

Cancer Treatment Related Pain

A pharmacological approach

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Acute

Common

- Flare due to XRT*
- Radiation mucositis*
- Chemotherapy mucositis*
- Chemotherapy
 - Taxanes*
 - Oxaliplatin*
 - Hand foot syndrome*
- Filgrastim
- Bisphosphonate (1st cycle)*
- Infusion vein phlebitis

Uncommon

- Pain at site of tumor* (vinorelbine)

* May limit treatment

Chronic

Common

- **Post surgical**
 - Breast surgery
 - Neck dissection
 - Thoracotomy
- **Aromatase inhibitors***
- **Peripheral neuropathy***
- Post chemotherapy

Uncommon

- XRT plexopathy, fibrosis
- **Osteonecrosis**
 - Bisphosphonates (jaw)
 - Radiation

* May limit treatment

Complexity Versus Cancer Pain

Easier

- Natural hx stable to improving
- Time to titrate
- Majority NED = fewer contraindications
- Less organ dysfunction

More challenging

- Substance abuse issues (ENT)
- Opioids 3rd to 5th line
- Sedation less well tolerated
- Fewer options

Drug approach to neuropathic pain

- As far as we know, the etiology/location does not determine efficacy i.e. neuropathic is neuropathic
- Few adequately powered RCTs

RCTs for Drug Rx of Chronic TRP

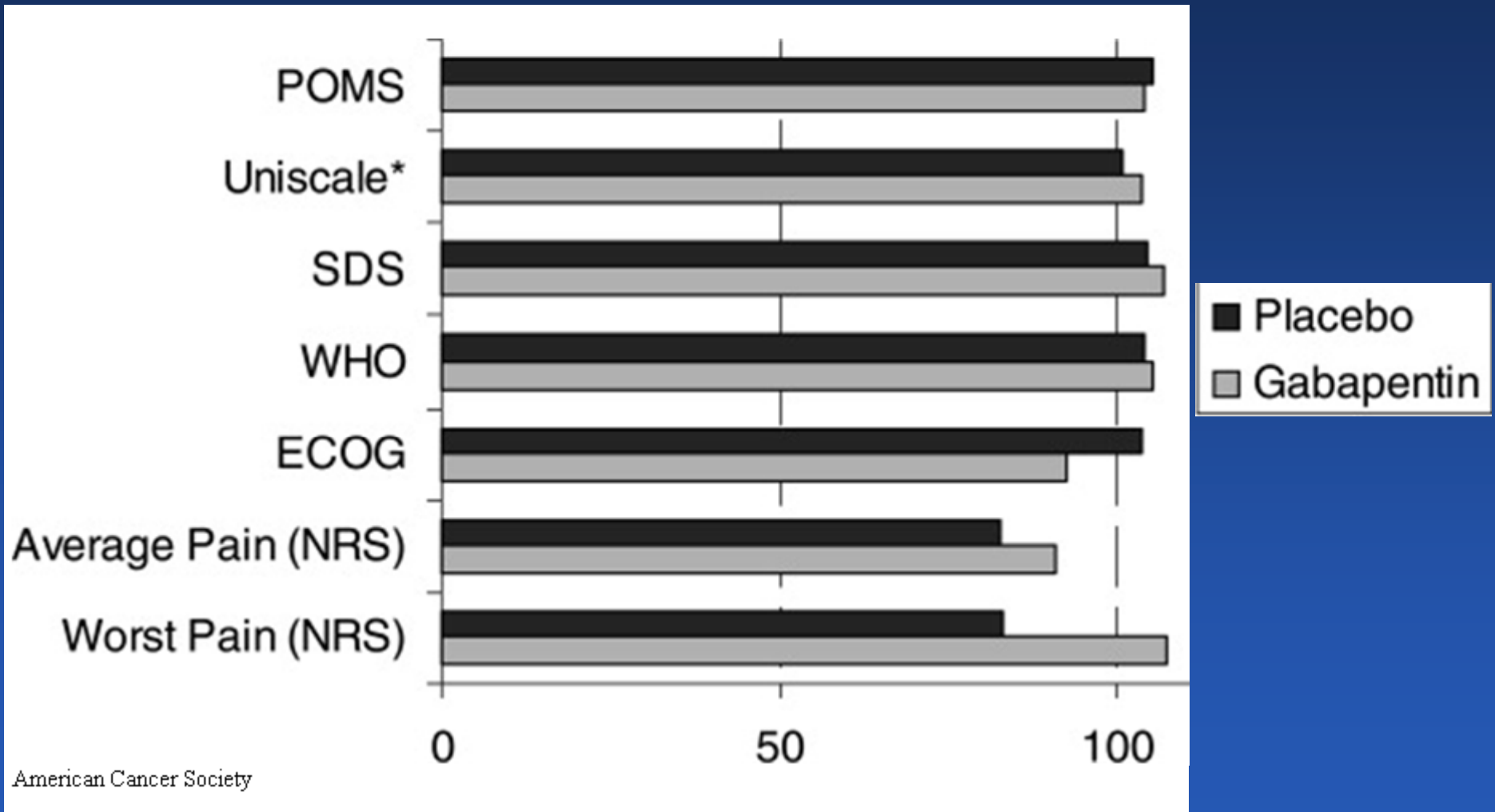
- Amantadine post surgical N = 15 xover
- Capsaicin post surgical N = 99 xover
- Venlafaxine post surgical?? N = 13 xover
- Levetiracetam post surgical N = 25 xover
- Lidocaine patch post surgical N = 18 xover
- Amitriptyline chemo neuropathy N= 44 (trend)
- Nortriptyline chemo neuropathy N = 51 xover
- Lamotrigine chemo neuropathy N= 131
- Gabapentin chemo neuropathy N= 115 xover

