Sistema Socio Sanitario

Ospedale Niguarda Cancer Center

Regione Lombardia

IL DOLORE ONCOLOGICO CRONICO: ESPERIENZE CONDIVISE

CIPN (Chemotherapy Induced Peripheral Neuropathy) Management

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Key points

- CIPN (Chemotherapy Induced Pheripheral Neuropathy) background
- Chemotherapeutic agents involved and potential pathophysiology of CIPN
- CIPN treatment
- CIPN prevention
- Future directions
- Conclusions

Background

- **CIPN is an adverse event of commonly used cancer treatments (platinum agents, taxanes, vinca alkaloids, thalidomide and bortezomib): prevalence of 48%; 68% within the first CT month; 60% at 3 months; 30% at 6 months[1]**
- **Manifestation: sensory symtoms in the hands and/or feet typically in a stocking-glove pattern, with sharp pain, numbness, burning, tingling; occasionaly pts present motor symptoms, autonomic involvement, or cranial neuropathies.**
- **Risk factors: diabetes, prior exposure to neurotoxic agents, B12/ folate, B1, B6 deficiencies, paraproteinemia, thyroid disfunction, alcohol exposure, preexisting hereditary neuropathy, decreased creatinina clearance, HIV**
- **CIPN is dose dependent and progressive while receiving and after such treatments (symptoms may resolve after CT discontinuation or continue for years)[2]**
- **CIPN can lead to dose reductions, changes in CT protocols, therapy discontinuation and can have long-term effects on quality of life influencing the activities of daily living**

1. Seretny M et al. Pain 2014. 2. Kautio A et al. Support Care Cancer 2011

Background

- **CIPN can be assessed by objective measures including physical examination, neurophysiological testing and subjective measures: the National Cancer Institute-Common terminology Criteria for Adverse Events (NCI-CTCAE) grading scale and patient-reported outcome measures is the most used.**

Nervous system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.					
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation or degeneration of the peripheral motor nerves.					
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.					

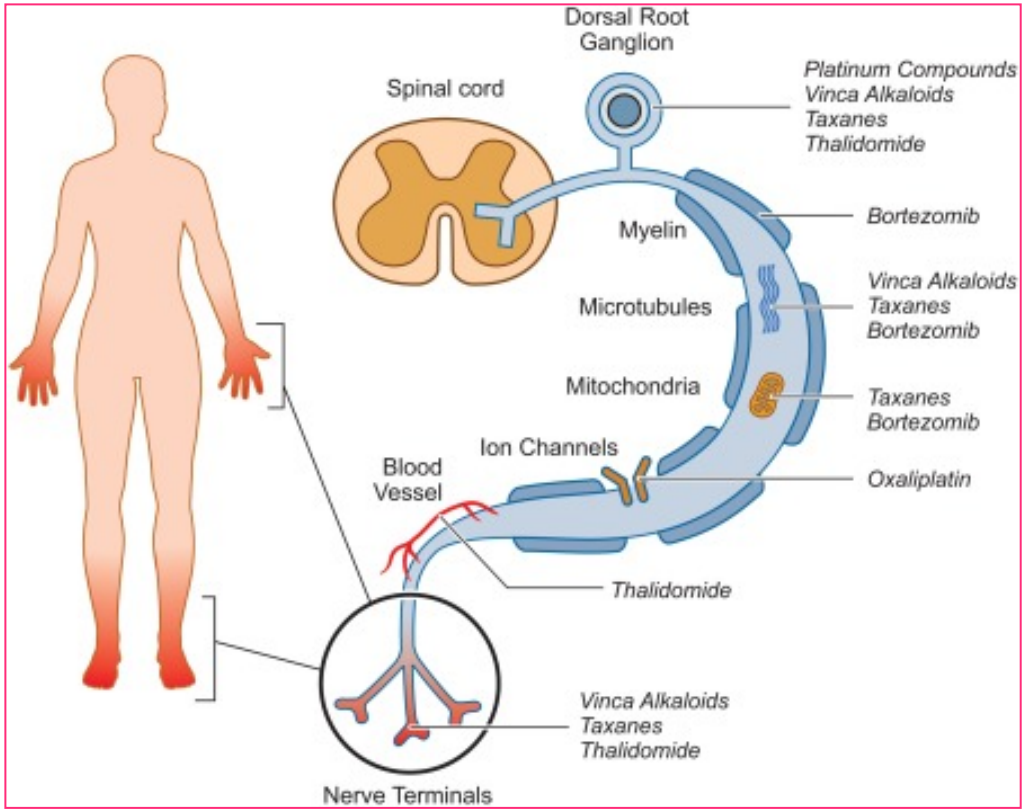
- **Nerve conduction studies (NCS) and an electromyogram (EMG) are well-tolerated electrophysiologic tests useful in the diagnostic evaluation, especially when the timing and course of symptoms are unusual**

Neurotoxic chemoterapeutic agents

	Incidence of Peripheral Neuropathy	Sensory Symptoms	Motor Symptoms
ANTIMICROTUBULE AGENTS Paclitaxel (Taxol®) Docetaxel (Taxotere®) Abraxane™ Vincristine (Onkovin®) Vinorelbine (Navelbine®) Ixabepilone (Ixempra®)	 60%[4] 50%[5] 71%[6] Not listed 25%[9] 63%[10]	Mild to moderate numbness, tingling, burning/stabbing pain of hands and feet are common and can become severe with increased doses[9,11]	Weakness of distal muscles, decreased deep tendon reflexes, and foot drop have been noted with high doses[5,9,11]
PLATINUM COMPOUNDS: Cisplatin (Platinol®) Carboplatin (Paraplatin®) Oxaliplatin (Eloxatin®)	 Not listed 4%[12] 74%[13]	Mild to moderate numbness and tingling of hands and feet can occur after prolonged (4-6 months) therapy and may develop 3-8 weeks after last dose.[14] Symptoms can become severe with high cumulative doses[14] Reduced or absent Achilles tendon reflex[15]. Oxaliplatin can cause acute hypersensitivity to cold stimuli in the mouth, throat and hands[1]	Weakness is rare but can occur with high doses of Cisplatin and Oxaliplatin[13,14]
TARGETED THERAPIES: Bortezomib (Velcade®)	31-55%[10]	Decreased sensation and numbness and tingling of the hands and feet. Those with preexisting neuropathy may experience a worsening of their neuropathy[16]	Myalgias and muscle cramps are less common side effects[16]
IMMUNOMODULATORY AGENTS: Thalidomide (Thalomid®)	25-83%[10]	Numbness and tingling and pain in the feet or hands[16]	Weakness[16]

Pathophysiology

One of the challenges in managing CIPN is that the exact pathophysiology is not well understood



- **Oxaliplatin and Cisplatin/Carboplatin exert their antineoplastic effects by forming platinum-DNA adducts that lead to cell cycle arrest and apoptosis**

- **Platinum agents are thought to cause CIPN by exerting damage in the dorsal root ganglion through mitochondrial dysfunction and neuronal apoptosis, either by DNA crosslinking or oxidative stress**

