Pain in Fibrous Dysplasia/McCune-Albright Syndrome

Alison Boyce, MD
FDSS 2015 Convention
How Do We Define Pain?

• An unpleasant sensory and emotional experience associated with actual or potential tissue damage

• Chronic pain: Persistent or recurrent pain lasting weeks to years (3 months)
## Pain in FD: Prevalence and Treatment

### Pain Anywhere (Y/N)
- Adults: 81%
- Children: 49%

### Mean Pain Scores
- Adults: 4.1 *
- Children: 2.8

### % that used treatment
- Adults: 26%
- Children: 44%

- Pain increases with age
- Pain is undertreated in children

*Kelly, Osteoporosis Int, 2007*
No correlation between amount of FD and pain

Kelly, Osteoporosis Int, 2007
Causes of Pain in FD: Many

• Orthopedic
  – Fractures (acute or impending)
  – Bone cysts
  – Surgical hardware problems

• Metabolic
  – Phosphate Wasting
  – “Intrinsic” FD pain

• Functional
  – Abnormal gait
  – Deformities
  – Muscle weakness
  – Arthritis
Approach to Pain Management in FD

1. Prevent & treat fractures & deformities
2. Evaluate & treat endocrine disease
3. Optimize physical function
4. Optimize psychosocial and emotional function
5. Pharmacologic and non-pharmacologic treatments

There are no therapies to fix the underlying problem in FD
But we can be proactive in preventing secondary complications that lead to pain
And we can be proactive to develop skills to cope with pain
Phosphate Wasting in FD

Low Blood Phosphorus

FD + rickets

Osteomalacia, Bone Pain

renal phosphate wasting

o = osteoid  b = bone
FGF23 causes Phosphate Wasting in FD

FGF23 is made by FD cells

May show up during times of rapid growth (ex: infancy, puberty)
May resolve in adulthood
Hypophosphatemia Increases Fractures

Fracture rate (# fractures/patient/year)

Age (years)

- 0-5
- 6-10
- 11-15
- 16-20
- 21-25
- 26-30
- 31-35
- 36-50

- hypophosphatemia
- normal phosphorus

(Leet, JBMR, 2004)
Hypophosphatemia: Treatment

1. Phosphorus Supplements
   - Pills, powder, or liquid
   - Short-acting, must give 3-5 times a day
   - Diarrhea, GI discomfort

2. Calcitriol
   - Prevents hyperparathyroidism (major side effect of Phosphorus supplements)
   - May increase urine calcium
     • Monitor urines and kidney ultrasounds
Pharmacologic Management of FD Pain
FD Pain Management: Pharmacologic Therapy

<table>
<thead>
<tr>
<th>Pain Treatments</th>
<th>Adults (n=35)</th>
<th></th>
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<th>Children (n=43)</th>
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<tbody>
<tr>
<td></td>
<td>% that used it</td>
<td>% reported relief</td>
<td>% that used it</td>
<td>% relief reported</td>
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<tr>
<td>NSAIDs</td>
<td>57%</td>
<td>56%</td>
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<td>56%</td>
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<td>Narcotics</td>
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<td>47%</td>
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<td>Bisphosphonates</td>
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<td>Alternative Treatments</td>
<td>17%</td>
<td>52%</td>
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<td>11%</td>
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</table>
FD Pain Treatment 3 Step Ladder

1 mild
ASA
Paracetamol
NSAIDs
± Adjuvants

2 moderate
Bisphosphonates
- Zoledronate
- Pamidronate
± Adjuvants

3 severe
Opioids
- Morphine
- Fentanyl
- Oxycodone
- etc
± Adjuvants
FD Pain Management: Pharmacologic Therapy

• Paracetamol (Tylenol)
  – Analgesic
  – Monitor liver enzymes

• Non Steroidal Anti-inflammatory Drugs (NSAIDs, ibuprofen, etc.)
  – Analgesic & anti-inflammation effects
  – Possible GI and kidney side effects
  – Many formulations; may act differently
Pharmacologic Therapy: Opioids (Narcotics)

• Block pain perception in the brain
• Very effective
• Central Nervous System effects
  – Sedation
  – Tolerance
  – Dependence (versus Addiction)

Children who require chronic narcotic therapy should be under the care of a pain medicine team
What about bisphosphonates?

- Synthetic analogues of pyrophosphate
- Used to treat disorders of low bone mass or high bone activity
- Taken up into skeletal matrix and inhibit osteoclasts (bone breakdown cells)
- Half life >10 years
Bone Remodeling Cycle

Osteoclasts chew the bone up

Osteoblasts fill in the holes
Types of Bisphosphonates

**Intravenous**
- Pamidronate (Aredia)
  - 3 hr infusion, ~every 3 months
- Zoledronic acid (Reclast)
  - 30 min infusion, ~every 6 months
- Ibandronate (Boniva)
  - Rapid infusion, ~every 3 months

**Oral**
- Alendronate (Fosamax)
  - Weekly pill
- Risedronate (Actonel)
  - Daily or weekly pill
What types of patients use bisphosphonates?

