

## Clinical Guidance on the Sequential and Combined Use of Anti-resorptive and Anabolic Agents for the Prevention and Treatment of Osteoporosis

The purpose of this guidance is provide-evidence based criteria-for-use for the selection of pharmacotherapy to prevent and treat osteoporosis. Anti-resorptive agents are bisphosphonates and denosumab, and anabolic agents are teriparatide and abaloparatide. Osteoporosis is considered to be **severe** when the patient's T-scores is  $< -3.0$  or their T-score  $< -1.5$  with evidence of  $>2$  mild vertebral fractures or  $>1$  moderate<sup>b</sup> vertebral fractures or other nontraumatic osteoporotic or fragility fracture.<sup>1-3</sup> Mild vertebral fractures (Grade 1) consist of  $\sim 20$ - $25\%$  decrease in anterior middle and/or posterior vertebral height and reduction of area  $10$ - $20\%$ .<sup>4</sup> Moderate vertebral fractures (Grade 2) consist of  $\sim 25$ - $40\%$  decrease in height and  $20$ - $40\%$  decrease in area.<sup>4</sup> A fragility fracture is defined by the World Health Organization as "a fracture caused by injury that would be insufficient to fracture a normal bone...the result of reduced compressive and/or torsional strength of bone".<sup>5</sup> Clinically, a fragility fracture may be defined as a fracture "...that occurs as a result of a minimal trauma, such as a fall from a standing height or less, or no identifiable trauma".<sup>6</sup>

### Treatment-Naive Patients

#### General Guidance for all treatments:

- The patient's total daily dietary and supplemental calcium intake is  $1000$  to  $1200$  mg/day.<sup>7,8</sup>
- Patient's with osteopenia have a 25-hydroxyvitamin D concentration  $>20$  ng/mL AND an active prescription for cholecalciferol (Vitamin D<sub>3</sub>) or ergocalciferol (vitamin D<sub>2</sub>) to prevent deficiency when indicated.
- Patient's with osteoporosis have a 25-hydroxyvitamin D concentration  $>30$  ng/mL AND an active prescription for cholecalciferol (Vitamin D<sub>3</sub>) or ergocalciferol (vitamin D<sub>2</sub>) to prevent deficiency when indicated.<sup>9,10</sup> Patients are **not** required to have a 25-hydroxyvitamin D concentration  $>30$  ng/mL to initiate treatment.
- T-scores are based on DXA scan at the lumbar spine or hip, or distal radius (when other sites are not reliable), with repeat scans performed at the same anatomical site on the same DEXA machine.
- Consider referring patients with a T-score  $< -1.5$  with evidence of  $>2$  mild vertebral fractures or  $>1$  moderate vertebral fractures or other nontraumatic osteoporotic fracture (e.g., hip or Colle's fracture) or a T-score  $< -3.0$  to the local osteoporosis specialist for consultation and treatment plan or management.

#### Oral Bisphosphonates

The oral bisphosphonates are the first choice for treatment naïve patients without a history of osteoporotic fracture. Once-weekly oral alendronate is on the VA National Formulary and is the primary agent for osteoporosis prevention and treatment in treatment-naïve patients. Once-weekly alendronate should be prescribed to the following patients:

- Have a T-score  $< -2.5$ , i.e., osteoporosis, or who have experienced a fragility fracture (independent of T-score).<sup>11,12</sup>  
OR
- Have a T-score  $\leq -1.0$  with no evidence of an osteoporotic fracture and a 10-year probability of hip fracture is  $> 3\%$ , or a FRAX 10-year probability of major osteoporotic fracture of  $\geq 20\%$ . Note: some younger patients may not meet the FRAX criteria because of their age.<sup>11,12</sup>

AND

- Have a creatinine clearance (CrCl)  $\geq 35$  mL/min, AND
- Have no gastrointestinal, swallowing, or other conditions that contradict or complicate oral administration.