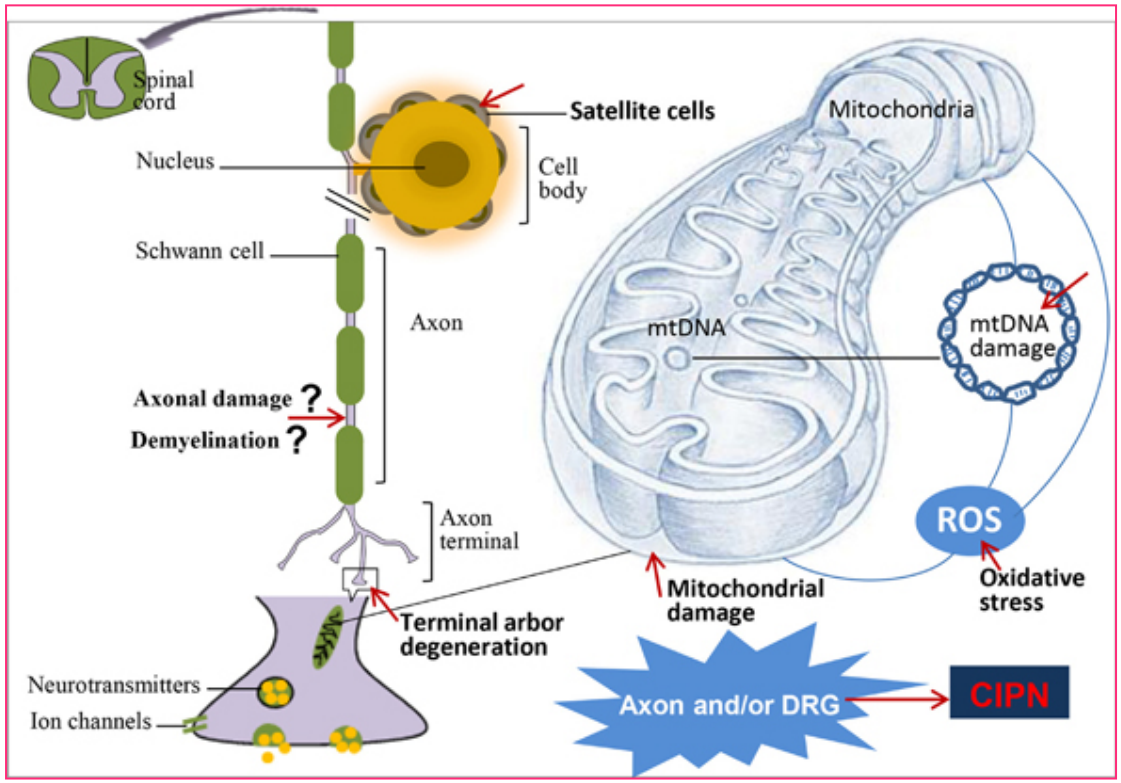
Addington J et al, F1000 Research 2016

Platinum agents

- **The dorsal root ganglion is not protected by the blood-brain barrier, making the DNA within the cell body of the dorsal root ganglion preferentially susceptible to these toxic agents**
- **The result of the dorsal root ganglion damage is a sensory neuropathy with anterograde axonal degeneration**
- **Oxaliplatin cause a rapid sensory neuropathy in up to 90% of pts, with a 10% with a chronic neuropathy at 2 years post administration**
- **Oxaliplatin can exert its neurotoxicity through alterations in transmembrane receptors and channels: its metabolite oxalate prolongs the open phase of voltage-gated Na+ channels leading to prolonged depolarization and nerve hyperexcitability**
- **CIPN can be related to the functioning of transient receptors potential (TRP) channels, affected by the platinum agents**
- **Platinum agents may involve membrane transporters: both copper and organic cation transporters have been shown to facilitate the transport of carboplatin into the dorsal root ganglion of sensory nerves**

McDonald ES et al, Neurobiol Dis 2002; Cersosimo RJ, Ann Pharmacother 2005.

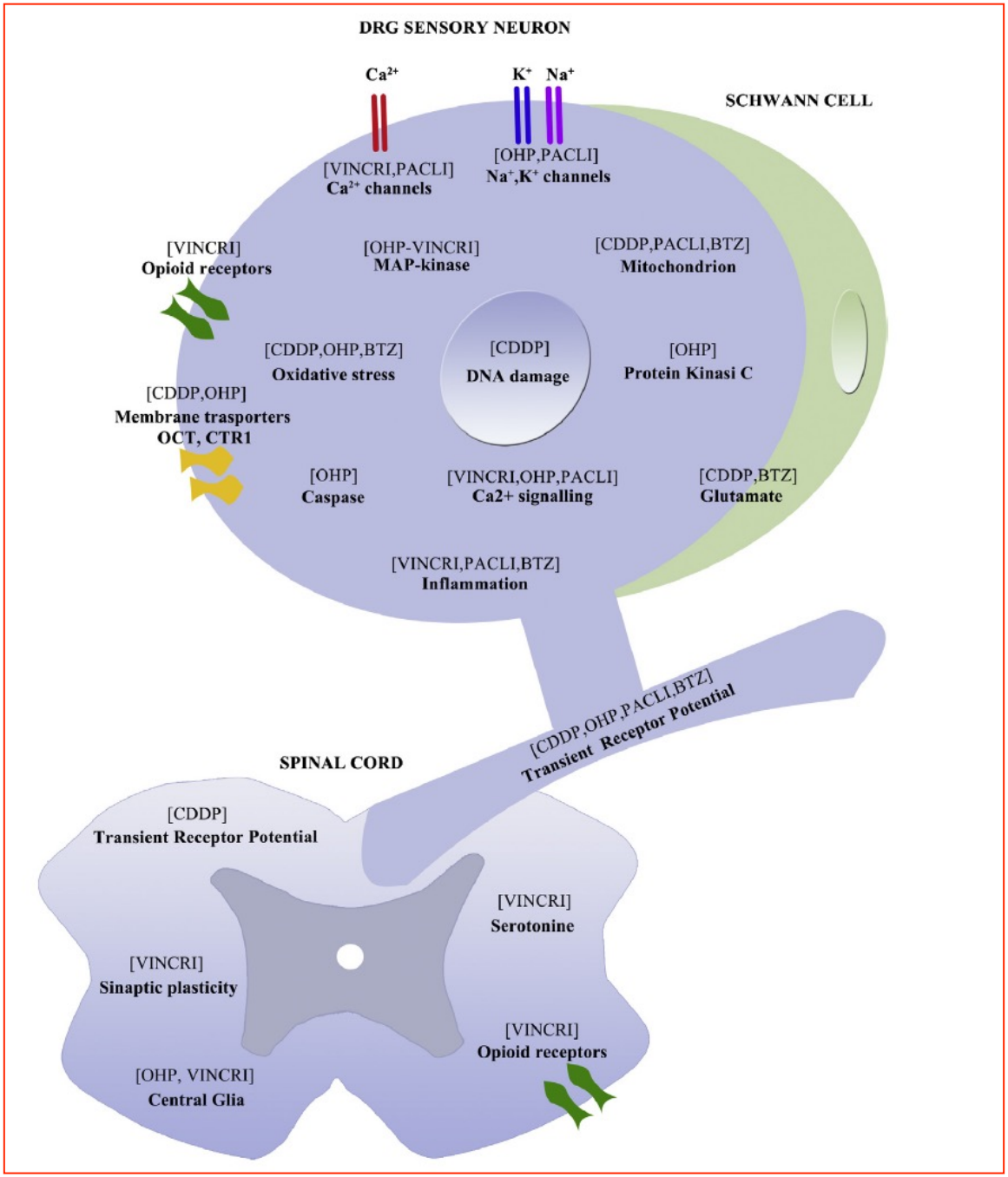
Pathophysiology



Taxanes (Docetaxel and Paclitaxel) exerts their antineoplastic effects on the microtubule during the cell cycle, loss of depolymerization of the microtubule leads to mitotic arrest during the G2/M phase. The microtubule maintains the integrity and health of functioning axons

- **Hypothesized mechanisms of taxane-induced neuropathy: disruption of the axonal microtubule structure and a deficit in axonal energy supply from the toxic effect of CT on mitochondria in primary afferent neurons**

Addington J et al, F1000 Research 2016



Carozzi VA et al, Neuroscience Letters 2015

CIPN Treatment-Phase III trials

Drug Class	Pharmacologic Agent and Dosage	Authors and Year of Publication	Number of Patients and Study Design	Drug Causing CIPN	Primary Study Outcome Measure and Results	Overall Results	Adverse Effects of Intervention
Antidepressant	Amitriptyline 10 mg daily with dose escalation of 10 mg/week up to target maximum dosage of 50 mg daily for 8 weeks	Kautio et al, 2008[39]	Total: 33 Placebo: 16 Amitriptyline: 17 Double-blind study	Vinca alkaloids, platinum agents, or taxanes	• Global improvement as assessed by numeric scales (scale, 0-10) in diary data: no significant difference in mean score between groups (3.4±3.6 vs 1.9±3.1 in placebo arm; *P* = NS). • Global improvement at final visit assessed by verbal rating scale (scale, complete relief-symptoms worse): no significant difference between groups (47% vs 31% in placebo arm; *P* = NS).	Negative	Tiredness Tachycardia
	Nortriptyline (N) 25 mg daily with dose escalation of 25 mg/week up to target maximum dosage of 100 mg during treatment period	Hammack et al, 2002[38]	Total: 51 Group A (N/PL): 26 Group B (PL/N): 25 Double-blind crossover study after 4 weeks	Cisplatin	• Paresthesia as assessed by visual analog scale: in first treatment period, no significant reduction in paresthesia (49 vs 55 [scale, 0-100] in placebo arm; *P* = .78).	Negative	Dry mouth Dizziness Constipation

