## Topic 10:
**Comparative effectiveness of narrow-spectrum antibiotics versus broad-spectrum antibiotics in the treatment of community-acquired pneumonia in adults**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overview/definition of topic</td>
<td>DESCRIPTION OF CONDITION(^1)(^-)(^4)</td>
</tr>
<tr>
<td></td>
<td>• Community-acquired pneumonia (CAP) is the acute infection of the lung in persons who have not been hospitalized recently and have not been regularly exposed to the health care system. A wide range of microorganisms can cause CAP, including bacteria (20-50%) and viruses (15-23%). In 30-65% of CAP cases, an etiologic organism cannot be identified.</td>
</tr>
<tr>
<td></td>
<td>• Typical symptoms of CAP include fever, cough, sputum production, shortness of breath, with lung infiltrate or consolidation on chest imaging and, leukocytosis. However, the diagnosis of CAP can be challenging, as some patients, especially those who are elderly, may not present with these symptoms.</td>
</tr>
<tr>
<td></td>
<td>• Antibiotics are only effective for CAP caused by bacteria, among which <em>Streptococcus pneumonia</em>, <em>Haemophilus influenzae</em>, and <em>Moraxella catarrhalis</em> are considered to be the most common.</td>
</tr>
<tr>
<td></td>
<td>• Broad-spectrum antibiotics used to treat CAP include tetracyclines, fluoroquinolones, and third- and fourth-generation cephalosporins. Narrow-spectrum antibiotics used to treat CAP are penicillin, aminopenicillins, ampicillin sulbactam, and amoxicillin clavulanate. Some might consider azithromycin to be narrow-spectrum in this context.</td>
</tr>
<tr>
<td></td>
<td>• According to the 2007 consensus based Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guidelines, empirical treatment of CAP with narrow-spectrum antibiotics is recommended in young patients with no previous history of antimicrobials and no comorbidity.(^2) Broad-spectrum antibiotics are used empirically in older patients, patients who received antibiotics within the previous 3 months, those with comorbidity, patients with severe disease who require hospitalization or an intensive care unit (ICU), and when there is concern for <em>Pseudomonas</em> infection.(^2)</td>
</tr>
<tr>
<td></td>
<td>• There is a general trend towards broader and longer duration antibiotic therapy for CAP. Public health experts are concerned about the use of antibiotics in patients who do not really have pneumonia, especially because excess use of broad-spectrum antibiotics can lead to antibiotic resistance.</td>
</tr>
</tbody>
</table>
Spectrum antibiotics can lead to emergence of multidrug-resistant bacteria. Using narrow-spectrum antibiotics is one of several ways to reduce bacteria resistance.

<table>
<thead>
<tr>
<th>Relevance to patient-centered outcomes</th>
<th>SYMPTOMS&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tiredness and weakness</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td>Body aches</td>
</tr>
<tr>
<td></td>
<td>Wheezing</td>
</tr>
<tr>
<td></td>
<td>Weak appetite</td>
</tr>
<tr>
<td></td>
<td>Fever and chills</td>
</tr>
<tr>
<td></td>
<td>Shortness of breath</td>
</tr>
</tbody>
</table>

**PATIENT-CENTERED OUTCOMES**
- Hospital admission rate
- ICU admission rate
- Length of hospital stay
- Hospital readmission rate
- Days away from work/school/normal activities
- Short-term disability and productivity lost
- Cost of care
- Patient satisfaction, including emergence of antibiotic resistance (patients often are upset when they learn they have a drug-resistant organism, and they may be subjected to special contact precautions as a result)
- Infection (e.g., *Clostridium difficile* infection) as a result of antibiotic treatment
- Drug toxicity and adverse effects
- Mortality

**Burden on Society**

**Recent prevalence in populations and subpopulations**

**INCIDENCE AND PREVALENCE**
- One study estimated that 915,900 episodes of CAP occur in adults greater than or equal to 65 years of age each year in the U.S.<sup>5</sup>
- The estimated CAP incidence is between 5-10 cases per 1000 person-years in a working population<sup>6,7</sup> and increases to over 20 cases per 1000 person-years among individuals aged 65-69 years, and to over 50 cases per 1000 person-years among those 85 years old or older.<sup>8</sup>
### Effects on Patients’ Quality of Life, Productivity, Functional Capacity, Mortality, Use of Health Care Services

- Patients diagnosed with CAP have a significant short-term decrease in quality of life due to symptoms, and typically miss at least one week of work or school even when not admitted. If admitted to a hospital, loss of productivity can go up to 2 or 3 weeks.\(^9\) Older age, non-white race, low education, low income, and unemployment were associated with worse outcomes.\(^{12}\)
- In 2013, CAP was the 9\(^{\text{th}}\) leading cause of death in the US, causing around 53,000 deaths (the mortality rate is 16.9 per 100,000). Despite recommendations to use broad-spectrum antibiotics for CAP, mortality from CAP has not decreased significantly over years.
- In 2012, 1.1 million persons were diagnosed with CAP, resulting in 327,840 hospital admissions.\(^{13}\)
- In the working population, CAP is a frequent and costly event with a national cost of $10.6 billion a year. The cost is higher in individuals with comorbid conditions, and in individuals admitted to hospitals.\(^5\),\(^7\),\(^{10}\)

### How Strongly Does This Overall Societal Burden Suggest That CER on Alternative Approaches to This Problem Should Be Given High Priority?

- CAP is a major cause of death and bears substantial clinical and economic burden. CER on alternative approaches to treating CAP should be given high priority, taking into consideration that broad-spectrum antibiotics are frequently used because it often is difficult to identify a causative organism.
- High priority also should be given to CER on the new techniques that have been under development to better determine the pathogen and establish a faster diagnosis in patients presenting with symptoms of CAP. This would help clinicians better differentiate colonization from infection, and help them choose the most appropriate antibiotic for patients most likely to have bacterial CAP, and help avoid unnecessary treatment of patients unlikely to benefit from antibiotics.

### Options for Addressing the Issue

#### Based on Recent Systematic Reviews, What Is Known About the Relative Benefits and Harms of the Available Management Options?

- A 2014 Cochrane systematic review evaluated the efficacy and safety of different antibiotic treatments for CAP in patients more than 12 years of age treated in outpatient settings. Although this review included 11 randomized controlled trials (RCTs) of good quality with 3352 participants, many different antibiotics pairs were examined, including clarithromycin vs. amoxicillin, clarithromycin vs. amoxicillin vs. azithromycin vs. levofloxacin, erythromycin vs. clarithromycin, clarithromycin vs. azithromycin microspheres, clarithromycin vs. telithromycin, azithromycin microspheres vs. levofloxacin, telithromycin vs. levofloxacin, cethromycin vs. clarithromycin, solithromycin vs. levofloxacin, and nemonoxacin vs. levofloxacin.
The variable comparisons have limited the ability to pool data across RCTs. In the individual RCTs, there was no significant difference in the comparative efficacy of various antibiotics for the treatment of CAP in outpatient settings. The authors concluded that there is insufficient evidence to recommend the choice of antibiotics for the treatment of CAP in outpatient settings.3

- A 2012 Cochrane systematic review evaluated the comparative effectiveness of antibiotic regimens containing coverage for atypical bacteria relative to those regimens not covering atypical bacteria for the treatment of CAP in hospitalized adults. Atypical bacteria include Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydia pneumoniae. The main typical bacteria causing CAP is Streptococcus pneumoniae. The review included 28 RCTs with a total of 5939 participants. The antibiotics with activity against atypical organisms were administered as monotherapy in all but three RCTs (mostly the comparison between quinolone and beta-lactam monotherapy). One RCT assessed a beta-lactam combined with a macrolide compared to the same beta-lactam. The authors concluded that there is no evidence of benefit in survival or clinical efficacy with empirical atypical coverage in hospitalized patients with CAP.14

- A 2012 systematic review including both RCTs and observational studies found that macrolide-based regimens were associated with survival benefit in observational studies but not in RCTs for the treatment of CAP in hospitalized patients. Also, there was no mortality benefit for patients treated with IDSA/ATS guideline-concordant antibiotics (macrolide and beta-lactam combination) compared with fluoroquinolones.15

- The duration of antibiotics is relevant to reducing bacteria-resistant. A 2012 systematic review including 5 RCTs compared short-course (3-7 days) versus long-course (7-10 days) antibiotic therapy for CAP. The review found no difference in effectiveness and safety in patients with CAP of mild to moderate severity.16

- A 2009 systematic review including 13 cohort studies found that blood cultures for patients hospitalized with CAP had limited value: the blood cultures were true-positive in 0-14% of cases, and that led to antibiotic narrowing in 0 -3% of patients. The review concluded that hospital quality measures that include blood cultures should be reassessed.17
### What could new research contribute to achieving better patient-centered outcomes?

- Diagnostic tests with high sensitivity and specificity are available to detect the causative organisms.\(^{18}\) However, whether these new diagnostic tests could improve patient-centered outcomes is unclear. There is a need for further research on establishing CAP diagnosis rapidly in clinical practice with respect to whether CAP is present, whether hospital admission is required, the type of pathogen (i.e., bacteria or virus, colonization or infection), and the causative bacteria, with a focus on patient-centered outcomes.
- In patients with CAP, new research could help to improve patient-centered outcomes by providing information about the comparative effectiveness of
  - narrow versus broad-spectrum antibiotic for empiric therapy and/or definitive therapy,
  - shorter versus longer antibiotic therapy, and
  - approaches to de-escalate antibiotic therapy on patient-centered outcomes including measures of the success of therapy, reducing the days of treatment according to patient’s response, association of therapy with side-effects such as *C. difficile* infection, and emergence of antibiotic resistance.

### Have recent innovations made research on this topic especially compelling?

- A recent cohort study from Australia found that, based on the etiology results, broad-spectrum antibiotics are not necessary for the vast majority of Australian patients with CAP.\(^ {19}\) Furthermore, the choice of antibiotics and outcomes were comparable regardless of whether a pathogen was isolated. This study has stimulated discussion and interest in the U.S.
- The availability of sensitive diagnostic tests such as procalcitonin (a marker of bacterial infection with a sensitivity of up to 89% and a specificity of up to 94%)\(^ {18}\) is likely to reduce unnecessary antibiotic therapy and reduce the length of antibiotic therapy. However, clinicians must be trained in how to interpret and respond correctly to the tests for them to be of value.
### How widely does care now vary?

- The 2007 IDSA/ATS guidelines recommend that once the diagnosis of CAP is made, antimicrobial therapy should be initiated promptly and at the point care where the diagnosis is first made. Outpatients with CAP are generally treated empirically because of the substantial cost and inadequacies of diagnostic testing for pneumonia. For outpatients without coexisting illnesses or recent use of antibiotics, IDSA/ATS guidelines recommend the administration of a macrolide or doxycycline; for those with coexisting illnesses or recent use of antibiotics, the guidelines recommend the use of levofloxacin or moxifloxacin alone or a beta-lactam plus a macrolide.²⁰

- Hospital CAP core measures (a set of measurements developed by the Centers for Medicare and Medicaid Services to reflect the quality of care in hospitals) have contributed to a greater uniformity of empiric treatment, although this treatment has been with broad-spectrum antibiotics as described in the bullet point above. However, because diagnosis of CAP is difficult and not always accurate, care still varies across hospitals and centers.²¹-²⁴ In addition, the core measures did not address management of CAP, including antibiotic management, after the initial selection of antibiotics.

