**EFFECTS OF DRUGS ON BONE REMODELING:**

A. Young adult female

- BMU activation is relatively low
- In each unit, balance between bone resorption and bone formation

B. Untreated post-menopausal osteoporosis

- Increase rate of initiation of cycles = more bone remodeling
- Resorption > formation

C. Anti-resorptive drugs

- Suppress osteoclast activity = reduce BMU activation
- Decrease bone resorption without affecting bone activation = positive bone balance (short-term effect)

**ANTI-RESORPTIVE (ANTI-CATABOLIC) DRUGS**

**EFFECT OF ANTI-RESORPTIVE DRUGS ON BONE:**

- Decrease activation frequency of BMU (reducing bone turnover) by inhibiting osteoclast activity
- Decrease resorption w/o affecting formation
- Preservation of architecture

**EFFECT ON BMD IS TRANSIENT**

A-B: rapid increase in BMD as anti-resorptive drug suppresses formation of new remodeling sites, and re-filling of sites already resorbed continues

B-D: slower secondary mineralization of new bone continues for years, and some remodeling takes place but with fewer, shallower resorption cavities

**HRT AND OSTEOPOROSIS:**

<table>
<thead>
<tr>
<th></th>
<th>Estrogen alone or with progestins (0.625 mg conjugated equine estrogens + 2.5 mg medroxy-progesterone acetate)</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>↑ (&gt; 5 years therapy)</td>
<td>↓ (but less than estrogen or alendronate)</td>
</tr>
<tr>
<td>BMD</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Fracture</td>
<td>↓ hip, vertebral, non-vertebral</td>
<td>↓ vertebral only (by 50%)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Menopausal symptoms</td>
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</tr>
</tbody>
</table>

**NOTES**

- Use of HRT restricted to treatment of mod-severe vasomotor symptoms
  - Use lowest possible dose and normally limit to < 5 years
  - Osteoporosis prevention = secondary benefit
- Selective estrogen receptor modifier (SERM) that mimics actions of estrogen in bone, but opposes actions in breast
BISPHONATES (ANTI-RESORBIC DRUGS CONT):

**GENERAL STRUCTURE:** Aminobisphosphonates (alendronate, risedronate, zoledronate)
- OH in R1 = better binding and enhanced potency
- N in R2 = increased potency

**ETIDRONATE:**
- First-generation bisphosphonate
- Doses that inhibit bone resorption also impair bone mineralization
  - If used continuously, results in accumulation of unmineralized osteoid (osteomalacia)
  - To avoid, give cyclically: 14 days etidronate 400 mg/d, followed by 76 days of calcium carbonate 500 mg/day
- In women with T-score ≤ 2.0 or previous fracture: decreased risk of vertebral fracture (RR 50%, ARR 5%)

**ADME of oral bisphosphonates:** etidronate, alendronate, risedronate
- Very poorly absorbed (1-5%) so MUST be taken on AN EMPTY STOMACH with water only (= 30 – 60 min before first meal of day to allow for adequate absorption)
  - EXCEPT delayed release risedronate is taken with food
- Plasma life is 1 hr
  - 50% is excreted by kidney
  - 50% taken up by bone, where half-life is very long (> 10 yrs)

**USES OF BISPHOSPHONATES:**
- Prevention & treatment of osteoporosis in postmenopausal women
  - Anti-fracture efficacy shown for 7-10 years
  - Optimal duration of treatment not fully established
  - Clinical trials suggest that on discontinuation after 5 yrs, bone remodeling remains suppressed for at least 5 yrs
    > Associated with increased risk of vertebral but not non-vertebral or all fractures compared to women who remained on the drug
- To increase BMD in men with osteoporosis
- Prevention & treatment of glucocorticoid-induced osteoporosis
- Paget’s disease of the bone in men and women
- Treatment of bone metastases of various types of cancer
  - High doses of high potency preparations
  - Reduce bone pain and risk of fractures

**POSSIBLE EFFECTS OF LONG-TERM THERAPY ON BONE QUALITY:**
- Mineralization
- Accumulation of microdamage
- Brittness of bone
- Risk of fracture
- Ability to heal

**MECHANISM OF ACTION:**
1. Incorporated into bone, then released when hydroxyapatite dissolved by osteoclast acid
2. Taken up into osteoclasts preferentially (by endocytosis)
   - Impair recruitment, differentiation & activity of osteoclasts
   - Increase osteoclast apoptosis
3. Osteoblast activity continues = re-filling of remodeling space
4. Results in reduction in activation of new BMU = decreased bone turnover

**ALENDRONATE, RISEDRONATE, ZOLEDRONATE EFFICACY:**
- 2nd and 3rd generation bisphosphonates
- Much more potent inhibitors of bone resorption than etidronate
- Inhibit bone resorption at doses that do not affect bone mineralization
  - Alendronate: 10 mg daily or 70 mg weekly
  - Risedronate: 5 mg daily, 35 mg weekly, or 150 mg monthly
  - Zoledronate: 5 mg once/year by IV infusion
- In women with T-score ≤ 2.0 or previous fracture: decreased risk
  - Hip RR 25-50%, ARR 1%
  - Vertebral RR 45-70%, ARR 5-7%
  - Non-vertebral RR 20-25%, ARR 2%

