

Rotation 9 (Emergency Medicine, Week 4)

CAT Final – PICO Rotation 7, Week 1

Name: Emily Yeung

Clinical & PICO Question:

82 year old female with PMHx of HTN, HLD, osteoporosis admitted to the floor s/p fall on left hip. She was started on bisphosphonates years ago (doesn't recall when) but wants to know if there is a recommended amount of time in which bisphosphonates have been found to be useful without having significant side effects.

What is the optimal duration of bisphosphonate use for osteoporosis before possibly experiencing significant side effects such as atypical femoral fracture, subtrochanteric/femoral shaft fractures or osteonecrosis of the jaw?

PICO Search Elements:

P	I	C	O
Osteoporosis	Bisphosphonate use	Medication continuation vs. discontinuation	Optimal duration
Post-menopausal women	Bisphosphonate therapy	Discontinued bisphosphonate use	Benefits of long term bisphosphonate use
		Drug holiday	Risk of atypical femoral fracture
			Risk of osteonecrosis of the jaw
			Risk of subtrochanteric/femoral shaft fracture

Search Strategy:

Database	Terms Used	Filters Applied	# of Articles
PubMed	Optimal duration of bisphosphonates for osteoporosis	5 years, humans	22
Cochrane Library	Optimal duration of bisphosphonates for osteoporosis	-	15
ScienceDirect	Optimal duration of bisphosphonates for osteoporosis	5 years, review articles	169
Trip Database	Optimal duration of bisphosphonates for	-	245

	osteoporosis		
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After choosing my search term of “optimal duration of bisphosphonates for osteoporosis” and applying the filters that I wanted, I narrowed down my search by looking into articles that were of the most recent and of the highest levels of evidence. Thus, I included 2 very recent systematic reviews from 2019 and another systematic review from 2016 that evaluated whether there is an optimal time period for the use of bisphosphonates and explain whether there are adverse effects in long-term use in addition to any rebound effects. Two of the articles was conducted in New York, which is a plus. I also decided to include a set of clinical guidelines set forth by the American Association of Clinical Endocrinologists and American College of Endocrinology to see if the conclusions drawn match what is recommended.

Additionally, I was looking for inclusion of many studies within the systematic reviews and consistent primary or secondary outcomes throughout each of the articles as it makes it easier to analyze and formulate my clinical bottom line. My articles also have a strong focus on evaluating osteoporosis in post-menopausal women as part of the patient demographics, which will help me form a stronger clinical bottom line, as the findings will be more relevant to my patient.

Articles Chosen:

Citation	<p>1. Long-Term Drug Therapy and Drug Discontinuations and Holidays for Osteoporosis Fracture Prevention: A Systematic Review. Fink HA, MacDonald R, Forte ML, Rosebush CE, Ensrud KE, Schousboe JT, Nelson VA, Ullman K, Butler M, Olson CM, Taylor BC, Brasure M, Wilt TJ. Ann Intern Med. 2019 Apr 23. doi: 10.7326/M19-0533. [Epub ahead of print] PMID: 31009947</p>
Abstract	<p>Abstract BACKGROUND: Optimal long-term osteoporosis drug treatment (ODT) is uncertain. PURPOSE: To summarize the effects of long-term ODT and ODT discontinuation and holidays. DATA SOURCES: Electronic bibliographic databases (January 1995 to October 2018) and systematic review bibliographies. STUDY SELECTION: 48 studies that enrolled men or postmenopausal women aged 50 years or older who were being investigated or treated for fracture prevention, compared long-term ODT (>3 years) versus control or ODT continuation versus discontinuation, reported incident fractures (for trials) or harms (for trials and observational studies), and had low or medium risk of bias (ROB). DATA EXTRACTION: Two reviewers independently rated ROB and strength of evidence (SOE). One extracted data; another verified accuracy.</p>

