Can We Pave the Pathway to Fracture Prevention?

Clinicians and patients face many challenges regarding the optimal duration of osteoporosis drug treatment (ODT) and the appropriate role of drug "holidays." The National Institutes of Health Pathways to Prevention Workshop "Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention" took place on 30 and 31 October 2018 and is summarized by Siu and colleagues in this issue (1). The associated systematic literature review by Fink and colleagues is also in this issue (2). The workshop identified important gaps in our understanding of the long-term treatment of osteoporosis, where "long-term" was defined as longer than 3 years. The systematic review focused on men and postmenopausal women aged 50 years or older.

Let us consider some key clinical questions. First, does long-term continuation of ODT enhance the efficacy of fracture prevention? In treatment-naive women who have received zoledronic acid or alendronate for 3 to 5 years, continuation for an additional 3 to 5 years decreased some vertebral fracture outcomes but not others and did not reduce nonvertebral fractures. We cannot counsel patients that long-term continuation decreases hip fracture risk. Second, how common are atypical femoral fractures (AFFs), which are serious adverse effects of long-term antiresorptive therapy, and do they vary by medication or medication class? The review (2) estimates that for every 1000 women with osteoporosis who are treated with alendronate for 4 years or zoledronic acid for 6 years (vs. placebo), 50 to 70 will avoid a clinical fracture at the cost of an additional 2 having a subtrochanteric or femoral shaft fracture. Similar estimates are not available for denosumab. However, because of inconsistent data—often derived from observational studies that may have methodological shortcomings—and because not all subtrochanteric or femoral shaft fractures that are reported will be confirmed to be AFF, the true ratio of vertebral fracture benefit to AFF harm may be markedly larger or smaller than this estimate. Third, can a drug holiday avert serious adverse effects of the medications without unduly increasing fracture risk? In a trial of zoledronic acid administered for 3 years to postmenopausal women with osteoporosis, continuation for 3 more years (vs. discontinuation) did not lower risk for nonvertebral or clinical vertebral fractures but halved risk for radiographic vertebral fractures (3). In 2 trials of alendronate, which was initially administered for 5 years to postmenopausal women, nonvertebral fractures were not reduced after continuation for 5 more years versus discontinuation, although continuation reduced clinical vertebral fractures in one of the trials (which included postmenopausal women with either osteopenia or osteoporosis) (4).

This review (2) provides insight into what approaches are *not* effective. Long-term treatment with alendronate (vs. placebo) did not reduce clinical fractures in women with osteopenia. Raloxifene does not reduce hip fracture risk, and it increases risk for venous thromboembolism (5). Patients receiving denosumab should not have drug holidays. In the FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months) trial of long-term denosumab therapy (6), patients who discontinued therapy had an increased rate of vertebral fracture after discontinuation, similar to the rate seen in participants who never received denosumab. So, should clinicians replace denosumab with a bisphosphonate, or should they continue denosumab in perpetuity, essentially framing osteoporosis as a chronic medical condition similar to hypertension? The challenge with the former approach is that the patients who receive denosumab have probably already declined bisphosphonates, and they may be averse to initiating bisphosphonate therapy at the time of denosumab withdrawal. The challenge with the latter approach is that AFFs are duration-dependent, and risks and benefits of "permanent" denosumab therapy are unknown.

The workshop summary (1) mentions that inadequate time is likely the biggest contributing factor to the lack of attention primary care physicians give to osteoporosis. However, although not proven, lack of knowledge among physicians about the absolute risks for osteonecrosis of the jaw and AFFs probably also leads to patient misperceptions. Such misperceptions exist regarding ineffectiveness and adverse effects of ODT (7).

Important special populations require study. Most participants in osteoporosis clinical trials were white postmenopausal women, and risks and benefits of ODT are unclear among minority populations and women aged 80 years or older. It is also unclear how clinicians should approach shared decision making for women with multiple comorbid conditions, who may be at especially high fracture risk. Although observational studies suggest that risk for incident AFF decreases after initiation of drug holidays, clinical trials on this topic are lacking. The information we have about long-term risks and benefits is often available only for some therapies that are approved by the U.S. Food and Drug Administration.

Why should clinicians care about the research gaps highlighted in the workshop? If studies do not use a standardized definition of AFF, or if clinical trials have insufficient numbers of participants to determine the true risk for AFF of the medications, clinicians cannot engage in shared decision making with patients to balance risks and benefits. Because we have only the few trials mentioned here regarding drug holidays, we cannot determine how long a bisphosphonate drug holiday should last. Should it last 2 years? The National Institutes of Health should support research to answer these high-impact clinical questions, in addition to encouraging approaches for clinicians to determine which

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individual patients are at greater risk for harms related to long-term bisphosphonate use. The need to rigorously study patient preferences in the context of ODT is pressing because of the complex dosing instructions of oral bisphosphonates and the dramatic underutilization of ODT among persons who have already had a vertebral or hip fracture (8, 9).

In conclusion, the good news is that in treatment-naive, postmenopausal women, long-term alendronate (4 years) and zoledronic acid (6 years) each reduced nonvertebral fractures more than they increased absolute risk for AFF and osteonecrosis of the jaw. However, important research gaps exist. Clinical trial data are insufficient to inform clinicians about who should be considered for drug holidays, when drug holidays should be initiated, how long they should last, and how patients should be monitored during drug holidays.

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