- In practice, the duration of treatment varies from 5-7 days to 10-14 days; the doses and choice of antibiotics also vary.²¹-²⁴

- The use of antibiotics for CAP may also vary according to patient comorbidity, with clinicians likely to favor broad-spectrum antibiotics when patients have serious comorbidity that could increase their risk of having complications.

### What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?

- We searched clinicaltrials.gov on March 18, 2015 and found 75 studies using the strategy “community acquired pneumonia” as the condition AND “antibiotics” as the interventions AND “adults OR senior” as the age groups. Forty (64%) trials have completed recruitment and 11 (15%) have results available. Most of these trials have focused on clinical cure/response or duration of antibiotic therapy as the primary outcome. Fifty-four (72%) trials received industry funding.

- In terms of the comparisons, 30 (40%) trials compared different monotherapies; 10 (13%) trials compared combination antibiotic therapy versus monotherapy or another combination therapy; 3 (4%) trials compared different durations of antibiotic therapy.

- Five (7%) studies, some observational, evaluated the use of diagnostic tests (polymerase chain reaction) or procalcitonin level for guiding antibiotic therapy.

- Two (3%) studies evaluated programs/strategies to improve antibiotic use.
(antimicrobial stewardship) at hospitals.

- It is important to note that new antibiotics for CAP are all broad spectrum. Only one trial (1%) compared a narrow against a broad-spectrum antibiotic (ampicillin/amoxicillin vs moxifloxacin) in hospitalized patients with non-severe CAP (NCT00887276). Pharmaceutical companies have great interest in research on these new antibiotics, but less interest in research on older narrow-spectrum antibiotics.

<table>
<thead>
<tr>
<th>How likely it is that new CER on this topic would provide better information to guide clinical decision making?</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP is a common disease, even with guidelines and hospital core measures, both broad and narrow treatment have potential pitfalls and evidence gaps exist. If new CER could show that selected narrow-spectrum antibiotics are non-inferior to broad-spectrum antibiotics, that would give clinicians a stronger evidence-based rationale for using narrow-spectrum antibiotics at least for certain subsets of patients who may not need a broad-spectrum antibiotic.</td>
</tr>
<tr>
<td>It is important to minimize inappropriate use of antibiotics to reduce the risk of developing more resistant organisms, which could in turn reduce future effectiveness of the available antibiotics. Thus, studies of strategies to reduce inappropriate use of antibiotics (and unnecessary use of broad-spectrum antibiotics) would help provide information that could improve clinical decision-making. Given the paucity of new antibiotics in development, approaches to prolong the useful lifespan of antibiotic classes should be encouraged.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Potential for New Information to Improve Care and Patient-Centered Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FACILITATORS:</strong></td>
</tr>
<tr>
<td>- Recent studies from Europe and Australia have demonstrated that narrower and shorter duration antibiotics are as good as broader and longer duration antibiotic therapy. Guidelines from the United Kingdom and Sweden also recommend amoxicillin or penicillin as empirical therapy for CAP in outpatients. Although the epidemiology of CAP differs between the U.S. and Europe/Australia, experience from these countries still may help to facilitate implementation of new approaches to the management of CAP in the U.S.</td>
</tr>
<tr>
<td>- Use of narrow-spectrum antibiotics and shorter durations of antibiotics are associated with a lower risk of <em>C. difficile</em> infection and lower risk of antibiotic resistance, and that information could help to facilitate greater use of narrow-spectrum antibiotics and shorter durations of antibiotics if new research shows that they also are non-inferior in effectiveness.</td>
</tr>
<tr>
<td>- The increasing interest of public health experts in preventing antibiotic resistance</td>
</tr>
</tbody>
</table>
could help to facilitate implementation of new strategies for treating CAP.

**BARRIERS:**

- Previous adoption of hospital core measures (abandoned on 1/1/2014) and existing practice guidelines have made research on use of narrow-spectrum empiric therapy challenging. There is a general trend toward broader and longer duration antibiotic therapy.
- The trade-off between the societal benefit of using narrow-spectrum antibiotics and the potential individual benefit (whether real or perceived) of using broad-spectrum antibiotics may not be well understood by prescribers and/or patients.
- It can be challenging to standardize treatment for CAP in populations having different comorbidity and different risks of complications.
- Changes in the recommended choice of antibiotics for CAP need to account for potential local/regional variation in the epidemiology of CAP and the prevalence of antibiotic resistance.

| How likely is it that the results of new research on this topic would be implemented in practice right away? | Implementation of new findings in this area likely would depend on how the new research findings are incorporated into practice guidelines at the national and local level, and could be affected by the quality of care measures being used by hospitals and health systems at the time that new research is reported.
- Recommendations for hospital-based care of CAP will be easier to implement than recommendations for outpatient-based care because hospitals tend to devote more resources to quality improvement activities than community-based practices. It is challenging to influence antibiotic prescribing practices in diverse outpatient settings.
- Depending on the strength of evidence from new research, hospitals and health systems could make changes in guidelines and quality of care measures within a relatively short period of time. The IDSA/ATS guidelines on the management of CAP are being updated and are projected to release in fall 2015. |

| Would new information from CER on this topic remain current for several years? | If new information from CER supported a paradigm shift toward greater use of a narrow-spectrum antibiotic, or shorter course of antibiotic therapy, it would take time to be widely embraced in practice, but could remain current for many years. |
References for topic 10: Comparative effectiveness of narrow-spectrum antibiotics versus broad-spectrum antibiotics in the treatment of community-acquired pneumonia in adults


Research Prioritization Topic Brief

Topic 20: “Osteoarthritis”

Comparative effectiveness of treatment strategies for stabilization of symptoms from osteoarthritis.

PCORI Scientific Program Area: Assessment of Prevention, Diagnosis and Treatment Options

Dr. Gillian Sanders Schmidler, PhD and Team
The Duke Clinical Research Institute

April 18, 2013
**Criteria** | **Brief Description**
---|---
**Introduction** | **DESCRIPTION OF CONDITION**
• Osteoarthritis (OA) is characterized by damage to cartilage and bones of joints, causing symptoms of pain and stiffness in the affected joints. OA is also referred to as degenerative joint disease or wear-and-tear arthritis.
• OA is a very common condition, particularly in people over age 45 and is a major cause of physical disability, decreased quality of life, and increased health care costs.

**Relevance to patient-centered outcomes** | **SYMPTOMS**
• Pain and stiffness of affected joints—the most commonly affected joints are knees, hips, hands, spine, and feet
• Usually begins in a single joint

**OUTCOMES**
• OA has an impact on many aspects of patients’ lives including:
  o Quality of life
  o Daily functioning
  o Mental health (including depressive symptoms)
  o Fatigue
  o Limitations with work
  o Quality of sleep
  o Ability to engage in other health behaviors (like physical activity)
• Other conditions more common in patients with OA include:
  o Impact of disease on quality of life:
    ▪ Impaired functioning (pain, limited mobility)
    ▪ Depression, anxiety, sleep disorders¹
  o Related to treatments used for OA symptoms:
    ▪ Nonsteroidal antiinflammatory drugs (NSAIDs) like aspirin, ibuprofen, and the like, used to treat OA-related pain
    ▪ Long-term use of these medications can contribute to peptic ulcer disease, kidney disease
  o Relationship to OA is unclear. Other metabolic disorders (diabetes, hypertension, high cholesterol) are more common in patients with OA.²

**Burden on Society** | **INCIDENCE (NEW CASES)**
• OA increases with age, occurring most often in people over age 45.³
• OA of the hand has one new case per year per 1000 people (0.1%) aged 20-89; higher as age increases.¹

**PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION)**
• 27 million US adults (>10% of population) aged 18 years and older have one or more type of clinical OA.²
• Prevalence varies by definition of OA, location of OA, and populations studied:⁴
  o 19% of people aged 45 or older and 37% of people aged 60 or older had knee OA on x-ray.⁴
In populations with higher proportions of African American, rural, and obese residents, 28% of people aged 45 or older and 50% aged 75 or older had knee OA on x-ray; prevalence of hip OA was similar.

- Of those showing OA on x-ray, a smaller proportion report having symptoms (7-17%).

**Key risk subgroups:**
- Risk of progression and severity of symptoms is greater in African Americans than Caucasians.
- There is greater prevalence and associated limitations on activity in women, particularly after menopause.

### Effects on patients’ quality of life, productivity, functional capacity, mortality, use of health care services

<table>
<thead>
<tr>
<th>QUALITY OF LIFE</th>
<th>OOA leads to functional limitations, pain, disability, lost earnings, and is associated with other comorbid conditions, all of which can affect quality of life.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRODUCTIVITY</td>
<td>5.3% of US adults aged 18-64 report arthritis-attributable work limitations (AAWL). Among adults with arthritis, approximately 30% reported AAWL.</td>
</tr>
<tr>
<td></td>
<td>In 2003, indirect costs of earning losses due to all rheumatic conditions (with OA being the most common of these) for adults in the United States was over $47 billion.</td>
</tr>
<tr>
<td></td>
<td>OA is the third leading cause of “years of life lost to disability” (after depression and alcohol overuse).</td>
</tr>
<tr>
<td>FUNCTIONAL CAPACITY</td>
<td>Most common functional limitations affect walking, standing, bending, and stooping movements; people with OA are more than three times as likely to have trouble with walking as people without OA.</td>
</tr>
<tr>
<td></td>
<td>Among older adults, risk of disability attributable to knee OA is as great as that due to cardiovascular disease and greater than any other medical condition.</td>
</tr>
<tr>
<td></td>
<td>Data from the National Health Interview Survey show that people with arthritis-related disability (including disability from OA) have more numerous, longer, and more bothersome disabilities than people with heart disease-related disability.</td>
</tr>
<tr>
<td>MORTALITY</td>
<td>Increased age-specific mortality among patients with OA, particularly symptomatic hip and knee OA, compared to those without OA is at least partly attributable to:</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal conditions related to NSAID use</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular-related conditions related to obesity</td>
</tr>
</tbody>
</table>

### How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?

Given the high prevalence of OA and the impact on functional status, productivity, and quality of life, high priority should be given to optimizing treatments to slow progression of disease, reduce pain, and maintain functional status.

### Options for Addressing the Issue
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?

Four recent systematic reviews explored OA management options.\(^9\)\(^{-12}\)

- Limited evidence on the relative benefits and harms of different therapies within each category (drugs, physical therapy/exercise, weight loss, or surgery)
- Little evidence directly comparing relative effectiveness in terms of patient-centered outcomes between different categories, or between different combinations of categories

**SCREENING/EARLY DIAGNOSIS**

- Diagnosing OA can be complex due to a lack of specific physical or laboratory findings and discrepancies between symptoms and the results of radiographic examinations.
- OA is frequently diagnosed by an overall clinical impression based on the patient's age and history, findings on physical examination, and X-ray or MRI findings.

