National Institutes of Health Pathways to Prevention Workshop: Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention

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Introduction

Advances in the biology of osteoporosis resulted in osteoporosis drug therapies (ODT). However, concerns about their safety have coincided with a decrease in their use and a leveling off in the incidence of osteoporotic fractures. (1, 2)

Osteoporosis is a skeletal disorder that compromises bone strength (3) and increases the likelihood of fractures. It is diagnosed using a standardized T-score measure for bone mineral density (BMD) (T-scores ≤ -2.5 indicate disease, while T-scores from -1.0 to -2.49 indicate low bone mass). (4) Among U.S. adults age >50, 8 million women and 2 million men have osteoporosis, (4) and 27 million women and 16 million men have low bone mass. (4) It is

estimated that by 2025, five fractures will occur for every 100 people age >65, and total U.S. health care costs attributable to fractures will reach $25 billion annually. (5)

Getting adequate nutrition and regular exercise, quitting tobacco use, limiting alcohol use, and preventing falls help reduce a person's risk of osteoporotic fractures. Further, pharmacologic treatments may be prescribed to prevent fractures for people who have very low BMD or a prior fragility fracture, and the U.S. Food and Drug Administration has approved anti-resorptives that inhibit bone loss and anabolics that stimulate bone formation. Nevertheless, many people at high fracture risk are untreated. Less than 20% of women received osteoporosis treatment in the year following diagnosis of an initial fragility fracture, and compliance rates are low. (5)

On October 30 and 31, 2018, the National Institutes of Health (NIH) convened the Pathways to Prevention (P2P) Workshop: Appropriate Use of Drug Therapies for Osteoporotic Fracture Prevention to assess the available scientific evidence to better understand the clinical benefits and harms of ODTs. The workshop brought together osteoporosis experts and was co-sponsored by the NIH Office of Disease Prevention (ODP), the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Institute on Aging. The ODP commissioned a systematic evidence review on long-term ODT use and fractures. Speakers were invited to present evidence. Intermediate outcomes, such as BMD, and the more established side effects and adverse outcomes were not the major focus. To complement the review, this report relied on other systematic reviews and studies presented by speakers.

Evidence Regarding Benefits and Harms of Long-Term ODTs

Although varied in treatment regimens and outcomes assessment, trials have shown the effectiveness of several ODTs (selected bisphosphonates, estrogen, raloxifene, denosumab, and teriparatide) in reducing the incidence of vertebral fractures in postmenopausal white women. (6) A smaller number of studies (7–9) have shown that some ODTs reduce the incidence of non-vertebral, including hip, fractures. Notably, the workshop and trials provided no

information on non-fracture patient outcomes of interest or sequelae of fractures, such as functional status, mobility, hospitalizations, and nursing home placement. There was limited or no evidence on effect modification for fracture outcomes with these treatments, as individual studies were poorly powered to detect changes in effect estimates by tested factors or to protect against Type I error rates in post hoc analyses.

Many of the side effects and possible adverse outcomes associated with ODT are documented elsewhere. The workshop and this report focused on the uncommon and serious complications thought to be specific to selected anti-resorptives—atypical femoral fractures (AFFs) and osteonecrosis of the jaw (ONJ). These complications have been the subject of advisories from regulators and professional societies. Evidence of the incidence of these complications is limited due to their infrequency and lack of studies designed to systematically identify and ascertain these adverse events. These events have been variably defined; some studies report (10) on subtrochanteric and femoral shaft fractures that may not have had all the radiographic characteristics of AFFs.

For different classes of ODTs, evidence from trials is nonexistent or limited on AFF and ONJ. The best available data, despite their limitations, comes from observational studies and postmarket surveillance. This work suggests that the age-adjusted incidence rates for AFFs were 1.78/100,000/year (95% confidence interval [CI], 1.5-2.0) with bisphosphonate exposure of 0.1 to 1.9 years, and increased to 113.1/100,000/year (95% CI, 69.3-156.8) with bisphoshonate exposure of 8 to 9.9 years. (11) For ONJ, the incidence is between 1 to 69 per 100,000 patient years for oral bisphoshonates and 0 to 90 per 100,000 patient years for IV bisphoshonates. (These incidence rates are marginally higher than in the general patient population.) (6, 9, 10, 12) Moreover, there were few cases of ONJ and AFF in the FREEDOM trial of denosumab during the main trial and the extension. (13, 14)