Chronic Post chemotherapy Neuropathy

Rao Cancer 2007; 110:2110-8

- Entry criteria loss of sensation OR pain
- No opioids allowed pre-study
- Randomized to gabapentin target dose 2700 mg/day or placebo
- N = 115

Mean scores at 6 weeks (% of baseline)



* Higher score = less severe for uniscale; other scales the opposite

Mean scores at end of 6 weeks

- No sig difference in outcome measures
- CIPN doesn't cause upregulation of $\alpha 2\delta 1$ subunit?
- Cautionary notes
 - Modest sample size
 - Only 60% completed trial
 - Mean baseline avg and worst scores ~ 4/10 and 5/10 respectively (mainly loss of sensation, NOT pain in this group)

In practice

- No good evidence base.
- Use the same approach as you would in the non cancer patient

In practice

- Typical approach for neuropathic pain of benign origin
 - TCA with low anticholinergic activity
 - Gabapentin/pregabalin
 - Cannabinoid
 - Opioids
 - Methadone
- Note: a couple of reports of menthol for neuropathic pain (“Absorbine Jr?”)

Chronic Post Surgical Pain

- 65 year old man with Ca tongue
- Radical neck dissection 5 months ago for recurrent disease in a neck node
- Severe burning, electric shock, some allodynia over neck/shoulder region
- Not improving
- Surgeon concerned about ongoing opioids

Chronic Post Surgical Pain

- Some help with Tylenol #3
- Unsuccessful trial with carbamazepine, amitriptyline 75 mg and gabapentin 2700 mg
- What are the issues?
- How would you proceed?

Issues

- History of substance abuse? If so or other red flags, we do urine toxicology.
- Sometimes swallowing issues but usually not limiting unless trismus
- Xerostomia not a contraindication to TCA
- No cardiac or renal disease
- What about capsaicin cream?

