Women’s Health
What’s New in Medicine 2012

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Disclosure: Dr. Sutton has no significant financial interest in any of the products or manufacturers mentioned.
Objectives

• What is new in the management of osteoporosis?
• What is new in the management of menopause?
• What is new in cervical cancer screening?
What is new in the management of osteoporosis?

• Key reference:
How big a problem is osteoporosis?

- Estimated 1.5 - 2 million osteoporosis-related fractures occur in the United States each year.
- Among white women, prevalence of osteoporosis is:
  - ~20% for ages 60-69
  - ~33% for ages 70-79
  - ~50% for ages ≥ 80

What is new in the management of osteoporosis?

• A 65 year old woman whose recent DEXA scan showed osteoporosis of the hip (T-score -2.7) returned to discuss results and treatment.
• She has looked online and is concerned about risks of interventions. She has read that calcium causes heart attacks, drugs like Fosamax cause hip fractures and jawbone death, and calcitonin causes cancer.
• What about those risks?
Calcium & Vitamin D

• Calcium ~1200 mg/day
  – Crucial for heart, nerves, & muscle (and bone)
  – 1 kg of calcium in body, urinary loss 200 mg/dy
  – Only route in is via GI tract, but absorption is poor
    • Needs acid environment (e.g. with food) + Vitamin D
    • 1200 mg/dy ingested -> ~200 mg/dy absorbed
    • Best absorbed when spread out (absorption maxes out with 400-600 mg ingested at a time)
      • Diet may be preferable source, but is difficult for many

• Vitamin D ~800 IU/day
Does calcium raise cardiovascular risk?

- News in 2010-2011 seemed to suggest this
- No RCTs have specifically examined effect of Ca supplement use on CVD events or related mortality
  - WHI CaD arm: No difference on first blush; higher risk reported on relook in 2010
    - Only 59% of subjects took \( \geq 80\% \) of prescribed Ca doses
    - Controls could take Ca (54% did, at entry)
  - BMJ 2011 meta-analysis: 25-30% increase
    - Most studies didn’t use CVD as a primary outcome
    - Nor were groups assigned to balance CVD risks

Does calcium raise cardiovascular risk?

• Prospective observational studies: Neutral to positive effect

• Iowa Women’s Health Study: 33% reduction
  • 34.4K postmenopausal women observed over 8 yrs
  • Study was designed to look for CVD events
  • Risk lower for highest quartile of Ca intake vs lowest
    (>1425 mg/dy vs <696 mg/dy)
  • Same risk reduction for dietary & supplemental Ca

• Neither milk intake nor vitamin D intake reduced risk after adjustment for calcium intake

Other effects of Ca supplementation

• Adverse (from supplement as opposed to diet):
  – Possible higher risk of nephrolithiasis
    • Hypercalciuria predisposes to bone loss and stones
    • 17% higher risk in WHI CaD study
    • Neutral to beneficial effect in other studies
    • Dietary calcium reduces stone risk (binds oxalate in gut)

• Beneficial (whether supplement or diet):
  – Improvement in lipids and blood pressure
    • Small but statistically significant
  – Reduced risk of osteoporosis and fractures
  – Reduced PTH level
What about osteoporosis medications?  
AHRQ 2012 Update: Level of Evidence for Benefit

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Vertebrae fracture</th>
<th>Non-vertebrae fracture</th>
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<tbody>
<tr>
<td>Bisphosphonates:</td>
<td>High level</td>
<td>High level</td>
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<tr>
<td>Alendronate (Fosamax)</td>
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<td>Risedronate (Actonel)</td>
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<td>Zoledronic acid (Reclast)</td>
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<tr>
<td>Ibandronate (Boniva)</td>
<td>High level</td>
<td>Insufficient evidence</td>
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<tr>
<td>Denosumab (Prolia)</td>
<td>High level</td>
<td>High level</td>
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<tr>
<td>Teriparatide (Forteo)</td>
<td>High level</td>
<td>High level</td>
</tr>
<tr>
<td>Raloxifene (Evista)</td>
<td>High level</td>
<td>No benefit shown</td>
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</tbody>
</table>

1) Calcitonin (Miacalcin) **excluded**: “most authorities no longer consider [it] to be appropriate treatment for osteoporosis”
2) Estrogen as effective as bisphosphonates overall, but efficacy unproven in women with established osteoporosis (& has risks)
How effective are the 4 bisphosphonates approved for osteoporosis in US?

