Conflicts-donations to Mayo

- Pfizer - pregabalin to prevent paclitaxel-induced neuropathy
- Competitive Technologies - donated Scrambler machines
Symptom Management of Therapy-Related Toxicities

Charles L Loprinzi MD
Regis Professor of Breast Cancer Oncology
Mayo Clinic
Rochester, MN
cloprinzi@mayo.edu
Issues

- Hot Flashes
- Vaginal Dryness
- AI arthralgias
- Paclitaxel neuropathy
Hot Flash Topics

- Overview of Mayo/NCCTG Randomized Hot Flash Studies
- Newer antidepressant meta-analysis
- CYP 2D6/Tamoxifen metabolism
- Gabapentin meta-analysis
- Gabapentin vs venlafaxine
- Stellate ganglion block
- Clinical hypnosis
Basic Study Design

Eligible Patients → Stratify → Randomize

Double Blind

Agent
Placebo
Mean Hot Flash Score % Reduction
Randomized Studies (positive trials)

- Placebo (n=420)
- Clonidine (n=75)
- Fluoxetine (n=36)
- Citalopram (n=57)
- Ven (vs MPA) (n=94)
- Venlafaxine (n=48)
- Megestrol (n=74)
- MPA 400 mg (n=94)
- Pregabalin (n=63)
Mean Hot Flash Score % Reduction
Randomized Studies (negative trials)

Week

0 1 2 3 4 5 6

Mg oxide

Flaxseed (n=69)

Vitamin E (n=53)

Soy (n=78)

Placebo (n=420)

Black Cohosh (n=58)
Mean Hot Flash Score % Reduction Randomized Studies (all trials)

Week

Mg oxide

Black Cohosh (n=58)
Placebo (n=420)
Soy (n=78)
Vitamin E (n=53)
Clonidine (n=75)
Fluoxetine (n=36)
Citalopram (n=57)
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Hot Flash Topics

- Overview of Mayo/NCCTG Randomized Hot Flash Studies
- **Newer antidepressant meta-analysis**
- CYP 2D6/Tamoxifen metabolism
- Gabapentin meta-analysis
- Gabapentin vs venlafaxine
- Stellate ganglion block
- Clinical hypnosis
Loprinzi, Fluoxetine 20 mg/g

Stearns, Paroxetine 10 mg/d
Stearns, Paroxetine 20 mg/d
Stearns, Paroxetine 12.5 mg/d
Stearns, Paroxetine 25 mg/d
Paroxetine total

Gordon, Sertraline 50 mg/d
Kimmick, Sertraline 50 mg/d
Grady, Sertraline 100 mg/d
Sertraline total

Loprinzi, Venlafaxine 37.5 mg/d
Loprinzi, Venlafaxine 75 mg/d
Loprinzi, Venlafaxine 150 mg/d
Venlafaxine total

Antidepressants total

Are there other placebo-controlled trials published after this meta-analysis?
Subsequent Placebo-controlled Hot Flash Antidepressant Studies with Similar Outcomes

- Desvenlafaxine
- Citalopram
- Escitalopram

Freeman, et al; JAMA 2011; 305; 267-74
The U.S. Food and Drug Administration today approved Brisdelle (paroxetine) to treat moderate to severe hot flashes (vasomotor symptoms) associated with menopause.
Hot Flash Topics

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- Gabapentin meta-analysis
- Gabapentin vs venlafaxine
- Stellate ganglion block
- Clinical hypnosis
Active Tamoxifen Metabolite Plasma Concentrations After Coadministration of Tamoxifen and the Selective Serotonin Reuptake Inhibitor Paroxetine

Vered Stearns, Michael D. Johnson, James M. Rae, Alan Morocho, Antonella Novielli, Pankaj Bhargava, Daniel F. Hayes, Zeruesenay Desta, David A. Flockhart
Hot Flash Topics