Triveldi MS et al, Americal J Hematology Oncology 2015

CIPN Treatment-Phase III trials

Drug Class	Pharmacologic Agent and Dosage	Authors and Year of Publication	Number of Patients and Study Design	Drug Causing CIPN	Primary Study Outcome Measure and Results	Overall Results	Adverse Effects of Intervention
Antiepileptic	Gabapentin (G) 300 mg with dose escalation of 300 mg to a target maximum dosage of 2700 mg daily for 6 weeks during treatment period	Rao et al, 2007[36]	Total: 115 Group A (G/PL): 57 Group B (PL/G): 58 Double-blind crossover study after 6 weeks	Vinca alkaloids, taxanes, or platinum agents	• "Average" pain by NRS and ENS: no difference in NRS or ENS score at baseline, 6 weeks, or 14 weeks between groups.	Negative	No significant differences in toxicities between groups
	Lamotrigine 25 mg at bedtime for 2 weeks, then 25 mg twice daily for 2 weeks, then 50 mg twice daily for 2 weeks, then 100 mg twice daily for 2 weeks, then 150 mg twice daily for 2 weeks	Rao et al, 2008[37]	Total: 125 Placebo: 62 Lamotrigine: 63 Double-blind study	Vinca alkaloids, taxanes, or platinum agents	• "Average" pain by NRS and ENS: no difference in NRS or ENS score at baseline or 10 weeks between groups.	Negative	No significant differences in toxicities between groups

Triveldi MS et al, Americal J Hematology Oncology 2015

CIPN Treatment-Phase III trials

Drug Class	Pharmacologic Agent and Dosage	Authors and Year of Publication	Number of Patients and Study Design	Drug Causing CIPN	Primary Study Outcome Measure and Results	Overall Results	Adverse Effects of Intervention
Topical	Baclofen, amitriptyline, and ketamine gel, 1.31 g of compounded gel containing 10 mg baclofen, 40 mg amitriptyline HCL, and 20 mg ketamine twice daily for 4 weeks	Barton et al, 2011[41]	Total: 203 Placebo: 102 BAK gel: 101 Double-blind study	Vinca alkaloids, platinum agents, taxanes, or thalidomide	• EORTC CIPN sensory subscale mean neuropathy change from baseline to 4 weeks: 8.1 vs 3.8 in placebo arm ($P = .053$).	Negative	No significant differences in toxicities between groups
	Amitriptyline and ketamine (AK) cream 4 g twice daily for 6 weeks	Gewandter et al, 2014[42]	Total: 458 Placebo: 231 AK: 227	Taxanes or nontaxanes	• Mean pain, numbness, and tingling score at week 6: no significant reduction in mean score ($P = .363$)	Negative	No significant differences in toxicities between groups

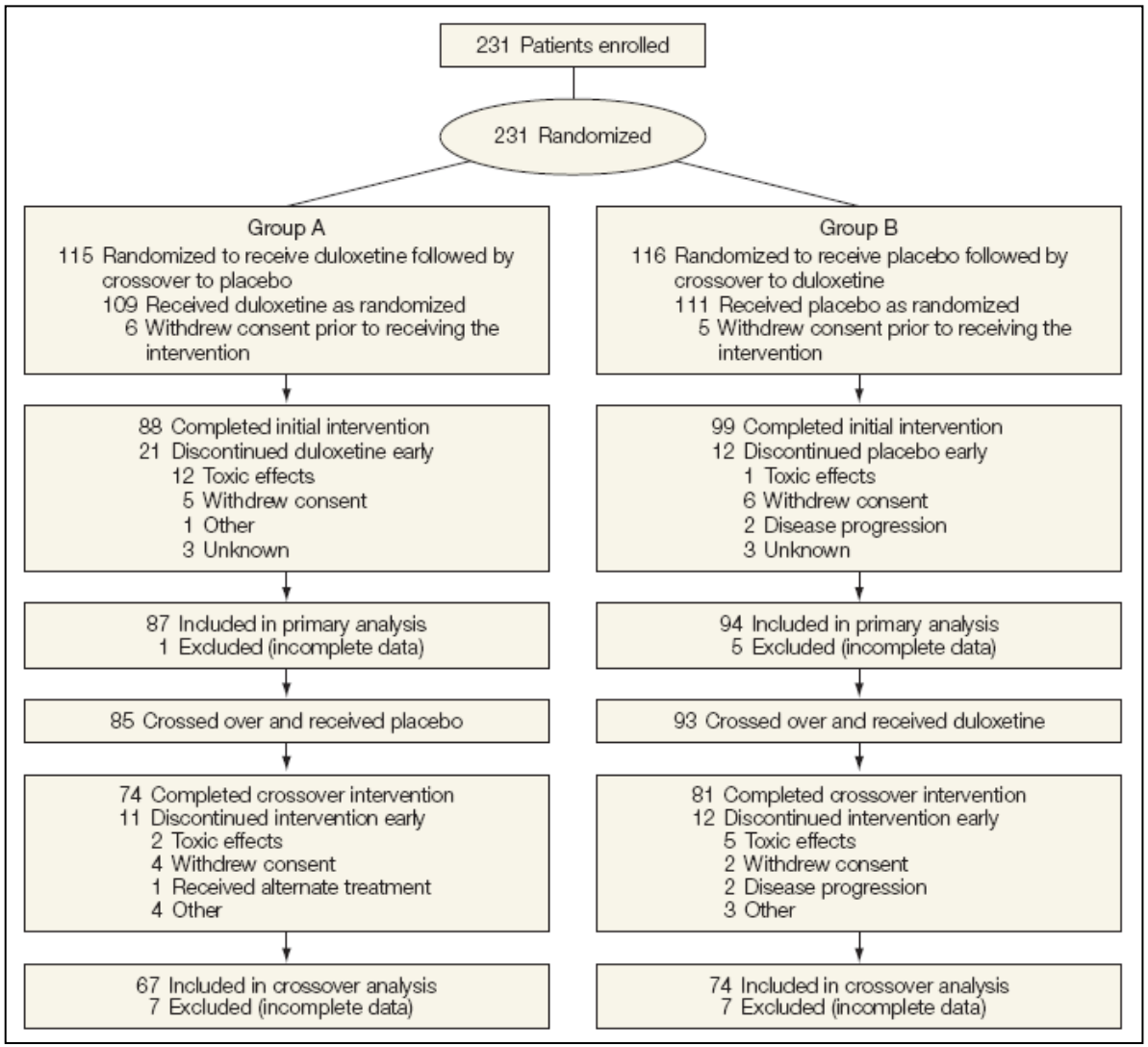
Triveldi MS et al, Americal J Hematology Oncology 2015

CIPN Treatment-Phase III trials

Drug Class	Pharmacologic Agent and Dosage	Authors and Year of Publication	Number of Patients and Study Design	Drug Causing CIPN	Primary Study Outcome Measure and Results	Overall Results	Adverse Effects of Intervention
	Venlafaxine 50 mg 1 h prior to oxaliplatin infusion and 37.5 mg extended-release twice daily on days 2 through 11	Durand et al, 2012[40]	Total: 48 Placebo: 24 Venlafaxine: 24 Double-blind study	Oxaliplatin	• Full relief of acute neurotoxicity: 31.3% vs 5.3% in placebo arm (P = .03).	Positive	Grade 1-2: nausea and vomiting, asthenia, somnolence
	Duloxetine (D) 30 mg daily for 1 week, then 60 mg daily for 4 weeks during treatment period	Smith et al, 2013[46]	Total: 220 Group A (D/PL): 109 Group B (PL/D): 111 Double-blind crossover study after 5 weeks	Paclitaxel, docetaxel, nanoparticle albumin-bound paclitaxel, cisplatin, oxaliplatin	• Reduction in average pain as measured by BPI-SF: in initial treatment period, larger mean reduction in BPI-SF pain score in duloxetine group than placebo group (1.06 vs 0.34 [scale, 0-10]; P = .003) with moderately large effect size (0.513).	Positive	Fatigue (7%) Insomnia (5%) Nausea (5%)

