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Hitting a Nerve: Management of Chemotherapy-Induced Neuropathic Pain

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Disclosure

- I have no actual or potentially relevant conflict of interest in relation to this activity

Learning Objectives

- Explain the pathophysiology and consequences of chemotherapy-induced neuropathic pain.
- Describe the clinical features, risk factors, causative agents, and natural course of history for CIPN.
- Discuss a therapeutic approach to managing CIPN including evidence for use of analgesics for treatment and prevention.

Abbreviations

- BAK: Baclofen, amitriptyline, ketamine
- DRG: Dorsal Root Ganglia
- DTR: Deep Tendon Reflexes
- Px: Prophylaxis
- Sx: Symptoms
- Tx: Treatment

Chemotherapy-Induced Peripheral Neuropathy (CIPN)

- A common side effect of chemotherapy (occurs in 30-40% of patients)
- Prevalence of CIPN is increasing
  - Due to increased cancer incidence and improved survival
- Painful and dose-limiting
  - Dose reduction or therapy cessation may compromise treatment response and survival
- May persist after treatment with chemotherapy
- No recommended preventive therapies and only limited treatment options

Pain 2019; 160(Suppl1): SI-S10

J Clin Oncol 2014; 32:1941-1967.

British Journal of Anaesthesia 2017; 119(4): 737-749.

For chemotherapy overall, CIPN is observed in ....

68% of patients **1 month** after finishing chemo

60% of patients **3 months** after finishing chemo

30% of patients **≥6 months** after finishing chemo

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Pain 2014; 155 (12): 2461-2470

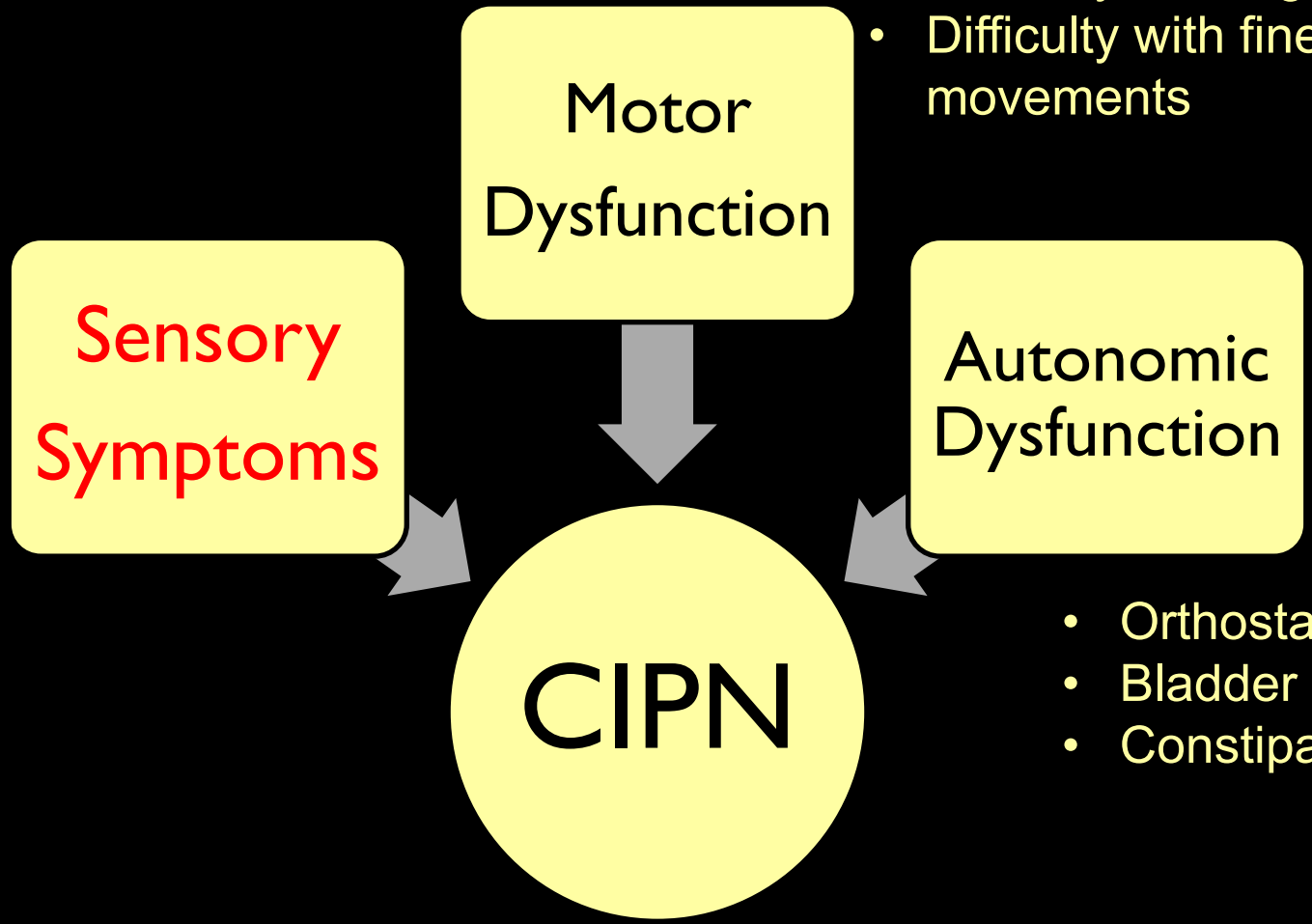
Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Chemotherapy	Prevalence	
Oxaliplatin	Acute: 85-96%	Chronic: 40-93%
Cisplatin	12-85%	
Paclitaxel	61-92%	
Bortezomib	47%	
Vincristine	20%	
Cisplatin + Paclitaxel	69-76%	