**MANAGEMENT OPTIONS\(^11\)**

- **Pain relievers and anti-inflammatory drugs:**
  - Most trials were primarily short-term, conducted in ideal settings (few real-world effectiveness studies)
  - Potential benefits:
    - Pain control and reducing swelling
  - Potential harms:
    - Gastrointestinal bleeding
    - Peptic ulcer disease
    - Hypertension
    - Swelling
    - Renal disease
- **Weight loss:**
  - Identifying effective weight-loss strategies is no easier in an OA population than any other (ie, extremely difficult)
- **Exercise and physical therapy:**
  - Unclear which type of exercise or physical therapy is best:
    - Reviews report that no single physical therapy intervention improves all key clinical and patient outcomes.
    - Studies tended to focus on a single exercise therapy, but typical practice uses combined interventions.
    - Unclear if effects of exercise therapies on quality of life differ by key patient populations or if outcomes are sustained over time.
  - Potential benefits for preserving physical function
  - Few harms were reported except for increased pain or swelling during and after exercise, but these did not deter participation in exercise programs.
- **Combination management:**
  - Using medications with exercise and physical therapy interventions
- **Joint Surgery:**
  - When medication and exercise or physical therapy are not enough to decrease pain and improve quality of life, joint surgery is another option.

What could new research

- There are currently few studies that compare multimodal treatments (eg, combinations of physical therapies) with exercise alone.
### PCORI Topic Brief: Assessment of Prevention, Diagnosis and Treatment Options

**Contribute to achieving better patient-centered outcomes?**

- Few studies explored how effects differed by key subgroups
- Few studies evaluated optimal duration and intensity on interventions

  - Existing evidence does not allow for conclusions about the following:
    - Comparative effectiveness of strategies to help patients engage in key behaviors for managing OA (physical activity, weight management), in real-world settings (community, primary care)
    - Comparative effectiveness of strategies to increase patient adherence to nonmedication-based strategies
    - Comparative effectiveness of methods to assist patients with informed decision making regarding OA treatments (eg, medication use, joint injections, physical therapy, joint replacement surgery), with a focus on individuals with low health literacy and limited health care access
    - Methods for identifying and engaging patients early in the OA disease process, particularly fostering healthy behaviors (physical activity, weight management) to slow disease progression
    - Comparative benefits of different exercise and physical therapy interventions
    - Which exercise therapies work best for key subgroups (sex, severity of disease, age, obesity)
    - Long-term benefits of exercise therapy interventions and strategies for helping patients adhere to exercise recommendations
    - How outcomes of pharmacotherapies will work outside of ideal study settings (need for more real-world research)

**Have recent innovations made research on this topic especially compelling?**

- There have been no recent high-impact innovations related to strategies for improving patient-centered outcomes.
- Yet, there is a compelling argument for fostering comparative effectiveness research in this area, given the following:
  - High burden of disease and large burden on patient-centered outcomes (pain, functional ability)
  - Existence of strategies to effectively improve these outcomes
  - High level of nonadherence to these strategies (both at the patient and health care levels)

**How widely does care now vary?**

**VARIABILITY IN CARE**

- Clinical practice often does not reflect guideline recommendations for care.13
- In particular, there is low use of conservative, nonmedication strategies like exercise and weight loss.

**What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?**

**RECENT PUBLICATIONS**

- MEDLINE search from 1/1/2008 – 4/9/2013: total 4,570 citations
  - 901 labeled as randomized controlled trials/therapy (RCTs)
  - 406 labeled as meta-analyses or systematic reviews

**ONGOING TRIALS**

- There are at least 628 ongoing studies listed in ‘clinicalTrials.gov’
- NIH Reporter (a database of NIH funded studies) lists:
  - 449 projects
  - 495 publications

**How likely is it that**

**KEY UNCERTAINTIES IN CLINICAL DECISION MAKING**
new CER on this topic would provide better information to guide clinical decision making?

| What management strategy or combination of management strategies works best for key subgroups of patients? |
| What are effective strategies to foster long-term adherence rates to management strategies? |
| What are the comparative benefits and harms of different management strategies? |
| What are the best methods for engaging patients in the decision making process regarding management strategies? |

LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES

- Effective treatments and behavioral strategies exist, but methods for employing and sustaining these in real-world clinical settings are lacking; comparative-effectiveness research (CER) can help patients and providers by giving practical guidance in these areas.
- There are few comparative effectiveness studies of exercise and physical therapy strategies; understanding the best interventions in this area could improve care and outcomes by establishing a set of “best practices” to be employed in health care and community settings.
- Beyond compliance with interventions, there is little evidence regarding which patients do best with what management strategies (e.g., joint injections, pharmacotherapies, physical therapy); CER in this area could help patients and providers to better select strategies according to patient characteristics.

### Potential for New Information to Improve Care and Patient-Centered Outcomes

| What are the facilitators and barriers that would affect the implementation of new findings in practice? |
| FACILITATORS |
| OA is a prevalent disease with wide impact on patient quality of life, functioning, and productivity. Therefore patients are often motivated to engage in treatments that may improve their symptoms. |
| Many nonmedication therapies can be delivered by individuals other than a physician and can be delivered in multiple settings to increase patient access. |
| There are already evidence-based interventions for patients with OA. These “off-the-shelf” programs can be adapted to different settings and patient groups and can be readily used in comparative effectiveness research and implementation strategies. |

| BARRIERS |
| OA is primarily treated in primary care settings (until patients need certain types of joint injections or are considering surgery). In primary care settings there are often many competing demands and little time; therefore any strategies need to consider this limitation. |
| Long-term adherence to exercise and weight loss in OA is a challenge, just as it is among other patient groups. |

| How likely is it that the results of new research on this topic would be implemented in practice right away? |
| Provider-based interventions are more likely to be implemented right away if they are easy to implement for both the provider and the patient. |
| Several professional societies have developed recommendations for the care and management of OA, and the core components of these recommendations are in agreement. However, there is a need to give providers: |
  - Reminders to implement these recommendations |
  - Specific guidance on when each management strategy may be appropriate for patients. These types of reminders, particularly if automated and integrated into practice settings, could be feasibly implemented. |

---

*PCORI Topic Brief: Assessment of Prevention, Diagnosis and Treatment Options*
Patient-based research that compares the effectiveness of different therapies is likely to be implemented right away if there are improvements in outcomes that are easy to achieve and can be customized to the individual patient.

<table>
<thead>
<tr>
<th>Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?</th>
</tr>
</thead>
<tbody>
<tr>
<td>CER priority areas that seek to identify best strategies for implementing existing recommendations for care and patient interventions (physical activity and weight management) are needed.</td>
</tr>
<tr>
<td>Other CER priority areas include comparative effectiveness of specific therapies (e.g., type of exercise or physical therapy intervention) and identification of optimal strategies for different patient subgroups.</td>
</tr>
<tr>
<td>These types of findings are not likely to become obsolete quickly.</td>
</tr>
</tbody>
</table>

**REFERENCES:**


APPENDIX: TOPIC QUESTION

Nominated by Institute of Medicine (IOM)

1) Compare the effectiveness of different treatment strategies in the prevention of progression and disability from osteoarthritis.
Research Prioritization Topic Brief

Topic 3: “Hip Fracture”

Comparative effectiveness of surgical options for hip fracture in the elderly.

PCORI Scientific Program Area: Assessment of Prevention, Diagnosis and Treatment Options

Dr. Gillian Sanders Schmidler, PhD and Team
The Duke Clinical Research Institute

April 19-20, 2013
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td><strong>DESCRIPTION OF CONDITION(^1,2,3)</strong></td>
</tr>
<tr>
<td>Overview/definition</td>
<td>• “Hip fracture” refers to a break of the upper part of the femur (large bone of the upper thigh)</td>
</tr>
<tr>
<td>of topic</td>
<td>• Classified into different types depending on location</td>
</tr>
<tr>
<td></td>
<td>• Treatment options vary by fracture type</td>
</tr>
<tr>
<td></td>
<td>• Two main causes:</td>
</tr>
<tr>
<td></td>
<td>o Simple falls (90%)—affect mostly the elderly, more common in women</td>
</tr>
<tr>
<td></td>
<td>o Major trauma (eg, motor vehicle accident)—mostly younger, more common in men</td>
</tr>
<tr>
<td>**Patient-centered</td>
<td><strong>SYMPTOMS/OUTCOMES(^1,2,3)</strong></td>
</tr>
<tr>
<td>outcomes</td>
<td>• Hip fracture can result in:</td>
</tr>
<tr>
<td></td>
<td>o Pain</td>
</tr>
<tr>
<td></td>
<td>o Functional impairment</td>
</tr>
<tr>
<td></td>
<td>o Prolonged rehabilitation</td>
</tr>
<tr>
<td></td>
<td>o Loss of ability to live independently</td>
</tr>
<tr>
<td></td>
<td>o Premature death</td>
</tr>
<tr>
<td></td>
<td>• Goal of treatment usually to return patients to pre-fracture level of functioning</td>
</tr>
<tr>
<td><strong>Burden on Society</strong></td>
<td><strong>INCIDENCE (NEW CASES)(^1,2)</strong></td>
</tr>
<tr>
<td>Recent incidence and prevalence in</td>
<td>• 957 per 100,000 for women and 414 per 100,000 for men from 1986 to 2005</td>
</tr>
<tr>
<td>populations and subpopulations</td>
<td>• Increased risk in women due to changes in bone strength (osteoporosis) after menopause</td>
</tr>
<tr>
<td></td>
<td>o Unclear if decreased use of postmenopausal hormone replacement therapy after findings of Women’s Health Initiative in 2002 will lead to increased incidence in women</td>
</tr>
<tr>
<td>**Effects on patients’ quality of life,</td>
<td><strong>QUALITY OF LIFE(^1,2,3)</strong></td>
</tr>
<tr>
<td>productivity, functional capacity,</td>
<td>• 80% of elderly women surveyed preferred death to a “bad” hip fracture that would result in nursing home need</td>
</tr>
<tr>
<td>mortality, use of health care services</td>
<td><strong>FUNCTIONAL CAPACITY</strong></td>
</tr>
<tr>
<td></td>
<td>• 50% of previously independently living elderly patients able to walk unaided after fracture, but many (25–75%) never completely recover full pre-injury functional status</td>
</tr>
<tr>
<td></td>
<td><strong>MORTALITY</strong></td>
</tr>
<tr>
<td></td>
<td>• 20% one-year mortality after a hip fracture</td>
</tr>
<tr>
<td></td>
<td>• 2–3% in-hospital mortality among patients 65 and over(^4)</td>
</tr>
<tr>
<td></td>
<td><strong>USE OF HEALTH CARE SERVICES(^4)</strong></td>
</tr>
<tr>
<td></td>
<td>• 304,000 hospitalizations in the United States (in 2010) secondary to hip fractures</td>
</tr>
<tr>
<td></td>
<td>o Ages 65–84: 0.9% of all hospitalizations for men, 1.8% for women</td>
</tr>
<tr>
<td></td>
<td>o Ages 85 and older: 2.7% of all hospitalizations for men, 4.5% for women</td>
</tr>
</tbody>
</table>
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?

- Common condition with potential for severe consequences and overall high societal burden
- Also high potential for decreasing the incidence of hip fractures via fall prevention measures
- Multiple different treatment options and potential for wide variety of different outcomes depending on nature, quality, and extent of medical/surgical care provided
- CER on alternative approaches may have significant impact on clinical outcomes, societal costs, and patient and provider decision making

<table>
<thead>
<tr>
<th>Options for Addressing the Issue</th>
<th>Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?</th>
<th>Four Key Questions in 2009 AHRQ “Treatment of Common Hip Fractures” report ³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Four Key Questions in 2009 AHRQ “Treatment of Common Hip Fractures” report ³</td>
<td>1) Relationship between patient variables, fracture type, and patient outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Relationship between fracture type and patient outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3) Relationship between implant variables and patient outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4) Relationship between intervention type and patient outcomes</td>
</tr>
<tr>
<td>Results:</td>
<td>Five of the included trials were conducted in the United States</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limited evidence to answer most of the key questions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High degree of uncertainty regarding the best way to treat unstable hip fractures and about which treatment options are most appropriate for various clinical populations</td>
<td></td>
</tr>
</tbody>
</table>

What could new research contribute to achieving better patient-centered outcomes?