Triveldi MS et al, Americal J Hematology Oncology 2015

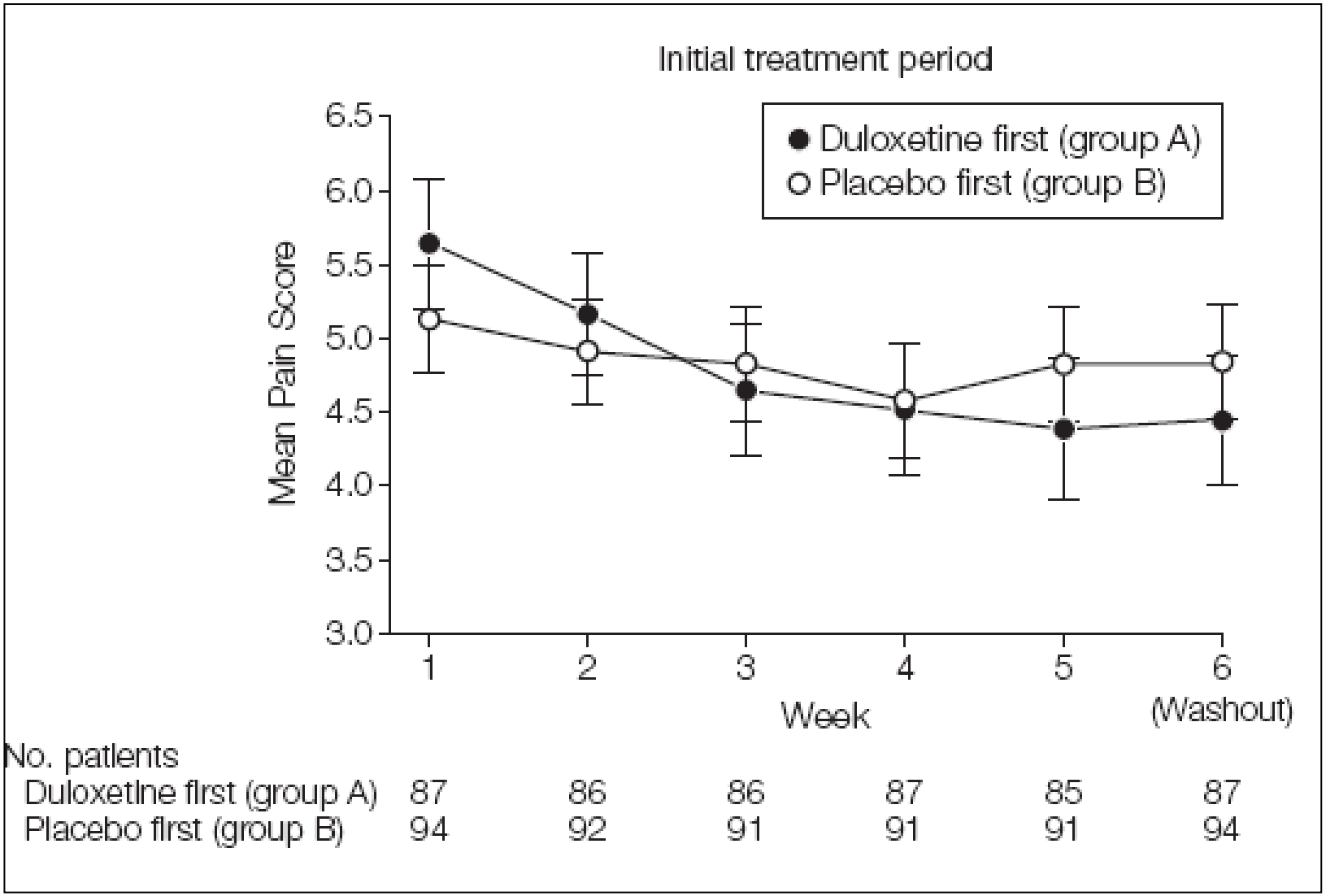
Effect of Duloxetine on pain, function and QOL among pts with CT induced CIPN



- **Randomized double blind placebo-controlled cross-over trial on 231 pts treated with duloxetine (60 mg daily) followed by placebo or placebo followed by duloxetine**
- **Pts with G1 or higher sensory neuropathy according to NCI CTC AE, at least 4 (0-10) CT-induced pain after taxanes (paclitaxel) or platinum agents (oxaliplatin)**

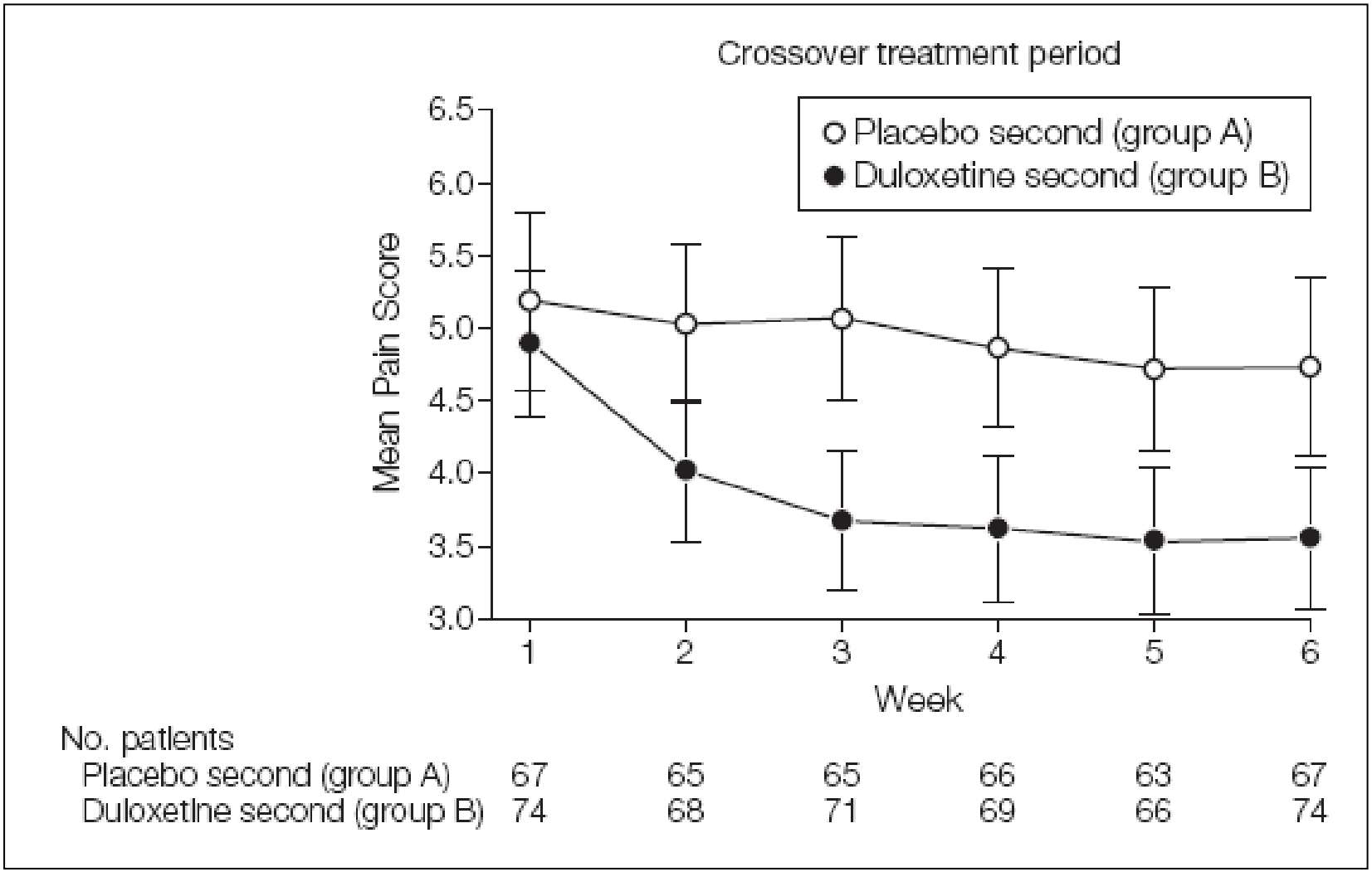
Smith EML et al, Jama 2013

Duloxetine and Placebo effects on average pain severity during initial treatment period



