Osteoporosis Treatment—What We Don’t Know

A “body of high-quality evidence” has established the general safety and effectiveness of osteoporosis drug therapy (ODT)—yet many people at high risk for fracture are not prescribed, or are not taking, or are not sticking with, the available drugs. Why?

A five-member panel of experts in primary care, geriatrics, and behavioral sciences, among others, convened by the National Institutes of Health (NIH), sought to answer that question. In the Pathways to Prevention Workshop: Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention, they discussed the available evidence on long-term drug therapies, in hopes of identifying research gaps and ways to “advance the field.” They then published a report summarizing their findings, along with recommendations for “new strengthened research.”

Trials have found that three to five years of ODT is safe and effective, the panel notes, and some ODTs reduce the incidence of nonvertebral fractures. However, those studies have been carried out mainly among white, postmenopausal women. Men, people of other races and ethnicities, residents in long-term care facilities, people with advanced and multiple comorbid conditions, and other populations are absent or under-represented. Thus, estimates regarding benefits and harm may differ in actual practice. Moreover, study results presented no data on non-fracture patient outcomes or sequelae, such as mobility, hospitalizations, and nursing-home placement. The studies also offered limited or no evidence on whether patient characteristics would result in different fracture outcomes.

In addition, few trials extended beyond five years, although some observational studies provided “limited evidence” on the potential benefits and harm of longer-term ODT use. Knowledge gaps exist on how to use information on bone biomarkers and other patient characteristics, such as concurrent medication use, which might modify ODT effects, the panelists concluded.

One of the main issues they investigated was how to ensure that people at the highest risk of fracture get the medicine they need. Only about one-third of women at high risk have reported receiving treatment with osteoporosis medication. And among older adults with a hip fracture, only 11% to 13% filled any prescription for osteoporosis medication within three months of the fracture.

Information on ODT use and adherence was not included in the systematic evidence review, however, so the report relies on material provided by the workshop speakers, who say that the low rates of diagnosis and treatment likely stem from multiple clinician and patient factors. For instance, regarding clinicians, problems may include lack of time, knowledge gaps, and a lack of appropriate systems in primary care.

The panelists also cited another gap—in communications between clinicians about treatment as patients transition from one setting to another. One solution could be a hospital based fracture-liaison service to coordinate care, they suggest.

Among patients, factors include perceptions that osteoporosis is a normal part of aging, or that drugs don’t work or are harmful/risky. Studies on decision-making have found that people often overestimate their risk for rare adverse effects and underestimate their likelihood of having a fracture.

In their assessment of the studies, the panelists found that education-based interventions sometimes increase filled-prescription rates, but not adherence rates six or 10 months down the road. They also found that coaching and counseling have been “largely ineffective.”

“We need to identify the reasons why,” the panelists concluded, and made a number of recommendations on how the research should be done. For instance, they suggest using a broader array of trial designs, such as the innovative platform trials used in cancer research where the target of the investigation is the disease and not the drug. Studies should also focus on fracture sequelae, and include diverse populations that “more closely match” the characteristics of people who actually have fractures.

Gaps in knowledge about the uncommon side effects reported with bisphosphonates and other drugs indicate that questions to be answered include which class of drugs to use first, when to start treatment and how long it should last, and which doses are preferable.

Knowing how to treat can help clinicians and their patients decide whom to treat, the report suggests. Addressing the research gaps will improve the shared decision-making that is required to answer those questions.

Source: Annals of Internal Medicine, April 23, 2019

Navajo Nation, NIH Sign Data-Sharing Agreement

“The U.S. biomedical research community has traditionally been slow to involve American Indian and Alaska Native people in research in a way that respects their beliefs and customs or improves their health,” says NIH Principal Deputy Director Lawrence Tabak, DDS, PhD.

But a new data-sharing and use agreement between the Navajo Nation and NIH grantees of the Environmental influences on Child Health Outcomes (ECHO) program is aimed at changing that. The agreement, signed by the Navajo Nation, Johns Hopkins University, and RTI International, was created to respect Navajo Nation cultural beliefs, tribal sovereignty, and community values while sharing information from the Navajo Birth Cohort Study (NBCS). It’s the first tribal data-sharing agreement for a nationwide research consortium that is creating a large-scale database, NIH says. The agreement also “lays the groundwork for discussion with other tribal nations considering participation in biomedical research programs.”

The ECHO program, launched in 2016, consists of 71 observational studies, as well as a pediatric clinical trials network. Research focuses on five key pediatric outcomes with a high public health impact: pre-, peri-, and postnatal outcomes; upper
and lower airway health; obesity; neurodevelopment; and positive health, such as happiness and a sense of well-being. The agreement enables NBCS to continue as part of ECHO and individual participant data to be shared with consortium members; but it does not cover genetic data or the sharing of biospecimens.

For instance, NBCS, with the University of New Mexico, is investigating the effects of environmental exposure to uranium and other toxicants on pregnancy outcomes and child development. Navajo Nation President Jonathan Nez says the data sharing will “benefit our Navajo people and allow us to further understand the relationship between uranium exposure, birth effects, and childhood development.”