### Zoledronic Acid

Intravenous zoledronic acid should be reserved for patients with a CrCl  $> 35$  mL/min who meet one of the following:

- Are unable to take an oral bisphosphonate.
- AND**
- Have a T-score  $< -2.5$ , i.e., osteoporosis, or who have experienced a fragility fracture (independent of T-score).<sup>11, 12</sup> OR
  - Have a T-score  $< -1.0$  with no evidence of an osteoporotic fracture and a 10-year probability of hip fracture is  $> 3\%$ , or a FRAX 10-year probability of major osteoporotic fracture of  $> 20\%$ . Note: some younger patients may not meet the FRAX criteria because of their age.<sup>11, 12, 13</sup>
- OR
- Zoledronic acid may be a reasonable choice for patients with a T-score  $< -3.0$ .<sup>1</sup> (Consider referral to the local osteoporosis expert for consultation and treatment planning, or management.)
- OR
- Independent of T-score, evidence of  $\geq 2$  mild vertebral fractures or  $\geq 1$  moderate vertebral fractures or other nontraumatic osteoporotic fracture, e.g., hip or Colle's fracture, regardless of ability to take an oral bisphosphonate.<sup>14, 15</sup> (Consider referral to the local osteoporosis expert for consultation and treatment planning, or management.)
- OR
- Zoledronic acid is advised for patients who have had an osteoporotic-related hip fracture within the past 90 days after ruling out other bone pathology, e.g., multiple myeloma and bone metastases.<sup>17</sup>
- OR
- A diagnosis of Paget's disease<sup>18</sup>

### Denosumab

Subcutaneous denosumab should be reserved for the following patients:

- Are unable to take a bisphosphonate.
- AND**
- Have a T-score  $< -2.5$ , i.e., osteoporosis, or who have experienced a fragility fracture (independent of T-score).<sup>11, 12</sup> OR
  - Have a T-score  $< -1.0$  with no evidence of an osteoporotic fracture and a 10-year probability of hip fracture is  $> 3\%$ , or a FRAX 10-year probability of major osteoporotic fracture of  $> 20\%$ . Note: some younger patients may not meet the FRAX criteria because of their age.<sup>11, 12</sup>

OR

- Independent of T-score, evidence of  $> 2$  mild vertebral fractures or  $> 1$  moderate vertebral fractures or other nontraumatic osteoporotic fracture, e.g., hip or Colle's fracture, **and** a CrCl  $< 35$  mL/min **or** unable to take zoledronic acid.<sup>14, 15</sup> (Such patients should be referred to their local osteoporosis expert for consultation and treatment planning, or management.)
- OR
- Denosumab may be an appropriate choice for patients with a T-score  $< -3.0$  independent of

fracture history.<sup>1</sup> (Consider referral to the local osteoporosis expert for consultation and treatment planning, or management).

- Denosumab should not be abruptly discontinued unless replaced by a bisphosphonate (See Treatment Duration and Treatment Holiday).

### *Anabolic Agents: Teriparatide and Abaloparatide*

Subcutaneous teriparatide and abaloparatide should be reserved for patients with severe osteoporosis in whom an increase in bone mineral density is paramount to sustained risk reduction for osteoporotic fracture, or for patients who cannot take a bisphosphonate or denosumab. Use of the drug for more than 2 years during a patient's lifetime is not recommended. Use for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture.

- A T-score < -3.0 regardless of fracture history for whom zoledronic acid or denosumab is deemed inappropriate or insufficient.<sup>1</sup> (Consider referral to the local osteoporosis expert for consultation and treatment planning, or management.)

## **Treatment Experienced Patients**

### *General Guidance for All Treatments*

- The patient's total daily dietary and supplemental calcium intake is 1000 to 1200 mg/day.<sup>1</sup>
- Patient's with osteopenia have a 25-hydroxyvitamin D concentration >20 ng/mL AND an active prescription for cholecalciferol (Vitamin D<sub>3</sub>) or ergocalciferol (vitamin D<sub>2</sub>) to prevent deficiency when indicated.
- Patients with osteoporosis have a 25-hydroxyvitamin D concentration >30 ng/mL AND an active prescription for cholecalciferol (Vitamin D<sub>3</sub>) or ergocalciferol (vitamin D<sub>2</sub>) to prevent deficiency when indicated.<sup>9, 10</sup> Patients are **not** required to have a 25-hydroxyvitamin D concentration >30 ng/mL to initiate treatment.
- T-scores are based on DXA scan at the lumbar spine, or hip, or distal radius (when other sites are not reliable), with repeat scans performed at the same anatomical site on the same DEXA machine.
- Consider referring patients with a T-score < -1.5 with evidence of >2 mild vertebral fractures or >1 moderate vertebral fractures or other nontraumatic osteoporotic fracture (e.g., hip or Colle's fracture) or a T-score < -3.0 should to the local osteoporosis specialist for consultation and treatment plan or management.