QID capsaicin cream vs placebo N=99

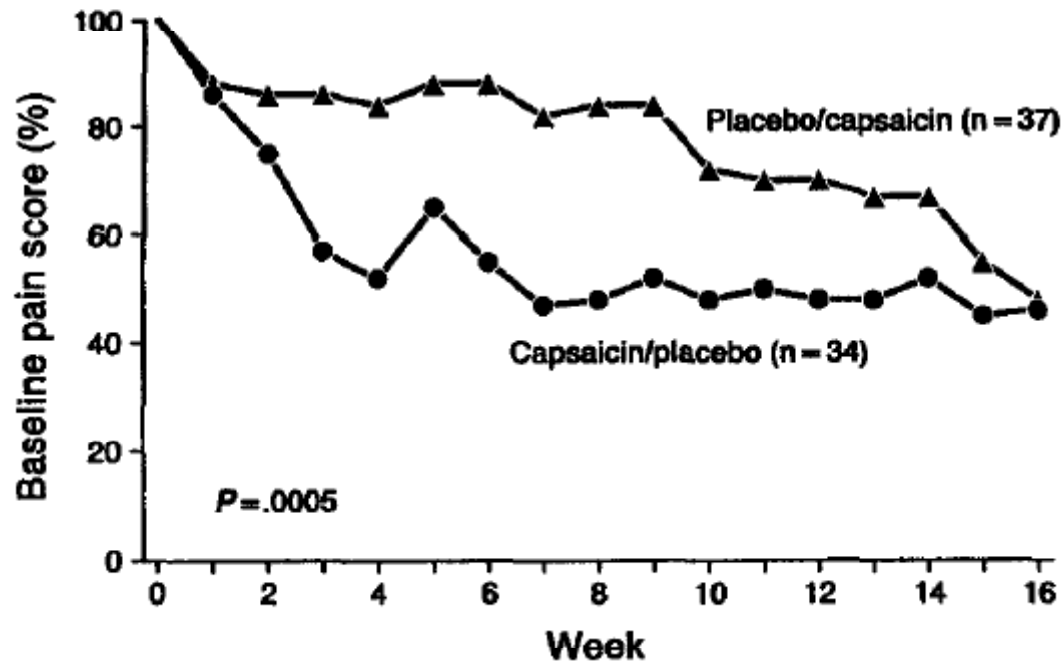