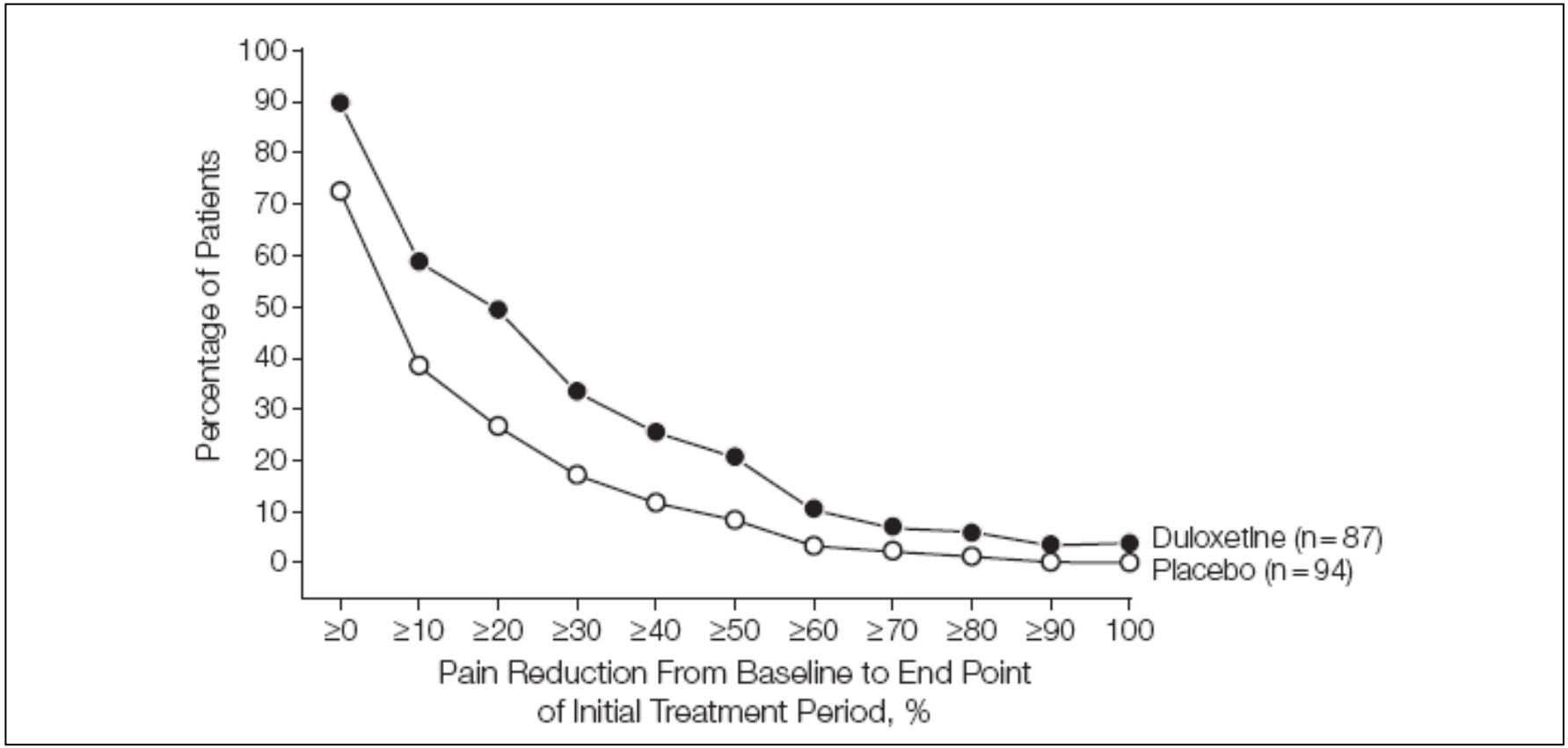
Smith EML et al, Jama 2013

Duloxetine and Placebo effects on average pain severity during crossover treatment period



Smith EML et al, Jama 2013

Decreasing in pain score due to Duloxetine vs Placebo



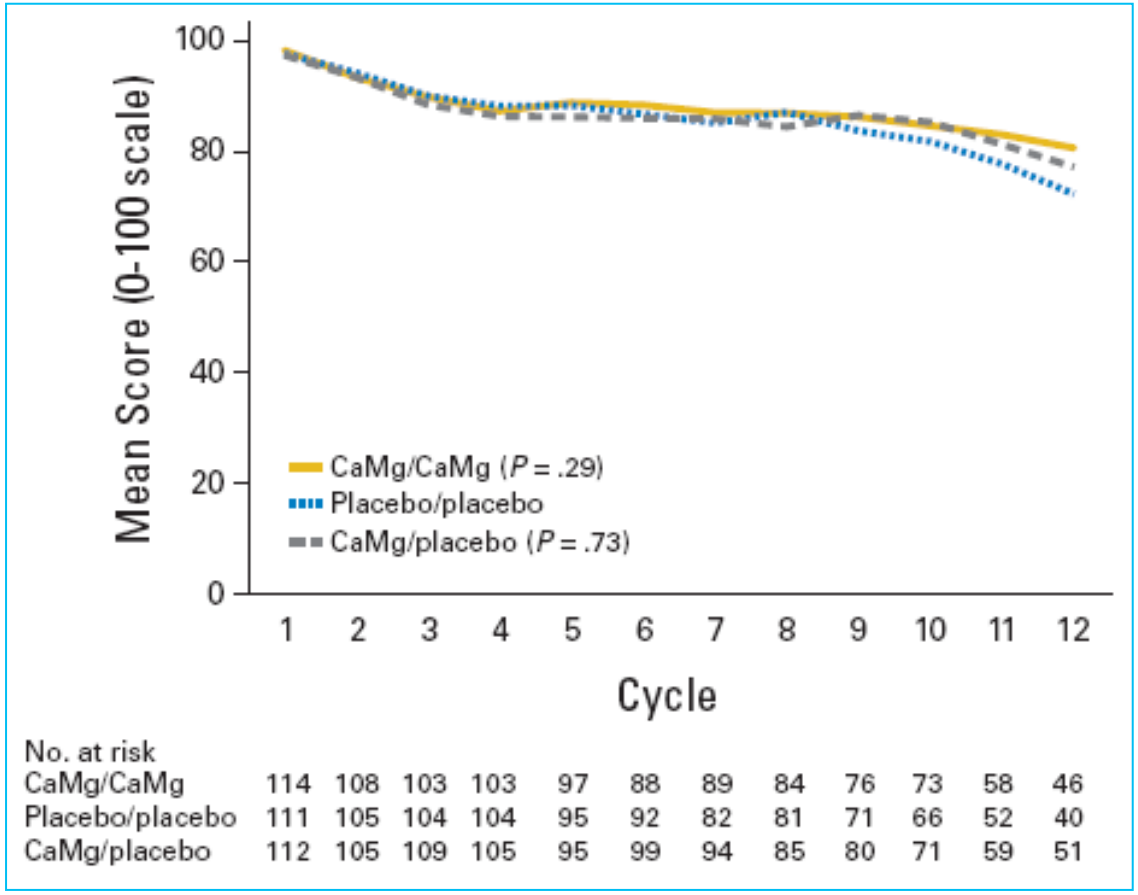
Pts receiving Duloxetine at initial 5 weeks treatment had a mean decrease in average pain of 1.06 vs 0.34 of those receiving placebo (p=0.003)