### *Oral Bisphosphonates*

Patients who experience an osteoporotic fracture within 2 years after starting an oral bisphosphonate should be assessed for adherence, malabsorption, and have any issues addressed; consultation with the local osteoporosis expert is advised. The decision whether to continue to treat with an oral bisphosphonate is based on the patients risk for fracture (T-score and fracture history) and response to existing or previous treatment. Consider discontinuing oral bisphosphonates after 5 or 10 years of treatment (See Treatment Duration and Drug Holiday).

1. Oral bisphosphonates should be continued if after  $\geq 2$  years the patient's:
  - Tolerating the medication AND

- Bone mineral density (BMD) has remained stable without a clinically significant loss (a decrease >3% or locally calculated value based on precision analysis of local DEXA) or has increased in the absence of an osteoporotic fracture AND
- T-score is  $\geq -3.0$  at the femoral neck, lumbar spine, or distal radius (when other sites are not reliable) AND
- CrCl >35 mL/min AND
- Adherence has been  $\geq 80\%$ ; if not, institute local measures to improve adherence and repeat DXA scan after 2 years. If adherence cannot be increased, then consider zoledronic acid or denosumab.

2. An oral bisphosphonate is advised for patients who have completed a course of treatment with an anabolic agent. There is some evidence that starting the anti-resorptive in the last six months of anabolic therapy may provide additional benefits, but this finding needs confirmation.<sup>21-23</sup>

### **Zoledronic Acid**

Intravenous zoledronic acid should be reserved for patients with a creatinine clearance (CrCl) >35 mL/min who meet one of the following:

- Consider switching to zoledronic acid for patients who have a T-score > -3.0 but have experienced an osteoporotic fracture after >2 years on an oral bisphosphonate even if their BMD has remained stable without a clinically significant loss (a decrease of >3%).
- Zoledronic acid is advised for patient's whose BMD has decreased >3% and who have a T-score > -3.0 after  $\geq 2$  years while on an oral bisphosphonate regardless of fracture status.
- Zoledronic acid can be considered for patients with a T score < -3.0 after >2 years on an oral bisphosphonate regardless of fracture status.
- Zoledronic acid is advised for patients who cannot take an oral bisphosphonate and have completed a course of treatment with an anabolic agent.
- Zoledronic acid is advised for patients who have had an osteoporotic-related hip fracture within the past 90 days after ruling out other bone pathology, e.g., multiple myeloma and bone metastases.

### **Denosumab**

Subcutaneous denosumab should be reserved for a patient with a CrCl <35 mL/min or who cannot take a bisphosphonate and one of the following:

- Consider denosumab for patients who have a T-score > -3.0 but have experienced an osteoporotic fracture despite previous treatment with a bisphosphonate even if their BMD has remained stable without a clinically significant loss (a decrease of >3%).
- Denosumab should be considered for patient's whose BMD has decreased >3% and T-score > -3.0 after  $\geq 2$  years despite previous treatment with a bisphosphonate regardless of fracture status.
- Denosumab can be considered for patients with a T score < -3.0 after >2 years on an oral bisphosphonate regardless of fracture status for whom a bisphosphonate is no longer appropriate.
- Denosumab is advised for patients who cannot take a bisphosphonate who have completed a course of treatment with an anabolic agent.

### **Anabolic Agents: Teriparatide and Abaloparatide<sup>a</sup>**

Subcutaneous teriparatide and abaloparatide should be reserved for patients with severe osteoporosis in whom an increase in bone mineral density is paramount to sustained risk reduction for osteoporotic fracture, or for patients who cannot take a bisphosphonate or denosumab. Use of the drug for more

than 2 years during a patient's lifetime is not recommended. Use for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture.

- Patients who despite treatment with a bisphosphonate or denosumab have continued to lose BMD, experienced an osteoporotic fracture, or have a T-score of  $< -3.0$ .<sup>3</sup> (Consider referring patients with a T-score  $< -3.0$  the local osteoporosis expert for consultation and treatment planning, or management.)