2010 AHRQ “Future Needs for the Treatment of Common Hip Fractures” report⁵ identified the following research gaps:

- Predictors of short time-to-recovery and functional outcomes
- Impact of suboptimal surgical quality on functional outcomes
- Optimal treatment for different types of fractures (eg, unstable intertrochanteric hip fractures) or defined populations (eg, frail elderly, patients with dementia)
- Between-class and within-class comparisons (eg, intramedullary nail vs. screws, cement vs. not, number and placement of screws, plate length and position, nail length, and other parameters)

Have recent innovations made research on this topic especially compelling?

- Comanaged geriatric fracture centers and organized geriatric fracture programs represent novel approaches that are associated with shorter times to surgery, fewer postoperative infections, fewer complications overall, and shorter lengths of stay.⁶
- Further research on health care redesign involving multidisciplinary collaboration is timely and may result in both improved outcomes and more efficient use of health care resources.

How widely does care now vary?

- Very large variation in quality, nature, and extent of care provided across the many clinical settings throughout the United States that offer hip fracture repair
- High variability in training and quality of surgeons and hospital-based clinicians who provide medical care to elderly patients with multiple comorbidities during hospitalization for hip fracture repair
<table>
<thead>
<tr>
<th>What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?</th>
<th>RECENT PUBLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Treatment of Common Hip Fractures (AHRQ, 2009)³</td>
</tr>
<tr>
<td></td>
<td>• Future Needs for the Treatment of Common Hip Fractures (AHRQ, 2010)⁵</td>
</tr>
<tr>
<td></td>
<td>• Pain Management Interventions for Hip Fractures (AHRQ, 2011)⁷</td>
</tr>
<tr>
<td></td>
<td>ONGOING TRIALS</td>
</tr>
<tr>
<td></td>
<td>• FAITH (Fixation using Alternative Implants for the Treatment of Hip Fractures)⁸</td>
</tr>
<tr>
<td></td>
<td>• HEALTH (Comparing Total Hip Arthroplasty and Hemi-Arthroplasty on Revision Surgery and Quality of Life in Adults with Displaced Hip Fractures)⁹</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How likely is it that new CER on this topic would provide better information to guide clinical decision making?</th>
<th>• The research gaps listed above were identified by key stakeholders. This suggests that CER on these topics is likely to inform stakeholder clinical decision making.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Many areas of uncertainty involve technical issues regarding surgical management; relative involvement of patients/capacity for shared decision making may vary</td>
</tr>
</tbody>
</table>
## Potential for New Information to Improve Care and Patient-Centered Outcomes

<table>
<thead>
<tr>
<th>Question</th>
<th>FACILITATORS</th>
<th>BARRIERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are the facilitators and barriers that would affect the implementation of new findings in practice?</td>
<td>• The current lack of consensus on questions identified by stakeholders as being important is likely to facilitate implementation of new, compelling findings. • 80% of hospitalizations have Medicare as primary payer—potential for CMS to help facilitate implementation</td>
<td>• Cost of implementation (e.g., to payers, providers, patients, caregivers, and others) • Lower barriers to market entry for surgical instruments and devices (e.g., hip implants), as opposed to drugs • Reimbursement structure for providers and financial incentives/disincentives associated with changing existing practices • Dissemination of findings across a large spectrum of providers, payers, and patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How likely is it that the results of new research on this topic would be implemented in practice right away?</th>
<th>EVIDENCE OF BENEFIT</th>
<th>EVIDENCE OF NO BENEFIT OR HARM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Highly likely to be implemented because most stakeholders likely to be motivated to improve decision making and patient outcomes • General sense that orthopedic surgeons are open to—and would welcome—greater clarity on treatment options</td>
<td>• Depending on balance, may be less likely to be implemented if findings do not provide additional clarity o Especially true if current financial/other incentives favor continued use of intervention with no benefit relative to other options</td>
</tr>
</tbody>
</table>

|Would new information from CER on this topic remain current for several years?| • New information from CER on this topic may remain current if it is compelling and clear, and if it addresses questions deemed relevant by stakeholders. • CER on certain technical questions may be rendered obsolete by unforeseeable technological advances (e.g., availability of new materials for hip replacement).|

## REFERENCES:


**APPENDIX: TOPIC QUESTIONS**

Nominated by the Agency for Healthcare Research and Quality (AHRQ)

1. What predicts short time-to-recovery after hip fracture?
2. What predicts functional outcomes after one year, especially one to two years after hip fracture?
3. What is the impact of suboptimal surgical quality on functional outcomes?
4. Do certain procedures (eg, internal fixation) work better than others for frail older patients?
5. Are most fragile patients more or less likely to have suboptimal fracture reduction/implant position than the most active, mobile patients (making them higher risk for implant failure?)
6. Which procedures are better for patients with dementia?
7. What is the optimal treatment for displaced femoral neck fractures?
8. What is the optimal treatment for unstable intertrochanteric hip fractures?
9. What is the optimal treatment for subtrochanteric hip fractures?
10. Between class comparisons (eg, IM nail vs. screws)
11. Within-class comparison of arthroplasty—cement vs. not
12. Within-class comparison of number and placement of screws
13. Within-class comparison of plate length, position
14. Within-class comparison of nail length (IMN)
Topic Brief
Comparative Effectiveness of Treatments for Non-Muscle-Invasive Bladder Cancer

PCORI Scientific Program Area:
Assessment of Prevention, Diagnosis and Treatment Options

Pacific Northwest Evidence-based Practice Center

October 10, 2016

This report was prepared by the Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, Portland, OR. All statements, findings and conclusions in this publication are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI) or its Board of Governors. This publication was developed through a contract to support PCORI’s work and is being made available free of charge for the information of the scientific community and general public as part of PCORI’s ongoing research programs.

Questions or comments may be sent to PCORI at info@pcori.org or by mail to Suite 900, 1828 L Street, NW, Washington, DC 20036.
Overview/definition of topic

DESCRIPTION OF CONDITION

Bladder cancer is the 4th most commonly diagnosed cancer in men and the 10th most commonly diagnosed cancer in women in the United States.\(^1\) The most common risk factor for bladder cancer is cigarette smoking; other risk factors include occupational exposures and family history.\(^2\) Bladder cancer is staged based on the extent of penetration or invasion into the bladder wall and adjacent structures.\(^3\) Bladder cancers that have not invaded the bladder smooth muscle layer are grouped as non-muscle-invasive bladder cancer (NMIBC), and include stage classifications Tis (carcinoma in situ), Ta (noninvasive papillary carcinoma), and T1 (cancer that invades the subepithelial connective tissue).

Approximately 75% of newly diagnosed bladder cancers are NMIBC.\(^4\) Individuals with NMIBC have 5-year survival rates higher than 88%.\(^5\) Prognosis is poorer for patients with muscle-invasive bladder cancers (MIBC), with 5-year survival rates from 63% to 15%.\(^5\) As many as 70% of NMIBC tumors recur after initial treatment, with a 10% to 20% risk of progression to MIBC.\(^4\) The likelihood of recurrence or progression to MIBC depends on a number of factors. These include cancer stage, tumor grade, whether the tumor is an initial tumor or a recurrence, number and size of tumors, and patient’s age and general health.

These factors may also affect treatment options. The main treatment for NMIBC is local resection with transurethral resection of the bladder tumor (TURBT), often with adjuvant intravesical therapy (i.e., the treatment solution is put inside the bladder) to destroy residual tumor cells using bacillus Calmette-Guérin (BCG), various chemotherapy agents (e.g., mitomycin C [MMC], apaziquone, paclitaxel, gemcitabine, thiotepa, valrubicin, doxorubicin, epirubicin), or interferon immunotherapy.\(^6\) Post-TURBT adjuvant intravesical therapy is associated with potential local side effects (e.g., dysuria, urinary frequency, or hematuria) and systemic side effects (e.g., fever, chills, rash, or fatigue). However, not using adjuvant intravesical therapy may increase the risk of bladder cancer recurrence or progression, particularly in patients with higher risk NMIBC. Radical cystectomy is a treatment option in patients with NMIBC who are at
high risk for progression to MIBC. In one recent study, approximately 10% of patients with high-risk bladder cancer underwent cystectomy.⁷

Various tools using clinical and pathologic variables have been developed for risk stratification and predicting bladder cancer recurrence and/or progression in persons with NMIBC. These include the European Organization for Research and Treatment of Cancer (EORTC) risk calculator,⁸ and a tool developed by the Spanish Urological Club for Oncological Treatment/Club Urologico Espanol de Tratamiento Oncologico (CUETO).⁹ In eight retrospective cohort studies of these two tools that were included in a recent systematic review,¹⁰ discrimination (how well a risk assessment method separates persons with from those without an outcome) was poor to fair for recurrence (C-index scores ranged from 0.52 to 0.66) and fair to good for progression (C-index scores ranged from 0.62 to 0.81). No study evaluated clinical outcomes associated with use of a formal risk assessment tool in a risk-adapted approach to management of NMIBC versus other approaches.¹¹

Recently, an expert panel of the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) created the AUA/SUO Guideline Risk Stratification System.¹² This system categorizes the risk of recurrence and/or progression of NMIBC as ‘low’, ‘intermediate’, and ‘high,’ and is meant for use in clinical practice for guiding patient counseling and treatment decisions. Unlike previous instruments, this system includes consideration of a patient’s prior treatment with BCG. Intermediate risk patients who have persistent or recurrent bladder cancer after intravesical therapy with BCG are reclassified as high risk. The risk categories in this system are based on the panel members’ consensus, not on meta-analyses or original data, and the panel recognized the need for validation of the model’s performance.¹² The AUA guideline recommends that patients with low-risk NMIBC receive a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin). In patients with intermediate-risk NMIBC, the AUA guideline recommends a six-week course chemotherapy (e.g., mitomycin C, epirubicin) or immunotherapy (BCG), with an option to continue for up to 1 year in responders to initial treatment. In high-risk patients, the AUA recommends intravesical BCG therapy for six-weeks, with continued therapy for three years in responders. Radical cystectomy is an option for patients with higher-risk NMIBC who have failed intravesical therapies (in some cases, including repeat treatment with BCG) or have features that put them at very high risk for progression.
<table>
<thead>
<tr>
<th>METHODS</th>
</tr>
</thead>
<tbody>
<tr>
<td>This Topic Brief is based on a review of a recent systematic review funded by the Agency for Health Research and Quality on NMIBC\textsuperscript{11} and a subsequent supplement funded by the American Urological Association,\textsuperscript{10} searches on ClinicalTrials.gov and selected databases from groups funding bladder cancer research (EORTC and SWOG), and consultation with experts (John Gore, M.D., M.S., University of Washington, and Sam Chang, M.D., Vanderbilt University).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relevance to patient-centered outcomes</th>
<th>SYMPTOMS\textsuperscript{3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The most common symptom of bladder cancer is painless hematuria (blood in the urine).</td>
<td></td>
</tr>
<tr>
<td>• Other symptoms include: increased frequency of urination, dysuria (pain or burning when urinating), urgency (feeling the need to urinate immediately, even though the bladder is not full), or difficulty urinating. However, each of these symptoms is more likely to be caused by problems other than bladder cancer.</td>
<td></td>
</tr>
<tr>
<td>• Bladder cancer that is far advanced may also cause a variety of other symptoms, such as: being unable to urinate, lower back pain, loss of appetite, weight loss, tiredness or weakness, swelling in the feet, or bone pain.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PATIENT-CENTERED OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mortality</td>
</tr>
<tr>
<td>• Need for cystectomy</td>
</tr>
<tr>
<td>• Progression to muscle-invasive bladder cancer</td>
</tr>
<tr>
<td>• Bladder cancer recurrence</td>
</tr>
<tr>
<td>• Quality of life</td>
</tr>
</tbody>
</table>

**Possible adverse effects of treatment include:** cystitis, urinary urgency, urinary frequency, incontinence, hematuria, pain, flu-like symptoms, surgical complications, urosepsis, and myelosuppression.