Apart from AFF and ONJ, the harms of estrogen and estrogen+progestin treatment should be considered (strokes, invasive breast cancer, pulmonary embolism, and dementia) as

they exceed benefits in postmenopausal women. Effect modification suggested short-term use of estrogen to reduce the risk of fractures remains in consideration for younger women who had a hysterectomy or those with postmenopausal symptoms. The American College of Obstetricians and Gynecologists has listed several contraindications for the use of estrogens for osteoporosis. (8)

Anabolic agents are limited to a 2-year lifetime exposure and have a black box warning, thus, cannot be considered for long-term use.

Current Gaps in Knowledge. Notably, in the case of both benefits and harms, trials provide evidence mainly for white postmenopausal women, while other populations (e.g., men, spectrum of race and ethnicities, residents in facilities, and people with advanced and multiple comorbid conditions) were absent or underrepresented. Evidence for ODTs is lacking for people who meet neither BMD nor fracture criteria for osteoporosis but are at high risk due to other health, genetic, or medication use factors. Given that trial subjects did not represent the true potential patient population, estimates on benefits and harms may differ in actual practice.

Few trials extended beyond 5 years, but a few observational studies provided limited evidence on potential benefits and harms from longer-term use. (6, 7) Evidence is lacking for non-fracture patient outcomes and fracture sequelae that patients may prioritize when making treatment decisions. Gaps exist in how to use information on bone biomarkers and other patient risk factors that modulate the effects of ODT on the risk of fractures and their sequelae.

Inability to rigorously estimate effect modification for subpopulations was in part due to limitations in trial designs. Although there have been many participants in ODT trials, analyses pooling patient-level data are limited to initial work on bone turnover markers. This approach would be potentially useful for addressing some of the gaps in knowledge of effect modification by increasing power.

Drug Holidays

Uncertainty regarding the long-term effects of ODTs has led to proposals for periods of medication discontinuation, or "drug holidays," as a means of minimizing potential harms. Drug holidays for bisphosphonates are of interest, as evidence suggests that accumulation of bisphosphonates in bone may impede normal remodeling and repair and potentially predispose to ONJ and AFF. Similar concerns exist for denosumab.

Bisphosphonate Drug Holidays. Evidence gaps limit evaluation of potential harms and benefits of drug holidays for anti-resorptive medications. The evidence comes from a limited number of efficacy trials and their extensions. Findings suggest that bisphosphonate discontinuation is associated with greater risk of some incident fractures and decrease in BMD. Discontinuation of alendronate for 5 years was associated with greater risk of incident vertebral fracture but not non-vertebral or hip fracture. (15) Similarly, discontinuation of zoledronate was associated with approximately 50% greater risk of vertebral fracture. (16) For both alendronate and zoledronate, discontinuation was associated with greater decreases in BMD compared to continued use. (15–17)

There is insufficient evidence from trials to determine whether bisphosphonate drug holidays reduce risk of rare events of ONJ, AFF, or other adverse events. Observational studies suggest that risk of incident AFF may decrease dramatically after initiation of drug holidays. (18, 19)

In addition, studies generally had insufficient or low strength evidence to assess effect modification by patient or clinical characteristics for drug holidays.

Drug Holidays for Other Medications. In the FREEDOM trial of long-term denosumab, patients who discontinued denosumab treatment after at least 1 year had a rapidly increased rate of vertebral fracture after discontinuation, (20) similar to the rate among those who never took denosumab. There is insufficient evidence to compare the effects of denosumab drug holidays following different treatment durations. The reduced risk of AFF or ONJ following denosumab discontinuation is also unclear.

Long-term anabolic treatment of osteoporosis is not advised, so discontinuation after long-term use cannot be evaluated. The evidence suggests that the benefits of anabolic medications, denosumab, and SERMs are quickly lost following discontinuation. (21–23)

Current Gaps in Knowledge. Few evidence-based guidelines exist to determine who should be considered for drug holidays, when to initiate them, the optimal duration, or the appropriate management of patients on drug holiday. This is due to insufficient empirical evidence on which to base such recommendations.