- Overview of Mayo/NCCTG Randomized Hot Flash Studies
- Newer antidepressant meta-analysis
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- Gabapentin meta-analysis
- Gabapentin vs venlafaxine
- Stellate ganglion block
- Clinical hypnosis
Favors gabapentin  Favors placebo

Pregabalin

Study

Pandya 300 mg/d
Pandya 900 mg/d
Guttuso 900 mg/d
Reddy 2400 mg/d
Total

HR (fixed) 95% CI

-70 -60 -50 -40 -30 -20 -10 0 10 20 30 40 50 60 70
Hot Flash Topics

• Overview of Mayo/NCCTG Randomized Hot Flash Studies
• Newer antidepressant meta-analysis
• CYP 2D6/Tamoxifen metabolism
• Gabapentin meta-analysis
• Gabapentin vs venlafaxine
• Stellate ganglion block
• Clinical hypnosis
Which do patients prefer better, gabapentin or venlafaxine?
A randomized crossover trial of venlafaxine versus gabapentin for hot flashes in breast cancer survivors

Louise Bordeleau
Kathleen Pritchard
David Warr
Charles Loprinzi

Olivera Jugovic
Marguerite Ennis
Rashida Haq
Pamela Goodwin

JCO 28; #9023; ASCO, 2010
Study schema: Crossover RCT

- **Venlafaxine**
  - 37.5mg daily X 7d ➔ 75mg daily

- **Gabapentin**
  - 300mg daily X 3d ➔ 300 mg BID X 3d ➔ 300mg TID

Timeline:
- **Screening**
- **Randomization**
- 2 weeks
- 4 weeks
- 2 weeks
- 4 weeks
Overall Efficacy

Mean of daily hot flash scores vs. Week
Patient Preference

- Number of preference forms completed: 58
  - Did not prefer one drug over another: 2
  - Expressed a preference: 56

- Patients with a preference: 56
  - Preferred venlafaxine: 38 (68%)
  - Preferred gabapentin: 18 (32%)  \( P=0.01 \)
Hot Flash Topics

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- Newer antidepressant meta-analysis
- CYP 2D6/Tamoxifen metabolism
- Gabapentin meta-analysis
- Gabapentin vs venlafaxine
- Stellate ganglion block
- Clinical hypnosis
Stellate ganglion blockade provides relief from menopausal hot flashes: a case report series.

Lipov E, Lipov S, Stark JT

J Womens Health 14:737-41, 2005

Lipov EG, Joshi JR, Sanders S, et al:

Stellate-ganglion block: a new treatment for hot flushes?

Loprinzi CL, Barton DL, Carns PE

MC08C8

Mayo Clinic Cancer Center

Pilot Evaluation of a Stellate Ganglion Block for the Treatment of Hot Flashes
Figure 1: Mean Percent of Baseline Score and Frequency

- **Baseline**
- **Week 1**
- **Week 2**
- **Week 3**
- **Week 4**
- **Week 5**
- **Week 6**

**Mean Percent of Baseline Score**

- **Score**
- **Frequency**
Figure 2: Percent of Baseline Score by Patient

Percent of Baseline Score by Patient

Percent of Baseline

Baseline Week 1 Week 2 Week 3 Week 4 Week 5 Week 6
Effects of Stellate Ganglion Block on Vasomotor Symptoms: Findings from a Randomized Clinical Trial in Postmenopausal Women

Maki et al

Abstract S-14

NAMS 2013
• Randomized
• Sham controlled
• 40 patients total
• Balanced arms at baseline
Moderate-severe hot flashes

- Baseline to 4-6 months
  - SGB-50% reduction
  - Sham-0% reduction
  - P < 0.001
Total number of objective hot flashes from baseline to 3 months

- Reduced more in the active versus sham arm

- RR 0.71 (CC 0.64-0.99); p = 0.05
SGB-Conclusions

• This looks like it actually works

• More data would be nice
Hot Flash Topics

• Overview of Mayo/NCCTG Randomized Hot Flash Studies
• Newer antidepressant meta-analysis
• CYP 2D6/Tamoxifen metabolism
• Gabapentin meta-analysis
• Gabapentin vs venlafaxine
• Stellate ganglion block
• Clinical hypnosis
Hypnosis for Hot Flashes

- 60 BCS with hot flashes
- Randomized to
  - hypnosis intervention (5 weekly sessions)
  - no treatment

Hot flash scores pre- and post-test by treatment condition.