<table>
<thead>
<tr>
<th>Burden on Society</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INCIDENCE AND PREVALENCE\textsuperscript{2}</strong></td>
</tr>
<tr>
<td>The American Cancer Society estimates 76,960 new cases of bladder cancer in the United States in 2016 (58,950 in men and 18,010 in women) and about 16,390 deaths (11,820 in men and 4,570 in women). Bladder cancer represents ~5% of all incident cancers in the U.S. The lifetime probability of developing bladder cancer is approximately 3.8% in men and 1.2% in women. Bladder cancer occurs primarily in people age 55 and older, and is roughly twice as common in whites compared with African Americans or Hispanic Americans.</td>
</tr>
<tr>
<td>Effects on patients’ quality of life, productivity, functional capacity, mortality, use of health care services</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>• Aside from the mortality rates cited above, NMIBC and treatments for NMIBC may have various effects on patients’ quality of life, functional capacity, and use of health care services.</td>
</tr>
<tr>
<td>• TURBT may cause dysuria and/or hematuria lasting for one or two weeks after the procedure; repeated TURBT may cause scarring of the bladder leading to urinary frequency and/or incontinence.</td>
</tr>
<tr>
<td>• Intravesical immunotherapy or chemotherapy may cause cystitis, urinary frequency, dysuria, hematuria, bladder pain, or flu-like symptoms, such as fever, chills, and fatigue.</td>
</tr>
<tr>
<td>• Patients with low-risk NMIBC often receive a single dose of intravesical therapy during TURBT; patients with higher-risk NMIBC typically receive at least an induction course.</td>
</tr>
<tr>
<td>• An induction course of intravesical therapy usually requires the patient to receive a treatment once per week for 6 consecutive weeks, beginning a few weeks after the TURBT. Each treatment requires the patient to hold the solution inside the bladder for approximately one to two hours. Additional induction courses and/or maintenance therapy may be utilized. The duration of maintenance therapy varies, commonly lasting for 1 year or longer. The frequency of maintenance therapy also varies, with treatments commonly given once per month (MMC) or every 3 to 6 months (BCG).</td>
</tr>
<tr>
<td>• After initial treatment for NMIBC, surveillance with cystoscopy is typically conducted every 3 to 6 months for at least a couple of years.</td>
</tr>
<tr>
<td>• Radical cystectomy may be an option in patients who have high-risk NMIBC and recurrent and/or progressive disease. Radical cystectomy may have profound adverse effects on a patient’s functional capacity and quality of life. Some of these effects are due to the surgical urinary diversion and urostomy, including the need to empty the urostomy bag or drain the urine pouch with a catheter. In addition, urinary diversion and urostomy may also lead to infections, urine leaks, pouch stones, and/or blockage of urine flow.</td>
</tr>
<tr>
<td>• Radical cystectomy and/or urostomy may also have adverse sexual effects for both men and women.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How strongly does this overall societal burden suggest that CER on alternative approaches to this</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bladder cancer is a common cancer, accounting for approximately 5% of all incident cancers in the U.S. It is an important health problem, with no substantial improvement in associated mortality since 1975.2,14</td>
</tr>
</tbody>
</table>
| • Economic analyses have shown bladder cancer to be the costliest cancer to treat in the United States on a per capita basis, taking into account diagnostic testing,
Given the overall societal burden of bladder cancer, CER to identify more effective and/or safer approaches to the treatment of NMIBC should be a high priority.

### Options for Addressing the Issue

Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?

<table>
<thead>
<tr>
<th>Intravesical immunotherapy/chemotherapy</th>
</tr>
</thead>
</table>
| • Intravesical therapy with any of several different agents was associated with reduced risk for bladder cancer recurrence versus no intravesical therapy (strength of evidence [SOE]: low for BCG; moderate for others).<sup>11</sup> These agents were BCG (3 trials; RR 0.56; 95% CI, 0.43 to 0.71), MMC (8 trials; RR 0.71; 95% CI, 0.57 to 0.89), doxorubicin (10 trials; RR 0.80; 95% CI, 0.72 to 0.88), and epirubicin (9 trials; RR 0.63; 95% CI, 0.53 to 0.75).
| • BCG was the only agent associated with reduced risk for bladder cancer progression versus no intravesical therapy (4 trials; RR 0.39; 95% CI, 0.24 to 0.64; SOE: low).<sup>11</sup> (For BCG and risk of recurrence and progression, the SOE was rated low due to methodological limitations in the studies; in addition, there were relatively few studies).
| • No intravesical agent was associated with decreased risk of all-cause or bladder cancer specific mortality versus no intravesical therapy.<sup>11</sup>
| • Evidence on gemcitabine, interferon alpha, and thiotepa was sparse, and the investigators found no randomized trials of valrubicin, paclitaxel, or apaziquone.<sup>11</sup>
| • Head-to-head trials of intravesical therapy using different drugs showed few clear differences. For BCG versus MMC, the most well-studied comparison, there was no difference on any outcome, including bladder cancer recurrence, progression, or mortality (SOE: moderate). However, BCG was associated with decreased risk of bladder cancer recurrence in the subgroup of trials that evaluated maintenance regimens (SOE: low). Other head-to-head comparisons were evaluated in fewer
trials, and showed few differences.\textsuperscript{11}

- Four trials of BCG versus no intravesical therapy found that local and systemic adverse events were relatively common (granulomatous cystitis or irritative symptoms in 27\% to 84\% of patients, macroscopic hematuria in 21\% to 72\%, and fever in 27\% to 44\%) (SOE: low). BCG was also associated with an increased risk of local adverse events and fever versus MMC (SOE: low). Few trials reported harms of intravesical agents other than BCG versus no intravesical therapy, or against another intravesical agent.\textsuperscript{11}

- Biomarkers such as FISH appear to predict response to intravesical therapies, but have not been evaluated for effects on clinical outcomes.\textsuperscript{11}

\textit{Treatment frequency and duration:}

- A single instillation of intravesical therapy for NMIBC plus TURBT was more effective than TURBT without intravesical therapy for reducing risk of recurrence, based on 15 RCTs (RR 0.74; 95\% CI 0.64 to 0.86; SOE: moderate); evidence was strongest for epirubicin and MMC. There were no clear effects of single instillation intravesical therapy on risk of progression or mortality and estimates were imprecise.\textsuperscript{10}

- Limited evidence suggested that BCG maintenance regimens (>6 weeks) are more effective than induction regimens (≤6 weeks) at reducing risk of bladder cancer recurrence in responders to induction therapy or in patients with higher risk tumors (2 trials; RR, 0.54; 95\% CI, 0.31 to 0.95; SOE: low).\textsuperscript{11}

- Evidence on the effectiveness of induction (multiple instillations over 4 to 8 weeks) versus maintenance (induction therapy plus additional instillations beyond 8 weeks) intravesical chemotherapy is limited (SOE: low). One trial that excluded patients with low-risk tumors (primary, solitary TaG1) found MMC maintenance therapy (6 weekly instillation followed by monthly instillations for 3 years) associated with decreased risk of recurrence vs. induction therapy (6 weekly instillations) (10\% vs. 26\%, RR 0.41, 95\% CI 0.24 to 0.69), but there were no differences in 3 trials of patients not selected for being at higher risk. Three of four trials (none focused on patients with higher risk tumors) found no difference between longer (1 year) versus shorter (3 to 6 months) maintenance chemotherapy.\textsuperscript{10}

\textit{Patient and tumor characteristics:}

- No trial evaluated how effectiveness of intravesical therapy may vary in subgroups defined by patient characteristics such as age, sex, race/ethnicity, performance status, and comorbidities.\textsuperscript{11}
Based on limited evidence, there were no clear differences in estimates of effectiveness of intravesical therapies in subgroups defined by tumor stage, grade, size, multiplicity, recurrence status, or DNA ploidy (SOE: low).11

**Fluorescent cystoscopy**

Fluorescent cystoscopy is a method for enhancing the visualization of tumors that may improve the likelihood of complete resection. It uses ultraviolet light (versus the traditional white light) and a dye injected into the bladder.

- Fluorescent cystoscopy was associated with decreased risk of bladder cancer recurrence versus white light cystoscopy at short-term follow-up (<3 months; 9 trials, RR 0.58; 95% CI 0.36 to 0.94; SOE: moderate), intermediate-term follow-up (3 months to <1 year; 6 trials; RR 0.70, 95% CI 0.56 to 0.88; SOE: moderate), and long-term follow-up (≥1 year; 12 trials, RR 0.82, 95% CI 0.69 to 0.97; SOE: moderate).10 However, findings were inconsistent and potentially susceptible to publication and performance bias (surgeons cannot easily be blinded to use of fluorescent cystoscopy).

- There were no differences between fluorescent cystoscopy versus white light cystoscopy in risk of progression or mortality, although fewer studies looked at these outcomes (SOE: low).10

**Treatment for recurrence or persistence after intravesical therapy**

- One trial of patients with high-risk Ta or T1 NMIBC who failed BCG therapy found gemcitabine maintenance associated with decreased risk of recurrence versus BCG (53% vs. 88%; RR 0.60; 95% CI 0.44 to 0.82), though there was no difference in risk of progression (33% vs. 38%).16

- One trial of patients with recurrent NMIBC after intravesical therapy who primarily received BCG (83% BCG) found a MMC maintenance regimen associated with increased risk for recurrence (40% vs. 28%; RR 1.44; 95% CI 0.84 to 2.47) and progression (18% vs. 11%; RR 1.64; 95% CI 0.64 to 4.19) versus gemcitabine, though neither finding was statistically significant.17

- An additional 9 trials assessed intravesical therapies in patients with recurrent bladder cancer, but none specified whether patients had received prior intravesical therapy or the type of intravesical therapy that was received.10
What could new research contribute to achieving better patient-centered outcomes?

- Although various risk stratification tools have been developed to inform treatment decisions, no study has evaluated clinical outcomes associated with use of a formal risk assessment tool versus other approaches. New research that evaluates and validates the accuracy of risk-adapted approaches in predicting recurrence and progression of NMIBC could help to achieve better patient-centered outcomes.

- Research on the effects of biomarkers on clinical outcomes for predicting response to intravesical therapy could help inform treatment choices, and guide decisions in patients who fail BCG.

- Additional head-to-head trials of intravesical therapies that use more standardized instillation regimens and doses, report outcomes in subgroups stratified by patient and tumor characteristics, and include more long-term outcomes related to progression and mortality would help clarify optimal treatment strategies, including optimal dosing and duration.

