Symptom Management of Therapy-Related Toxicities

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

• Pfizer - pregabalin to prevent paclitaxel-induced neuropathy
• Competitive Technologies - donated a Scrambler machine
Issues

• Hot Flashes
• Vaginal Dryness
• AI arthralgias
• Paclitaxel neuropathy
Basic Study Design

Eligible Patients → Stratify → Randomize

Double Blind

Agent
Placebo
Mean Hot Flash Score Reduction
Randomized Studies

% Reduction (Mean)

Week

0 1 2 3 4 5 6

Placebo (n=420)
Soy (n=78)
Vitamin E (n=53)
Clonidine (n=75)
Fluoxetine (n=36)
Venlafaxine (n=48)
Megestrol (n=74)
Mean Hot Flash Score Reduction
Randomized Studies

% Reduction (Mean)

Week

0 1 2 3 4 5 6

Black Cohosh (n=58)
Placebo (n=420)
Soy (n=78)
Vitamin E (n=53)
Clonidine (n=75)
Fluoxetine (n=36)
Citalopram (n=57)
Ven (vs MPA) (n=94)
Venlafaxine (n=48)
Pregabalin (n=63)
MPA 400 mg (n=94)
MPA 500 mg X 3 (n=7)
Megestrol (n=74)
Flaxseed (n=69)
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
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
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
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
CYP 2D6 Websites

- Google- ‘CYP 2D6 inhibitors’
- http://medicine.iupui.edu/clinpharm/ddis/table.asp
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
Favors gabapentin  Favors placebo

Pregabalin Median Hot Flash Score

Reduction from baseline (%)

Week

Baseline 1 2 3 4 5 6

Pregabalin 150 mg bid
Pregabalin 75 mg bid
Placebo

P = 0.002 (75 mg bid)
P = 0.007 (150 mg bid)

Favors gabapentin  
Favors placebo

HR (fixed)  
95% CI

Study

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

Pregabalin
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
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  Olivera Jugovic
Kathleen Pritchard  Marguerite Ennis
David Warr  Rashida Haq
Charles Loprinzi  Pamela Goodwin

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

Venlafaxine

Gabapentin

Venlafaxine

Gabapentin

2 weeks

4 weeks

2 – 4 weeks

4 weeks

Screening

Randomization

Venlafaxine: 37.5mg daily X 7d ➔ 75mg daily
Gabapentin: 300mg daily X 3d ➔ 300 mg BID X 3d ➔ 300mg TID
Overall Efficacy

Mean of daily hot flash scores

Week

0 5 10 15 20 25

Mean of daily hot flash scores

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%)  \(P=0.01\)
Issues
• Hot Flashes
• Vaginal Dryness
• AI arthralgias
• Paclitaxel neuropathy
Vaginal Dryness

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?
The Effects of Vaginal Estrogens (VE) on Serum Estradiol Levels Breast Cancer Survivors Receiving an Aromatase Inhibitor (AI) or a Selective Estrogen Receptor Modulator (SERM)

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

SABCS; 2009
Objective

- Determine the degree of estrogen absorption from
  - Chronic E2 tablet
  - Estrogen ring
- Postmenopausal breast cancer survivors
  - Adjuvant AI
  - Adjuvant SERM
Cases and Controls

- Postmenopausal women
  - No menstrual period for 1 year, or
  - Oophorectomy
  - ER positive breast cancer
- Completed
  - Local breast cancer therapy
  - Systemic chemotherapy
- Clinically NED
- Using a VE for atrophic vaginitis
Cases

- 14 Patients using E2 tablet
  - 1 tablet inserted 2 x per week ≥ 3 months

- 10 Patients using E2 ring
  - Ring inserted once every 90 days ≥ 3 months
Controls

• 24 postmenopausal breast cancer survivors
• After local therapy and/or chemotherapy
• Receiving an AI or SERM as adjuvant therapy
• Not on E2 tablet or ring
Controls on AI Only
Cases Using E2 Ring:
AI or SERM