Research is needed on identifying patients at greatest risk of harms with long-term bisphosphonate use. A validated risk profile, including patient characteristics and treatment preferences in combination with clinical factors, is needed. There is also a need for improved understanding of pathogenesis underlying risk and the role of hip geometry and genetics in the risk of serious adverse events.

There is a need to determine the optimal initiation, duration, and other conditions of drug holidays. While drug discontinuation is commonly a conscious decision made by patients and providers based on clinical information, most evidence regarding drug holidays comes from clinical trials, where discontinuation occurred at arbitrary time points. Further, the relevant period during which risk of AFF or ONJ might increase under bisphosphonates is unclear, and the appropriate timing and optimal duration of drug holidays is unknown. Without comparative evidence for alternative drug holiday durations, it is unclear whether increased risk of fractures would continue over longer periods of discontinuation, how long benefits of bisphosphonate use might persist, or at what point the risk of harms might be minimized.

Sequencing or combining different classes of medications is a variation on drug holidays, by shortening exposure to bisphosphonates and thus lessening potential harms; however, limited evidence exists on appropriate use of other medications, such as anabolic therapy, to complement bisphosphonate treatments. For instance, it is unclear whether treatment with anabolic drugs would be a more effective or safer alternative to bisphosphonate

discontinuation. Similarly, the evidence is limited on the effectiveness of different sequencing of osteoporosis medications (e.g., anabolics preceding anti-resorptives) or their use in combination (e.g., adding anabolics to bisphosphonates).

Patient and Clinician Barriers to Care

To the extent that effective drug therapies exist, they are only successful when the appropriate people use them. In the case of osteoporosis, many people at risk for future fractures go undiagnosed. Among those diagnosed with osteoporosis and prescribed medication, only about 50% fill their prescriptions even when medications are at no cost. (24) Of those filling their prescriptions, only about 50% continue taking medication 3 months later. (25) Information about ODT use and adherence was not included in the SER, so this report relied on material provided by workshop speakers.

Clinician factors. Low rates of diagnosis and treatment may stem from multiple clinician and patient factors. For the clinician, workshop speakers discussed problems with time, knowledge gaps, and appropriate systems in primary care. Inadequate time is most likely the biggest contributing factor to the lack of attention to osteoporosis among primary care physicians. (26) Workshop speakers discussed how knowledge gaps may exist, but particularly about osteoporosis risk in relatively younger adults. In addition, communication lapses about osteoporosis treatment between clinicians may occur as patients transition from one setting to another after hospitalization. An innovative model of care suggests that the use of a hospital-based fracture liaison service (FLS) to coordinate care after a fall improves communication and would result in improved rates of osteoporosis testing, treatment, and prevention of future fractures. (27)

Patient factors. Patient factors include perceptions that osteoporosis is a normative consequence of aging, perceived drug ineffectiveness, side effects, complex dosing regimens, medication cost, and poor education and health literacy. (28, 29) Education-based interventions

sometimes increase rates of medication prescriptions being filled, but not medication adherence 6 or 10 months later. (30) Coaching, counseling, or educational interventions have been largely ineffective; (31) the more effective FLS and pharmacist-based interventions produce modest effects. (32)

Patients often perceive medication risks as outweighing any possible benefits, particularly for the rare but severe side effects of bisphosphonates, including ONJ and AFF. (33) In the decision-making literature, researchers find that people often overestimate the risks of medication side effects, and have a tendency to display an optimistic bias about the likelihood of experiencing negative effects from an untreated disease. (34)

Current Gaps in Knowledge. We know little about how to increase diagnosis and long-term medication adherence in osteoporosis. The few successful interventions have yielded only modest outcomes***.*** Time constraints for primary care physicians point to the need to develop new models for preventive care. Models exist, but more research is needed regarding their effectiveness. In addition, research is needed that ties the efficacy of ODT, currently assessed by fracture, to outcomes most valued by patients, such as change in functional status, hospital stays, and pain. Finally, more research is needed in factors necessary for effective shared decision-making processes between patients and clinicians.