Source: NIH, May 7, 2019

Emergency Protocol Improves Survival After Severe Head Injury

Preventing low oxygen, low blood pressure, and hyperventilation in people with head injury has been shown to improve survival rates, according to observational studies. The guidelines for prehospital management of traumatic brain injury (TBI), developed in 2000, were updated in 2007 to reflect those findings. But are they being followed? And, if they are being followed, do they help?

The Excellence in Prehospital Injury Care (EPIC) study—the first time the guidelines were assessed in real-world conditions—trained emergency medical service (EMS) responders in Arizona and compared patient outcomes before and after implementation of the guidelines.

The researchers found “a therapeutic sweet spot” in that the guidelines had an “enormous impact” on people with severe TBI. Implementing them did not affect overall survival of the entire group, which included more than 21,000 patients with moderate, severe, and critical injuries. However, further analysis showed that the guidelines helped double the survival rate of people with severe TBI, and tripled the survival rate in patients with severe TBI who needed to have a breathing tube inserted by EMS personnel.

Daniel Spaite, MD, who led the study, said that patients with moderate injuries would most likely have survived anyway; but before the guideline implementation, those in critical condition may have had injuries too serious to overcome.

The guidelines were also associated with an overall increase in survival to hospital admission.

According to Bentley Bobrow, MD, co-principal investigator, “It was exciting to see such dramatic outcomes resulting from a simple two-hour training session with EMS personnel.”

The study “demonstrates the significance of conducting studies in real-world settings and brings a strong evidence base to the guidelines,” said Patrick Belligowan, PhD, program director at the National Institute of Neurological Disorders and Stroke, which supported the study. “It suggests we can systematically increase the chances of saving the lives of thousands of people who suffer severe traumatic brain injuries.”

Source: NIH, May 8, 2019

Interprofessional Medication Review Works Better With ‘Collegial Mentoring’

Nursing-home patients take, on average, eight different drugs every day and two drugs on demand. But often, they are prescribed those drugs without a proper clinical evaluation, and dementia reduces their ability to report effects and side effects, say researchers from the University of Bergen in Norway.

Various trials of medication reviews have shown that it is possible to reduce the number of drugs without detriment to the patient’s health. But interventions that rely on multiple components (e.g., electronic prescribing aids and explicit prescribing criteria) might fail simply because they have too many elements to implement cohesively, say the researchers. To ensure that complex interventions are successful and sustainable over time, they add, different approaches have to be combined. Their solution: incorporating clinical assessment using tools that have been validated for people with dementia, and testing to ascertain whether the intervention was carried out successfully.

The study strategy involved an interprofessional medication review based on a systematic clinical evaluation of the patient and the collegial mentoring of the nursing-home team. The researchers included data from 297 patients in 36 Norwegian nursing-home units in COSMOS, a nine-month multicenter trial testing a five-part approach: Communication, Systematic pain assessment and treatment, Medication review, Organization of activities, and Safety.

The implementation began with a two-day seminar for managers, nurses, physicians, and pharmacists, with the prerequisite that at least two nurses (“COSMOS ambassadors”) from each unit participate. The seminar consisted of four hours of lectures, role-playing, and problem-solving, with discussions on such topics as pharmacodynamics and pharmacokinetics, multimorbidity, clinical challenges, and drug–drug interactions. The COSMOS ambassadors, in turn, trained other staff in short sessions.

Next, the researchers trained the nursing-home staff in assessing pain, neuropsychiatric symptoms, cognition, daily functioning, and quality of life for each patient. The nursing-home physician, nurses, and researchers performed medication reviews, using the results from clinical assessments to guide prescription evaluations. Each patient’s condition was discussed in detail.

After two months, the nursing-home staff were gathered for a midway evaluation to discuss promoters of and barriers to implementation, giving them an opportunity to share their experiences and learn from each other.
The ambassadors were supported by twice-monthly telephone calls from the researchers, who gave advice on overcoming barriers. For instance, they recommended that if a drug had to be stopped, staff members should use the word “pause.” This would ensure that the patient had to be re-evaluated after cessation, and that both patient and relatives would be less likely to interpret the change as a denial of treatment.

All units in the intervention group participated, with an average of three participants per unit. (No pharmacists participated, the researchers say; in-house pharmacists are seldom available in Norwegian nursing homes.) However, only seven of the 21 physicians attended, with the remainder citing a lack of time or lack of relevance. Also, the doctors depended on the nurses to attend the medication reviews, said the researchers, as they had varying degrees of knowledge about electronic records and some found it difficult to alter prescriptions.

After four months, 92% of the patients had had a medication review. Changes in health were documented for 77%, and 30% were put back on a prescribed drug that had previously been stopped.

Participants reported barriers such as a lack of time and ethical dilemmas. In general, nursing staff described improved communication, and particularly that the interprofessional discussions helped facilitate difficult decisions, such as those relating to treatment levels. The nurses’ observations “influenced the prescribing routines positively,” say the researchers. Overall, physicians were receptive and the collegial monitoring was mostly viewed as positive.