- Pre-Insertion
- 30 Days
- 60 Days

pmol/l

AI or SERM
Cases Using E2 Tablet:
AI or SERM

![Bar graph showing cases using E2 tablet with AI or SERM. The graph includes bars for 'Pre-Insertion pmol/l' and 'Post-insertion pmol/l'.]
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
Menopause; Vol 16 #5

• 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
Vaginal DHEA For Vaginal Symptoms:
A Phase III Randomized, Double Blind, Placebo-Controlled Study

Debra Barton, et al
Women with cancer and vaginal dryness

Randomize

Placebo

DHEA 0.25% 3.25 mg vaginally X 12 W

DHEA 0.25% 6.5 mg vaginally X 12 W
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
Location of Joint Symptoms

% of Patients With AI-Related Joint Symptoms

Hands | Knees | Back
--- | --- | ---
Pain | Stiffness

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

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

Pain

Stiffness

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

• Acupuncture
• Testosterone
• Omega 3 FA
• Vitamin D
Randomized Placebo-Controlled Trial of Acupuncture for AI-related Joint Symptoms

Eligibility:
• Postmenopausal
• Adjuvant AI for > 6 mo
• Worst joint pain score ≥ 3
• N=40

Primary Outcome:  Change in joint pain score (BPI-SF)

Crew...Hershman et al. *JCO* Mar 1, 2010:1154
Percent change in the group mean Brief Pain Inventory–Short Form (BPI-SF) scores from baseline to 3 and 6 weeks for the true and sham acupuncture groups: (A) BPI-SF worst pain, (B) BPI-SF pain severity, and (C) BPI-SF pain-related interference.

Crew K D et al. JCO 2010;28:1154-1160
Acupuncture

Multi-institutional confirmatory trial underway
Promising-Appearing Study Ideas

• Acupuncture
• Testosterone
• Omega 3 FA
• Vitamin D
Testosterone undecanoate treatment reduces joint morbidities induced by anastrozole therapy in postmenopausal women with breast cancer: results of a double-blind, randomized phase II trial

Birrell SN and Tilley WD.

Australia
Trial Design

90 women on adjuvant anastrozole 1mg per day plus

3 months of placebo or testosterone undecanoate (TU)

30 = placebo  
30 = 40 mg TU  
30 = 80 mg TU
Percentage of patients with a PAIN VAS >50mm

- Placebo
- 40 mg TU
- 80 mg TU

Baseline
1 month
3 months

P=0.04
Percentage of patients with a Stiffness VAS >50mm

- Placebo
- 40 mg TU
- 80 mg TU

P=0.06
Estradiol concentrations

Baseline
1 month
3 months

Placebo  40 mg TU  80 mg TU
Free Testosterone Concentrations

- Placebo 40 mg TU 80 mg TU
- Baseline
- 1 month
- 3 months

Graph showing Free Testosterone Concentrations at baseline, 1 month, and 3 months for Placebo, 40 mg TU, and 80 mg TU.
A randomized double-blind placebo controlled, Phase II/III, study of aromatase inhibitors and transdermal testosterone in the adjuvant treatment of postmenopausal women with aromatase inhibitor induced arthralgias: N10C7

Stephen Birrell, M.D. Ph.D.

Charles Loprinzi, M.D.
Randomized Placebo-Controlled Trial of Testosterone for AI-related Joint Symptoms

Eligibility:
- Postmenopausal
- Adjuvant AI
- Worst joint pain score ≥ 50/100

Primary Outcome: Change in joint pain score at 3 mos

N=226
Promising-Appearing Study Ideas

- Acupuncture
- Testosterone
- Omega 3 FA
- Vitamin D
S0927: Randomized Placebo-Controlled Trial of Omega-3-Fatty Acid for the control of Aromatase Inhibitor-Induced Musculoskeletal Pain in Women with Early Stage Breast Cancer

Eligibility:
- Age > 21 years
- Postmenopausal
- Stage I-III ER+ and/or PR+ breast cancer
- Taking an AI for > 3 mo
- Worst joint pain score ≥ 5
- N=~246

Follow-up: 0, 6, 12, 24 weeks

Primary Endpoint: Change in worst joint pain/stiffness at 12 weeks

Stratification: history osteoarthritis and prior taxane use
Promising-Appearing Study Ideas

- Acupuncture
- Testosterone
- Omega 3 FA
- Vitamin D
The VITAL trial
Randomized trial of vitamin D3 to prevent worsening of musculoskeletal symptoms and fatigue in women with breast cancer starting adjuvant letrozole.