	<p>DATA SYNTHESIS: Thirty-five trials (9 unique studies) and 13 observational studies (11 unique studies) had low or medium ROB. In women with osteoporosis, 4 years of alendronate reduced clinical fractures (hazard ratio [HR], 0.64 [95% CI, 0.50 to 0.82]) and radiographic vertebral fractures (both moderate SOE), whereas 4 years of raloxifene reduced vertebral but not nonvertebral fractures. In women with osteopenia or osteoporosis, 6 years of zoledronic acid reduced clinical fractures (HR, 0.73 [CI, 0.60 to 0.90]), including nonvertebral fractures (high SOE) and clinical vertebral fractures (moderate SOE). Long-term bisphosphonates increased risk for 2 rare harms: atypical femoral fractures (low SOE) and osteonecrosis of the jaw (mostly low SOE). In women with unspecified osteoporosis status, 5 to 7 years of hormone therapy reduced clinical fractures (high SOE), including hip fractures (moderate SOE), but increased serious harms. After 3 to 5 years of treatment, bisphosphonate continuation versus discontinuation reduced radiographic vertebral fractures (zoledronic acid; low SOE) and clinical vertebral fractures (alendronate; moderate SOE) but not nonvertebral fractures (low SOE).</p> <p>LIMITATION: No trials studied men, clinical fracture data were sparse, methods for estimating harms were heterogeneous, and no trials compared sequential treatments or different durations of drug holidays.</p> <p>CONCLUSION: Long-term alendronate and zoledronic acid therapies reduce fracture risk in women with osteoporosis. Long-term bisphosphonate treatment may increase risk for rare adverse events, and continuing treatment beyond 3 to 5 years may reduce risk for vertebral fractures. Long-term hormone therapy reduces hip fracture risks but has serious harms.</p>
PDF Link	Article 1 - Fink

Citation	2. Fracture risk following intermission of osteoporosis therapy. Dennison EM, Cooper C, Kanis JA, Bruyère O, Silverman S, McCloskey E, Abrahamsen B, Prieto-Alhambra D, Ferrari S; IOF Epidemiology/Quality of Life Working Group. Osteoporos Int. 2019 Jun 7. doi: 10.1007/s00198-019-05002-w. [Epub ahead of print] PMID: 31175404
Abstract	<p>Abstract Given the widespread practice of recommending drug holidays, we reviewed the impact of medication discontinuation of two common anti-osteoporosis therapies (bisphosphonates and denosumab). Trial evidence suggests the risk of new clinical fractures, and vertebral fracture increases when osteoporosis treatment with bisphosphonates or denosumab is stopped.</p> <p>INTRODUCTION: The aim of this paper was to review the available literature to assess what evidence exists to inform clinical decision-making with regard to drug holidays following treatment with bisphosphonates (BiP) or denosumab.</p>

	<p>METHODS: Systematic review.</p> <p>RESULTS: Differing pharmacokinetics lead to varying outcomes on stopping therapy. Prospective and retrospective analyses report that the risk of new clinical fractures was 20-40% higher in subjects who stopped BiP treatment, and vertebral fracture risk was approximately doubled. Rapid bone loss has been well described following denosumab discontinuation with an incidence of multiple vertebral fractures around 5%. Studies have not identified risk factors for fracture after stopping treatment other than those that provide an indication for treatment (e.g. prior fracture and low BMD). Studies that considered long-term continuation did not identify increased fracture risk, and reported only very low rates of adverse skeletal events such as atypical femoral fracture.</p> <p>CONCLUSIONS: The view that patients on long-term treatment with bisphosphonates or denosumab should always be offered a drug holiday is not supported by the existing evidence. Different pharmacokinetic properties for different therapies require different strategies to manage drug intermission. In contrast, long-term treatment with anti-resorptives is not associated with increased risk of fragility fractures and skeletal adverse events remain rare.</p>
PDF Link	Article 2 - Dennison