Elkins G et al. JCO 2008;26:5022-5026
Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial

Methods

• Randomized, single-blind
• 187 postmenopausal women
• ≥ 7 hot flashes/d
• 5 weekly sessions of
  • Clinical hypnosis
  • Structured-attention control

Results from baseline to week 12

- Hot flash frequency reduction
  - 74 % for hypnosis
  - 17 % for controls ($P < 0.001$)

- Hot flash score reduction
  - 80 % for hypnosis
  - 15 % for controls ($P < 0.001$)

- Physiologically monitored hot flashes reduction
  - 57 % for hypnosis
  - 10 % for controls ($P < 0.001$)

Mayo study

Deb Barton, et al
Schema

Randomize

- placebo pill + focused attn training/practice
- 75 mg venlafaxine + focused attn training/practice
- placebo pill + self-hypnosis training/practice
- 75 mg venlafaxine + self-hypnosis training/practice

7 weeks study duration
Hot flash score percent of baseline

**p = .04 compared to placebo/focused attention**
Issues

• Hot Flashes
• Vaginal Dryness
• AI arthralgias
• Paclitaxel neuropathy
The reported incidence of vaginal dryness was 36-71% in two studies that looked at menopausal symptoms in breast cancer survivors.

Vaginal Dryness

- Non-estrogenic vaginal lubricants
- Vaginal estrogen
- DHEA
Fig 1. Changes in mean vaginal dryness scores during the study period.
Vaginal Dryness

- Non-estrogenic vaginal lubricants
- Vaginal estrogen
- DHEA
Vaginal estrogen appears to work better than does Replens.


Is there concern regarding vaginal estrogen use with AIs?
Effects of vaginal estrogens on serum estradiol levels in postmenopausal breast cancer survivors and women at risk of breast cancer taking an aromatase inhibitor or a selective estrogen receptor modulator.

S Wills, A Ravipati P Venuturumilli, C Kresge, E Folkerd, M Dowsett, D Hayes, D Decker

J Oncol Prac; 8 (3); pp144-148; 2012
Vaginal Dryness

- Non-estrogenic vaginal lubricants
- Vaginal estrogen
- DHEA
Menopause; Vol 16 #5

- Intravaginal dehydroepiandrosterone, a physiologic and highly efficient treatment of vaginal atrophy
- Labrie, et al
Menopause; Vol 16 #5

- Effect of intravaginal dehydroepiandrosterone on libido and sexual dysfunction in postmenopausal women
- Labrie, et al
Menopause; Vol 16 #5

- Serum steroid levels during 12-week intravaginal dehydroepiandrosterone administration
- Labrie, et al
• Transvaginal dehydroepiandrosterone: an unconventional proposal to deliver a mysterious androgen that has no receptor or target tissue using a strategy with a new name: Hormone Precursor Replacement Therapy (HPRT)

• Editorial
ASCO 2014; # 9507  Impact of vaginal dehydroepiandosterone (DHEA) on vaginal symptoms in female cancer survivors: Trial N10C1 (Alliance)

Presenting Author: Debra L. Barton, Mayo Clinic, Rochester, MN
N10C1 Alliance Trial
Registration and randomization

DHEA 3.25 mg in bioadhesive moisturizer base

DHEA 6.5 mg in bioadhesive moisturizer base

Bioadhesive moisturizer base alone

Each treatment taken daily at bedtime for 12 weeks
Primary Outcome Results at 12 weeks