Pain 2019; 160(Suppl1): SI-S10

CIPN: the Clinical Syndrome

- Weakness of extremities
- Difficulty walking
- Difficulty with fine motor movements



- **Tingling**
- **Pain**
- **Numbness**

- Orthostatic hypotension
- Bladder dysfunction
- Constipation

Journal of Pain & Palliative Care Pharmacotherapy, 2020 DOI: 10.1080/15360288.2020.1734144

British Journal of Anaesthesia 2017; 119(4): 737-749.

Pain 2019; 160(Suppl1): SI-S10

CIPN: the clinical syndrome

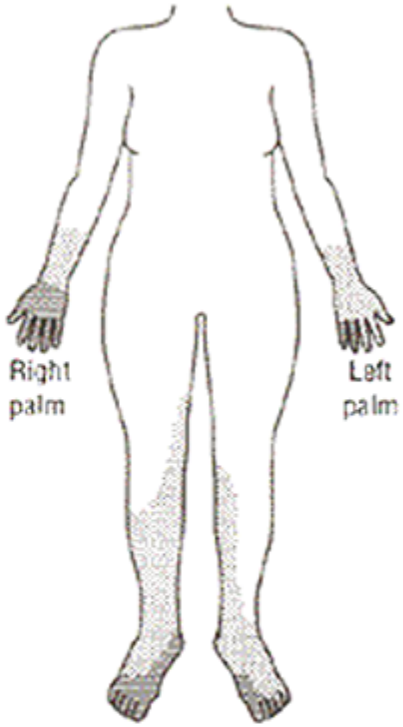
- Pathogenesis and toxicity differ based on agent
- Distinguishing features (that help to differentiate from other neuropathies)
  - Symmetrical, distal, length-dependent "glove and stocking presentation"
  - Sensory neuropathy > motor symptoms
  - Dose-dependent
- As chemotherapy continues…
  - Symptoms get progressively worse
  - Symptoms do not improve between doses
- Acute neuropathy syndromes (paclitaxel and oxaliplatin) and chronic
- "Coasting" = new or worsening neuropathy after cessation of chemotherapy

J Clin Oncol 2014; 32:1941-1967.

CIPN: Glove and Stocking Neuropathy

Examples of descriptors used

- Burning
- Shooting
- Stabbing
- Electric shocks
- "Like walking on glass"
- "As if wearing gloves with bees inside"



Sensory symptoms and signs

+ve

- Mechanical allodynia e.g. clothes on skin are painful
- Thermal allodynia especially cold hypersensitivity with acute oxaliplatin treatment
- Hyperalgesia
- dysaesthesia

-ve

- Numbness
- Paraesthesia
- Inability to detect temperature changes
- Loss of fine motor function (peg board)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6499732/

Pain 2019; 160(Suppl1): SI-S10

Assessment: Is this CIPN?