<sup>a</sup>Abaloparatide has not been studied in men or for drug-induced osteoporosis.

### Sequencing and Combination Pharmacotherapy

Sequencing refers to switching a patient from zoledronic acid or denosumab to the other or to an oral bisphosphonate or anabolic agent and which treatment a patient receives after up to 2 years of an anabolic agent.

- It is advised that any patient who receives a course of an anabolic agent be started on an oral bisphosphonate, zoledronic acid, or denosumab immediately thereafter. There is some evidence that starting the anti-resorptive in the last six months of anabolic therapy may provide additional benefits, but this finding needs confirmation.
- It is advised that patients who are taking denosumab but require treatment with an anabolic agent continue with denosumab during the course of anabolic treatment to prevent bone resorption.
- There is evidence that combining a bisphosphonate with an anabolic may not result in the anticipated gains in BMD.

### Treatment Duration and Treatment Holiday<sup>2,11</sup>

- Consider discontinuing **oral bisphosphonates** after 5 or more years of treatment *if the patient did not have* a hip, spine, or multiple other osteoporosis fractures before or during therapy AND their hip T-score is  $> -2.5$  or they are not at high fracture risk (e.g., age  $< 70$  years, FRAX below threshold or other strong risks). This is a risk: benefit decision. Reassess every 2-3 years.
- Consider continuing **oral bisphosphonates** for up to 10 years (cumulative), or change to an alternative treatment, in patients who after 5 or more years of treatment had a hip, spine or multiple other osteoporosis fractures before or during therapy AND their hip T-score is  $\leq -2.5$  or they are at high fracture risk (e.g., age  $> 70$  years, FRAX above threshold or other strong risks). Reassess every 2-3 years.
- Consider discontinuing **zoledronic acid** after 3 or more years of treatment if the patient did not have a hip, spine, or multiple other osteoporosis fractures before or during therapy AND their hip T-score is  $> -2.5$  or they are not at high fracture risk (e.g., age  $< 70$  years, FRAX below threshold or other strong risks). This is a risk: benefit decision. Reassess every 2-3 years.
- Consider continuing **zoledronic acid** for up to 6 years (cumulative), or change to an alternative treatment, in patients who after 5 or more years of treatment had a hip, spine or multiple other osteoporosis fractures before or during therapy AND their hip T-score is  $< -2.5$  or they are at high fracture risk (e.g., age  $> 70$  years, FRAX above threshold or other strong risks). Reassess every 2-3 years.
- **Denosumab** should be continued indefinitely as discontinuation will result in a rapid loss in BMD and potentially increased fracture risk unless it is replaced by a bisphosphonate or an anabolic agent.<sup>13</sup>

- **Teriparatide and abaloparatide** use for more than 2 years during a patient's lifetime is not recommended due to concerns of osteosarcoma. Use for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture. It is advised that any patient who receives a course of an anabolic agent be started on an oral bisphosphonate, zoledronic acid, or denosumab immediately thereafter. There is some evidence that starting the anti-resorptive in the last six months of anabolic therapy may provide additional benefits, but this finding needs confirmation.<sup>19-21</sup>

### **Treatment and Prevention of Surgical/Drug-induced Osteoporosis<sup>a</sup>**

Oral bisphosphonates are the primary choice to the treatment and prevention of osteoporosis secondary to surgery or drug-induced osteoporosis. Zoledronic acid, denosumab and anabolic agents should generally be reserved for patients with severe osteoporosis based on T-score and fracture history, and on renal function, i.e., CrCl < 35 mL/min, as outlined above. Drug holidays are not recommended for patients taking a bisphosphonate for drug-induced osteoporosis.

### ***2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-induced Osteoporosis<sup>22</sup>***

The American College of Rheumatology recommends that all adults taking prednisone  $\geq 2.5$  mg/day (or equivalent) for  $\geq 3$  months have optimal intake of calcium (1000 – 1200 mg/day) and vitamin D<sub>3</sub> (600-800 IU/day) along with lifestyle modifications (balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing, or resistance training, limiting alcohol intake to 1-2 drinks/day).