59% pts receiving first Duloxetine reported decreased pain of any amount vs 38% pts initially receiving placebo

Smith EML et al, Jama 2013

CIPN Prevention-Phase III trials

Phase III Randomized, Placebo-Controlled, Double-Blind Study of Intravenous Calcium and Magnesium to Prevent Oxaliplatin-Induced Sensory Neurotoxicity (N08CB/Alliance)



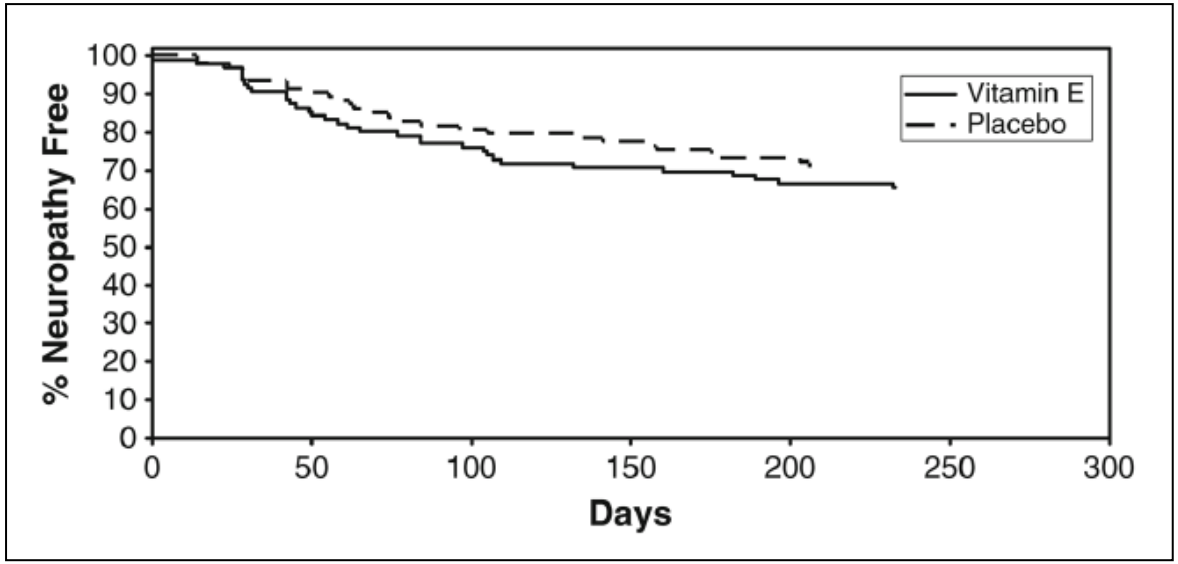
No. at risk												
CaMg/CaMg	114	108	103	103	97	88	89	84	76	73	58	46
Placebo/placebo	111	105	104	104	95	92	82	81	71	66	52	40
CaMg/placebo	112	105	109	105	95	99	94	85	80	71	59	51

353 CRC pts treated with adjuvant FOLFOX (oxaliplatin, leucovorin, 5-fluorouracil) randomly assigned to iv calcium/ magnesium before and after oxa, a placebo before and after oxa, or calcium/magnesium before and placebo after

Primary endpoint: cumulative neurotoxicity measured by EORTC sensory scale

Loprinzi CL et al, J Clin Oncol 2014

The use of vitamin E for the prevention of chemotherapy-induced peripheral neuropathy: results of a randomized phase III clinical trial

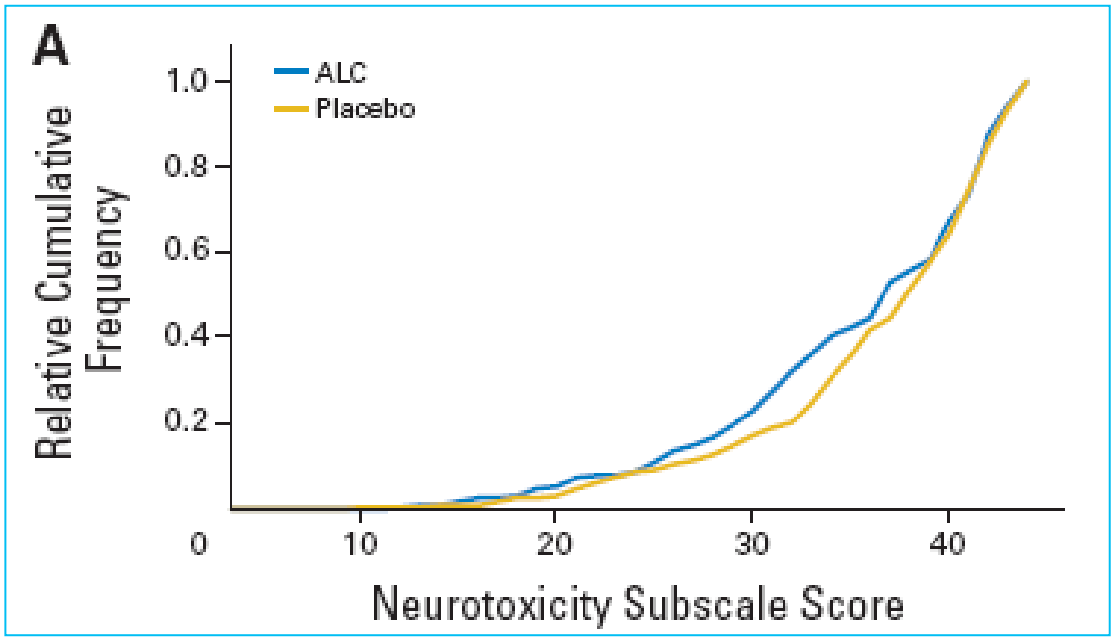


207 pts treated with neurotoxic CT (taxanes, cisplatin, carboplatin, oxaliplatin or combination) randomly assigned to vitamin E (400 mg)/placebo.

Primary endpoint: incidence of grade 2+ sensory neuropathy toxicity (CTCAE v 3.0)

Kottschade LA et al, Support Care Cancer 2011

Randomized Double-Blind Placebo-Controlled Trial of Acetyl-L-Carnitine for the Prevention of Taxane-Induced Neuropathy in Women Undergoing Adjuvant Breast Cancer Therapy