• ~50% reduction in fracture risk in 3-5 yrs of use in postmenopausal women with osteoporosis (range 25-77%), in many trials
  – Additional benefit with extension of use
  – Zoledronic acid 1x/yr: 30-35% reduction in 2 yrs
  – Exception: Ibandronate (Boniva) for non-vertebral fractures (BMD ↑ 3.5% but no difference in fracture rate at 3 yrs vs placebo)

Bilezikian Am J Med 2009 Feb;122(2 Suppl):S14-21
What are the benefits & risks of bisphosphonates?

• **Benefits:**
  – Reduced risk of osteoporosis-related fractures
  – Prevent or slow skeletal involvement in cancer

• **Risks:**
  – Atypical femoral fractures – we’ll discuss today
  – Osteonecrosis of the jaw – we’ll discuss today
  – Hypocalcemia
  – Renal insufficiency
  – Fever, musculoskeletal symptoms
  – Esophagitis, ?cancer (oral not advised in Barrett’s?)
  – Esophageal ulceration
  – Unclear association: Atrial fib; ophthalmic side effects
What about osteonecrosis of the jaw?

• Risk factors include:
  – IV >> oral route for the bisphosphonate
  – Longer duration of use
  – Cancer (esp myeloma, metastatic breast cancer)
  – Cancer therapies (chemotherapy, radiation)
  – Dental or jaw bone issues: extractions, implants, poor dentition, poorly fitting dentures, injury
  – Ongoing bone loss risk factors: glucocorticoids, smoking

• AHRQ 2012 Update:
  – The risk of “osteonecrosis of the jaw in patients taking bisphosphonates for osteoporosis prevention or treatment...[is] small, ranging from less than one to 28 cases per 100,000 person-years of treatment.”
What about dental surgery?

• American Association of Oral and Maxillofacial Surgeons in position paper (2006) and update (2009) advise:
  – Oral bisphosphonate use $< 3$ yrs and have not taken corticosteroids concomitantly: Perform dental surgery (extractions and implants) as usual
  – Oral bisphosphonate use $< 3$ yrs and have taken corticosteroids concomitantly: Discontinue oral bisphosphonate 3 months before performing dental surgery; restart it when bone has healed
  – Oral bisphosphonate use $>3$ yrs: Discontinue oral bisphosphonate 3 months before performing dental surgery; restart it when bone has healed
What about atypical fracture risk?

• Case reports starting in 2009

• Subsequent observational studies vary: “no increase in relative risk” to “small increase in absolute risk”

• Currently, many sources advise stopping a bisphosphonate after 5 yrs (except for patients still at high fracture risk)
  – FDA (5/2012) advises stopping after 3-5 yrs in patients at lower risk (younger without history of fracture, or BMD close to normal)
  – FDA (5/2012) advises that those at higher risk (older pts, those with fracture history, and BMD still in the osteoporotic range) may benefit from continuing
What does the AHRQ report say?

- “Limited data...support a possible association...Data are not consistent...[yet] were sufficient for FDA to issue a Warning...”

- “One large RCT showed that after 5 years of initial alendronate therapy, vertebral fracture risk and nonvertebral fracture risk were lower if alendronate was continued for an additional 5 years instead of discontinued” ... if T-score was \( \leq -2.5 \)

  Schwartz J Bone Miner Res 2010 May;25(5):976-82

- Another study cited found “approximately one new fragility fracture for every 100 fewer hip fractures”

  Wang J Bone Miner Res 2011 Mar;26(3):553-60
What’s the data for atypical fractures like?

• Case-control study in Ontario of women ≥ 68 yrs with subtrochanteric or femoral shaft fractures over 6 yr period

• Bisphosphonate use for ≥ 5yrs (vs short use) associated with:
  – AOR* 2.74 for atypical fracture (95% CI: 1.25-6.02)
  – AOR* 0.76 for typical osteoporotic fracture (95% CI: 0.63-0.93) *Adjusted odds ratio

• Absolute risk of atypical fracture in 52.6K women:
  0.13% in 6th year, 0.22% in 6th or 7th yr

  Park-Wyllie et al. JAMA 2011 Feb 23;305(8):783-9
What about calcitonin?

- Calcitonin-like protein family
  - Calcitonin, 32 amino acids
    - Made in C cells in thyroid
    - Receptors in osteoclasts, kidney, some areas of brain
    - Was approved for osteoporosis without having to demonstrate fracture reduction (1984 & 1991)
  - Calcitonin gene-related peptide, 37 amino acids
    - Alternate splicing of same gene
    - Role as pain modulator, possibly neurotransmitter
    - Found in elevated levels in some cancers
Oral calcitonin is being studied...