- Fluorescent cystoscopy may decrease risk of recurrent NMIBC, but more research is needed to determine its effects on risk of bladder cancer progression and mortality. RCTs that adequately safeguard against performance bias associated with the use of photosensitizers for fluorescent cystoscopy are needed to better define its utility.

- Evidence on the management of patients with recurrence or progression of bladder cancer after induction intravesical therapy with BCG or other agents is sparse. New research into the comparative effectiveness of various treatments after failure of first-line intravesical therapy could help to improve patient outcomes. This research should assess the comparative effectiveness of various intravesical agents, cystectomy or bladder-preserving alternatives to cystectomy, and/or novel agents (e.g., immune checkpoint inhibitors).

- The effectiveness of intravesical therapy in reducing the risk of progression in high risk patients is uncertain, and recent guidelines recommend considering initial radical cystectomy for such patients. However, these guidelines are based on limited evidence (grade C) that does not compare initial radical cystectomy with other treatments. New randomized trials that compare initial cystectomy with intravesical therapy or other bladder-preserving therapies for high risk NMIBC could provide needed information to inform treatment decisions.

- Cystoscopy, bladder tumor resection, intravesical therapy, and cystectomy are each associated with discomfort and possible adverse effects. New research into approaches that might reduce discomfort and/or adverse effects could improve patient-centered outcomes. This research could look into optimal dosing of...
intravesical agents that considers adverse effects; supplemental agents to reduce local or systemic side effects; and new technologies designed to reduce adverse effects and/or improve patient recovery time, such as PlasmaKinetic (PK) button vaporization in TURBT or robotic cystectomy.

- New research into the comparative effectiveness of novel or understudied approaches to treatment of NMIBC (e.g., enhanced cystoscopy with narrow band imaging, electromotive intravesical chemotherapy, chemohyperthermia, and external beam radiation therapy) could improve patient-centered outcomes.

### Have recent innovations made research on this topic especially compelling?

- As part of The Cancer Genome Atlas project, molecular alterations in 131 muscle-invasive bladder cancers have been characterized, with potential for the development of molecularly-targeted agents for treating NMIBC, as well as muscle-invasive bladder cancer.\(^{18}\)
- Newer immunotherapeutic agents – immune checkpoint inhibitors – have been developed and may hold promise for the treatment of NMIBC.
- Device assisted approaches to intravesical therapy (e.g., electromotive drug administration [EMDA] or hyperthermic intravesical chemotherapy [HIVEC]) may hold promise for increasing the absorption of chemotherapeutic agents and, thereby, improving outcomes.
- New technologies designed to reduce adverse effects and/or improve patient recovery time, such as PlasmaKinetic (PK) button vaporization in TURBT or robotic cystectomy hold promise.
- Use of these innovations in clinical practice and evidence on their effectiveness from well-conducted RCT’s appear to be limited at this time.

### How widely does care now vary?

- Women with bladder cancer have worse survival than men, likely due to delays in diagnosis and consequent diagnosis at later stages.\(^{19}\) In one study of a university-affiliated managed care organization, women received fewer referrals to urologists for evaluation of hematuria than did men (28% versus 47%).\(^{20}\) These disparities may be due to higher rates of urinary tract infections (which may have similar symptoms as bladder cancer) and the lower incidence of bladder cancer in women.
- African Americans are more likely to be diagnosed with bladder cancer of higher grades and stages and have worse survival rates compared with whites.\(^{19,21}\) They are also less likely to undergo radical cystectomy for localized muscle-invasive bladder cancer. However, there is less information on disparities in care specifically for NMIBC. One study of early stage bladder cancer that used SEER-Medicare data from 1992 through 2002, found differences in initial treatment between African Americans and whites. African Americans were more likely to undergo restaging.

| Have recent innovations made research on this topic especially compelling? | As part of The Cancer Genome Atlas project, molecular alterations in 131 muscle-invasive bladder cancers have been characterized, with potential for the development of molecularly-targeted agents for treating NMIBC, as well as muscle-invasive bladder cancer.\(^{18}\) Newer immunotherapeutic agents – immune checkpoint inhibitors – have been developed and may hold promise for the treatment of NMIBC. Device assisted approaches to intravesical therapy (e.g., electromotive drug administration [EMDA] or hyperthermic intravesical chemotherapy [HIVEC]) may hold promise for increasing the absorption of chemotherapeutic agents and, thereby, improving outcomes. New technologies designed to reduce adverse effects and/or improve patient recovery time, such as PlasmaKinetic (PK) button vaporization in TURBT or robotic cystectomy hold promise. Use of these innovations in clinical practice and evidence on their effectiveness from well-conducted RCT’s appear to be limited at this time. |
| How widely does care now vary? | Women with bladder cancer have worse survival than men, likely due to delays in diagnosis and consequent diagnosis at later stages.\(^{19}\) In one study of a university-affiliated managed care organization, women received fewer referrals to urologists for evaluation of hematuria than did men (28% versus 47%).\(^{20}\) These disparities may be due to higher rates of urinary tract infections (which may have similar symptoms as bladder cancer) and the lower incidence of bladder cancer in women. African Americans are more likely to be diagnosed with bladder cancer of higher grades and stages and have worse survival rates compared with whites.\(^{19,21}\) They are also less likely to undergo radical cystectomy for localized muscle-invasive bladder cancer. However, there is less information on disparities in care specifically for NMIBC. One study of early stage bladder cancer that used SEER-Medicare data from 1992 through 2002, found differences in initial treatment between African Americans and whites. African Americans were more likely to undergo restaging. |
resection (12% versus 6.5%) and urine cytology (37% versus 30%), and received fewer endoscopic examinations (4 versus 5). However, these differences “did not appear to be systematic and had unclear clinical significance”. There was no difference in “aggressive therapy” between African American and white patients.

- Intravesical chemotherapy to reduce risk of recurrence is underutilized, with analyses of claims data showing fewer than 5% of patients with NMIBC receiving an installation of intravesical chemotherapy after TURBT. Similarly, less than one third of patients with NMIBC receive induction courses of intravesical BCG according to NCCN guidelines, and fewer still receive maintenance BCG.

What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?

ClinicalTrials.gov
On October 3, 2016, we searched ClinicalTrials.gov using the search term “non-muscle invasive bladder cancer” and identified 88 studies, of which 72 studies (30 RCTs identified below in bold) were of known status and related to treatment of NMIBC. Results were available for 6 of these studies; however, in 4 of those studies no actual results were reported due to inadequate enrollment or inadequate outcome events.

- Thirty-two of these studies (14 RCTs) evaluate various agents for intravesical therapy for primary and/or recurrent NMIBC. Most are of induction therapy and a few are of maintenance therapy. Most are not restricted to patients with intermediate- and/or high-risk tumors. Studies include: NCT02371447, NCT02138734, NCT02891460, NCT01458847, NCT02316171, NCT02214602, NCT01314664, NCT01498172, NCT01469221, NCT01410565, NCT01438112, NCT00974818, NCT02808143, NCT02075060, NCT02365818, NCT01731652, NCT02720367, NCT00782587, NCT01475266, NCT02307487, NCT01803295, NCT01373398, NCT02716961, NCT02563561, NCT01310803, NCT01648010, NCT02202772, NCT02695771, NCT01162785, NCT01304173, NCT02311101, NCT00794950.

- An additional 10 studies (2 RCTs) evaluate various agents administered via other routes (oral, intravenous, intradermal, or percutaneous), including: NCT02343614, NCT02753309, NCT02605863, NCT02197897, NCT02657486, NCT01373294, NCT02792192, NCT02009332, NCT02010203, NCT02326168.

- Eleven studies evaluate treatments specifically for patients who have failed BCG therapy. Most (n = 8 [3 RCTs]) of these trials are of various intravesical treatments (NCT01625260, NCT02015104, NCT02773849, NCT01200992, NCT02449239, NCT02143804, NCT00406068, NCT01687244), while two trials are of intravenous agents (NCT02625961 [pembrolizumab] and NCT02451423 [an anti-PD-L1 antibody]) and one (NCT02844816) is of an orally-administered agent (atezolizumab).

- Studies also evaluate various other therapies and treatment approaches, including

PCORI Topic Brief: Treatment of Non-Muscle-Invasive Bladder Cancer
electromotive drug administration (3 RCTs) (NCT01149174, NCT01920269, NCT02202044, NCT01442519), hyperthermic chemotherapy (3 RCTs) (NCT02471495, NCT01094964, NCT02254915, NCT00384891), photodynamic therapy (NCT00322699), narrow band imaging (2 RCTs) (NCT01004211, NCT01180478). One study (NCT01166230) of fluorescent cystoscopy (n = 255) versus white light cystoscopy (n = 261) reported results and found improved recurrence-free survival for fluorescent cystoscopy (16.4 months versus 9.6 months).

- Three studies evaluate differences in quality of life related to treatment with different intravesical agents (NCT01697306 [RCT]) or possible benefits of interventions for reducing local side effects of BCG (1 RCT) (NCT02207608, NCT01939756). One of these studies (NCT02207608) reported results and found no effect of hyaluronic acid in reducing serious side effects.

- One study (NCT02070120 [RCT]) compares chemo-resection (i.e., not adjuvant therapy) with intravesical MMC versus surgical intervention (TURBT or ablation, according to local practice), and another study (NCT02113501) evaluates the effectiveness of treatment based on sub-staging with a 2nd TURBT after BCG induction therapy.

**Other databases**

- A search of the European Organisation for Research and Treatment of Cancer (EORTC) clinical trials database found 19 trials of treatments for NMIBC. The majority (n = 16) of these trials evaluate various intravesical agents and/or various doses or timings of treatment. Two studies are of chemo-resection and one is of treatment with YAG-laser versus TURBT.

| How likely it is that new CER on this topic would provide better information to guide clinical decision making? | It is very likely that a new CER on this topic would provide better information to guide clinical decision making. A recent systematic review and associated supplement identified numerous gaps and methodological limitations in the research related to various aspects of treatment for NMIBC. Many of the recent AUA/SUO guidelines are based on limited evidence (grade C). New research could provide a better evidence base particularly related to: the accuracy and value of formal risk-adapted approaches to treatment decisions; the comparative effectiveness of enhanced cystoscopy techniques such as fluorescent cystoscopy; the effectiveness of various treatments for persistent or recurrent disease after intravesical therapy with BCG or other agents; the comparative effectiveness of initial cystectomy in patients with high-risk NMIBC; and approaches for reducing discomfort and adverse effects associated with treatments for NMIBC. |
What are the facilitators and barriers that would affect the implementation of new findings in practice?