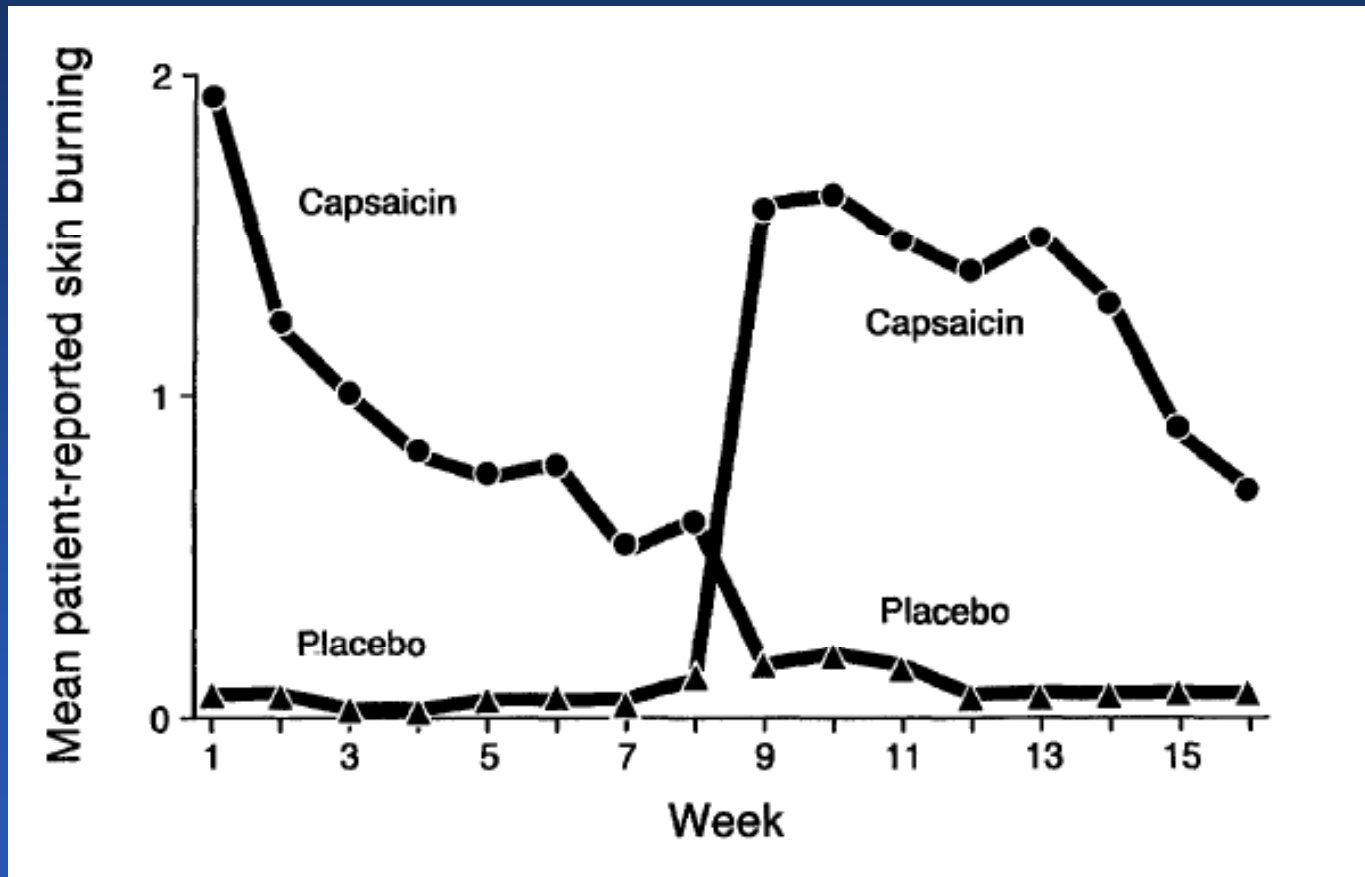