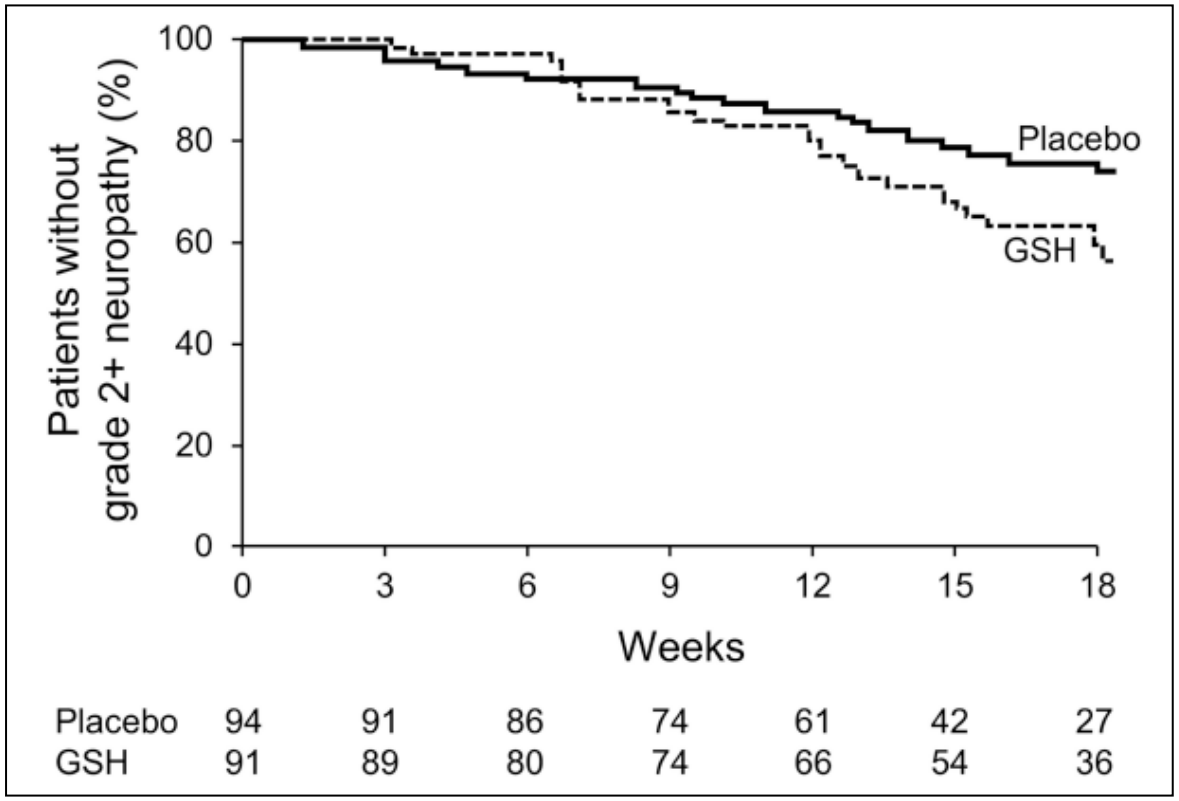


409 BC pts treated with adjuvant taxane-based CT randomly assigned to ACL (3000 mg)/placebo.

Primary endpoint: if ALC prevents CIPN measured by 11 item neurotoxicity component of functional assessment of cancer therapy (FACT)-taxane scale at 12 weeks

Herschman DL et al. J Clin Oncol 2013

NCCTG N08CA (Alliance): The use of Glutathione for Prevention of Paclitaxel/Carboplatin Induced Peripheral Neuropathy: A Phase III Randomized, Double-Blind Placebo-Controlled Study



185pts treated with carboplatin and paclitaxel randomly assigned to glutathione iv (1.5 g/m2)/ placebo.

Primary endpoint: CIPN assessed by both EORTC-QLQ-CIPN20 and CTCAE scales v4.0

Leal AD et al. Cancer 2014

Future Directions and Ongoing Trials

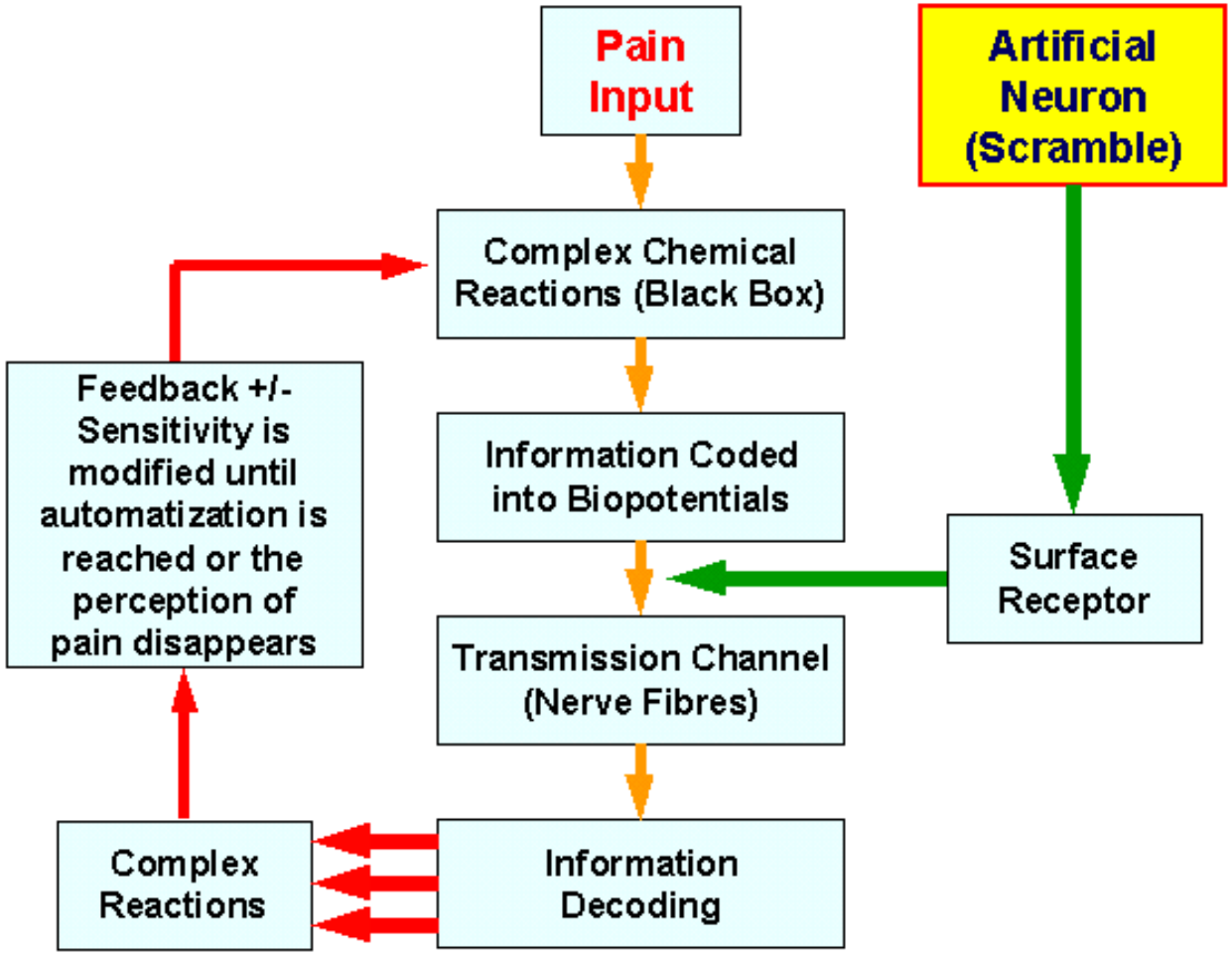
- Acupunture (NCT02129686)
- Massage Therapy (NCT02221700)
- Scrambler Therapy (NCT02111174)
- Topical Menthol (NCT01855606)

Scrambler therapy

Scrambler Therapy is a non invasive neurocutaneous electrical pain intervention effective for the treatment of neuropathic pain

It substitutes pain information with synthetic "non pain" information

Scrambler therapy - theory



….but rather to control its properties by manipulating a metavariable system……

Marineo G et al. Journal of the Pancreas 2003

Scrambler therapy

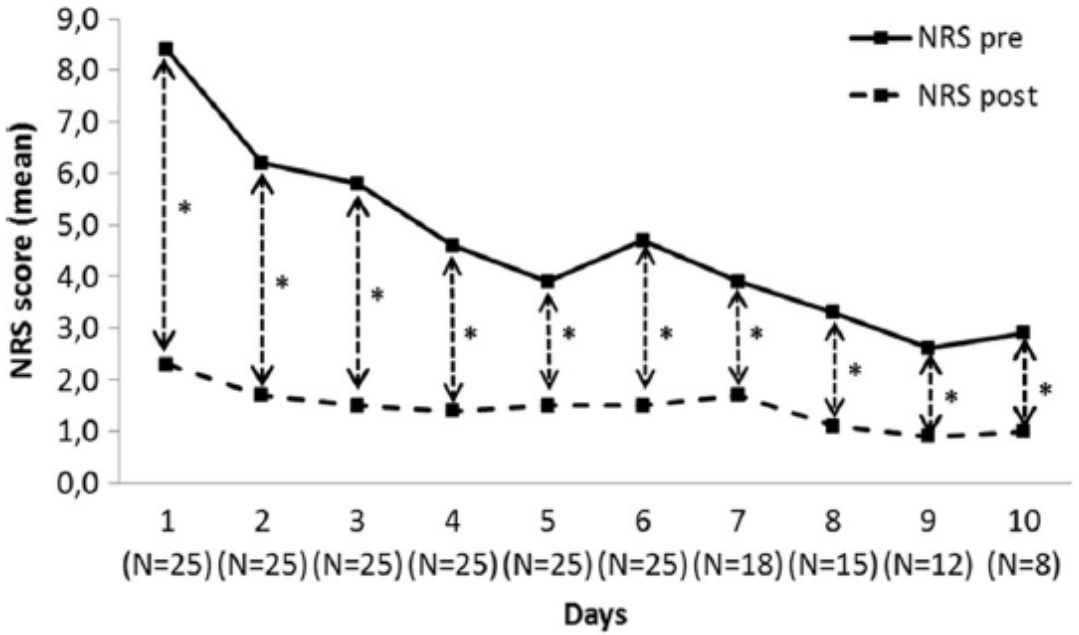
- It consists on positioning electrodes bilaterally outside the pain area to the proximal and distant area and works converting a “pain” information in “non-pain” information via electrical stimulation to the central nerve system
- The intensity of the electrodes is set to the maximum value at which the patient doesn’t feel discomfort
- Frequency: 43 to 52 Hz
- 10 daily sessions of 30-40 minutes
- The efficacy can be evaluated with pain scale (VAS-visual analogue scale, NRS-numerical rating scale)