<table>
<thead>
<tr>
<th>Time</th>
<th>Severity of Primary Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.00 (No DHEA/ES 1.3)</td>
</tr>
<tr>
<td>Week 2</td>
<td>3.50 (3.25 mg)</td>
</tr>
<tr>
<td>Week 4</td>
<td>3.00 (3.25 mg)</td>
</tr>
<tr>
<td>Week 8</td>
<td>2.50 (3.25 mg)</td>
</tr>
<tr>
<td>Week 12</td>
<td>2.00 (6.5 mg)</td>
</tr>
</tbody>
</table>

P-values:
- P = .48 (3.25 mg)
- P = .08 (6.5 mg)
- P = .11 (3.25 mg)
- P = .005 (6.5 mg)
# Female Sexual Function Index

Higher = better function

<table>
<thead>
<tr>
<th>FSFI Subscale</th>
<th>No DHEA Mean (SD)</th>
<th>3.25 mg DHEA Mean (SD)</th>
<th>6.5 mg DHEA Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desire</td>
<td>0.2 (0.9)</td>
<td>0.3 (1.0)</td>
<td>0.5 (1.0)**</td>
</tr>
<tr>
<td>Arousal</td>
<td>0.4 (1.6)</td>
<td>0.7 (1.4)*</td>
<td>1.0 (.16)**</td>
</tr>
<tr>
<td>Lubrication</td>
<td>1.1 (1.7)</td>
<td>1.3 (1.8)</td>
<td>3.0 (2.0)*</td>
</tr>
<tr>
<td>Orgasm</td>
<td>0.7 (1.8)</td>
<td>0.8 (1.9)</td>
<td>1.0 (1.7)</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>0.5 (1.5)</td>
<td>0.9 (1.5)</td>
<td>1.1 (1.6)*</td>
</tr>
<tr>
<td>Pain</td>
<td>1.0 (1.8)</td>
<td>1.4 (1.7)*</td>
<td>2.0 (1.6)**</td>
</tr>
<tr>
<td>Overall Total</td>
<td>3.8 (7.4)</td>
<td>5.5 (7.5)</td>
<td>7.1 (7.3)**</td>
</tr>
</tbody>
</table>

Significant difference than no DHEA: * ≤.05, **≤.01, ***≤.001
## Overall Quality of Life

Negative Numbers Indicates Worsening

<table>
<thead>
<tr>
<th>Week 12: Mean change from Baseline (SD)</th>
<th>No DHEA</th>
<th>DHEA 3.25 mg</th>
<th>DHEA 6.5 mg</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.3 (2.2)</td>
<td>0.2 (1.7)</td>
<td>0.3 (1.9)**</td>
<td>.01</td>
</tr>
</tbody>
</table>
# Subjective Impression of Change

<table>
<thead>
<tr>
<th></th>
<th>No DHEA</th>
<th>DHEA 3.25 mg</th>
<th>DHEA 6.5 mg</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td># (%) Perceiving a moderate to very much better change</td>
<td>47 (40%)</td>
<td>67 (55%)</td>
<td>69 (58%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
DHEA vs Placebo Hormone changes

- Increased DHEA concentrations
- Increased testosterone concentrations
- Estrogen
  - Slightly increased estrogen concentrations in pts not on an AI
- No increase in pts on an AI
- No change in markers of bone turnover
Lessons Learned

• Vaginal DHEA is absorbed vaginally

• DHEA 6.5 mg improved symptoms more quickly and to a non-significant greater degree

• DHEA 6.5 mg improved sexual function and overall QOL beyond what the moisturizer did
Lessons Learned

- All arms were equally well tolerated aside from significant differences in voice changes (both DHEA doses) and headaches (3.25 mg)

- These data support the use of DHEA clinically
Issues

• Hot Flashes
• Vaginal Dryness
• AI arthralgias
• Paclitaxel neuropathy
What is the natural history of AI arthralgias?
Aromatase Inhibitor Arthralgias

• Large early trials
  • Incidence ~5-20%

• Patients report: “I feel like an old lady”

• True incidence is probably ~50%

• ~10-20% discontinue therapy because of toxic effects
  • Usually with symptom resolution

