begun to shift, given the emerging evidence on patient and societal harms from opioid use and lack of evidence on benefits. A summary of eight more recent (2009-2012) chronic pain guidelines (four of which included systematic reviews) by the Centers for Disease Control[14] found that all included statements about considering benefits/risks and alternatives to opioids, such as considering using opioids only when alternative treatments are ineffective. However, most statements about indications for opioids are broad, and most guidelines do not address the duration of initial prescribing or limiting initial opioid use. Key elements are summarized in Table 1.

Table 1. Key elements relevant to initiation of opioids for chronic pain from practice guidelines[14]

Guideline Element	APS/ AAPM	Utah	VA/DoD	WA State	Canadian	ACOEM	NYC	ASIPP
Opioid Indication	Consider alternatives to opioids and trial when benefits are likely to outweigh risks and no alternative therapy likely to pose favorable benefit/ harm balance	Consider all options, including non-pharmaceutical treatment; opioids considered only when other therapies not beneficial	Inadequate response to non-drug or non-opioid modalities, or when benefits outweigh risks of opioid therapy	Consider when other physical, behavioral, and non-opioid measures have failed and no contra-indication to use (e.g., substance abuse)	Use in mild to moderate or severe pain.	Anatomical/ physiologic abnormalities; other non-opioids, adjuvants, and alternative pain control modalities inadequate; no contra-indications	Consider when potential benefits likely to outweigh potential harm; when other approaches to analgesia are ineffective	Establish medical necessity based on moderate/ severe pain, organic problem, failure to respond to non-controlled substance, adjuvants, physical therapy/ exercise, and other interventions
Duration of Initial Treatment	Several weeks to months	Short-term trial	Not addressed	Not addressed	Not addressed	Not to exceed 4 weeks; in rare situations, extend by 2 weeds	Not addressed	8-12 weeks

APS/AAPM = American Pain Society/American Academy of Pain Medicine Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain
Utah = Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain
VA/DoD = Veteran's Administration/Department of Defense Management of Opioid Therapy for Chronic Pain
WA State = Washington State Agency Medical Directors Group Interagency Guideline on Opioid Dosing for Chronic Noncancer Pain
Canadian = Canadian Guideline for Safe and Effective Use of Opioids for Chronic Noncancer Pain
ACOEM = American College of Occupational and Environmental Medicine Guidelines for the Chronic Use of Opioids*
NYC = New York City Department of Health and Mental Hygiene Opioid Prescribing Guidelines
ASIPP = American Society of Interventional Pain Physicians Guidelines for Responsible Opioid Prescribing in Chronic Non-cancer Pain
*Have changed since this review

A 2014 systematic review of 13 opioid prescribing guidelines for chronic pain including these and others[15] found only two guidelines rated as high quality and deemed by more than half of the guideline appraisers to be usable without modification: one from 2009 by the American Pain Society – American Academy of Pain Medicine (APS-AAPM) and another from 2010 by the

Canadian National Opioid Use Guideline Group, both of which were based on systematic reviews conducted using accepted standards, unlike the other guidelines. Most recommendations in all 13 of the guidelines were supported only by observational studies or expert opinion.[15] Statements relevant to initiation of opioids included in at least some of the guidelines included using a trial period for opioids, individualizing therapy, engaging multidisciplinary pain management teams, and regular follow-up.[15]

The most recent healthcare professional organization position statements relevant to initiation of opioids for chronic pain are:

- A 2013 updated statement from the American Academy of Pain Medicine[16] states that prescription of opioids for chronic, intractable pain is appropriate when other methods are not effective and the treatment plan includes elements to avoid diversion and addiction, and opioids should be prescribed only after a thorough evaluation and consideration of alternatives.
- A 2014 position paper from the American Academy of Neurology on opioids for chronic noncancer pain considered multiple systematic reviews and concluded that although there is evidence for significant pain relief from opioids up to a few months, there is no evidence supporting long-term pain relief, and major concerns about safety. The position paper concluded that headaches, low back pain, and fibromyalgia should not be treated chronically with opioids, as the risks outweigh the benefits.[17]

As of February 2016, the Centers for Disease Control and Prevention have released a draft guideline for prescribing opioids for chronic pain and the public comment period has closed, but the final guideline has not yet been released.[18] The Food and Drug Administration is also increasing initiatives to address opioid overuse,[19] along with many other federal and state agencies.

