



## UPDATE ON DRUG-INDUCED OSTEOPOROSIS (DIO)

Many commonly prescribed drugs are known to cause bone loss. The aim of this newsletter is to review drugs associated with osteoporosis (OP), the frequency of occurrence, prevention and management.

### Glucocorticoids (GCCs):

- Most common cause of DIO; occurs in 30 – 50% of patients who receive chronic GCCs, with an annual average bone loss rate of ~12% in the first year.<sup>1</sup>
- Some studies suggest topical or inhaled corticosteroids are safer than systemic glucocorticoids but the evidence is contradictory.<sup>2</sup>

### Antiepileptic drugs (AEDs):

- Phenytoin, phenobarbital, primidone and carbamazepine are the agents most frequently associated with DIO.<sup>3</sup> Valproate and oxcarbazepine have also been reported to cause bone loss.<sup>4</sup>
- Evidence suggests the risk of OP is doubled in patients on AEDs in comparison to those not on any type of antiepileptic medications.<sup>3</sup>
- A few qualitative studies which evaluated effects of AEDs on bone mineral metabolism and bone mineral density found no significant effects with gabapentin, lamotrigine, topiramate and vigabatrin.<sup>4</sup> Currently no human data exists for potential effects of clobazam and levetiracetam.

### Progestins:

- Depot medroxyprogesterone acetate (DPMA) is associated with bone density loss.<sup>5</sup>
- Use of DPMA for > 5 years resulted in 5-6% decrease in mean BMD; the decrease was more pronounced in the first two years with smaller declines seen in following years.<sup>6</sup>
- Various other methods of contraception have less effect on bone health and would be an alternative if compliance is not an issue.

### Thiazolidinediones (TZDs):

- Rosiglitazone: a 4 – 6 year comparative study reported fracture rates in women of 2.7 per 100 patients-years (PY) compared to 1.54 per 100 PY for metformin and 1.29 per 100 PY for glyburide.<sup>7</sup>
- Pioglitazone: studies that ranged in duration from 16 weeks to 3.5 years reported fracture rates in women of 1.9 per 100 PY of use compared to 1.1 per 100 PY in placebo or active control groups.<sup>8</sup>
- Affects primarily post-menopausal women; fracture rates were not significantly higher in men.<sup>9</sup>

### Proton Pump Inhibitors (PPIs):

- A large observational study has reported a small but significant increase in the risk of hip fracture associated with the long-term PPI use, particularly with higher doses of PPIs. More research is needed to confirm this result.<sup>9</sup>
- Authors recommend use of lowest effective dose and PRN rather than daily use when appropriate.<sup>10</sup>
- To avoid absorption problems with calcium supplements, calcium citrate can be recommended.<sup>11</sup>

### Anticoagulants:

- Unfractionated heparin used for > 3 months has been associated with osteoporosis and spontaneous vertebral fractures.<sup>12</sup>

- Osteoporosis is reversible upon discontinuation but the overall effect is unknown.<sup>12</sup>
- Preliminary evidence suggests that low molecular weight heparins are less likely than unfractionated heparin to cause osteoporosis.<sup>13</sup>
- Evidence is conflicting as to whether or not warfarin causes osteoporosis.<sup>14</sup>

#### Thyroid Hormone:

- In a population based study, endogenous and exogenous TSH suppression, but not thyroid hormone therapy was associated with an increased fracture risk in women.<sup>15</sup>
- Optimal therapy with thyroid hormone is needed and maintaining TSH levels during replacement therapy above 1mU/mL is also recommended.<sup>15</sup>

#### Antidepressants:

- In studies of older men and women, SSRI but not TCA use is linked to increased bone loss at the hip.<sup>16,17</sup>
- A population-based cohort study in adults 50 years of age and older reported daily SSRI use was associated with a 2-fold increased of fragility fractures.<sup>18</sup>
- A large case control Danish study found a dose-dependent increase in fracture risk with citalopram, fluoxetine and sertraline (borderline for paroxetine).<sup>19</sup>

#### Other medications:

- Immunosuppressants, vitamin A and retinoids, loop diuretics like furosemide, chemotherapy agents and aluminum containing antacids have also been linked to OP.<sup>20</sup>

#### Prevention of DIO:

- Alternative medications, when available, should be considered in place of drugs that can precipitate OP, especially in patients at high risk.<sup>21</sup>
- If a patient requires long term therapy with a drug that induces bone loss, provide education about the risk of OP and lifestyle modifications to reduce risk. These include adequate intake of calcium, vitamin D and protein; increased weight-bearing exercise activities; limiting alcohol consumption; avoiding excessive intake of caffeine; smoking cessation, and measures to prevent falls.<sup>21,22</sup>
- Baseline BMD and regular evaluation of bone disease severity throughout the course of treatment is recommended especially for long term glucocorticoid therapy.<sup>24</sup> Patients on long term AEDs should be monitored for BMD, calcium, phosphate, and vitamin D status.<sup>4</sup>
- Recommend pharmacological therapy for osteoporosis prevention or treatment based on individual circumstances.
  - **Bisphosphonates** are indicated for prevention and treatment of glucocorticoid-induced OP.<sup>2</sup> They may be effective for patients on AEDs as well but are not recommended at this time due to concerns regarding long-term use particularly in the younger population typical of AED users.<sup>4</sup> There is some evidence antiresorptive agents are effective for increasing BMD in patients with diabetes, but may not be effective for bone loss induced by TZDs.<sup>22</sup>
  - **Calcitonin** may prevent bone loss during glucocorticoid treatment, but results from the literature are conflicting. A metaregression analysis showed that calcitonin was less effective in comparison to bisphosphonate.<sup>22</sup>
  - **Selective Estrogen Receptor Modulators** (e.g., raloxifene) have been reported to be of benefit in postmenopausal women taking AEDs.<sup>3</sup> Similarly, there is data to support efficacy of hormone replacement therapy (HRT) in postmenopausal women on AEDs.<sup>3</sup> However, HRT is associated with increased risk of cardiovascular events and breast cancer and may also increase seizure activity.<sup>3</sup>
  - **Teriparatide** may be effective in preventing GCC-induced bone loss. A study of 428 men and women with osteoporosis who had used long term glucocorticoid >3 months, suggested that teriparatide was more effective in preventing bone loss than alendronate.<sup>23</sup> However, this was a secondary outcome and more research is needed to determine the role of teriparatide in DIO.

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