<table>
<thead>
<tr>
<th>FACILITATORS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• There exists considerable uncertainty about various aspects of treatment for patients with NMIBC and urologists are eager to have better evidence to guide treatment decisions.</td>
</tr>
<tr>
<td>• Groups such as the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) have a great interest in the topic and are active in synthesizing and disseminating research findings among urologists. The Bladder Cancer Advocacy Network (BCAN) also has a great interest in the topic and includes patient stakeholders.</td>
</tr>
<tr>
<td>• New treatments have historically faced difficulty in gaining FDA approval. A recent approval of a drug for treating metastatic bladder cancer (atezolizumab) may open doors for additional approval for treatment of NMIBC.</td>
</tr>
<tr>
<td>• Formal risk stratification tools would be clinically useful and potentially effective in refining treatment for improved outcomes.</td>
</tr>
<tr>
<td>• Patients would be interested in using interventions that have been shown to reduce the discomfort and/or adverse effects associated with treatments for NMIBC.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BARRIERS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The cost of newer techniques (e.g., enhanced cystoscopy, EMDA, HIVEC, PlasmaKinetic button vaporization, robotic cystectomy) or novel agents may be a barrier to their implementation. Cost-benefit analyses could be useful for guiding policies regarding certain treatments.</td>
</tr>
<tr>
<td>• New findings might provide evidence in support of particular treatment options (e.g., initial radical cystectomy over intravesical therapy) that could be less acceptable or attractive to patients. In such circumstances, it would be important to develop appropriate and effective tools for shared decision making.</td>
</tr>
</tbody>
</table>
### How likely is it that the results of new research on this topic would be implemented in practice right away?

- Results of new research that addresses limitations in the current evidence and clarifies some of the uncertainty around treatment questions for NMIBC are likely to be implemented in practice right away.
- Research that validates the accuracy and utility of formal risk-adapted approaches to treatment would likely be implemented right away.
- The best management of patients with intermediate- or high-risk NMIBC that have failed induction intravesical therapy with BCG remains uncertain. Results of new research that helps to clarify the comparative effectiveness of various chemotherapeutic, immunotherapeutic, and/or surgical treatments would likely be implemented in practice right away.
- Similarly, the results of CER examining initial cystectomy versus intravesical therapy in patients with high risk NMIBC would likely be implemented in practice right away.

### Would new information from CER on this topic remain current for several years?

- New information related to formal risk-adapted approaches and/or the influence of patient and tumor characteristics on the effectiveness of intravesical therapy would likely remain current for several years. This information would likely be adaptable and relevant for use with new chemotherapeutic or immunotherapeutic agents, and thereby remain current for years.
- Given the moderate number of ongoing clinical trials (and some comparative effectiveness studies) evaluating various intravesical agents for NMIBC, to remain current for several years it would be important for new CER of intravesical agents to anticipate and avoid possible overlap with current ongoing studies.
- Similarly, there are a number of ongoing trials of various types of enhanced cystoscopy, particularly of blue light cystoscopy, and efforts should be made avoid possible overlap with current ongoing studies.
- Well-done RCTs of initial cystectomy versus intravesical therapy in patients with high risk NMIBC would likely to remain current for several years.
- New information on methods to reduce discomfort and/or adverse effects of various treatments is likely to remain current for several years.

### Conclusions

- NMIBC is a common cancer for which there are a number of important research gaps that could be addressed in comparative effectiveness research.
- Research is needed to validate the accuracy and utility of risk-adapted approaches to treatment, understand optimal approaches to management of patients with intermediate- or high-risk NMIBC who fail BCG, and determine the role of cystectomy for high-risk or recurrent NMIBC, the effects of fluorescent cystoscopy on clinical outcomes, and the use of biomarkers to predict response to treatments.
- Research is needed to understand effects of management strategies for NMIBC on patient-centered outcomes such as quality of life and on methods for reducing adverse effects associated with intravesical therapy and cystectomy.
REFERENCES


Treatment for Chronic Insomnia: Topic Brief

June 13, 2017

“This document was prepared for informational purposes only and should not be construed as medical advice or used for clinical decision-making.”
I. Background

Insomnia is a common health problem in the United States; its prevalence varies based on the definition of insomnia used. Approximately one-third of adults suffer from occasional symptoms of insomnia—trouble falling asleep or staying asleep—each year.\(^1\) About 9 to 15 percent of adults experience insomnia that results in daytime consequences such as fatigue, sleepiness, irritability, and feelings of anxiety or depression.\(^2\) Finally, about 6 percent of adults experience chronic and persistent insomnia accompanied by daytime dysfunction that meets the diagnostic criteria for insomnia outlined in the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders.\(^3\)

The prevalence of insomnia symptoms increases with age and is higher among women. Approximately 50 percent of people over the age of 65 experience symptoms of insomnia, and women are 1.4 times more likely to suffer from insomnia than men.\(^4\) Insomnia is also more common among those with comorbid health conditions, including pulmonary disease, heart disease, and diabetes, and among those with mental health disorders, especially depression and anxiety.\(^5\)

Individuals with insomnia report trouble falling asleep (sleep onset insomnia), difficulty staying asleep (sleep maintenance insomnia), or waking too early (sleep maintenance insomnia). Sleep maintenance insomnia is particularly prevalent among older adults.\(^6\)

Given the functional, mood, and quality-of-life implications of insomnia, many patients who suffer from insomnia seek treatment. While many different treatments are available, prescription sleeping aids are widely used. A Centers for Disease Control and Prevention (CDC) report found that approximately 4 percent of U.S. adults aged 20 or older reported using prescription sleep aids in the past month. The percentage of adults using prescription sleep aids increases with age, and is higher among women and non-Hispanic whites.\(^7\)

The following brief explores the decisional dilemmas faced by clinicians and patients when choosing a treatment for chronic insomnia, the quality of evidence for each treatment, current clinical guidelines, and existing evidence gaps, in addition to some emerging issues regarding the comparative safety of various dosing regimens for pharmacologic treatment options.

II. Overview of Current Treatment Options and Evidence Base

In December 2015, the Agency for Healthcare Research and Quality (AHRQ) published a Comparative Effectiveness Review that explored the comparative effectiveness and harms of treatment options for the management of chronic insomnia. Per the review, current treatments for insomnia fall into three broad categories: pharmacologic, psychological, and complementary and alternative medicine (CAM).\(^8\) Methodological limitations to efficacy studies of CAM approaches yielded evidence that was insufficient for inclusion in the review. Accordingly, the review and this topic brief focus on pharmacologic and psychological interventions.
Psychological Interventions

Overview of Available Psychological Interventions

Psychological interventions for the treatment of insomnia include cognitive behavioral therapy that is tailored to the needs of those with insomnia (CBT-I), sleep restriction therapy aimed at improving sleep efficiency, stimulus control therapy that attempts to change behaviors associated with sleep and the sleep environment, and brief behavioral therapy (BBT) that combines elements of sleep restriction and stimulus control therapy.

Findings of the AHRQ Review: Psychological Interventions

The AHRQ review found moderate strength of evidence that CBT-I improves global and sleep outcomes compared to passive controls within the general adult population, and low-to-moderate strength of evidence for CBT-I compared to passive controls among older adults. In addition, multi-component behavioral therapy and BBT were found to improve several sleep outcomes in older adults, but the strength of this evidence was low given the small number of studies and the small sample sizes of existing studies. Evidence was insufficient to assess the adverse effects of psychological treatments.

Barriers to the Uptake of Psychological Interventions for Insomnia

In spite of evidence supporting the efficacy of psychological interventions to treat insomnia, especially CBT-I, few providers are currently trained in delivering CBT-I. Limited numbers of trained providers, the cost of treatment, and time necessary to seek face-to-face treatment all present barriers to the uptake of face-to-face CBT-I. In light of this, alternative methods of delivering CBT-I are being explored. Trials have indicated that computer and telephone delivery of CBT-I are efficacious and have suggested that they may be an alternative to face-to-face CBT-I.

| Table 1. Effects of Psychological Interventions for Insomnia in the General Adult Population and Among Older Adults, pooled results from RCTs |
|-----------------------------------|----------------|----------------|-----------------------------------|
|                                   | General Adult | Older Adults   |                                    |
|                                   | CBT-I         | CBT-I          | Multicomponent Behavioral or BBT   |
| Insomnia Severity Index*          | -5.15 [-7.13, -3.16]; Moderate SOE | -3.60 [-2.13, -5.07]; Low SOE | Insufficient                      |
| Sleep onset latency (minutes)     | -12.70 [-18.23, -7.18]; Moderate SOE | -9.98 [-16.48, -3.48]; Low SOE | -10.43 [-16.31, -4.55]; Low SOE |
| Total sleep time (minutes)        | 14.24 [2.08, 26.39]; Moderate SOE | NS; Low SOE | Insufficient                      |
| Wake time after sleep onset (minutes) | -22.33 [-37.44, -7.21]; Moderate SOE | -26.96 [-35.73, -18.19]; Moderate SOE | -14.90 [-22.66, -7.14]; Low SOE |
| Adverse Effects SOE               | Insufficient  | Insufficient   | Not Reported                      |

SOE = strength of evidence; NS = no statistically significant difference between groups


* The Insomnia Severity Index (ISI) is a global outcome measure assessing daytime functioning and sleep quality with a validated minimum clinical difference of 7 points. Other sleep measures do not have a validated minimum clinical difference.
Pharmacologic Interventions

Overview of Available Pharmacologic Interventions

Pharmacologic treatment options for insomnia include over-the-counter remedies containing diphenhydramine (a sedating antihistamine) or melatonin (a hormone), and prescription sleep aids. While many patients self-medicate with sleep aids containing diphenhydramine, there is little evidence that this is effective for the treatment of insomnia and it may cause sedation the next day due to its long half-life. While melatonin has been found to be safe for short-term use (three months or less), it has not been found to be effective for sleep onset insomnia (except in those who have a delayed sleep-wake phase syndrome) or in sleep maintenance insomnia. Given the limitations of over-the-counter treatments for insomnia, prescription sleep aids are widely used.

Numerous prescription sleep aids from an array of classes are approved by the FDA for the short-term treatment of insomnia (typically one month or less). These drugs include benzodiazepines (e.g., triazolam and temazepam), non-benzodiazepine hypnotics (e.g., zaleplon, zolpidem, and eszopiclone), ramelteon (a melatonin agonist), doxepin (an antidepressant), and suvorexant (an orexin receptor agonist).

<table>
<thead>
<tr>
<th>Class</th>
<th>Brand Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Halcion</td>
<td>triazolam</td>
</tr>
<tr>
<td></td>
<td>Restoril, Normison</td>
<td>temazepam</td>
</tr>
<tr>
<td>Nonbenzodiazepine</td>
<td>Sonata</td>
<td>zaleplon</td>
</tr>
<tr>
<td>Hypnotics</td>
<td>Ambien</td>
<td>zolpidem</td>
</tr>
<tr>
<td></td>
<td>Lunesta</td>
<td>eszopiclone</td>
</tr>
<tr>
<td>Melatonin agonists</td>
<td>Rozerem</td>
<td>ramelteon</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Sinequan</td>
<td>doxepin</td>
</tr>
<tr>
<td>Orexin receptor agonists</td>
<td>Belsomra</td>
<td>suvorexant</td>
</tr>
</tbody>
</table>

Typically, clinicians base the selection of a first-line drug on the type of insomnia that a patient presents with. For patients with difficulty falling asleep (sleep onset insomnia), a short-acting medication such as zolpidem, zaleplon, or ramelteon is often prescribed first. For patients who have trouble staying asleep or who wake early (sleep maintenance insomnia), a longer-acting medication such as extended release zolpidem, eszopiclone, suvorexant, or low-dose doxepin is frequently tried first.