Citation	<p>3. A systematic review and meta-analysis of the effect of bisphosphonate drug holidays on bone mineral density and osteoporotic fracture risk. Nayak S, Greenspan SL. Osteoporos Int. 2019 Apr;30(4):705-720. doi: 10.1007/s00198-018-4791-3. Epub 2019 Jan 8. PMID: 30623214</p>
Abstract	<p>Abstract We performed a systematic review on the effect of drug holidays (discontinuation) on bone mineral density (BMD) and fracture risk. Bisphosphonate discontinuation may be considered for women who do not have low hip BMD after 3-5 years of initial treatment, while women who have low hip BMD may benefit from treatment continuation.</p> <p>INTRODUCTION: We performed a systematic review and meta-analysis on the effect of drug holidays (discontinuation) on BMD and fracture risk.</p> <p>METHODS: We searched PubMed, Embase, and Cochrane Library databases to locate controlled clinical trials and cohort studies evaluating the effect of drug holidays/discontinuation versus osteoporosis treatment continuation. We performed random-effects meta-analyses of hazard ratios of hip and any clinical osteoporotic fracture for individuals who discontinued bisphosphonates compared to persistent users.</p>

	<p>RESULTS:</p> <p>Thirteen records reporting results from eight different studies met inclusion criteria. The FLEX study found a reduced clinical vertebral fracture risk with 10 years of alendronate therapy compared to 5 (RR 0.45, 95% CI 0.24-0.85), and the HORIZON extension studies found a reduced risk of morphometric vertebral fracture with 6 years of zoledronic acid therapy compared to 3 (OR = 0.51, 95% CI 0.26-0.95); subgroup analyses showed that women with low hip BMD T-scores after the initial treatment period benefitted from continued treatment in terms of reduced vertebral fracture risk. Meta-analysis of adjusted hazard ratios of hip and any clinical osteoporotic fracture for women who discontinued bisphosphonates revealed no significant differences in the risk of hip fracture (summary estimate of HR 1.09, 95% CI 0.87-1.37) or any clinical fracture (summary estimate of HR 1.13, 95% CI 0.75-1.70) compared to persistent users.</p> <p>CONCLUSIONS:</p> <p>Bisphosphonate discontinuation may be considered for women who do not have low hip BMD after 3 to 5 years of initial treatment, while women who have low hip BMD may benefit from treatment continuation.</p>
PDF Link	Article 3 - Nayak

Citation	<p>4. Update on long-term treatment with bisphosphonates for postmenopausal osteoporosis: a systematic review.</p> <p>Eriksen EF, Díez-Pérez A, Boonen S. Bone. 2014 Jan;58:126-35. doi: 10.1016/j.bone.2013.09.023. Epub 2013 Oct 9. Review. PMID: 24120384</p>
Abstract	<p>Abstract</p> <p>INTRODUCTION:</p> <p>Osteoporosis is a progressive skeletal disorder that requires long-term treatment. However, there is little guidance regarding optimal treatment duration and what the treatment discontinuation and retreatment criteria should be. Given that bisphosphonates are the most commonly prescribed class of agent for the treatment of osteoporosis, we reviewed the long-term data relating to these therapies and discussed the considerations for using bisphosphonates in postmenopausal women with osteoporosis.</p> <p>METHODS:</p> <p>A PubMed search, using the search terms 'bisphosphonate', 'postmenopausal osteoporosis' and 'long term' and/or 'extension' was conducted in January 2013. Results from nine controlled studies that prospectively assessed alendronate, risedronate, ibandronate or zoledronic acid in women with postmenopausal osteoporosis were reviewed.</p> <p>FINDINGS:</p> <p>Clinical studies in postmenopausal women with osteoporosis showed that long-term use of bisphosphonates resulted in persistent antifracture and bone mineral density (BMD) increasing effects beyond 3 years of treatment. No unexpected adverse events</p>

	<p>were identified in these studies and the long-term tolerability profiles of bisphosphonates remain favorable. Data from the withdrawal extension studies of alendronate and zoledronic acid also showed that residual fracture benefits were seen in patients who discontinued treatment for 3 to 5 years after an initial 3- to 5-year treatment period. BMD monitoring and fracture risk assessments should be conducted regularly to determine whether treatment could be stopped or should be reinitiated. Patients exhibiting T-scores < -2.5 or who have suffered a new fracture while on treatment should continue treatment, while patients with T-scores > -2.5 could be considered for discontinuation of active treatment while undergoing continued monitoring of their bone health. The duration and potential discontinuation of treatment should be personalized for individual patients based on their response to treatment, fracture risk and comorbidities.</p>
PDF Link	Article 4 - Eriksen

