BONE DENSITY & OSTEOPOROSIS:

An Update for Manitoba Physicians

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“When is a Holiday Bad for Your Health?”

What are the types of anti-osteoporosis medications?	The most widely used classes of medications to treat osteoporosis and reduce fracture risk act through inhibition of bone turnover, and are called antiresorptive (or anticatabolic). Two general categories exist, bisphosphonates and non-bisphosphonates (including estrogen, raloxifene and denosumab). The bisphosphonates are unique since they persist in the skeleton for years (possibly lifelong) and continue to act after an adequate initial course of therapy has been completed (usually defined as 3 - 5 years of intravenous or oral therapy). In contrast, non-bisphosphonate antiresorptive medications cease to act on the skeleton as soon as they are stopped, followed by a rapid increase in bone turnover. As a result, only bisphosphonates can be considered for a "drug holiday" as discussed below.
Rapid bone loss and rebound vertebral fractures after stopping denosumab	Denosumab, which is the most potent inhibitor of bone turnover, is typically given at 6 monthly intervals subcutaneously. Shortly after the end of the 6-month dosing interval and without further treatment there is an increase in bone turnover that exceeds pre-treatment baseline rates (overshoot in bone turnover) with accelerated "catch up" loss in bone density. Bone density usually falls to the pre-treatment baseline by 1 year after stopping therapy. This increased bone turnover may put individuals at paradoxically increased risk for vertebral fracture, so-called rebound vertebral fractures. Rebound vertebral fractures, which can be multiple, have been most strongly associated with individuals who had vertebral fractures at baseline. Patients should be advised that abrupt discontinuation of denosumab may put them at risk and should discuss their treatment with their healthcare provider prior to delaying therapy, stopping therapy or missing a scheduled dose.
Managing patients stopping denosumab	Individuals discontinuing denosumab should consider "bridging" to another antiresorptive medication to blunt the rapid bone turnover. Typically this is with a bisphosphonate, but the timing can be difficult to determine. An intravenous dose may not be retained by the skeleton if denosumab is still inhibiting bone turnover, and may need to be delayed. Some have suggested that oral bisphosphonate therapy for 1 year after discontinuing denosumab may be more effective. Additional information can be found in the references provided below and on the Osteoporosis Canada website: https://osteoporosis.ca/increased-risk-of-vertebral-fracture-after-stopping-denosumab/

When a drug holiday might be appropriate?	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 and cumulative use. Although bisphosphonates have been shown to have a good safety profile, 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 perhaps not for those who are at high fracture risk – see below), though no evidence-based guidelines regarding the duration of the drug holiday, monitoring and when treatment should be reinitiated currently exist.
When a drug holiday may not be appropriate?	A drug holiday is not appropriate for medications that do not have ongoing skeletal effects after cessation, including estrogen, raloxifene and denosumab. Withdrawal of the latter leads to accelerated bone loss. An individualized approach with shared-decision making is needed for individuals receiving bisphosphonates who remain at high fracture risk after an initial course of therapy (≥20% ten-year risk of fracture, previous vertebral or hip fracture, multiple fragility fracture episodes, very low bone density measurements or new fractures despite therapy). Limited data suggest a benefit of continued treatment on vertebral fracture risk, but uncertain benefit for non-vertebral fractures. Benefits need to be weighed against the small but cumulative risk of atypical femur fractures (AFFs), cost and inconvenience of another 3–5 years of therapy.

References (1-5):

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