Decreasing the initiation of opioids is a key strategy for changing prescribing behavior to improve outcomes for patients where risks and harms may exceed benefits (and where other treatment options should be offered first) and for decreasing the societal burden of high opioid availability and sharing, selling, misuse, and addiction. Clearly, any strategies to reduce initiation must account for many patients currently on long-term opioid treatment who should not be cut off; and that these issues do not apply in the same way to those with very limited life expectancy, particularly advanced cancer with severe pain (who are out of the scope of this topic brief). Any initiatives must also recognize that suffering from acute and chronic pain is substantial and should be addressed by other means if opioids are not used, and that services to address these conditions, such as comprehensive, holistic pain management programs or

cognitive behavioral therapy, are often not available. Patient risk assessment tools for chronic pain or opioid misuse, and alternative specific clinical strategies for pain management (i.e., rehabilitation), are outside the scope of this topic brief as well.

Strategies for decreasing prescriber initiation of long-term opioids can be categorized as in the Agency for Health Care Research and Quality's Closing the Quality Gap series,[20] which focused on evidence about effective strategies to close the "quality gap"—the difference between what is expected to work well for patients based on known evidence, and what actually happens in day-to-day clinical practice across populations of patients. Broad categories include[21] strategies at the macro level (state or federal policies, or organizations such as insurers or health systems) and the micro level, including providers and patients.

The adapted taxonomy[22,23] below describes strategies[24-26] most relevant to decreasing initiation of opioids. Many initiatives to date have focused on prevalent (rather than incident) prescribing and risk of abuse, but some of these may also affect incident prescribing.

- Provider reminder systems (manual or computerized interventions that prompt health workers to perform an action during a consultation with a patient, for example, computer decision support systems) or protocols (algorithms, checklists, or pathways that specify elements of care) to systematize guideline recommendations
  - Protocols for limiting number of pills in opioid prescriptions for acute conditions
  - Protocols for initiating other pain management strategies (e.g., non-steroidal anti-inflammatory agents or physical therapy) before or concomitantly with initial acute opioid prescriptions
- Audit and feedback (summary of a healthcare provider's or institution's clinical performance that is reported, either publicly or confidentially, to or about the clinician or institution (e.g., the percentage of a provider's patients who have achieved or have not achieved some clinical target); can be population-based or on individual patients
  - Insurer-based programs
  - Internal performance measurement with benchmarking

- Provider education and behavior change (educational materials, interventions, or outreach visits)
  - Academic detailing (outreach to providers in their settings) and other initiatives to promote alternatives to opioids and appropriate prescribing
  - Teaching communication skills on pain management and opioid prescribing
- Organizational change (changes in the structure or delivery of care)
  - Leadership, provider attitude, or behavior change initiatives

- Investment in alternative pain management strategy availability and support through health systems
- Case management or other targeted interventions that use additional providers such as nurses to help manage care for high-risk patients

- Patient education and promotion of self-management or patient engagement (distribution of materials or access to a resource that enhances patients' knowledge, skills, or ability to manage their condition)
- Community-based initiatives[24]
  - Invest in surveillance
  - Convene a stakeholder meeting with broad representation to create guidance to help communities undertake comprehensive approaches that address the supply of, and demand for, prescription opioids in their locales; implement and evaluate demonstration projects that model these approaches.
  - Convene an inter-agency task force to ensure that current and future national public education campaigns about prescription opioids are informed by the available evidence and that best practices are shared.
- Regulatory or legislative initiatives
  - Prescription drug monitoring programs (state-run electronic databases used to track the prescribing and dispensing of controlled prescription drugs to patients, that are designed to monitor this information for suspected abuse or diversion)[27]
  - "Pill mill" laws (designed to shut practices prescribing opioids outside accepted norms)
  - Quality measures (population-based measures that enable users to quantify the quality of a specific aspect of care by comparing it to evidence-based criteria)
- Insurer or Medicaid policies
  - Prior authorization or precertification (pre-approval process to determine if an insurer will cover a prescribed medication)
  - Drug utilization review (authorized, structured, ongoing review of prescribing, dispensing, and/or use of medication) and/or monitoring for providers

Of note, these strategies must address a wide variety of settings and providers, including primary care, emergency departments, hospitals, pain management programs, surgeons, dentists, and others with significant opioid use.

3. Patient-Centeredness:

- Common adverse events from opioids include constipation, nausea and vomiting, drowsiness, confusion, depression, and sexual dysfunction.
- Opioids may also lead to hyperalgesia and worse pain.