Patients who, in addition to calcium, vitamin D and lifestyle modifications, should be treated with a bisphosphonate or an anabolic agent<sup>a,b</sup> if they meet one of the following:

- Age < 40 years with a
  - History of osteoporosis fracture (s) OR
  - Z –score < -3.0 at hip or spine and prednisone > 7.5 mg/day OR
  - > 10%/year loss of BMD at hip or spine and prednisone > 7.5 mg/day OR
  - Very high dose of glucocorticoid (>30 mg/day and cumulative dose of >5 gm in the past year).
- Age  $\geq 40$  years
  - History of osteoporosis fracture (s) OR
  - Men  $\geq 50$  years and postmenopausal women with T-score  $\leq 2.5$  at the hip or spine OR
  - Glucocorticoid-adjusted FRAX 10-year risk for major osteoporotic fracture  $\geq 10\%$  OR
  - Glucocorticoid-adjusted FRAX 10-year risk for hip fracture > 1% OR
  - Exposure to an equivalent daily dose of prednisone  $\geq 30$  mg and a cumulative dose of > 5 gm in the past year.
- For women of childbearing potential, the benefits and risk of osteoporosis treatment must be carefully weighed (see below).

<sup>a</sup> Abaloparatide has not been studied in men or for drug-induced osteoporosis including glucocorticoid-induced osteoporosis.

<sup>b</sup> Denosumab should be reserved for patients who cannot take a bisphosphonate or teriparatide.

### ***Patient's receiving pharmacologic androgen deprivation therapy (ADT) or have undergone orchiectomy, or an aromatase inhibitor for breast cancer***

- Daily intakes of calcium 1000 – 1200 mg and vitamin D<sub>3</sub> 800– 1000 IU are recommended
- Treatment with zoledronic acid or denosumab is indicated for men without bone metastases being treated with long-term ADT with a 10-year probability of hip fracture is  $\geq 3\%$  or the 10-year probability of a major osteoporotic fracture is  $\geq 20\%$ .

### ***Patients receiving antiestrogen therapy (surgical or chemical ovarian ablation, aromatase inhibitor therapy, or tamoxifen for pre-menopausal women) or chemotherapy-induced ovarian dysfunction***

- Osteoclast inhibition with either bisphosphonates or denosumab is recommended for women with early breast cancer and treatment-related bone loss
- Daily intake of calcium 1000 – 1200 mg and vitamin D<sub>3</sub> 800– 1000 IU is recommended
- For premenopausal women, initiate anti-resorptive therapy after conservative measures in high-risk patients (Z score of -2.5 or lower or history of fracture due to low BMD)
- For post-menopausal women on aromatase inhibitor therapy, screen for fracture risk and add anti-resorptive therapy after modifications in nutrition, exercise, and lifestyle

### ***Antiepileptic Drugs and Osteoporosis Prevention and Treatment***

There are no clinical practice guidelines on the prevention or treatment of bone loss secondary to antiepileptic drugs (AEDs). Both enzyme-inducing AEDs (e.g., phenytoin, carbamazepine, oxcarbazepine, and topiramate at a dose >200 mg) and nonenzyme-inducing AEDs (e.g., valproate, levetiracetam, lamotrigine, zonisamide and topiramate at a dose <200mg) are thought to affect bone loss by accelerating vitamin D metabolism or inducing hypocalcemia and stimulating parathyroid hormone, respectively. The following recommendations apply to patients who have been or are expected to be treated with AEDs for >2 years:<sup>23, 24</sup>

- All patients should receive calcium supplementation of 1000-1500 mg/day and vitamin D<sub>3</sub> supplementation of 500 – 750 IU/day sufficient to increase vitamin concentrations to  $\geq 20$  ng/mL.
- Patients who are at risk for osteoporosis fracture or have had previous osteoporosis fracture should receive an oral bisphosphonate or alternative as appropriate.

### ***Osteoporosis Prevention and Treatment in Premenopausal Women***

#### ***Women of Child-bearing Potential Who Are Not Pregnant***

- Lifestyle modifications including adequate daily intake of calcium (1000 mg) and vitamin D<sub>3</sub> (600 IU), smoking cessation, regular weight-bearing or resistance training, limiting alcohol intake to 1-2 drinks/day and maintaining weight in the recommended range.
- Bisphosphonates have long terminal half-lives, storage in bone, and recirculation during bone remodeling after their discontinuation has raised concern about their use even before pregnancy. Consider the potential for future pregnancy when prescribing any osteoporosis treatment to women of childbearing potential.