Fig 2. Changes from the baseline pain score are illustrated for the two study arms. After 8 weeks of treatment with one compound, patients were crossed over to the alternative compound in a double-blind manner.

Capsaicin

- Strong preference in “responders” to capsaicin (60% vs 18%)
- ~ 50% severe to very severe burning sensation in skin (decreases over time)
- 35% had a moderate cough
- Withdrawal rate on capsaicin similar to placebo (trial effect)
- Outside of a clinical trial there is a LOT of withdrawal plus its fussy (QID)

QID capsaicin cream vs placebo



In this case

- The primary raises concerns about substance abuse but no red flags
- Unsuccessful trial of nabilone, amantadine, hydromorphone 5 fold titration (? 25% relief or “none”)
- Started on oxycodone, section 16 application for outpatient methadone

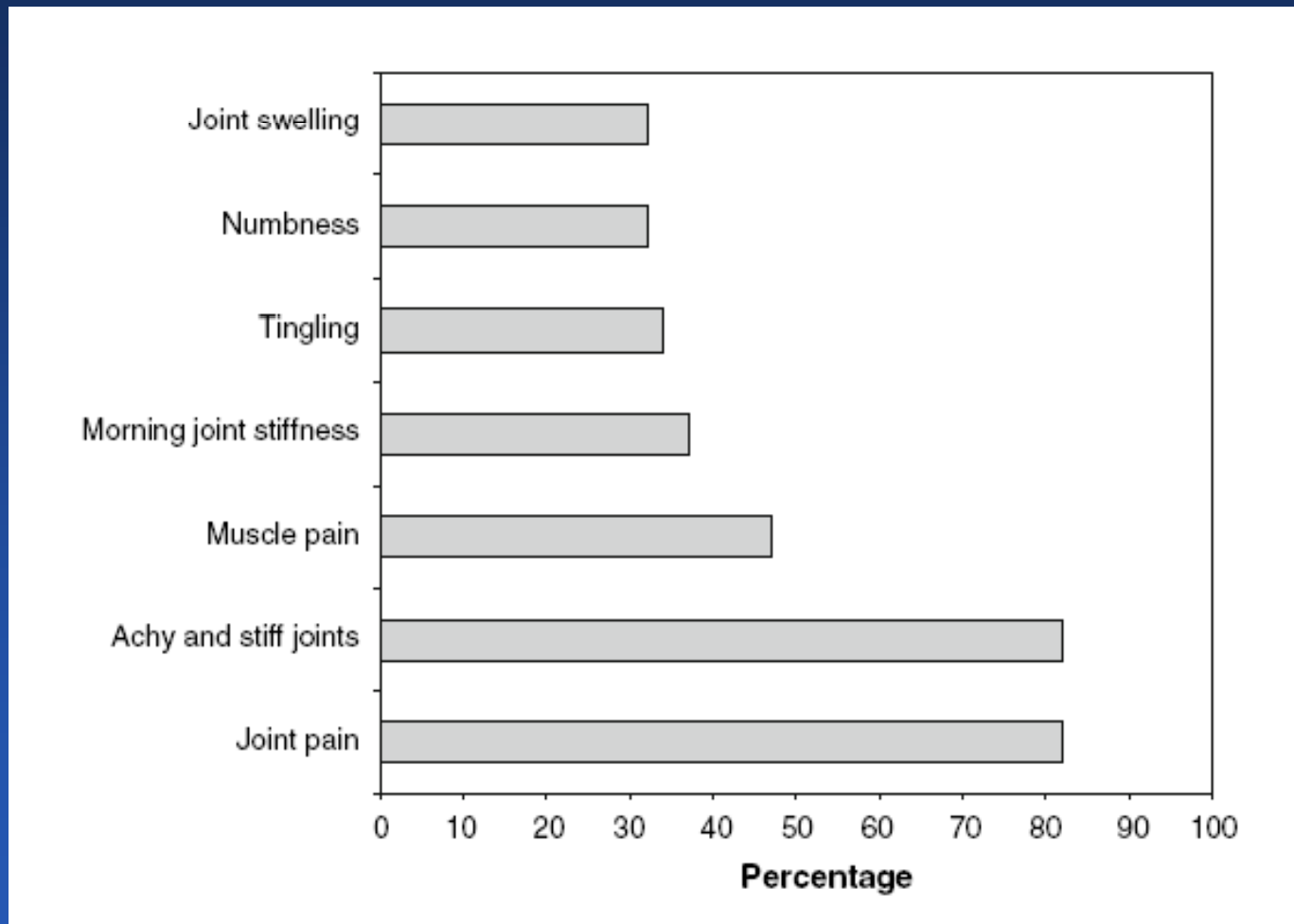
Breast cancer patient on letrozole

- Adjuvant therapy in a 55 year old with a 1 cm, grade II, node negative cancer
- After 3 months on the AI develops severe knee pain (past osteoarthritis there), shoulder pain and finger stiffness
- Function is impaired – walking, sleeping, golfing
- Confidence is high that this is NOT due to recurrent cancer. Why?

Incidence of MSK Symptoms with AIs

- Henry *Breast Cancer Res Treat* 2008
- 100 patients with 6 month follow up on adjuvant AI
- Completed HAQ and VAS @ baseline, 1, 3, 6, 12 months
- 38 referred to rheumatology
- 10% stopped therapy

Symptom frequency in those referred to hematology (n=38)