• FDA-approved for treatment of adults with:
  – Osteoporosis
  – Paget’s disease
  – Bone tumors and bone metastases
  – High blood calcium levels

All other uses are “off-label”
Side Effects of Bisphosphonates

• Flu-like symptoms (first 1-2 doses)
  – Temporary, manageable with Tylenol/Motrin

• Low blood calcium
  – Adequate dairy, vitamin D and calcium supplements

• GI disease (reflux, ulcerations): Oral forms
  – Can be severe!
  – STOP drug if developing symptoms
Osteonecrosis of the Jaw

- **Very** rare, few cases in FD
- Assoc w long-term, high dose, IV infusions, invasive dental procedures
- No cases in kids or adolescents
- Complete planned dental work prior to starting
Bisphosphonates in FD

• Early case reports
  – Most show improvement in pain
  – Conflicting reports about radiographic effects on FD lesions

• Clinical trial in alendronate (oral form) at NIH:
  – 40 patients
  – Placebo-controlled
Placebo-Controlled Trial of Alendronate in FD

Compared to placebo, alendronate decreased markers of bone resorption in the blood

Boyce, JCEM 2014
Alendronate Did Not Improve FD Appearance

Start of Study

Alendronate-Treated

After 2 years

Placebo-Treated
Alendronate did not improve pain
NIH Experience with Bisphosphonates

• Use only for pain
• Use only IV forms (Zoledronate, Pamidronate)
• Do not try to normalize bone resorption markers
• It may take more than one infusion to start working
• Try to use lowest dose at lowest frequency that is needed
Non-Pharmacologic Management of FD Pain
Chronic Pain Cycle

- Activity Avoidance
- Progressive Deconditioning
- More Pain with Activity
- Anxiety, Fear, Anger
- Increased Perception of Pain
- Depression & Social Avoidance

Physical
Psychological
Chronic Pain Cycle

Physical
- Activity Avoidance
- Progressive Deconditioning
- More Pain with Activity

Psychological
- Anxiety, Fear, Anger
- Depression & Social Avoidance
- Increased Perception of Pain

PAIN
Physical Activity

• Low/no impact weight bearing exercise as tolerated
  – Improve muscle strength and range of motion
  – Improve coordination, prevent falls
  – Improve non-FD bone health
  – Psychological benefits
Rehabilitation (PM&R, Physiatry): Function & Mobility

- Orthotics
- Assistive ambulation (cane, crutches, wheelchairs)
- Coordinate with PT: strength, ROM
- Coordinate with OT: activities of daily living, self care

Leg length discrepancy
Rehabilitation: Hydrotherapy

• Water is
  – Buoyant
  – Shock absorbing
  – Pain relieving
  – A force which resists bodily movement

• Can participate at any age
• Both swimming and upright activities are beneficial
Psychological Management in Chronic Pain

• Recognition of stress and negative emotion
• Problem solving
• Coping skills
• Behavioral
  – Relaxation training
  – Biofeedback
• Play therapy
• Individual, group, family
Psychological Therapy is Effective for Treatment of Chronic Pain

Cochrane Review, 2012
Other Non-Pharmacologic Techniques

• Massage Techniques
• Acupuncture
• Transcutaneous Electrical Nerve Stimulation
• Temperature modalities
  – Cold: reduce swelling and numb area
  – Heat: relaxes muscle and soft tissues
Energy conservation and work simplification

• Metabolic bone diseases are tiring. Endurance can be a problem.

• Be mindful about activities so you get the most bang for your buck!
  – Sit rather than stand
  – Keep frequently used items within easy reach
  – Plan the steps of an activity starting and be flexible
  – Consider adaptive equipment, school accommodations
Orthopedic Surgery

• Goals:
  – Correct fractures
  – Correct and prevent deformity
• May need to use specialized techniques
  – Osteotomy and intramedullary rods
  – Plates & screws -> bone might not hold them well, may cause stress risers
Pharmacologic and Non-Pharmacologic Pain Treatments: General Principles

• It’s a balancing act
  – **Risks** (known & unknown)
  – **Benefits** (certain & uncertain)
  – **Cost** (money, time, & energy)
HRQOL for FD Patients and US Population

Adults

- Physical Function *
- Mental Health
- Role-Physical *
- Role-Emotional
- Social Function
- Bodily Pain *
- General Health *
- Vitality

- US Population
- FD Patients
HRQOL for FD Patients and US Population

Children
Compassionate use study of denosumab for FD

Concerning side effects

Boyce, JBMR, 2012
Pilot Study of safety and efficacy of Denosumab to treat FD: T-D-0041

**on-drug phase**

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<th>Month</th>
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**D** = denosumab dose

**off-drug phase**

<table>
<thead>
<tr>
<th>Month</th>
<th>6</th>
<th>6.25</th>
<th>6.5</th>
<th>6.75</th>
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**End points**: bone turnover, pain relief, lesion size (18F-sodium fluoride PET/CT bone scan), biopsies (histomorphometry, Ki67 index), safety (calcium and phosphate)

**Status**: IRB-approved, Amgen support pending, projected start date fall 2015
Questions?