- ❑ What **risk factors** does the patient have?
- ❑ Are there other **possible causes** of neuropathy?

Ann Neurol . 2017 June ; 81(6): 772–781.

Risk Factors for Developing CIPN

Patient-Related Factors

- Older age
- History of neuropathy before starting chemotherapy
- Co-morbid health conditions that may be associated with increased risk of neuropathy
  - Diabetes
  - HIV
  - Alcoholism
  - Impaired renal function
  - Smoking
- Higher BMI
- Low serum albumin

Drug-Related Factors

- Higher chemotherapy dose
- Longer duration of chemotherapy
- Route of administration
- Treatment schedule
- Formulation

Cancer-Related Factors

- Paraneoplastic neuropathies
- Direct neoplastic infiltration
- Multiple Myeloma

Ann Neurol . 2017 June ; 81(6): 772–781. *Pain* 2019; 160(Suppl1): SI-S10 *British Journal of Anaesthesia* 2017; 119(4): 737-749.

Assessment: Is this CIPN?

- ❑ Has the patient received a **neurotoxic chemotherapy**?

Ann Neurol . 2017 June ; 81(6): 772–781.

Classical Chemotherapy Classes Associated with CIPN*

Platinum	Taxanes	Vinca Alkaloids
Cisplatin	Paclitaxel	Vincristine
Oxaliplatin	Docetaxel	Vinblastine
Carboplatin	Cabaliztaxel	Vinorelbine

***In decreasing order of neurotoxicity**

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Pain 2019; 160(Suppl1): SI-S10

Crit Rev Oncol Hematol 2012; 82: 51-77

Raffa et al, eds. *Chemotherapy-Induced Neuropathic Pain*. Boca Raton, F: CRC Press, 2013.

Other Chemotherapy Classes Associated with CIPN

Proteasome Inhibitors	Epotilones	Immunomodulators
Bortezomib	Eribulin	Thalidomide
Carfilzomib	Ixabepilone	Pomalidomide
Ixazomib		Lenalidomide

Pain 2019; 160(Suppl1): S1-S10

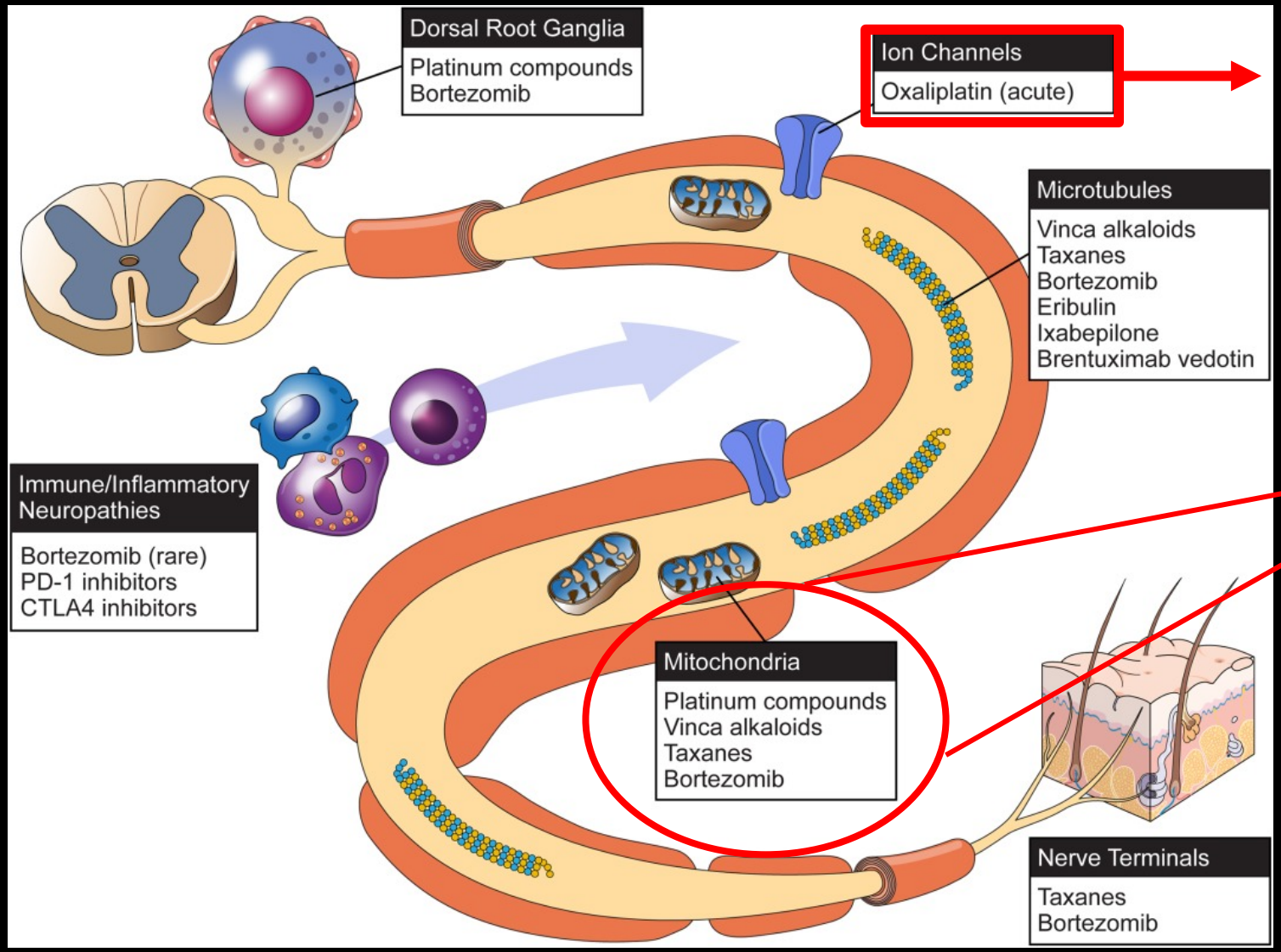
Raffa et al, eds. *Chemotherapy-Induced Neuropathic Pain*. Boca Raton, F: CRC Press, 2013.