Support Care Cancer
DOI 10.1007/s00520-015-2952-x

ORIGINAL ARTICLE

Pilot evaluation of scrambler therapy for pain induced by bone and visceral metastases and refractory to standard therapies

Paolo Notaro[1,3] · Carlo Alberto Dell'Agnola[1] · Alessandro J Dell'Agnola[1] · Alessio Amatu[2] · Katia Bruna Bencardino[2] · Salvatore Siena[2]



After 10 sessions of scrambler therapy pain score significantly reduced from 8.4 to 2.9 (p=0.008), with a pain relief of 89%

Notaro P et al. Support Care Cancer 2015

Scrambler therapy for CT-induced neuropathy

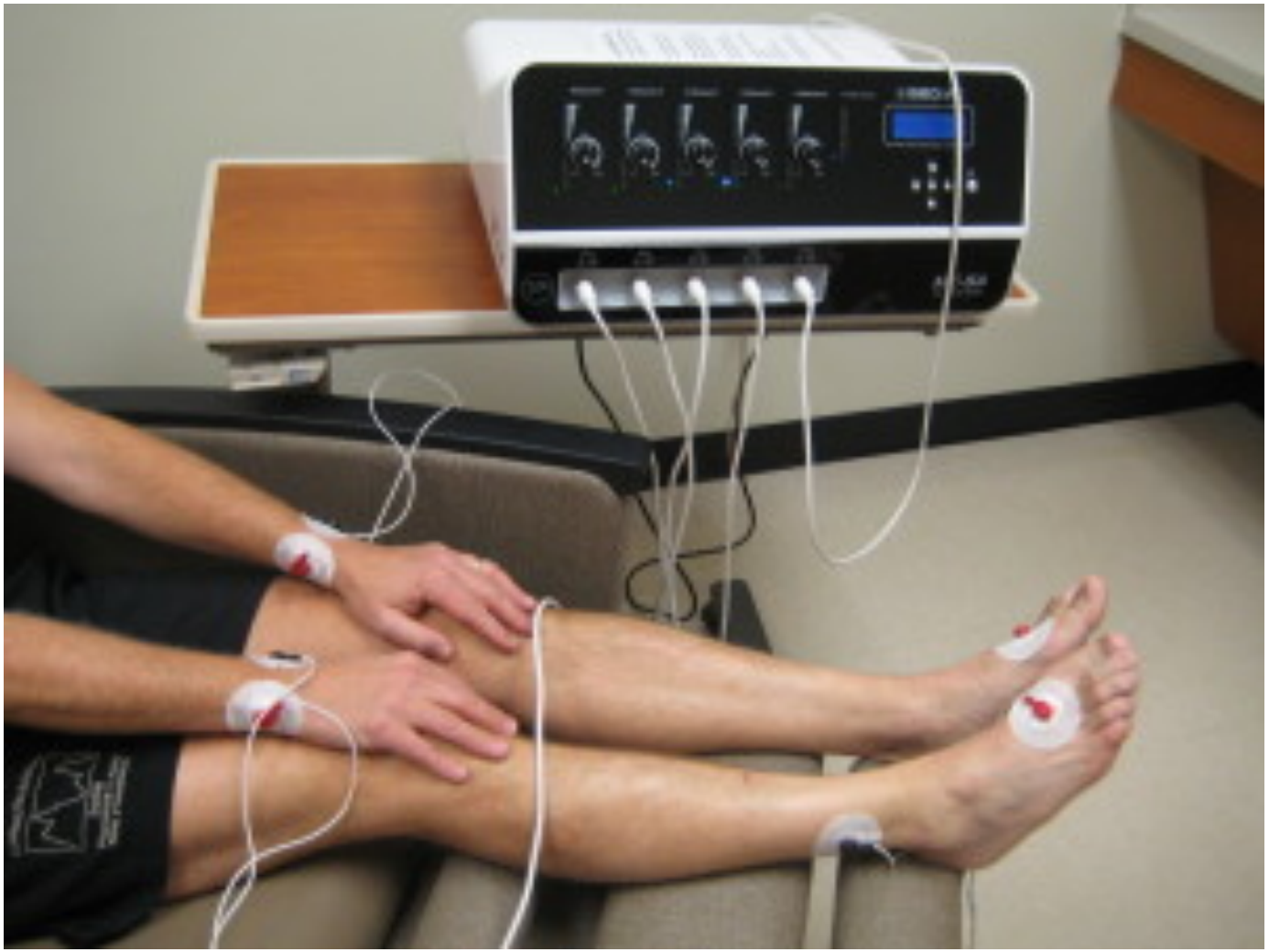
Current Treatment Options in Oncology
DOI 10.1007/s11864-014-0303-7

Neuro-oncology (GJ Lesser, Section Editor)

Therapeutic Strategies for Cancer Treatment Related Peripheral Neuropathies

*Deirdre R. Pachman, MD**
James C. Watson, MD
Charles L. Loprinzi, MD

Scrambler therapy – electrodes positioning



Case Report -1

- MDP, woman, 47 y
- 2000, March: left emicolectomy for colon adenocarcinoma pT3N1G2M0
- 2000, May-July: 6 courses of adjuvant FOLFOX (oxaliplatin, lederfolin, 5-fluorouracil) stopped for allergic reaction to oxaliplatin and G3 neuropathy (paresthesia of the four limbs)
- 2000, September: lung nodulectomy for metastases of colon adenocarcinoma
- 2002, October: lung metastsectomy for metastasis of colon adenocarcinoma
- 2002 November-2003 April: adjuvant chemotherapy with oral capecitabine
- 2012 May: right inferior lung lobectomy for lung adenocarcinoma pT1N0M0.

Case Report -2

- 2000-2015: persistence of peripheral neuropathy (paresthesia of the four limbs) documented by several neurologic visits (hypoesthesia lower limbs with a stocking pattern, Achilles' reflexes absent, hands hypodisthesia) and EMG (sensitive neuropthy, axonal, of the four limbs), treated with pregabalin, gabapentin, duloxetine, without benefit.

- 2015 November-December: 7 sessions of Scrambler Therapy with a substantial benefit (NRS 2 vs 5, hands and feet sensitivity improvement , greater use of the fingers, tingling reduction, forefoot sensitivity appearance, walking improvement)

Conclusions

- CIPN is a relatively common and potentially serious adverse event of cancer treatment, causing a reduction or dicontinuation of therapy
- Symptoms are frequently disabling, affecting patients' daily activities and quality of life
- The exact pathophysiology is not clear
- Duloxetine is the only intervention with efficacy for CIPN treatment demonstrated from a randomized, double-blind, placebo-controlled trial
- Additional supporting data are required before recommending venlafaxine
- It is resonable to try to control symptoms with tricyclic antidepressants, gabapentin, pregabalin, opioids, topical BAK after discussing the limited evidence, risks and benefits with the patient, considering scrambler therapy employment
- No effective drugs are available for CIPN prevention

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MOTRICOLOR

Grazie per l'attenzione!

ROL

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