- Caprylic acid derivative to ↑ bioavailability
- 565 women (mean 66.5 yr) randomized to oral calcitonin tablet (OCT), nasal calcitonin spray (NCS), or placebos, followed 48 weeks
- Higher blood levels from oral than nasal form
- Lumbar spine BMD improved on OCT
  - OCT ↑ 1.5% ± 3.2%
  - NCT ↑ 0.78% ± 2.9% & placebo ↑ 0.5% ± 3.2%
- Trend toward ↑ trochanteric BMD with OCT

Binkley et al J Bone Miner Res 2012 Aug;27(8):1821-1829
...which led to concerns in Europe

- In July 2012, a committee of the European Medicines Agency (EMA) recommended removal of osteoporosis as indication for calcitonin
- Preliminary (unpublished) findings from two studies of an oral calcitonin tablet suggested possible higher risk of prostate cancer vs placebo
- Committee then analyzed RCTs of osteoarthritis and osteoporosis, concluding there was an 0.7 – 2.4% increase in absolute risk of cancer for long-term treatment with nasal or oral calcitonin vs placebo
- Low efficacy, more potent options also played a role (benefit not felt to outweigh potential risk)
AHRQ treatment of Calcitonin

• In 2007 report, rated as “fair” for reduction of vertebral fractures

• In 2012 update, “calcitonin [was] excluded from [the] report at the subject matter experts’ request, as most authorities no longer consider calcitonin to be appropriate treatment for osteoporosis”
What is new in the management of osteoporosis?

• Calcium:
  – Concern over CVD risk was based on studies not designed to look for this outcome
  – Older studies: safe & beneficial via diet, safe & beneficial via supplement (except kidney stone risk)
• Calcitonin is falling out of favor (little benefit)
• Bisphosphonates are favored approach:
  – Alendronate and risedronate show fracture reduction at all sites and are oral so pose less risk of osteonecrosis of the jaw (than IV)
  – Consider stopping after 5 yrs (unless high fracture risk)
What about benefits vs risks of bisphosphonates?

• Bisphosphonates reduce fracture risk significantly: ~50%
• Risk of atypical femoral fracture: ~1 new case for every 100 hip fractures prevented
• Risk of osteonecrosis of the jaw from bisphosphonates taken for osteoporosis prevention or treatment: <1 case to 28 cases per 100,000 person-years of treatment
What is new in the management of menopause?

• 49 yo woman presents with hot flashes and sweats which waken her several times a night. Her menses are now occurring infrequently and irregularly, typically around every 3-4 months over the past year. She has already tried eating soy and taking an OTC herbal product without relief, and wonders what she can take that’s safe. She has been healthy. FMH negative. Her annual exam and mammogram were normal 8 months ago.
Where does menopausal hormone therapy (HT) stand?

- Management should be individualized.
- When vasomotor or genitourinary symptoms are moderate to severe and not controlled by other measures, hormone therapy is an option.
- If hormone therapy is considered, the risks of hormone therapy should be discussed.
- The lowest dose of estrogen offering symptom relief should be used, for the shortest period of time necessary.
When is HT indicated?

• Systemic HT is indicated, short term, for the treatment of moderate-severe vasomotor symptoms in women without contraindications (CHD, CVA, DVT/PE history, breast cancer, liver disease...)

• Vaginal estrogen is indicated for the treatment of women with symptomatic atrophic vulvovaginitis for which OTC lubricants are not sufficient.
Not for primary prevention of disease (including osteoporosis)

• “Estrogen plus progestin and estrogen alone decreased risk for fractures but increased risk for stroke, thromboembolic events, gallbladder disease, and urinary incontinence. Estrogen plus progestin increased risk for breast cancer and probable dementia, whereas estrogen alone decreased risk for breast cancer.”

Any newly recognized cancer risks?

• Lung cancer risk higher on HT: 75% ↑ risk in lung adenocarcinoma in a systematic review & meta-analysis (studies pooled various subgroups)
  Greiser et al, Maturitas 2010 Mar;65(3):198-204

• WHI: 70% ↑ risk of death from lung CA
  – No difference in rate of diagnosis with lung CA
  – No increase on estrogen only (few cases)
  – Difference was in non-small cell (not small cell)
  – Estrogen + progestin: 87% ↑ mortality from NSC lung CA
Are there safer forms of HT?

• Several large studies have found estradiol patch safer than oral forms of estrogen (for HT):
  – No increase risk in DVT/PE on patch
  – No increase in risk of CVA (in doses up to 0.05 mg/dy)
  – Less increase in risk of gallbladder disease

• Micronized progesterone may be safer
  – No increase in DVT/PE or in breast cancer?
    Simon Cimacteric 2012 Apr;15 Suppl 1:3-10

• Topical gel, cream, foam not specifically studied for these outcomes (and more expensive)
What forms of HT are there?