### *Women who are Pregnant*

Anti-resorptive and anabolic agents should be used during pregnancy only if benefits outweigh risks. Based on animal data, bisphosphonates, denosumab, or teriparatide may cause fetal harm if administered during pregnancy. Bisphosphonates long terminal half-lives, storage in bone, and recirculation during bone remodeling after their discontinuation has raised concern about their use even before pregnancy. Consider the potential for future pregnancy when prescribing any osteoporosis treatment to women who are pregnant.

### **References**

1. Kanis JA, Bianchi G, Bilezikian JP, et al. Towards a diagnostic and therapeutic consensus in male osteoporosis. *Osteop Int* 2011;22:2789-98.
2. Adler RA, Fuleihan GE-H, Bauer DC, et al. Managing osteoporosis inpatients on long-term bisphosphonate treatment: report of a taskforce on of the American Society for Bone and Mineral Research. *J Bone Min Res* 2016;31(1):16-35.
3. Kendler L, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicenter, double-blind, double-dummy, randomized controlled trial. *The Lancet* published online November 9, 2017. Accessed January 10, 2018.
4. Genant HK, Wu CY, Kijik CV, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Min Res* 1993;8(9):1137-48
5. Guidelines for preclinical evaluation and clinical trials in osteoporosis. World Health Organization Geneva. 1998.
6. Brown JP, Josse RG. 2002 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *CMAJ* 2002;167:S1–34.
7. IOM (Institute of Medicine). 2011. Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press.
8. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. 2012;97(6):1802-22.
9. Carmel AS, Shieh A, Bang H, Bockman RS. The 25 (OH) D level needed to maintain a favorable bisphosphonate response is > 33ng/ml. *Osteoporos Int* 2012; 23:2479-2487.
10. Peris P, Martinez-Ferrer A, Monegal A, Martinez de Osaba MJ, Muxi A, Guanabens N. 25 hydroxyvitamin D serum levels influence adequate response to bisphosphonate treatment in postmenopausal osteoporosis. *Bone* 2012; 51:54-58.
11. Qaseem A, Forciea MA, McLean RM, et al. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med* 2017;166:818-39.
12. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician’s guide to prevention and treatment of osteoporosis. *Osteo Int* 2014;25(10):2359-81.
13. Grey A, Bolland MJ, Wattie D, et al. The antiresorptive effects of a single dose of zoledronate persist for two years: a randomized, placebo-controlled trial in osteopenic postmenopausal women. *J Clin Endocrinol Metab* 2009;94:538-44.

14. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809-22.
15. Boonen S, Reginster J-Y, Kaufman J-M, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. *N Engl J Med* 2012;367:1714-23.
16. Miller PD, Pannacciulli N, Brown JP, et al. Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. *J Clin Endocrinol Metab* 2016; 101:3163-3170.
17. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007;357-1799-1809.
18. Reid IR, Miller P, Lyles K, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med* 2005;353:898-908.
19. Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomized controlled trial. *Lancet* 2015;386:1147-55.
20. Leder BZ, Tsai JN, Jiang LA, Lee H. Importance of prompt anti-resorptive therapy in postmenopausal women discontinuing teriparatide or denosumab: the Denosumab and Teriparatide Follow-up study (DATA-Follow-up). *Bone* 2017;98:54-8.
21. Cosman F, Miller PD, Williams GC, et al. Eighteen months of treatment with 6 months subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: results of the ACTIVEExtend trial. *Mayo Clin Proc* 2017;92(2):200-210.
22. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arth & Rheum* 2017;69(8):1521-37.
23. Lazzari AA, Dussault PM, Thakore-James M, et al. Prevention of bone loss and vertebral fractures in patients with chronic epilepsy – antiepileptic drug and osteoporosis prevention trial. *Epilepsia* 2013;54(11):1997-2004.
24. Dussault PM, Lazzari AA. Epilepsy and osteoporosis risk. *Curr Opin Endocrinol Diabetes Obes* 2017;24:395-401.