Citation	<p>5. Bisphosphonate Treatment in Osteoporosis: Optimal Duration of Therapy and the Incorporation of a Drug Holiday. Villa JC, Gianakos A, Lane JM. HSS J. 2016 Feb;12(1):66-73. doi: 10.1007/s11420-015-9469-1. Epub 2015 Dec 9. Review. PMID: 26855630</p>
Abstract	<p>Abstract</p> <p>BACKGROUND: Bisphosphonates are the most widely used treatment for osteoporosis. They accumulate in the bone for years, and therefore, their inhibitory effects on osteoclasts may persist after drug discontinuation. The ideal duration of therapy remains controversial.</p> <p>QUESTIONS/PURPOSES: The purpose of this study is to review the literature to determine the (1) indications for drug holiday, (2) the duration of drug holiday, (3) the evaluation during drug holiday, and (4) the proper treatment and maintenance after drug holiday.</p> <p>METHODS: A review of two electronic databases (PubMed/MEDLINE and EMBASE) was conducted using the term "(Drug holiday)," in January 29, 2015. Inclusion criteria were as follows: (1) clinical trials and case control, (2) human studies, (3) published in a peer-review journal, and (4) written in English. Exclusion criteria were as follows: (1) case reports, (2) case series, and (3) in vitro studies.</p> <p>RESULTS: The literature supports a therapeutic pause after 3-5 years of bisphosphonate treatment in patients with minor bone deficiencies and no recent fragility fracture (low risk) and in patients with moderate bone deficiencies and/or recent fragility fracture (moderate risk). In these patients, a bone health reevaluation is recommended every 1-3 years. Patients with high fracture risk should be maintained on bisphosphonate therapy without drug holiday.</p>

	<p>CONCLUSION:</p> <p>The duration and length of drug holiday should be individualized for each patient. Evaluation should be based on serial bone mass measurements, bone turnover rates, and fracture history evaluation. If after drug therapy, assessments show an increased risk of fracture, the patient may benefit from initiating another treatment. Raloxifene, teriparatide, or denosumab are available options.</p>
PDF Link	Article 5 - Villa

Citation	<p>6.AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS - 2016.</p> <p>Camacho PM, Petak SM, Binkley N, Clarke BL, Harris ST, Hurley DL, Kleerekoper M, Lewiecki EM, Miller PD, Narula HS, Pessah-Pollack R, Tangpricha V, Wimalawansa SJ, Watts NB.</p> <p>Endocr Pract. 2016 Sep 2;22(Suppl 4):1-42. doi: 10.4158/EP161435.GL.</p> <p>PMID: 27662240</p>
Abstract	<p>Abstract</p> <p>AACE = American Association of Clinical Endocrinologists AFF = atypical femur fracture ASBMR = American Society for Bone and Mineral Research BEL = best evidence level BMD = bone mineral density BTM = bone turnover marker CBC = complete blood count CI = confidence interval DXA = dual-energy X-ray absorptiometry EL = evidence level FDA = U.S. Food and Drug Administration FLEX = Fracture Intervention Trial (FIT) Long-term Extension FRAX® = Fracture Risk Assessment Tool GFR = glomerular filtration rate GI = gastrointestinal HORIZON = Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly IOF = International Osteoporosis Foundation ISCD = International Society for Clinical Densitometry IU = international units IV = intravenous LSC = least significant change NBHA = National Bone Health Alliance NOF = National Osteoporosis Foundation 25(OH)D = 25-hydroxy vitamin D ONJ = osteonecrosis of the jaw PINP = serum carboxy-terminal propeptide of type I collagen PTH = parathyroid hormone R = recommendation RANK = receptor activator of nuclear factor kappa-B RANKL = receptor activator of nuclear factor kappa-B ligand RCT = randomized controlled trial RR = relative risk S-CTX = serum C-terminal telopeptide SQ = subcutaneous VFA = vertebral fracture assessment WHO = World Health Organization.</p>
PDF Link	Article 6 - AACE/ACE