Rheumatologic diagnoses

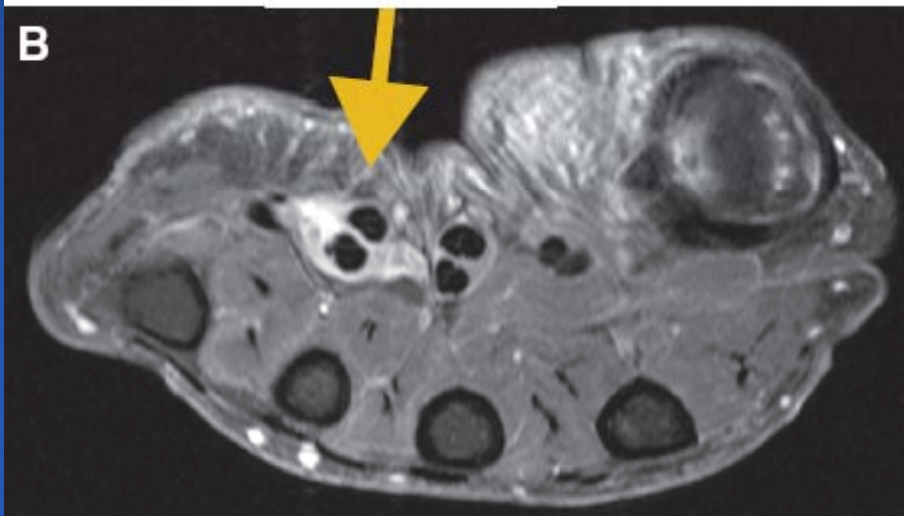
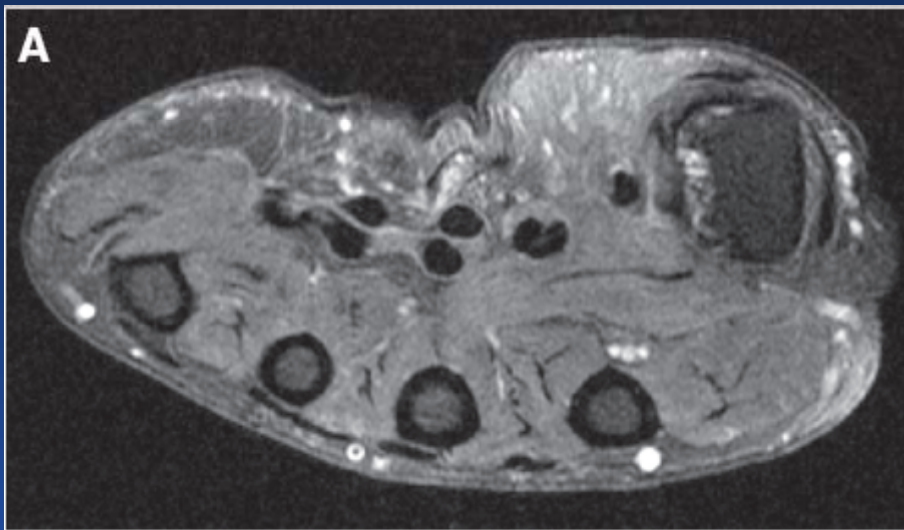
Diagnosis	Number of patients (%)
Bursitis	8 (21.1%)
Trochanteric	6 (15.8%)
Carpal tunnel syndrome	8 (21.1%)
Osteoarthritis	11 (28.9%)
Knee	3 (7.9%)
Hand	2 (5.3%)
Tendonitis	14 (36.8%)
Rotator cuff/shoulder	8 (21.2%)
Wrist	3 (7.9%)
Elbow	2 (5.3%)
Patellofemoral syndrome	7 (18.4%)

Some subjects had more than one diagnosis

Aromatase inhibitor associated pain

- Aromatase inhibitors associated with musculoskeletal complaints in ~1/3 of patients (more if recent paclitaxel).
- Can start days to many months later
- Can improve spontaneously
- Outside of clinical trials may lead to 20% stopping the drug
- Enhancing tendons/synovia on MRI and increased intra-articular fluid

Pre/post MRI flexor tendon changes



Morales J Clin Oncol 2008

Approach

- No imaging unless true uncertainty
- Educate: recurrence rate of cancer much lower in those experiencing Sx
- Treat with NSAID/codeine
- Or stop medication x 3 weeks. If major improvement, switch to another aromatase inhibitor
- ?? Role for vitamin D

Summary

- Treatment related pain is common
- Diverse etiologies - neuropathic is common
- Little high quality data on efficacious Rx
- Management of neuropathic pain is the same whether cancer or treatment related except for leaving opioid titration until later and futility of dexamethasone
- Reassurance that cancer is NOT the cause is often important

Questions?