BONE DENSITY & OSTEOPOROSIS:

An Update for Manitoba Physicians

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"FRAX, Repeat BMD Testing and Drug Holidays"

What is FRAX?	The World Health Organization (WHO) fracture risk assessment tool, called "FRAX", estimates a patient's 10-year fracture risk from the input of several risk factors: age, sex, body mass index, prolonged glucocorticoid use, current smoking, high alcohol intake, parental hip fracture, rheumatoid arthritis, prior fragility fracture and femoral neck BMD (if available). The Canadian FRAX tool (http://www.sheffield.ac.uk/FRAX/tool.jsp?country=19) has been utilized for BMD reporting in Manitoba since 2012 using the following Fracture Risk categories: "Low risk" = <10% chance of an osteoporotic fracture "Moderate risk" = 10 - 19% chance of an osteoporotic fracture "High risk" = ≥ 20% chance of an osteoporotic fracture "Not applicable" = premenopausal women and men < 50 years
How is BMD monitored in those not on treatment?	The average rate of BMD loss in older adults is approximately 0.5% per year, though this can increase perimenopause and in the presence of medications such as glucocorticoids and aromatase inhibitors. Since the measurement error associated with BMD testing (referred to as the "least significant change" that can be detected with 95% confidence) is 3-10% depending upon measurement site and baseline BMD, it follows that short term change in BMD can be difficult to detect. In individuals not receiving therapy a sufficiently long testing interval is required to see a significant change in BMD and fracture risk. The usual BMD re-testing interval is: • At least 3 years in the absence of high risk medications (1-2 years in the presence of glucocorticoids and aromatase inhibitors until rapid BMD loss has been excluded, usually 2-3 measurements); • At least 5 years if individuals are found to be at low risk for fracture or developing osteoporosis; • For individuals over age 65 with normal BMD and no other risk factors, the chance of developing osteoporosis is so small that additional testing is not required in the absence of new risk factors.

How is BMD monitored in those with treatment?	Currently approved treatments for osteoporosis modestly increase BMD, but this can be difficult to detect given measurement error. Moreover, the reduction in fracture risk is much greater than expected from the small change in BMD and is largely due to stabilization in bone structure through suppression in bone turnover. In individuals on treatment, stable or increased BMD is consistent with effective therapy. It often requires at least 3 years to detect an increase and at least 5 years to equate stable BMD with response. Once treatment effect is documented, additional BMD monitoring is not required while the patient remains on the same treatment unless there are new risk factors or clinical concerns (such as a fracture).
Does FRAX change in people on treatment?	The FRAX tool does not reflect change in fracture risk in individuals on effective treatment for osteoporosis. Most of the risk factors (except for BMD) are not affected by treatment, while any improvement in BMD is offset by increasing age. That said, the fracture risk generated by FRAX can be interpreted as what an individual's risk would be in the absence of treatment and can guide decisions regarding continuation or withdrawal of drug therapy.
What is a drug holiday?	Bisphosphonate medications (which includes alendronate, risedronate and zoledronate) persist in the skeleton for several years after the last administered dose, and continue to suppress bone turnover for 1-5 years depending upon the agent. Although the safety profile of the bisphosphonates is excellent, there have been concerns about long term use and the potential for adverse events including atypical femur fractures (AFFs) that increase with duration of use. A temporary cessation in bisphosphonate therapy after 3-5 years of use has been proposed for some individuals (although not those who are at high fracture risk – see below), though guidelines regarding the duration of the drug holiday and when treatment should be reinitiated are unclear.
When is a drug holiday not appropriate?	A drug holiday is not appropriate for medications that do not have persistent effect after cessation, including estrogen, raloxifene and denosumab. In fact, withdrawal of the latter leads to accelerated "catch up" BMD loss which can be harmful. For individuals receiving bisphosphonates who are at high fracture risk ($\geq$20% ten-year risk of fracture, previous vertebral or hip fracture, or multiple fragility fracture episodes) the benefit of continued treatment is considered to outweigh the risk, and continuation of drug therapy is generally encouraged.
How is BMD monitored during a drug holiday?	BMD loss during a bisphosphonate drug holiday is similar to or even less than average for an untreated individual. Therefore, the usual rules for BMD monitoring would apply (see above).