Crew...Hershman, JCO 2007
Prevalence of joint symptoms in women on AI’s for early stage BC

- Cross-sectional survey of 200 consecutive pts receiving adjuvant AI therapy

- Self-administered 25-item survey

Crew…Hershman, JCO 2007
Location of Joint Symptoms

% of Patients With AI-Related Joint Symptoms

- Pain
- Stiffness

Hands  Knees  Back

Crew...Hershman, JCO 2007
Severity of Joint Symptoms

- **Mild** (1-4) % of Patients With AI-Related Joint Symptoms
- **Moderate** (5-7)
- **Severe** (6-10)

Crew...Hershman, JCO 2007
Are there any promising appearing therapies for AI arthralgias?
Promising-Appearing Study Ideas

- Acupuncture
- Testosterone
- Duloxetine
- Vitamin D
Promising-Appearing Study Ideas

- Acupuncture
- Testosterone
- Duloxetine
- Vitamin D
Promising-Appearing Study Ideas

• Acupuncture
• Testosterone
• Duloxetine
• Vitamin D
Promising-Appearing Study Ideas

- Acupuncture
- Testosterone
- Duloxetine
- Vitamin D
What is the current recommended treatment for AI arthralgias?
Current Recommendations

• Try analgesics, exercise

• If the patient is having substantial trouble, stop the AI and give a few weeks to resolve

• Consider re-starting another AI

• Consider tamoxifen

• Re-consider magnitude of benefit of adjuvant hormonal therapy
Issues

• Hot Flashes
• Vaginal Dryness
• AI arthralgias
• Paclitaxel neuropathy
Topics

- Natural history investigation results
- Important clinical study results
Introduction

• Paclitaxel infusion commonly is followed, in 2-4 days, by an acute pain syndrome, with symptoms usually resolving in 3-7 days

• This pain has been called paclitaxel-induced arthralgia or myalgia
ATF3

24 hr post-paclitaxel (18 mg/kg; i.v.)

Injured neurons (blue nuclei)

Rat DRG

Control
The Paclitaxel Acute Pain Syndrome: Sensitization of Nociceptors as the Putative Mechanism

Paclitaxel-Associated Acute Pain Syndrome: Natural History Study

N08C1

Patients scheduled to receive IV paclitaxel at one of 2 dose/schedules

- 175+ mg/m² Q 3 wks
- 70-90 mg/m² weekly

Patient questionnaires looking at the incidence and severity of paclitaxel-associated acute pain and sensory neuropathy.
P-APS Data
Worst P-APS Scores for Cycle 1 (Weekly)

Worst Pain Score (mean)

Time (Days)

n= 91 91 90 91 91 91 90
Analgesic Use (Weekly)

- **OTC meds**
- **Opioids**

Patients (%)

<table>
<thead>
<tr>
<th>Cycles</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
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<td>Patients (%)</td>
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<td>OTC meds</td>
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<td>Opioids</td>
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</table>

n = 91 89 85 87 88 85 85 82 79 73 67 59
CIPN Data
EORTC CIPN-20 Data (Weekly)

- **Sensory**
- **Autonomic**
- **Motor**

Baseline values (%) over cycles:

<table>
<thead>
<tr>
<th>Cycles</th>
<th>Sensory</th>
<th>Autonomic</th>
<th>Motor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>99</td>
<td>95</td>
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<tr>
<td>1</td>
<td>99</td>
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<tr>
<td>12</td>
<td>88</td>
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<td>88</td>
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**P < 0.0001**
Individual questions from the CIPN20 sensory subscale used for this analysis

- Did you have tingling fingers or hands?
- Did you have tingling toes or feet?
- Did you have numbness in your fingers or hands?
- Did you have numbness in your feet or toes?
- Did you have shooting or burning pain in your fingers or hands?
- Did you have shooting or burning pain in your toes or feet?
EORTC CIPN-20 Tingling, Numbness and Pain Scores – Hands (Weekly)