**ADVERSE EFFECTS:**
- **ORAL ADMINISTRATION:**
  - GI upset (abdominal pain, NVD)
  - Severe esophagitis: pt must take it in upright position with full glass of water and remain upright for further 30 min

**ZOLEDRONATE:** transient flu-like symptoms on injection

**OSTEONECROSIS OF JAW:** < 1:10,000 in pts treated for osteoporosis
- Exposed necrotic bone in jaw region, not healing after 6-8 wk
- 90% of cases seen on IV administration of high doses for > 2 years in CA pts
  - Most after dental extraction (therefore recommended to avoid)
- May be due to highly suppressed bone turnover
- Can lead to severe pain and other complications, and is difficult to treat

**ATYPICAL FEMUR FRACTURES:**
- Overall < 1% of all hip fractures
- Bisphosphonate use increase absolute risk by 1.5 cases per 10,000 pt/year
  - Risk increases with increasing duration of use
  - Risk decreases on discontinuation
- NOTE that risk of typical hip fracture is 75-420 per 10,000 high risk pts/yr
  - Therefore benefit of bisphosphonate >> risk of this fracture
**DENOSUMAB (ANTI-RESORPTIVE DRUGS CONT):**

**MECHANISM:**
- Monoclonal antibody to RANKL that mimics the actions of OPG
  - Binds to RANKL and prevents its binding to RANK
- Results in a marked decrease in osteoclast formation and bone resorption

**USES:**
- Approved for severe osteoporosis in postmenopausal women
  - In clinical trials, reduced risk of vertebral fracture by 60%, non-vertebral fracture by 20% and hip fracture by 40% in women with T-score < -2.5
- In higher doses, to prevent skeletal-related events in pts with bone metastases from solid tumors
- May be useful in conditions characterized by temporary, rapid bone resorption (e.g. aromatase inhibitor treatment)

**DOSE FOR OSTEOPOROSIS:**
- Given as 60 mg SC injection every 6 months
- Suppressive effect on bone resorption wears off by 6m after last dose

**ADVERSE EFFECTS:**
- Hypocalcaemia (2%)
- Serious infections including cellulitis (because RANK-RANKL system is used by immune cells)
- Eczema (10%)
- Osteonecrosis of jaw when used in higher doses for bone metastases in cancer treatment (expected because it’s a potent inhibitor)
- Atypical fractures reported (expected because bone turnover is suppressed almost completely)

**ANABOLIC DRUGS:**

**EFFECT OF ANABOLIC DRUGS ON BONE:**
- Increase activation frequency (number of BMUs)
- Increase amount of bone formed by each BMU (due to stimulation of osteoblast activity)

**MECHANISM OF ANABOLIC DRUGS:**
- Intermittent administration of PTH and teriparatide increases bone remodeling, with a relatively greater increase in bone formation than resorption (anabolic effect)
  - Acts by increasing recruitment and differentiation of osteoblasts and decreasing their apoptosis
  - Anabolic window appears to last about 12-18 months, after which effects fade
- This is followed by a subsequent stimulation of bone resorption

**TERIPARATIDE: rPTH(1-34):** sequence identical to the 34 n-terminal amino acids of human PTH

**MECHANISM OF ACTION:**
- Intermittent administration of PTH and teriparatide increases bone remodeling, with a relatively greater increase in bone formation than resorption (anabolic effect)
  - Acts by increasing recruitment and differentiation of osteoblasts and decreasing their apoptosis
  - Anabolic window appears to last about 12-18 months, after which effects fade
- This is followed by a subsequent stimulation of bone resorption

**EFFECTIVENESS:**
- In postmenopausal women with prior vertebral fractures (secondary prevention):
  - Decreased risk of both vertebral fracture by 65% and non-vertebral fracture by 53%
  - No significant decrease in risk of hip fracture (but study not powered for this)

**USES:**
- Severe osteoporosis in post-menopausal women
- Glucocorticoid-induced osteoporosis in high-risk patients
  - Given by once daily SC injection and is expensive

**ADVERSE EFFECTS:**
- Well tolerated but may induce hypercalcemia and/or hypercalciuria
- Treatment duration limited to 2 years
- Bone density increase will be lost on D/C unless followed with anti-resorptive agent
<table>
<thead>
<tr>
<th>Agent</th>
<th>Efficacy</th>
<th>Vertebral</th>
<th>Non-vertebral</th>
<th>Hip</th>
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<tbody>
<tr>
<td>HRT (CEE + MPA)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Raloxifene</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Bisphosphonates</td>
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<tr>
<td>Etidronate</td>
<td>+</td>
<td>50% RR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5% ARR</td>
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<tr>
<td>Alendronate, Risedronate, Zoledronate</td>
<td>+</td>
<td>25-50% RR</td>
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<td></td>
<td>1% ARR</td>
<td>45-70% RR</td>
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<td>60% RR</td>
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<td>Teriparatide</td>
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<tr>
<td></td>
<td>65% RR</td>
<td>53% RR</td>
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</tbody>
</table>

SUMMARY OF AGENTS USED FOR OSTEOPOROSIS: (1 - RR = RRR) (use McCormack’s lecture for exam purposes??)