- Increasing evidence of serious long-term outcomes has been emerging, including issues such as hypogonadism, cardiac issues (including myocardial infarction, QT prolongation from methadone, falls and fractures, significant rates of abuse and addiction, and overdose hospitalizations and deaths).[11,28]
- Guilt, stigma, and burden of opioid dependence, including challenges of obtaining prescriptions, turnover of providers, and risk of withdrawal, can also cause patient harm.
- Societal issues include diversion and the subsequent risk of addiction, abuse and overdose to other contacts, neonatal abstinence syndrome, and, potentially, worsening rates of heroin addiction and overdose.[24,29]

4. Impact/ Burden of the Condition:

Chronic pain affects a substantial proportion of Americans. The costs of pain treatment, lost productivity, and disability are estimated at up to $635 billion each year in the United States.[1] Disparities in pain prevalence and treatment are a major issue, with worse pain and outcomes and fewer opioid prescriptions for vulnerable populations, including racial and ethnic minorities.[5]

In 2013, more than 16,000 Americans died from overdoses related to prescription opioids, a fourfold increase since 1999.[30] Recent research has also reported a trend for people transitioning from misuse and abuse of prescription painkillers to heroin abuse.[8,31] Heroin abuse, overdose, and deaths nearly quadrupled from 2000 to 2013.[8] In a 2014 survey of people in treatment for opioid addiction, 94 percent of respondents said they chose to use heroin because prescription opioids were “far more expensive and harder to obtain.”[8]

Opioid abuse is costly for the healthcare system and society. A recent systematic review of economic studies estimated the annual US overall societal costs at 55.7 billion, with $23.7 billion in healthcare costs, $5.1 billion in criminal justice costs, and $25.6 billion in workplace costs.[3]

5. Evidence Gaps:

Of multiple recent comprehensive systematic reviews on opioids,[4,11,15,32-34] only one addressed any of the strategies for decreasing initiation of opioids described in the above taxonomy.

- A systematic review conducted for the APS-AAPM Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain through October 2008 summarized and updated existing reviews. Several key questions are relevant to this topic:[4,35]

- Provider protocols: In patients being considered for opioids for chronic noncancer pain, how effective is risk assessment for improving clinical outcomes? The review found no systematic reviews, randomized trials, or controlled observational studies addressing this question.
- Organizational change—alternative strategies: What are the benefits associated with behavioral therapy, multidisciplinary rehabilitation, and/or functional restoration/work hardening in addition to or instead of opioids for chronic noncancer pain? The review found no systematic reviews, randomized trials, or controlled observational studies that addressed the effectiveness of such interventions in decreasing initiation of opioids.
- Insurer or Medicaid policies: What are the effects of opioid prescribing policies on clinical outcomes? The review found no systematic reviews, randomized trials, or controlled observational studies that addressed the effectiveness of such policies for decreasing initiation of opioids.

We did not identify any information from systematic reviews or targeted searching of the published or grey literature on evidence for any other strategies for decreasing initiation of opioids. Although some studies described evidence for improving management of chronic pain management, reducing opioid use in patients already on opioids, or reducing rates of opioid misuse, these studies did not evaluate rates of initiation of opioids.

6. Ongoing Research:

In the search of ongoing studies from clinicaltrials.gov, PCORI, the Health Services Research Projects in Progress (HSRProj) database, the National Institute for Drug Abuse, and Robert Wood Johnson Foundation, most studies identified addressed clinical interventions, patients already on opioids, chronic pain management issues more generally, or preventing prescription drug abuse but did not address decreasing initiation of opioids.

We identified two ongoing interventions to reduce initiation of opioid use, relevant to strategies in the taxonomy:

- Patient education and promotion of self-management: The PreACT trial (NCT02437188) is a pilot study of the feasibility and preliminary efficacy in veterans who are anxious or depressed of a preoperative one-day workshop of Acceptance and Commitment Therapy (ACT) with a booster session to reduce pain and opioid use after orthopedic or open abdominal surgery. The ACT intervention includes behavioral change training to reduce behavioral avoidance and acceptance and mindfulness training to enhance acceptance-based coping.

- Provider protocol: The SPACE (Strategies for Prescribing Analgesics Comparative Effectiveness) Trial is a randomized comparison of two strategies in the Veterans Affairs system: one that emphasizes early use of strong opioids, and one that delays and minimizes opioid use (opioid-avoidant, optimizing non-opioid medications) for chronic back, hip, or knee pain (estimated study completion date 5/17) (NCT01583985)

We did not identify any studies addressing other strategies in the taxonomy.