<table>
<thead>
<tr>
<th>Cycles</th>
<th>Tingling</th>
<th>Numbness</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>85</td>
<td>83</td>
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<tr>
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<td>12</td>
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</tbody>
</table>
CIPN-20 Burning/Shooting Pain Scores Segregated by Cycle-1 P-APS Scores – Feet (Weekly)
Topics

- Natural history investigation results
- Important clinical study results
Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Dawn L. Hershman, Christina Lacchetti, Robert H. Dworkin, Ellen M. Lavoie Smith, Jonathan Bleeker, Guido Cavaletti, Cynthia Chauhan, Patrick Gavin, Antoinette Lavino, Maryam B. Lustberg, Judith Paice, Bryan Schneider, Mary Lou Smith, Tom Smith, Shelby Terstrijp, Nina Wagner-Johnston, Kate Bak, and Charles L. Loprinzi
• 1,225 potentially relevant citations
• 250 examined in detail
• 48 eligible for guideline evidentiary basis
  • 42 for CIPN prevention
  • 6 for CIPN treatment
Treatment agents reviewed: ASCO guidelines

• Acetyl-L-carnitine
• Lamotrigine
• Duloxetine
• Tricyclic antidepressants
• Gabapentin
• Topical BAK
CALGB 170601
A Phase III Double Blind Trial of Oral Duloxetine for Treatment of Pain Associated with Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Investigators
Ellen Lavoie Smith, PhD, APRN-BC, AOCN; Herbert Pang, PhD; Connie Cirrincione, MS; Camilo Fadul, MD; Tim Ahles, PhD; Stewart Fleishman, MD; Alice Kornblith, PhD; Charlie Shapiro, MD; Electra Paskett, PhD

Supported by:
National Cancer Institute Division Disease Control & Prevention & Lilly Pharmaceuticals
Chemotherapy-induced neuropathy

Duloxetine
30 mg/d for 1 week
60 mg/d for 4 weeks

Placebo
1/d for 1 week
2/d for 4 weeks

Smith et al JAMA; 2013;309:1359-67
**Pain Outcomes**

\[ p = 0.003 \quad \text{Effect Size} = 0.513 \]

**Mean Pain Score with SE During Initial Rx Period By Arm**

- **Duloxetine** → **Placebo**
- **Placebo** → **Duloxetine**

**Average Pain Interference**

- **Duloxetine**
- **Placebo**

BPI-SF Pain Interference Score = sum of 7 items: interference with general activity, mood, walking, normal work, relations with people, sleep, and enjoyment of life.

\[ N = 220 \]
Treatment agents reviewed: ASCO guidelines

- Acetyl-L-carnitine
- Lamotrigine
- Duloxetine
- Tricyclic antidepressants
- Gabapentin
- Topical BAK
If a patient/physician really wants to try something, even if it is not proven, then…

Pachman DR,… Loprinzi CL; Support Care Cancer. 2014 Aug;22(8):2281-95
Take-Home Points

• Newer antidepressants, gabapentin, and progesterone analogs decrease hot flashes

• Don’t mix tamoxifen and paroxetine

• Patients prefer venlafaxine over gabapentin

• Vaginal dryness: Vaginal estrogen works, but doesn’t make sense, to me, to use with AIs; DHEA is an option, esp in pts on AIs.
Take-Home Points

• AI arthralgias: acupuncture, vitamin D, and a testosterone preparation look promising
• P-APS appears to be of neurologic origin
• Duloxetine of some help for CIPN
• Gabapentinoids, TCAs, and a topical BAK preparation might help
Thank you
Prior to yesterday, had you heard of cryotherapy for decreasing paclitaxel-associated neuropathy?

___ Yes

___ No
For those of you who are using paclitaxel chemotherapy, are you using cryotherapy for decreasing paclitaxel-associated neuropathy?

___ Yes

___ No
Supportive Cryotherapy: A Review From Head to Toe

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Optum Oxaliplatin Injection and Same-Day CaMg Use by Month
(Timeframe: January 2003 - June 2014)