Crit Rev Oncol Hematol 2012; 82: 51-77

Pathogenesis of CIPN

- Pathogenesis and toxicity differ based on agent
- Typically dose-dependent with axonal degeneration after several cycles of neurotoxic chemotherapy
- Sensory Nerve Involvement:
  - Majority of symptoms due to damage to dorsal root ganglion neurons or axonal damage and dampening of sensory action potentials
    - Sensory loss, acral pain (feet/hands), and sometimes sensory ataxia
  - Larger nerve fiber involvement may also occur
    - Loss of reflexes, vibration, and proprioception, and muscle weakness
- Motor, autonomic, and cranial nerve symptoms are less common, but may occur
- Recovery may be complete or partial with long term-neuropathy possible

Ann Neurol . 2017 June ; 81(6): 772–781.
Crit Rev Oncol Hematol 2012; 82: 51-77
Raffa et al, eds. *Chemotherapy-Induced Neuropathic Pain*. Boca Raton, F: CRC Press, 2013.
J Clin Oncol 2014; 32:1941-1967.
Hale KE. Toxicities of Chemotherapy. In: Hall JB, Schmidt GA, Kress JP. eds. *Principles of Critical Care, 4e*. McGraw-Hill; Accessed Au
19, 2020. https://accessmedicine.mhmedical.com/content.aspx?bookid=1340&sectionid=8003708



Acute cold symptoms = effect on voltage-gated sodium channels

"Coasting" = damage to mitochrondia

From Annals of Neurology, Anthony Windebank, Wolfgang Grisold, Anna Gristold, et al, Chemotherapy-induced peripheral neuropathy: a current review 81 (6): 772-781 © 2017 John Wiley and Sons. Represented with permission from John Wiley and Sons.

Ann Neurol . 2017 June ; 81(6): 772–781.

Assessment: Is this CIPN?

- Is the **clinical presentation** and **time course** what I would expect for the chemotherapy received?
- Has the patient received a **dose** of chemotherapy associated with the development of CIPN?
- Is the **route** of administration consistent with CIPN?
  - CIPN rare with methotrexate, unless given intrathecally
  - CIPN with bortezomib: subcutaneous < intravenous

Ann Neurol . 2017 June ; 81(6): 772–781.