• Estrogen: systemic forms
  – *Transdermal* vs oral (also transvaginal, parenteral)
  – *Estradiol* vs conjugated or esterified
  – Generic vs brand name (cost; acceptability; adhesive)

• Progestin (to mitigate estrogen’s endometrial CA risk)
  – Oral vs intrauterine (also transdermal, intravaginal)
  – Micronized progesterone (oral) vs synthetic progestins

• Estrogen: vaginal forms
  – 3 forms as 4 brands, similar pricing: estradiol vaginal tablets (Vagifem 10 mcg), estradiol vaginal ring (Estring), estradiol vaginal cream (Estrace), Premarin vaginal cream
Non-hormonal approaches for vasomotor symptoms

• Behavioral
• Alternative
• Botanical
  – Phytoestrogens (soy, red clover, flax)
  – Black cohosh
  – Evening primrose oil
• Prescription medications
Prescription non-hormonal medications (all off-label for this indication)

• Gabapentin – best studied, esp in breast cancer
  – Dose range 300-2400 mg/dy; most studies 900 mg/dy
• SNRIs
  – Venlafaxine (Efexor) at 25-75 mg/dy (or higher)
  – Desvenlafaxine (Pristiq) (high rates of nausea)
• SSRIs – variable efficacy for vasomotor symptoms
  – Citalopram & es-citalopram (Lexapro) more effective?
  – Avoid SSRIs (esp paroxetine) if pt is on tamoxifen
• Clonidine - limited by side effects – best if HTN
What is new in management of menopause?

• Continue to try to limit HT use to moderate-severe symptoms not adequately treated by other approaches
• Consider transdermal estradiol as risks appear less (for CVA for $< 0.05 \text{ mg/dy}$, DVT/PE, gallbladder disease)
• Consider micronized progesterone (Prometrium) or intrauterine levonorgestrel (Mirena) in women on estrogen with intact uterus, to protect endometrium from estrogen
• Reliably lowest estrogen exposure from vaginal route is now vaginal estradiol tablets (Vagifem 10 mcg 2x/wk; ring remains low too (Estring, averages $\sim 7 \text{ mcg/dy}$)
What is new in cervical cancer screening?

• 35 yo woman presents for annual exam. Her last Pap smear was 3 years ago and was normal, after a series of normal Pap smears annually since she became sexually active at age 18. She has been married & monogamous for 8 years.

She has heard that it might be possible to do Pap smears even less frequently and wonders whether that’s really safe.
ACS/ASCCP & USPSTF guidelines: 3/2012

- For women 21-29: Pap every 3 yrs
- For women 30 – 65 with a cervix:
  - Pap every 3 yrs, or
  - “Co-screening” with both Pap and high-risk HPV
    - If both are negative/normal, next screen in 5 years
    - Co-screening preferable per ACS/ASCCP
- Stop screening after hysterectomy, and age 65
- However, annual/ongoing Pap still indicated if:
  - Immunosuppression (e.g. from medication or HIV)
  - PMH of CIN-2 or worse -> annual Pap x 20 years
Multiple large studies show HPV better than Pap at finding dysplasia

- HPV prevalence is higher at younger ages
  - Infection in younger women commonly clears
  - More likely to be persistent when present in older women
- HPV is more sensitive for identifying dysplasia than Pap; specificity depends on likelihood it’s persistent
- Screening with HPV in women ≥ 30 yrs old results in:
  - Detection of more dysplasia than Pap alone
  - Detection of dysplasia at an earlier stage
  - Better subsequent reduction in advanced dysplasia (CIN-2/3) in future years
What’s currently under investigation?

• Home collection of vaginal swab for HPV
  – Pap done only if HPV+
  – Sensitivity & specificity of this approach is comparable to standard screen & cost lower

• Biochemical markers of neoplasia

• Correlation between HPV+ and dysplasia in immunosuppressed women
What is new in cervical cancer screening?

• Stop screening average-risk women* after hysterectomy, and after age 65

• For average-risk women* age 30 – 65 with a cervix, “co-screening” with Pap + high-risk HPV has better sensitivity and specificity than Pap alone (though either approach is acceptable)
  – Extend screening interval to 5 yrs if both are negative
  *Not immunosuppressed; no CIN-2+ in past 20 yrs

• For women 21-29, do Pap only (not HPV) q3yrs
  – order HPV as reflexive only if Pap returns ASCUS
Thank you!

Questions?

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