Qamar J. Khan
Bruce F. Kimler
Pavan S. Reddy
Priyanka Sharma
Jennifer R. Klemp
Carol J. Fabian

The University of Kansas Medical Center
Cancer Center of Kansas, Wichita KS

ASCO 2012
Abstract # 9000
Postmenopausal stage I-III breast cancer starting adjuvant Letrozole 25OHD levels 40 ng/ml or less

Vit D3 30,000 IU/wk
RDA of Ca + D

Matching placebo/wk
RDA of Ca + D

24 weeks

Randomized, double-blind, placebo-controlled
Primary Endpoint (protocol defined): Incidence of a MS Event using Simple Descriptive Pain Intensity Scale*

*Worsening pain (Simple Descriptive Pain Intensity Scale), worsening disability (HAQ II), or discontinuation of letrozole due to musculoskeletal pain

Frequency of MS event, %

Placebo arm: 51%
VitD3 arm: 37%

P=0.069
Vitamin D

• Phase III trial in development, by verbal report
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
• Al 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
24 hr post-paclitaxel (18 mg/kg; i.v.)

Injured neurons (blue nuclei)
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 91 90 91 91 90 90
Worst P-APS Scores Per Cycle (Q 3 Weeks)
Daily Mean Pain Scores (Q 3 Week)

Mean P-APS Pain

- 7-10
- 5-6
- 1-4
- 0

Day

Cycle 1
Cycle 2
Cycle 3

*Cycle 4, day 2
<table>
<thead>
<tr>
<th>Pain Descriptor</th>
<th>Location of Pain</th>
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<td>Aching</td>
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<tr>
<td>Dull</td>
<td>Legs, upper</td>
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<tr>
<td>Sharp</td>
<td>Feet</td>
</tr>
<tr>
<td>Throbbing</td>
<td>Hips</td>
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<tr>
<td>Shooting</td>
<td>Back, lower</td>
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<tr>
<td>Heavy</td>
<td>Other</td>
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<tr>
<td>Cramping</td>
<td>Neck</td>
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<tr>
<td>Stinging</td>
<td>Shoulders</td>
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<tr>
<td>Gnawing</td>
<td>Head</td>
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<td>Hot</td>
<td>Abdomen</td>
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<tr>
<td>Pulsating</td>
<td>Arms, upper</td>
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<tr>
<td>Stabbing</td>
<td>Arms, lower</td>
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<tr>
<td>Splitting</td>
<td>Hands</td>
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</table>
Analgesic Use (Q 3 Weeks)

- OTC meds
- Opioids

Patients (%)

Cycles

1 2 3 4 5 6
CIPN Data
EORTC CIPN-20 Data (Weekly)

Baseline values (%)

Autonomic
Motor
Sensory

P < 0.0001

Cycles

Baseline values (%)

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<th>Sensory</th>
<th>Motor</th>
<th>Autonomic</th>
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n= 100 99 95 98 98 96 95 95 93 93 93 91 94
EORTC CIPN-20 Sensory, Motor and Autonomic Scores (Q 3 Weeks)

Weeks

CIPN-20 Scores

Autonomic
Motor
Sensory

<table>
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<tr>
<th>Weeks</th>
<th>Sensory</th>
<th>Motor</th>
<th>Autonomic</th>
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n= 81 60 60 54 45 31 29
n= 81 67 67 59 49 33 27
n= 81 67 67 59 49 33 27
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)