Platinum Drugs: Cisplatin

Mechanism	Risk Factors	Clinical Features	Time Course	Px	Tx
Preferential damage to the dorsal root ganglion (via cross-link and damage of DNA)	Cumulative dose >400 mg/m^2 (almost all patients) Onset may occur at 250-350 mg/m^2	Predominately large fiber sensory neuropathy • Tingling • Numbness • Paresthesias of upper/lower extremities • Reduced perception of vibration • Reduced proprioception • Decreased DTR • Gait disturbances	Earliest signs are in orange	Exercise[1] Amifostine[2] (with cyclosphosphamide) Glutathione[3] Vitamin E?[4]	Venlafaxine (with docetaxel and 5-FU)[5] Duloxetine[6]
Mitochondrial DNA damage (responsible for "coasting")			Progression or emergence 2-6 months after stopping treatment		
Neuronal cell death, irreversible ("neuronopathy")	Cumulative dose greatest risk factor		Frequently recovery is incomplete		

[1] *Support Care Cancer.* 2018 April ; 26(4): 1019–1028.
[2] *J Clin Oncol* 1996; 14:2101-2112
[3] *J Clin Oncol* 1995; 13(1):26-32
[4] *Neurology* 2010 74:762-766
[5] *Cancer Chemother Pharmacol* 2018; 82:787-79
[6] *Cancer Chemother Pharmacol* 2018; 82:787-79
Crit Rev Oncol Hematol 2012; 82: 51-77
Raffa et al, eds. *Chemotherapy-Induced Neuropathic Pain*. 2013.

Platinum Drugs: Oxaliplatin

Mechanism	Risk Factors	Clinical Features	Time Course	Px	Tx
Axonal hyper-excitability from altered voltage-gated sodium channels	Oxaliplatin infusion Every 2 week schedule *Not* related to cumulative dose	**Acute, cold-induced neuropathy (sensory/motor symptoms):** • cold sensitivity (hands, face, and oral cavity) • throat discomfort • discomfort swallowing cold liquids • muscle cramps/spasms	• Typically begins with 2nd or 3rd cycle • Peak 2-3 days after each dose • May occur during drug infusion • Symptom severity worsens with each cycle • Usually self-limiting over hours to days	Cryotherapy[1] Exercise[2] Metformin 500 mg TID[3] Oxcarbazepine[4] Glutathione[5] Calmangafodipir[6] L-carnosine[7] Ganglioside-monosialic acid (GM-1)[8] Venlafaxine??	Exercise[9] (minimize progression of CIPN) Duloxetine[10,12] Venlafaxine[11-12]
DRG and Mitochondrial DNA damage (responsible for "coasting")	Cumulative dose >510-750 mg/m^2	Chronic Sensory Neuropathy: • Paresthesias • Dysesthesias • Upper extremities > lower	• Partially reversible in 80% of patients and completely resolves in 40% at 6-8 months after discontinuation. • Coasting may occur for 2-3 months post-therapy • Hands improve faster than feet		

[1]*Ann* Oncol 2020; 31:131-136, [2]*Support Care Cancer.* 2018 April ; 26(4): 1019–1028. [5]*J Clin Oncol* 2002 20:3478-3483,[12]*Cancer Chemother Pharmacol* 2018; 82:787-79, *J Clin Oncol* 2020 Jul 14
[3]*Int J Colorectal Dis* 2018; 33:1675-1683, [6]*Acta Oncol* 2018; 57:393-402, [8]*World J Surg Oncol* 2013 11:19
[4]Neurology 2006; 67:2253-2255 [7]*Toxicol Appl Pharmacol* 2019; 365:41-50, [9]*Support Care Cancer* 2018 26:615–624 *Crit Rev Oncol Hematol* 2012; 82: 51-77
[10]*JAMA.* 2013;309(13):1359-1367 [11]*Annals of Oncology* 2012; 23: 200–205

Patient Counseling for Oxaliplatin Cold-Induced Neuropathy

- Avoid ice and all cold beverages and food (like ice cream)
  - If you forget, drink something warm
- Avoid washing hands with cold water
  - If you forget, rinse your hands with warm water
- Keep gloves near the fridge for getting items inside
- Wear gloves in the refrigerated section of the grocery store
- Wear gloves outside
- Avoid touching metal hand railings or other cold objects.
- Always wear socks to avoid contact with cold floors
- In the winter, dress warm with gloves, hats, and scarves
- Do not breathe deeply when exposed to cold air
- In the summer, avoid cold air conditioning

