Introduction
Bisphosphonates were first reported in the literature in the late 1960s and were initially used in patients for treatment of calcium metabolism. In the 1990s, bisphosphonates were approved for use in osteoporosis and have become the mainstay of treatment. However, concerns have recently been raised regarding long-term bisphosphonate use.

Background
Osteoporosis has an estimated prevalence of over 200 million people worldwide, impacting almost one-third of postmenopausal women in the United States and Europe. (IOF, 2017) It is estimated that in these women, at least 40% will sustain a fragility fracture during their lifetime. The estimated lifetime rate in men is 15 – 30 percent. (IOF, 2017)

Considering the absence of absolute treatment guidelines and absolute durations of treatment, more recently, concerns have surfaced regarding long-term bisphosphonate use. Rare complications of long-term bisphosphonate treatment include atypical femoral fracture (AFF) and osteonecrosis of the jaw (ONJ). These safety issues coupled with residual post-treatment fracture risk reduction have resulted in temporarily suspending the bisphosphonate, also known as a drug holiday.

Risk of Atypical Femoral Fracture & Osteonecrosis of the Jaw
Some studies show a twofold increased risk of AFF in patients treated with bisphosphonate use longer than 5 years. (Anagnostis, et al, 2017) In many patients, the risk of AFF is outweighed by the benefits of bisphosphonate use. (Tu, et al, 2010) In addition to long-term use of bisphosphonates, risks for AFF include use of proton pump inhibitor, glucocorticoids, history of contralateral AFF, collagen disease and varus deformity. (Tu, et al, 2010) ONJ is typically seen in oncology patients receiving high dose IV bisphosphonate treatment. (Anagnostis, et al, 2017) & Jagpal & Saag, 2018) Dental co-morbidity and history are important in identifying risk for ONJ. (Jagpal & Saag, 2018)

Drug Holiday
Drug holidays have been introduced to decrease the risk of AFF and ONJ. Some studies have suggested a lack of evidence for decreased risk for AFF during a drug holiday. (Adams, et al, 2018 & Schilcher, et al, 2015) While a drug holiday of 5 years is commonly believed to be appropriate, the decision for initiating a drug holiday and the duration of the drug holiday must be individualized. Candid and balanced discussion with patients about the risks and benefits of temporarily discontinuing bisphosphonate therapy is critically important in patient centered shared decision making. Lifestyle modifications including weight-bearing exercise, supplemental calcium and reducing fall risk should be continued during the drug holiday. Periodic risk reassessment during the drug holiday is also vital so that bisphosphonate treatment can be reinstated if the patient’s risk increases or bone mineral density declines.

Recommendations for bisphosphonate drug holidays

<table>
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<th>Organization</th>
<th>Drug holiday</th>
<th>Risk assessment</th>
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<tr>
<td>American Society for Bone Mineral Research (2019) <a href="http://www.asbmr.org">www.asbmr.org</a> Consensus clinical recommendation</td>
<td>Reassess treatment with bisphosphonates after 3 to 5 years</td>
<td>No specific drug holiday recommendation</td>
<td>No statement regarding testing during drug holiday</td>
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<td>Endocrine Society &amp; European Society of Endocrinology (2019) <a href="http://www.endocrine.org">www.endocrine.org</a> <a href="http://www.e-e-hormones.org">www.e-e-hormones.org</a> Guideline</td>
<td>After 5 years of oral treatment or 3 years of IV treatment, consider drug holiday up to 5 years in low to moderate risk women</td>
<td>Reassess fracture risk every 2 to 3 years during drug holiday</td>
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<td>American College of Physicians (2017) <a href="http://www.acponline.org">www.acponline.org</a> Guideline</td>
<td>Recommends 5 years of osteoporosis treatment in women</td>
<td>Appropriate treatment duration unknown</td>
<td>No statement</td>
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<tr>
<td>European Menopause and Andropause Society (2017) <a href="http://www.emas-online.org">www.emas-online.org</a> position statement</td>
<td>Drug holiday consideration after 5 years (alendronate or risedronate) or 3 years (zoledronate) in all treated patients</td>
<td>Suggested recommendation for duration of drug holiday is 2 – 3 years (shorter with risedronate), but optimal duration is unknown</td>
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<td>American Association of Clinical Endocrinologists and American College of Endocrinology (2016) <a href="http://www.aace.com">www.aace.com</a> Guideline</td>
<td>Consider after 5 years of oral treatment in low to moderate risk patients, or 6 – 10 years in higher risk patients</td>
<td>Consider alternative medication treatment (raloxifene or teriparatide) during drug holiday for higher risk patients</td>
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Analysis from DiGiulio, Loveless, Heider, Egan and Porschke (2020)

Discussion
There is no evidence based optimal timing or duration for bisphosphonate drug holidays at this time. Bisphosphonate drug holiday may not be appropriate for all patients. Some patients may benefit from alternative osteoporosis treatment with raloxifene or teriparatide during drug holiday. Treatment decisions must be individualized based on risk assessment which include bone mineral density, fracture risk, fall risk, co-morbidities, and bisphosphonate used.

References