Summary of the Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases

<p>Fink, et al., 2019</p>	<p>Systematic review</p>	<p>-Databases used include MEDLINE, Embase, Cochrane Library, Clinicaltrials.gov for relevant systematic reviews -Ultimately included 61 studies (including but not limited to 35 RCTs, 13 controlled observational studies)</p>	<p>-Outcomes studied included efficacy of long term ODT, harms, and effects on fractures</p>	<p>-The purpose of this study is to summarize optimal long-term osteoporosis drug treatment (ODT) and determine any harms of prolonged use of long-term bisphosphonate treatment -Additionally, the authors looked into variation in such outcomes based on patient demographics, bone, or drug characteristics -In women with personal history of osteopenia/osteoporosis, 4 years of alendronate compared with placebo was associated with reduced radiographic vertebral fractures but did not significantly reduce nonvertebral/hip fractures -Long-term bisphosphonate treatment may increase risk of atypical femoral fracture, subtrochanteric/femoral shaft fractures, or osteonecrosis of the jaw, although rare -Continuing long-term bisphosphonate treatment beyond 3-5 years may reduce risk of developing vertebral fractures</p>	<p>-There were few studies that actually examined long term ODT, its discontinuation, or its holidays although short-term efficacy has been proven -Several studies had low statistical power for outcome for clinical fracture -Reporting of harms was not consistent between the studies</p>
<p>Dennison, et al., 2019</p>	<p>Systematic review</p>	<p>-The authors used a PICO style approach for conducting their</p>	<p>-Outcomes studied included whether fracture risk increases</p>	<p>- This systematic review aims to review available literature to summarize whether to continue or</p>	<p>-Observational studies by nature are limited by contradicting</p>

		<p>systematic review</p> <ul style="list-style-type: none"> -Databases used include Pubmed, Embase, Cochrane Library, NHS Evidence, Epistemonikos, and NIH records on Clinicaltrials.gov -Ultimately included 38 RCTs and several observational studies 	<p>upon treatment discontinuation, whether fracture rate remains stable or decreases upon treatment continuation, whether certain patient/treatment characteristics are associated with increased fracture risk upon d/c, and any adverse events that occur with long-term exposure</p>	<p>discontinue long-term bisphosphonate treatment</p> <ul style="list-style-type: none"> -Currently, the risks of interrupting osteoporosis therapy are poorly studied, in part due to the large proportion of patients that remain at high fracture risk 5 years post-therapy -The decision to stop bisphosphonate use should take into consideration the clinical risk factors that determine risk of recurring fragility fractures -It is important to continue therapy among women with high risk of fracture due to increased fracture incidence after stopping therapy -Despite these recommendations, over 50% of patients will stop therapy after 2 years and most providers stop such therapy after 3-5 years due to risk of developing atypical femoral fracture and osteonecrosis of the jaw -However, this risk remains less than 1/1000 patients in those treated for up to 10 years -Risk of hip, subtrochanteric femur/femoral shaft fractures remain low as well 	<p>observations and reporting bias</p> <ul style="list-style-type: none"> -There is a lack of clinical trial data particularly in subgroups such as those of different ethnicities or steroid-induced osteoporosis -This study was funded by an unrestricted grant from the MSD, which is a pharmaceutical company
Nayak, et	Meta-	-Databases used	-Outcomes	-The purpose of this	-Number of