Cycles

CIPN-20 Scores

Pain
Numbness
Tingling

n= 91 85 83 80 87 87 84 84 77 79 70 66 58
n= 91 85 83 80 87 87 83 84 77 79 70 66 57
n= 91 85 83 80 87 87 84 84 77 79 70 66 58
EORTC CIPN-20 Tingling, Numbness and Pain Scores – Hands (Q 3 Weeks)

Weeks

CIPN-20 Scores

Pain

Numbness

Tingling

Weeks

CIPN-20 Scores

Pain

Numbness

Tingling

n= 81 67 67 58 49 32 28

n= 81 67 66 59 49 33 27

n= 81 67 66 59 49 33 28
CIPN-20 Burning/Shooting Pain Scores Segregated by Cycle-1 P-APS Scores – Feet (Weekly)
CIPN-20 Sensory Neuropathy Scores, Segregated by Cycle-1 P-APS Scores (Q 3 Weeks)
Topics

- Natural history investigation results
- Important clinical study results
Selected CIPN Clinical Trials

• Gabapentin

• Duloxetine
Is your practice commonly using gabapentin or pregabalin for pts with CIPN?

1. Yes

2. No
Efficacy of Gabapentin in the Management of Chemotherapy-Induced Peripheral Neuropathy: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Crossover Trial (N00C3)


Cancer 110(9):2110, 2007
Chemotherapy-induced neuropathy

R

6 wk Gabapentin 2700 mg/day

Placebo

6 wk Placebo

2 wk Washout

6 wk Gabapentin 2700 mg/day

Cancer 110(9):2110, 2007
Mean Pain Intensity

- **Placebo**: P=0.21
- **Gabapentin**: P=0.37

Mean pain intensity over weeks:
- **First period**
- **Wash-out**
- **Second period**

Cancer 110(9):2110, 2007
Pregabalin to Prevent the Paclitaxel Associated Acute Pain Syndrome and CIPN

Patients receiving paclitaxel chemotherapy

S → R

Pregabalin
Placebo
Selected CIPN Clinical Trials

• Gabapentin

• Duloxetine
CALGB 170601
A Phase III Double Blind Trial of Oral Duloxetine for Treatment of Pain Associated with Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Supported by the NCI Division of Cancer Prevention & Lilly Pharmaceuticals

Principal Investigator:
Ellen Lavoie Smith, PhD, APRN, AOCN®

Co-Investigators:
Herbert Pang, PhD; Constance Cirrincione, MS; Stewart Fleishman, MD; Electra D. Paskett, PhD; Tim Ahles, PhD; Camilo Fadul, MD; Chetaye Knox; Charles L. Shapiro, MD
Study Objectives

Primary Objective
• To assess whether duloxetine 60mg daily decreases CIPN-related neuropathic pain caused by paclitaxel or oxaliplatin

Secondary Objectives
• To assess treatment-related side effects
• To determine duloxetine’s influence on functional status and quality of life
Pain Outcomes

$p = 0.003$  
*Effect Size* $= 0.513$

$p = 0.015$

Mean Pain Score with SE During Initial Rx Period By Arm

Average Pain Interference

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.

$N = 220$
Most Common AEs – Initial Rx

- Fatigue: Duloxetine 7.5%, Placebo 5.7%
- Insomnia: Duloxetine 5.3%, Placebo 3.8%
- Nausea: Duloxetine 3.1%, Placebo 1.1%
- Somnolence: Duloxetine 11%, Placebo 1%
- Dizziness: Duloxetine 27%, Placebo 7%
- Drop-Out: Duloxetine 16%, Placebo 3%
Take-Home Points

• Newer antidepressants, gabapentin, and progestational agents decrease hot flashes
• Don’t mix tamoxifen and paroxetine
• Patients prefer venlafaxine over gabapentin
• Vaginal dryness: DHEA looks promising
Take-Home Points

• AI arthralgias: acupuncture, vitamin D, an omega 3 F. A., and a testosterone preparation being explored

• P-APS appears to be of neurologic origin

• Gabapentin was not helpful for treating CIPN in a prospective randomized trial

• Pregabalin is being studied for prevention of the P-APS

• Duloxetine of some help for CIPN
Thank you