Findings of the AHRQ Review: Pharmacologic Interventions

The December 2015 AHRQ report found that most trials comparing pharmacologic options for the treatment of insomnia were small, of short duration, and typically failed to establish or use minimum important differences to facilitate the interpretation of results. Data from benzodiazepine trials were insufficient to assess global outcomes, sleep outcomes, or adverse effects in either patients within the general adult population or among older adults. Ramelteon was not found to meaningfully improve global or sleep outcomes compared to placebo in the general adult population.
Low- to moderate-strength of evidence of efficacy for global and sleep outcomes in the general adult population was found for nonbenzodiazepine hypnotics compared to placebo, with greater improvements for eszopiclone and zolpidem than for zaleplon. Among older adults, eszopiclone improved one global outcome by a meaningfully important difference and improved several sleep outcomes, but did not improve sleep onset latency (low strength of evidence). In addition, zolpidem was shown to improve sleep onset latency in older adults (low strength of evidence).

Moderate strength of evidence was found for the improvement in global and sleep outcomes in patients within a combined general adult and older adult population taking suvorexant compared to placebo. Finally, within the general adult population there was low-strength of evidence that doxepin improved sleep outcomes compared to placebo; among older adults there was low- to moderate-strength evidence that doxepin improved sleep outcomes.

### Table 3. Effects of Pharmacologic Therapies for Insomnia in the General Adult Population, pooled results from RCTs

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Ramelteon, 4-16mg</th>
<th>Eszopiclone, 2-3mg</th>
<th>Zaleplon, 5-20mg</th>
<th>Zolpidem, 10-15mg</th>
<th>Suvorexant 15-20mg*</th>
<th>Doxepin 3mg or 6mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia Severity Index</td>
<td>Not reported</td>
<td>-4.6 [-5.3, -3.9]; Low SOE</td>
<td>Not reported</td>
<td>Not reported</td>
<td>-1.2 [-1.8, -0.6]; Moderate SOE</td>
<td>NR</td>
</tr>
<tr>
<td>Sleep onset latency (minutes)</td>
<td>-3.1 [-7.4, 1.2]; Low SOE</td>
<td>-19.1 [-24.1, -14.1]; Moderate SOE</td>
<td>10mg: -9.9 [-19.5, -0.4]; Insufficient</td>
<td>-15.0 [-22.1, -7.8]; Moderate SOE</td>
<td>-6.0 [-10.0, -1.9]; Moderate SOE</td>
<td>NR</td>
</tr>
<tr>
<td>Total sleep time (minutes)</td>
<td>0.1 [-10.0, 10.1]; Low SOE</td>
<td>44.8 [35.4, 54.2]; Moderate SOE</td>
<td>NS; Low SOE</td>
<td>23.0 [2.0, 43.9]; Moderate SOE</td>
<td>16.0 [4.7, 27.2]; Moderate SOE</td>
<td>3mg: 12 [CI NR]; 6mg: 17 [CI NR]; Low SOE</td>
</tr>
<tr>
<td>Wake time after sleep onset (minutes)</td>
<td>5.9 [-6.1 to 17.9]; Low SOE</td>
<td>-10.8 [-19.8, -1.70]; Low SOE</td>
<td>Not reported</td>
<td>Not reported</td>
<td>-4.7 [-8.9, -0.5]; Moderate SOE</td>
<td>3mg: -10 [CI NR]; 6mg: -14 [CI NR]; Low SOE</td>
</tr>
<tr>
<td>Study withdrawals due to adverse effects</td>
<td>RR 1.23 [0.47, 3.25]; Insufficient</td>
<td>RR 1.4 [0.97, 2.0]; Low SOE</td>
<td>RR 1.6 [0.7, 3.9]; Low SOE</td>
<td>RR 2.8 [1.2, 6.4]; Moderate SOE</td>
<td>RR 0.66 [0.31, 1.42]; Low SOE</td>
<td>RR 1.19 [0.36, 3.93]; Insufficient</td>
</tr>
</tbody>
</table>

SOE = strength of evidence; CI = confidence interval; NR = not reported; RR = relative risk; NS = no statistically significant difference between groups


*Data for suvorexant includes a mixed general and older adult population, with adults over the age of 65 taking the 15mg dose and adults under the age of 65 taking the 20mg dose.
Table 4. Effects of Pharmacologic Therapies for Insomnia in the Older Adult Population, pooled results from RCTs

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Eszopiclone, 2mg</th>
<th>Zolpidem, 5mg</th>
<th>Suvorexant, 15-20mg*</th>
<th>Doxepin, 1-6mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia Severity Index</td>
<td>-2.3 [-3.3, -1.3]; Low SOE</td>
<td>Not reported</td>
<td>-1.2 [-1.8, -0.6]; Moderate SOE</td>
<td>-1.7 [-2.6, -0.9]; Moderate SOE</td>
</tr>
<tr>
<td>Sleep onset latency (minutes)</td>
<td>-4.7 [-14.1, 4.7]; Insufficient</td>
<td>-18.3 [-31.5, -5.4]; Low SOE</td>
<td>-6.0 [-10.0, -1.9]; Moderate SOE</td>
<td>-14.7 [-24.0, -5.4]; Low SOE</td>
</tr>
<tr>
<td>Total sleep time (minutes)</td>
<td>30.0 [19.7, 40.3]; Low SOE</td>
<td>18.2 [-3.2, 39.6]; Insufficient</td>
<td>16.0 [4.7, 27.2]; Moderate SOE</td>
<td>23.9 [12.0, 35.7]; Moderate SOE</td>
</tr>
<tr>
<td>Wake time after sleep onset (minutes)</td>
<td>-21.6 [-29.6, -13.6]; Low SOE</td>
<td>Not reported</td>
<td>-4.7 [-8.9, -0.5]; Moderate SOE</td>
<td>-17.0 [-29.3, -4.7]; Low SOE</td>
</tr>
<tr>
<td>Study withdrawals due to adverse effect</td>
<td>RR 1.56 [0.69, 3.51]; Insufficient</td>
<td>RR 0.34 [0.07, 1.64]; Insufficient</td>
<td>RR 0.66 [0.31, 1.42]; Low SOE</td>
<td>RR 0.73 [0.20, 2.69]; Insufficient</td>
</tr>
</tbody>
</table>

SOE = strength of evidence; RR = relative risk


*Data for suvorexant includes a mixed general and older adult population, with adults over the age of 65 taking the 15mg dose and adults under the age of 65 taking the 20mg dose.

**FDA Drug Safety Warnings: Dosing of Nonbenzodiazepine Hypnotics**

In January 2013, after numerous reports of impairment in patients, especially women, the day after taking zolpidem and new data showing that blood levels of the drug remained high enough the next day to cause such impairment, the FDA released a safety announcement recommending that the initial dose of zolpidem be reduced from 10 mg to 5 mg for women taking an immediate-release version of the drug and from 12.5 mg to 6.25 mg for women taking an extended-release version of the drug. In May 2013, the FDA added a second warning that patients taking the extended-release version of zolpidem should not drive or engage in activities requiring “complete mental alertness” the day after taking the drug due to potential next-day impairment.

The following year, in May of 2014, the FDA issued a safety announcement regarding the dosing of eszopiclone, recommending that the initial dose be reduced to 1 mg for both men and women after the 3 mg dose was shown to cause impairment to driving ability, memory, and coordination that can last for more than 11 hours after taking the drug, regardless of gender, in a post-marketing study. The guidance allows the dose to be increased to 2 or 3 mg, as needed.

Notably, the efficacy studies upon which both zolpidem and eszopiclone were approved, and those studies included in the AHRQ review, included doses of 10 to 15 mg of zolpidem and the higher 2 to 3 mg doses of eszopiclone. In addition, the approved dose of suvorexant is 10 mg, but efficacy studies and those studies in the review looked at 15 to 20 mg doses. Little is currently known about the effectiveness of the now-approved, lower-dose versions of these drugs.
III. Current Guidelines

The 2016 American College of Physicians (ACP) guidelines on the treatment of chronic insomnia disorder in adults recommends CBT-I as the first-line therapy (strong recommendation; moderate strength of evidence).¹⁹ When deciding whether to prescribe short-term therapy with a sleep aid in patients who do not respond to CBT-I, the ACP guidelines recommend that clinicians discuss the benefits, harms, and costs of available pharmacologic options with these patients (weak recommendation; low strength of evidence). These guidelines stress that, while prescription sleep aids may improve short-term global and sleep outcomes, the long-term safety and effectiveness of these drugs are currently unknown and they should not be used for extended periods of time.

Accompanying these guidelines, the ACP released an evidence report on the available pharmacologic treatments for insomnia disorder. This report, consistent with the AHRQ report, found the greatest strength of evidence for improvements in global and sleep outcomes with the short-term use of eszopiclone, zolpidem, and suvorexant, but noting that the absolute effect sizes of trials included in the evidence report were small and that the strength of evidence for these drugs is low to moderate, at best.²⁰ In addition, the ACP again highlighted that data on the benefits and harms of these drugs for longer-term use are not available.

Recently released guidelines from the American Academy of Sleep Medicine also highlight the uncertainty of data available on the relative benefits and harms of prescription sleep aids in the treatment of chronic insomnia. While these guidelines recommend the use of a number of available pharmacologic options over no treatment, the strength of the recommendations are universally weak and the quality of evidence is very low to low for many of the drugs considered, including eszopiclone, zolpidem, and suvorexant.²¹

IV. Evidence Gaps and Research Areas of Interest

Unanswered questions regarding the comparative effectiveness of the available pharmacologic and psychological treatment options, and the relative risks and benefits of each treatment, make determining the best treatment a challenge for clinicians and patients.

While the AHRQ review synthesized evidence from a large number of trials, most of these studies included small sample sizes and were of a short duration. Many drug trials were excluded from the review as they were shorter than four weeks in duration, and those that were included were typically only four to six weeks long. Evidence on the safety and effectiveness of prescription sleep aids for long-term use is limited. Trials involving a treatment duration of one year or more and observational studies evaluating the long-term safety and effectiveness of these drugs are highlighted as a key gap in both the AHRQ review and the ACP guidelines.

In addition, there are very few head-to-head comparisons of drugs or comparisons of drugs to psychological interventions. Only four small trials included in the AHRQ review compared CBT-I to pharmacologic options (either nonbenzodiazepine hypnotics or benzodiazepines). The results of these trials were mixed and the data from them were insufficient to provide definitive conclusions. The lack of head-to-head drug comparisons and comparisons of drugs to psychological interventions is clearly an evidence gap.
The limited availability of providers who deliver face-to-face CBT-I, in addition to the cost associated with these services and the required investment of time, present barriers to the uptake of CBT-I. Larger, more robust trials demonstrating the effectiveness of alternative methods of delivering CBT-I (e.g., online or via telephone), especially head-to-head comparisons, are needed.

Moreover, the outcomes assessed by the trials included in the review highlighted a number of gaps. The drug trials included in the review did not typically include the function, mood, and quality-of-life outcomes that are important to patients. In addition, baseline data on sleep onset latency, total sleep time, time to waking after sleep onset, and sleep efficiency typically were not reported, making it difficult to interpret whether the drugs delivered clinically meaningful improvements.

Finally, the FDA’s decision to recommend reducing the starting dose of both zolpidem and eszopiclone raises questions about safe and appropriate dosages of these drugs. While a reduced starting dose may be safer and result in fewer next-day effects, robust data on the effectiveness of these drugs at their lower dosages are not currently available.

2 Ohayon MM, Epidemiology of insomnia: what we know and what we still need to learn. Sleep Medicine Reviews. 2002;6(2):97-111.
4 Ohayon MM, Epidemiology of insomnia: what we know and what we still need to learn. Sleep Medicine Reviews. 2002;6(2):97-111.