7. Likelihood of Implementation of Research Results in Practice:

At the macro level, insurers, health systems, providers, and government agencies have high interest in reducing the burden of prescription opioid use. However, changing provider behavior and public attitudes about pain management is difficult, and alternatives to opioids, such as multimodal chronic pain management programs, are often not available or easily accessible. Additionally, the range of settings, providers, and types of patients involved in initiating opioids is vast, and therefore strategies need to be widely disseminated. Effectiveness studies, however, are generally targeted to specific acute non-cancer pain conditions, such as low back pain. At the micro level, prescribing an opioid is often much easier for providers than using more time-intensive strategies or referring to alternative programs. Limited time is available in primary care, the emergency department, or on hospital discharge for alternative approaches to pain management. Clinicians may discount the potential likelihood of addiction or other adverse events associated with opioid use, and other major classes of drugs used for pain, such as nonsteroidal anti-inflammatory drugs, also have significant adverse effects and risk of serious complications. Identifying incident pain cases for targeted interventions is challenging.

8. Durability of Information:

There is limited ongoing research specifically related to new strategies for decreasing initiation of opioids. Information from comparative effectiveness research would therefore have a high likelihood of remaining current.

9. Potential Research Questions:

The potential questions below are linked to key strategies in the taxonomy, particularly the use of audit (or monitoring) and feedback.

- Insurer-based programs—audit and feedback and improved alternative pain management availability:
    - What is the comparative effectiveness of insurer-based strategies for opioid management of pain that include elements of prescription monitoring and physician feedback, combined with better coverage of alternative methods for pain manage-

ment including mental health care, compared to usual coverage, on reducing rates of provider initiation of opioids for non-cancer pain?

- Organizational change:
    - What is the comparative effectiveness of health system strategies for management of pain that include elements such as protocols, prescription monitoring, and physician feedback, combined with increased availability of alternative methods for pain management, compared to voluntary programs on reducing rates of provider initiation of opioids for noncancer pain?
- Quality measures and standards:
    - What is the comparative effectiveness of quality measurement strategies and feedback, based on current guidelines and evidence, combined with quality improvement strategies for primary care provider behavior change, on reducing rates of provider initiation of opioids for those with noncancer pain without worsening outcomes for patients?
- Physician/patient-level strategies:
    - What is the comparative effectiveness of various primary care physician and patient communication and dissemination strategies to promote guideline concordant care for managing patients with chronic noncancer pain who are new or repeat users of opioids on reducing rates of provider initiation of opioids for chronic pain and improving patient outcomes?

10. Conclusions:

Given the rapid increase in opioid prescribing and increasing societal harms, particularly abuse, overdose, and deaths over the past two decades, strategies to decrease initiation of long-term opioids for acute and chronic pain are a public health imperative. Facilitators include the many stakeholders invested in this issue, and barriers include: the complexity of the issue, involving many agencies, settings, and types of providers; challenges of treating pain while reducing opioid use; lack of data on effective strategies; and feasibility of implementing strategies to address incident use for acute pain across many providers and settings. Promising emerging initiatives include strategies implemented by health systems, insurers, and prescription drug monitoring programs that may involve monitoring, feedback, protocols, and quality standards. Unfortunately, high-quality effectiveness and comparative effectiveness studies are lacking. Any strategies to decrease prescribing must also include increased availability of alternative pain strategy management, to ensure that patients are receiving adequate care, and not harm patients who require opioids currently, such as those already maintained on long-term opioids

for chronic pain and those with advanced cancer at the end of life.

APPENDIX

Methods

Literature search:

From December 2015 to February 2016, we conducted a literature review for systematic reviews and guidelines. We searched key sources including Cochrane, the AHRQ Evidence-Based Practice Center site, and websites for relevant government agencies, including the Centers for Disease Control and Substance Abuse and Mental Health Services Administration, and relevant professional associations involved in this issue (American Pain Society-American Academy of Pain Medicine, American Academy of Neurology). We also searched references and websites suggested by our experts, including the report, "The Prescription Drug Epidemic: An Evidence-Based Approach"[24] and the Robert Wood Johnson Foundation website (rwjf.org) and Brandeis Prescription Drug Monitoring Program Center of Excellence (www.pdmpexcellence.org/) website.

Ongoing clinical studies:

We searched clinicaltrials.gov and PCORI studies for the terms "opioid*" AND ("chronic pain" OR "persistent pain") OR ("opioid-avoidant" OR "prevention" AND "persistent pain") for studies addressing decreasing initiation of opioids, and open to recruitment or completed in the last two years, and addressing strategies (not individual treatments), on December 15, 2015. On February 18, 2016, we supplemented this with additional targeted searching using terms from the final list of strategies and "opioid*" and "pain." On February 18, 2016, we also searched NIHreporter, National Institute on Drug Abuse, and Robert Wood Johnson Foundation websites for relevant studies using similar criteria. Finally, to search for more health services-oriented studies, we searched HSRProj for the terms "pain" and "opioids."

References for Topic Brief- Comparative Effectiveness of Alternative Strategies for Decreasing Initiation of Opioids for Managing Chronic Pain

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