<p>al., 2019</p>	<p>analysis/ Systematic review</p>	<p>include Pubmed, EMBASE, Cochrane Library to evaluate RCTs and cohort studies, with final inclusion of 8 studies</p>	<p>studied included evaluating the effect of drug holiday or bisphosphonate discontinuation vs. osteoporosis treatment continuation with particular focus to clinical osteoporotic fractures</p>	<p>study was to review the effect of drug holidays on bone mineral density and fracture risk -There is no significant difference in risk of hip fracture/any clinical fracture in patients who d/c bisphosphonate use to persistent users after 3 years -For high risk patients, there is reduced risk of clinical vertebral fracture with 10 years of therapy with alendronate (as compared to 5), and reduced risk of morphometric vertebral fracture with 6 years of therapy with zoledronic acid (as compared to 3) -Ideal length of bisphosphonate use should be based on T-score, age, and other risks</p>	<p>studies included could be larger -Several of the RCTs included had relatively smaller sample sizes -The majority of the studies evaluated alendronate, thus conclusions may not be generalizable to other bisphosphonate</p>
<p>Erikson, et al., 2014</p>	<p>Meta-analysis/ Systematic review</p>	<p>- The main database used was PubMed, resulting in 107 studies screened with using the search terms 'bisphosphonate', 'postmenopausal osteoporosis' and 'long term' and/or 'extension' with a total of 9 final RCTs</p>	<p>- Outcomes studied included long-term efficacy of bisphosphonates, fracture risk reduction with long-term bisphosphonate treatment, adverse effects</p>	<p>- This is meta-analysis/systematic review that aims to evaluate long-term data bisphosphonate use in postmenopausal women with osteoporosis -Treatment continuation with alendronate beyond 3-5 years is associated with continued vertebral fracture risk reduction -Patients with low femoral neck scores (T-score < -2.5) after 3-5 years of treatment are still at increased risk of vertebral fractures and</p>	<p>-Although a majority of studies assessed incidence of fracture as endpoints, the clinical relevance of such results may be limited by statistical power and may not be generalized to populations as a whole -Not all studies focused on the same fracture</p>

				<p>may benefit in continuous bisphosphonate therapy</p> <ul style="list-style-type: none"> -Duration of treatment and discontinuation should be individualized based on response to treatment, fracture risk, comorbidities -Long-term use of bisphosphonates are not associated with any adverse effects and tolerability remains favorable 	<p>type</p> <ul style="list-style-type: none"> -Different studies focused on different bisphosphonate thus results may or may not be extrapolated to use of other bisphosphonate
Villa, et al., 2016	Systematic review	<ul style="list-style-type: none"> -Databases used included Pubmed, MEDLINE, and EMBASE with particular focus to “drug holiday” with total of 65 articles -Inclusion criteria: clinical trials, case control, human studies, published in peer-reviewed journal, written in English -Exclusion criteria: case reports, case series, in vitro studies 	<ul style="list-style-type: none"> -Outcomes studied included efficacy of bisphosphonate treatment, long-term effects of bisphosphonates, osteonecrosis of the jaw, atypical femoral fractures, esophageal cancer 	<ul style="list-style-type: none"> -The purpose of this review was to evaluate current literature to determine when drug holidays are indicated, the duration of such drug holiday, f/u during drug holiday, and proper treatment/maintenance after such drug holiday -After the use of FDA approved bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid), fracture risk reduction is 47-70% lower for vertebral fractures, 28-50% lower for hip fractures, and 19-38% lower for other non vertebral fractures -Discontinuation of bisphosphonate use for up to 5 years does not significant increase fracture risk for women with low risk but women with high risk of clinical 	<ul style="list-style-type: none"> -What consists of a “drug holiday” is not consistent between all studies included -Longer follow-up studies were limited -One of the authors in this review reported personal fees from various biotechnical companies with specific focus in rheumatology

				<p>fracture may benefit from continued bisphosphonate use</p> <ul style="list-style-type: none"> -Bisphosphonate use and subsequent development of osteonecrosis of the jaw remains unclear; rather it may be attributed to bone formation suppression instead - The absolute risk of developing atypical femoral fractures is low and there is no consensus on the extent of bisphosphonate use increases this risk -There is no evidence supporting increased risk of esophageal cancer with bisphosphonate use -Patients with femoral neck T score above -2.0 are unlikely to benefit from continued treatment over 5 years 	
AACE/ACE, 2016	Clinical practice guidelines	-This is a clinical practice guideline for the diagnosis and treatment of postmenopausal osteoporosis	Recommendations are organized into how fracture risk is assessed and diagnosed, who needs pharmacologic therapy, what medication should be used, how treatment is monitored, whether sequential use of therapeutic agents should be considered, and risks	<ul style="list-style-type: none"> -All women aged 50 and above should be evaluated for osteoporosis risk through detailed history, PE, FRAX tool -Pharmacotherapy is strongly recommended for patients with T-score of -2.5 or lower in spine, femoral neck, total hip -Treatment is monitored by obtaining baseline axial spine/hip DXA, repeat q1-2 years or less depending on clinical circumstance; also monitor serial changes in 	-Although this clinical practice guideline reviewed many types of articles (both of low and high evidence), shortcomings of such guidelines include expert opinion -Team of who establishes such clinical guideline may have other conflicting interests as mar of the people

				lumbar spine, total hip, femoral neck -Consider bisphosphonate holiday after 5 years of stability in mod-risk patients, 6-10 years in higher-risk patients -Ending of bisphosphonate holiday is based on individual patient, optimal duration of such holiday is still not established	responsible for this guideline have received financial incentives from various pharmaceutical or biotech companies
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Conclusions:

Fink, et al., demonstrated that in female patients with personal history of osteopenia or osteoporosis, 4 years of alendronate compared with placebo was associated with reduced radiographic vertebral fractures but did not significantly reduce nonvertebral or hip fractures. Although rare, long-term bisphosphonate treatment may increase risk of atypical femoral fracture, subtrochanteric/femoral shaft fractures, or osteonecrosis of the jaw. In addition, continuing bisphosphonate treatment beyond 3-5 years may reduce risk of developing vertebral fractures.

Dennison, et al., demonstrated that it is important to continue therapy among women with high risk of fracture due to increased fracture incidence after stopping therapy. The decision to stop bisphosphonate use should take into consideration the clinical risk factors that determine risk of recurring fragility fractures. Over 50% of patients will stop therapy after 2 years and most providers stop such therapy after 3-5 years due to risk of developing atypical femoral fracture and osteonecrosis of the jaw but this risk remains less than 1/1000 patients in those treated for up to 10 years.

Nayak, et al., demonstrated that there is no significant difference in risk of hip fracture or any clinical fracture in patients who discontinue bisphosphonate use as compared to persistent users after 3 years. However, for high-risk patients, there is reduced risk of clinical vertebral fracture with 10 years of therapy with alendronate (as compared to 5 years), and reduced risk of morphometric vertebral fracture with 6 years of therapy with zoledronic acid (as compared to 3 years).

Erikson, et al., demonstrated that patients with low femoral neck scores (T-score < -2.5) after 3-5 years of treatment are still at increased risk of vertebral fractures and may benefit from continued bisphosphonate therapy, especially with alendronate, which has been associated with continued vertebral fracture risk reduction. Ultimately, long-term use of bisphosphonates is not associated with any adverse effects and tolerability remains favorable.

Villa, et al., demonstrated that the use of alendronate, risedronate, ibandronate, zoledronic acid are associated with significantly lower risk for fractures in the short run. Discontinuation of bisphosphonate use for up to 5 years does not significant increase fracture risk for women with low

risk but women with high risk of clinical fracture may benefit from continued bisphosphonate use. There is no evidence linking long-term bisphosphonate use to developing osteonecrosis of the jaw, atypical femoral fractures, or esophageal cancer.

The AACE/ACE recommend that all women aged 50 and above should be evaluated for osteoporosis risk through taking a detailed history, physical exam, and using the FRAX tool. Pharmacotherapy is strongly recommended for patients with T-score of -2.5 or lower in spine, femoral neck, total hip. Treatment efficacy is monitored by obtaining baseline axial spine/hip DXA. They recommend bisphosphonate holiday after 5 years of stability in moderately risk patients and in 6-10 years in higher-risk patients.

In conclusion, there is little to no evidence supporting the continuation of long-term bisphosphonate therapy in low risk individuals, especially for patients with femoral neck T score above -2.0. Long-term bisphosphonate use is not associated with increased risk of developing osteonecrosis of the jaw, atypical femoral fractures, and esophageal cancer. However, it is important to continue therapy among women with high risk of fracture due to increased fracture incidence after stopping therapy. The ideal length of bisphosphonate use should be individualized based on age, comorbidities, T-score, fracture risk, and response to treatment. Ending of bisphosphonate holiday is based on individual patient, as optimal duration of such holiday is still not established for a generalized population.

Clinical Bottom Line:

The first article is one of the most recent systematic reviews to evaluate the efficacy of long term ODT, harms, and effects on fractures, including a total of 35 RCTs, 13 controlled observational studies, and more. Moreover, the authors looked into variations based on patient demographics and bone/drug characteristics, which is something unique to this study. Although rare, long-term bisphosphonate treatment may increase the risk of atypical femoral fractures, subtrochanteric/femoral shaft fractures, or osteonecrosis of the jaw. However, reporting of harms was not consistent between the studies included and in turn, may reflect the risks of developing such complications.