Source: BMC Geriatrics, May 7, 2019

**VA vs. HCV: Making a Deadly Disease a Memory**

The Veterans’ Administration (VA) is “within striking distance” of eliminating the hepatitis C virus (HCV) in all veterans who are “willing and able to be treated.” The expectation is that all eligible veterans will be cured by late 2019.

“This is terrific news,” said VA Secretary Robert Wilkie, noting that the VA is the largest single provider of HCV care in the U.S. “Diagnosing, treating, and curing HCV infection among veterans has been a significant priority for the VA.”

According to the Review of Hepatitis C Virus Care Within the Veterans Health Administration, published last month by the VA Office of Inspector General (OIG), the VA cares for more than 180,000 confirmed patients who are disproportionately affected by HCV infection at rates about three times the national average.

As of March 2019, approximately 116,000 veterans had started taking all-oral hepatitis C medications. Almost 100,000 patients have completed treatment and are now cured. That’s a very different story from one reported several years ago, when HCV treatment was out of reach for the tens of thousands of service members who were seriously ill with HCV, most of whom had contracted it through blood transfusions during the Vietnam War.

The good news is due largely to highly effective direct-acting antivirals (DAAs), which have revolutionized HCV treatment. Before 2014, HCV treatment required weekly interferon injections for up to a year, with low cure rates (35–55%) and significant physical and psychiatric side effects, which frequently led to early discontinuation. Of approximately 180,000 veterans in VA care at that time with chronic HCV infection, only 12,000 had been treated and cured. More than 30,000 of them had advanced liver disease.

In 2014, the VA launched an “aggressive program” to identify all undiagnosed veterans with HCV, link them to care, and offer them treatment with the new medications: sofosbuvir (Sovaldi) and simeprevir (Olysio). Both have few side effects and can be administered once daily for as little as eight weeks.

However, the drugs were incredibly expensive, prohibitively so for many people. Sofosbuvir, for example, cost $1,000 per pill. But the VA, who are allowed by law to negotiate prices, brought the cost down. The agency estimated that the drugs would cost roughly $750 million and provide almost 60,000 treatments during 2017 to 2018, at about $25,300 per veteran.

The VA then began treating close to 2,000 veterans with HCV every week—almost one treatment per minute every workday. By the following year, the overall death rate had dropped dramatically. Veterans cured of HCV were also 84% less likely to develop liver cancer.

Still, some patients have been left out. The OIG conducted a study to assess (among other things) why some patients with chronic HCV infection were not treated with DAAs. Acceptable reasons included pregnancy, being in hospice or palliative care, possible drug interactions with current medications, a diagnosis of liver cancer, and adherence challenges (e.g., being homeless). Unacceptable reasons included HIV co-infection and prior treatment failure with DAAs.

The decision to disqualify patients from HCV treatment must be made on a case-by-case basis by individual providers in consultation with their patients, the OIG says. Patients who are deferred for treatment based on “problematic levels of alcohol or substance use” should be referred for substance-use treatment and must have a plan for re-evaluation for hepatitis-C treatment within three to six months. However, the VA notes that patients with drug or alcohol addiction “should not be automatically excluded from hepatitis-C treatment.”

The VA says it is on track to treat more than 125,000 veterans with HCV by October of this year. As of March, fewer than 27,000 veterans remained to be treated.

Sources: VAntage Point, May 14, 2019; Forbes, March 1, 2018

**Anti-BTK Drug Helps Prevent MS Relapse**

Results from a phase 2 study in patients with relapsing multiple sclerosis (MS) show that 79% remained relapse-free during 48 weeks of treatment with evobrutinib.

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Evobrutinib is designed to inhibit primary B-cell responses such as proliferation and antibody and cytokine release, without directly affecting T cells. Bruton’s tyrosine kinase (BTK) inhibition is thought to suppress autoantibody-producing cells, which may be useful in some autoimmune diseases such as MS, rheumatoid arthritis, and systemic lupus erythematosus. The researchers say evobrutinib is the first BTK inhibitor to demonstrate clinical proof of concept in MS.

The initial analysis at 24 weeks found that evobrutinib 75 mg reduced the total cumulative number of TI gadolinium-enhancing lesions compared with placebo. By week 12, researchers were observing “rapid reductions.” The new data show that results were maintained through 48 weeks at 75 mg QD and 75 mg b.i.d.

The majority of 267 patients (85%) completed the 52 weeks of treatment. No new safety signals were identified, and no treatment-associated infections, infestations, or lymphopenia were observed over 52 weeks. The most common treatment-related effects were nasopharyngitis and increased liver aminotransferase values: 5.7% of the 25-mg QD group, 3.8% of the 75-mg QD group, and 13% of the 75-mg b.i.d. group moved from baseline to grade 2 or higher in alanine transaminase. In the placebo group, that number was 7.5% over 24 weeks. All effects were reversible on treatment discontinuation with no clinical consequences.

Sources: PR Newswire and The New England Journal of Medicine, May 10, 2019