Conclusions/Future Research Needs and Priorities

A body of evidence primarily in postmenopausal white women has established the general safety and effectiveness of ODT. Yet, this body of evidence has many gaps for guiding their duration of use for treatment and management decisions. Questions remain as to who specifically should be treated, when treatment should be initiated, what medication should be started, how long treatment should be maintained, how treatment should be monitored, and in what order treatments should be used. Answers to these questions are needed to realize the population benefits from ODT.

Who should be treated is hampered by gaps in the understanding of effect modification of the treatment benefits and harms, as well as by limits in homogeneity of patients included in trials and studies. Gaps in our understanding of the uncommon side effects reported with bisphosphonates leave questions about which class of drugs should be used initially, when treatment should be started, how long they should be continued, whether treatment interruptions would be beneficial, whether lower doses might be preferable, and whether sequencing drugs would be beneficial. Finally, questions exist on how best to implement many of these interventions in our complex health systems, taking into account patient and provider considerations affecting medication initiation and its continuation, especially in multimorbid adults and those in residential care.

Decisions about whether to prescribe ODTs will likely involve shared decision-making, and the balance of risks and benefits will vary by patient. Ideally, balancing risks and benefits would include estimates, not only of fracture rates, but also of future function, mobility, and other outcomes important to patients. The benefits relative to risks may differ in the setting of a recent fracture as opposed to primary prevention in a patient with no previous fracture. For some patients, the balance of benefits and risks will be favorable and many of those patients may opt for treatment. Some patients may weigh risks of harms more heavily and may choose to decline or defer treatment. In either case, the information used in shared decision-making can be better informed by additional research addressing some of the research gaps noted above. This is reflected in our recommendations.

Recommendations (also see Table 1)

For existing and possible new treatments to optimize treatment duration, new research should make use of innovative research designs and approaches, including modeling studies. Trials designed for drug approval and efficacy have yet to take advantage of preference designs, sequential intervention designs, adaptive trial methodology, or innovative platform trials

as used in cancer research, where the target of investigation is the disease and not the drug; endpoints should include fracture sequelae. Observational studies have yet to apply causal inference methods and include fracture sequelae. Studies should include diverse populations that more closely match the characteristics of people experiencing osteoporotic fractures—including men, the spectrum of races and ethnicity, people with multiple comorbidities taking multiple medications, people in a variety of residential settings, and those with high fracture risk who do not meet criteria for osteoporosis. These trials should specify possible effect modifiers *a priori*. Future trials of new agents estimating efficacy should measure uncommon side effects of bisphosphonates and denosumab.

Concerns about AFF and ONJ may contribute to decisions about initiating and continuing treatment with bisphosphonates, and research should prioritize these complications. Studies should employ standard case definitions for these complications and should estimate their incidence using specified methods for ascertainment and follow-up. Studies are needed on incidence by ethnicity, characterization of these complications, pathogenesis, risk factors and algorithms to predict risk, early detection, interventions to reduce their incidence (e.g., improved oral hygiene), and their management if complications occur. Improving understanding and management of these complications could potentially mitigate an important barrier to bisphosphonate or denosumab use.

Drug holidays and sequential therapies were suggested to reduce the incidence of these complications. Research should determine who is at greatest risk for adverse outcomes associated with long-term ODT, including but not limited to AFF and ONJ. Risks of harms should be considered along with the risk of osteoporotic fracture and patient preferences when deciding who may benefit from a drug holiday and who should continue medication use.

Consideration needs to be given to how drug holidays are implemented, including drug- and patient-specific determination of optimal timing, duration of holiday, and follow-up. Study of the efficacy of lower dose bisphosphonate treatment to delay or prevent the need for drug

holidays is warranted. Given the limitations of randomized controlled studies to evaluate these questions, alternative study designs and existing data capturing the naturalistic discontinuation of ODT initiated by patients and providers, rather than discontinuation at arbitrary time points, should be used. Development of a consensus definition of “drug holiday” will aid in the collection of data and allow standardization in the evaluation of drug holiday effects.