The second article included a good amount of RCTs in the systematic review, 38 RCTs and several observational studies. The authors acknowledge that current risks of interrupting osteoporosis therapy is poorly studied since a large proportion of patients remain at high risk for fracture development, even after 5 years post-therapy. However, risks of such complications still remain low after those treated for up to 10 years. The authors also acknowledge that there is a limitation in the amount of data readily available in particular subgroups, such as those from different ethnicities or in steroid-induced osteoporosis.

Although the third article only included 8 final studies in its systematic review/meta-analysis, which is less than the previous studies, it still provided valuable information in determining that the ideal length of bisphosphonate use should be based on T-score, age, and other risk factors. The majority of its studies evaluated the main bisphosphonate used today (alendronate), thus its conclusions may not be fully generalized to other bisphosphonates.

The fourth article included 9 final RCTs with a strong focus to evaluate long-term bisphosphonate

use in a specific population that is relevant to my initial patient: postmenopausal women with osteoporosis. Additionally, the authors specified which the femoral neck scores/T-score < -2.5 after 3-5 years of treatment that are still at increased risk of vertebral fractures, thus may benefit in continuous bisphosphonate therapy. However, because of the specific population studied, these conclusions may not be generalized to other populations, such as men with osteoporosis.

The fifth article is another systematic review that included the most articles, with a total of 65 articles. It provided specific percentages in terms of fracture risk reduction, which is 47-70% lower for vertebral fractures, 28-50% lower for hip fractures, and 19-38% lower for other non vertebral fractures after the use of approved bisphosphonates. However, what consists of a drug holiday is not consistent between all studies and should be further specified in future studies.

The last article is a clinical practice guideline for the diagnosis and treatment of osteoporosis in postmenopausal women. This was valuable to include since it provided recommendations on how fracture risk is assessed and diagnosed, when pharmacologic therapy is indicated, which medication to use, and other risks. However, this guideline does include expert opinion, which may be biased depending on conflict of interest as many of the people responsible for developing this guideline received financial incentives from pharmaceutical or biotech companies.

Annually, there are an estimated 8.9 million fractures that occur as a complication from osteoporosis. The mainstay of managing osteoporosis involves the use of bisphosphonates with a well-established efficacy of fracture reduction up to 50%. However, poor adherence to such medications, co-morbidities, and concomitant use of other medications lower potential efficacy rates. Additionally, there is little guidance as to what the optimal treatment duration should be and what the criteria is for treatment discontinuation or retreatment. Recently, long-term bisphosphonate treatment has been associated with rare risks, such as atypical femoral fracture and osteonecrosis of the jaw, prompting patients and providers to discontinue such therapy due to such rare adverse effects. However, this risk remains less than 1/1000 patients in those treated for up to 10 years.

Current studies demonstrate that in women with personal history of osteopenia/osteoporosis, four years of alendronate compared with placebo is associated with reduced radiographic vertebral fractures but does not significantly reduce nonvertebral/hip fractures. Additionally, treatment continuation with alendronate beyond 3-5 years is associated with continued vertebral fracture risk reduction, which may be especially beneficial for patients with low femoral neck scores (T-score < -2.5). Long-term use of bisphosphonates is not associated with any adverse effects and tolerability remains favorable. Risk of developing hip, subtrochanteric femur/femoral shaft fractures remains low as well. In the case of possible discontinuation of such therapy, this decision should be individualized, based on response to treatment, fracture risk, and comorbidities. However, these conclusions may not be generalized to other populations such as men since there was a strong focus in studying postmenopausal women with osteoporosis. In addition, we need to take extra precaution in patients with underlying pathologies of the bone in which continued duration of bisphosphonate use may be beneficial.

For this patient, I would need to know more information about when she was started on bisphosphonates and how her treatment response has been thus far. It would also be helpful to

review previous T-scores and other indicators of her osteoporosis before determining whether to continue or discontinue long-term bisphosphonate therapy.