Further, guidance is needed for the appropriate follow-up and management of patients during drug holidays, including timeframe for follow-up, screening measures, and the re-initiation or substitution of medication following the drug holiday.

Similarly, the use of other pharmacologic therapies to supplement bisphosphonate treatment or replace bisphosphonates during drug holidays should be evaluated. Limited evidence suggests that sequencing ODTs may enhance the success, but the appropriate timeframe, order, ODTs, and patient characteristics for sequential therapy are uncertain to maximize benefits and minimize drug exposure and risk of harms.

With respect to barriers to treatment, little evidence ties specific ODTs to long-term benefits in pain relief or function as a result of fracture prevention. Research addressing decision-making factors that predict who initiates treatment, who does not, and why will inform the relative importance of the factors weighed in these decisions. We currently know demographic factors related to adherence to ODTs, but less about attitudes and other appraisals influencing medication use. Adherence is low, and less is known on how to increase long-term medication use. Finally, research is needed as to the best context for shared decision-making between patients and health care professionals. Results would clarify the type of relationship necessary for effective communication, and how inclusion of family members or other informal caregivers influence decision-making processes.

Aging of the population increases the prevalence of osteoporosis and its consequences. Although ODTs may have played a part in more recent reductions in fracture incidence, uncommon but potentially serious side effects have been associated with these treatments.

Clinicians and patients need increased information on benefits and risks to inform shared decision-making about the use of these treatments, taking into account patients' values and preferences. The research outlined above is urgently needed to advance prevention of osteoporosis-related mortality and morbidity.

Table 1. Summary of Workshop Panel Recommendations To Advance the Field of Osteoporotic Drug Therapy

Item	Description
1.	In assessing both existing and potential treatments and optimizing duration, researchers should make use of innovative designs and approaches, including:
	a. Modeling studies: Include biologic and non-biologic determinants of fractures and how much of the biologic pathway a treatment mitigates.
	b. Clinical trials: Incorporate preference designs, sequential intervention designs, adaptive trial methodology, platform trials; include fracture sequelae outcomes (functional status, mobility, hospitalizations, and nursing home placement).
	c. Observational studies: Apply causal methods; include fracture sequelae; include diverse populations (e.g., men, racial/ethnic groups, people with multiple chronic conditions, people in various residential settings, people with high fracture risk who do not have osteoporosis).
2.	Future clinical trials should evaluate new agents that potentially lack the side effects of current bisphosphonates and may have greater efficacy.
3.	More research is needed to characterize AFF and ONJ as serious adverse events associated with long-term bisphosphonate or denosumab use.
	a. Studies should employ standard case definitions for these complications.
	b. Studies should assess: incidence by race/ethnicity, risk factors, pathogenesis, algorithms to predict risk, interventions to reduce incidence.
4.	More evidence and research are needed to determine which patients are optimal candidates for drug holidays and sequential therapies, and possible strategies for mitigating serious adverse events associated with long-term bisphosphonate or denosumab use (i.e., AFF and ONJ).
	a. Studies are needed that are drug- and patient-specific, and that establish optimal timing and duration of and follow-up for drug holidays.
	b. Concurrent study of the efficacy of lower-dose bisphosphonate therapy, as a means of delaying or preventing the need for drug holidays, is needed.
	c. Designs listed in 1a and 1b and analyses of existing data would provide a more real-world picture of drug therapy discontinuation.
	d. A consensus definition of "drug holiday" would facilitate data collection and interpretation.
	e. The use of other pharmacologic therapies to supplement bisphosphonate treatment or replace it during drug holidays requires evaluation.
	f. Studies to establish the appropriate timeframe, order, medication type, and optimal patient characteristics for sequential therapy are needed.

Item	Description
5.	More research on barriers to osteoporotic drug therapy is needed.
	a. Studies assessing who initiates treatment, who does not, and why will increase understanding of the numerous factors that influence decisions about osteoporotic drug therapy use.
	b. Studies that examine patient and provider attitudes and that identify ways of increasing long-term use of osteoporotic drug therapies are needed.
	c. Research that establishes the best context for shared decision-making among patients, providers, family members, and other informal caregivers would help to mitigate a number of patient- and provider-related barriers.

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