Platinum Drugs: Carboplatin

Mechanism	Risk Factors	Clinical Features	Time Course	Px	Tx
DRG and Mitochondrial DNA damage (responsible for "coasting")	Concurrent use with taxanes Less common at conventional doses, but may develop at higher doses (such as those used for hematopoietic stem cell transplant)	Sensory neuropathy Less frequent and less severe than cisplatin Reflexes usually normal	Similar to cisplatin Coasting may be less common	Exercise[1] Amifostine[2] (carboplatin + paclitaxel)	Exercise[3] (carboplatin + paclitaxel) Venlafaxine[4] Duloxetine[4]

[1] *Support Care Cancer.* 2018 April ; 26(4): 1019–1028.
[2] *Ann Oncol* 2003; 14:1086-1093
[3] *Cancer Nurs* 2020; 43(4): 269-280
[4] *Cancer Chemother Pharmacol* 2018; 82:787-79,

Raffa et al, eds. *Chemotherapy-Induced Neuropathic Pain.* 2013.
Ann Neurol . 2017 June ; 81(6): 772–781.
Crit Rev Oncol Hematol 2012; 82: 51-77

Taxane Drugs: Paclitaxol

Mechanism	Risk Factors	Clinical Features	Time Course	Px	Tx
Manifestation of acute neuropathy (although mechanism unclear)	Single dose >250 mg/m^2 Cumulative dose >1000 mg/m^2 Weekly treatment schedule > every 3 week schedule? (conflicting studies) Previous or concurrent use of platinum drugs	**Acute Pain Syndrome:** • Arthralgias and myalgias • Occurs in large axial muscles/joints (hip, back, shoulder, legs, feet)	• Develops within 1-3 days of each dose • Resolves in between cycles (~within a week) • Symptom severity does not worsen with each cycle	Cryotherapy[1-3] Cryo-compression[4] Compression only[5] Exercise[6] Gabapentin 300 mg TID[7] Ganglioside-monosialic acid (GM-1)[8]	Acupuncture[9] Duloxetine[10-11,13] Venlafaxine[11] Exercise[3] (carboplatin + paclitaxel)[12] Pregabalin[13]
Stabilization of microtubule polymers and interference with axonal transport (large sensory fibers affected > small fibers) "Dying back axonopathy" (starting with distal nerve endings)		**Chronic neuropathy:** • Lower extremities > upper • primarily sensory (numbness/ tingling > pain) • Loss of pain and temperature sensation • Decreased vibration perception, proprioception, and DTR/ankle reflexes • Motor involvement less frequent (occasional mild weakness in foot muscles)	• Numbness/tingling occur earlier than pain • Stocking glove distribution begins in fingers/toes and can progress proximally • After completion of treatment, CIPN improves over 3-6 months		

[1]*J Natl Cancer Inst* 2018; 110:141-148, [2]*Ann* Oncol 2020; 31:131-136, [3]*Front Oncol* 2017; 6:27, [4]*J Clin Oncol* 2018; 36, (15_suppl; abstr 10095) [5]*Breast Cancer Res Treat* 2016; 160:61-67 [6]*Support Care Cancer.* 2018 April ; 26(4): 1019–1028. [7]*Breast J* 2019; 25:226-231 [8]*J Natl Cancer Inst* 2020; 112:55-62 [9]*Oncologist* 2020; 25:310-318 [10]*JAMA.* 2013;309(13):1359-1367 [11]*Cancer Chemother Pharmacol* 2018; 82:787-79, [12]*Cancer Nurs* 2020; 43(4): 269-280 [13]Clinical Drug Investigation (2020) 40:249–257 NEJM 2008: 358: 1663-1671 Raffa et al, eds. *Chemotherapy-Induced Neuropathic Pain.* 2013. *Crit Rev Oncol Hematol* 2012; 82: 51-77

Taxane Drugs: Docetaxol

Mechanism	Risk Factors	Clinical Features	Time course	Px	Tx
Stabilization of microtubule polymers and interference with axonal transport (large sensory fibers affected > small fibers) "Dying back axonopathy" (starting with distal nerve endings)	Cumulative dose >400 mg/m^2 Previous or concurrent use of platinum drugs *(schedule does not appear to influence toxicity)*	Same toxicity profile as paclitaxel	Spontaneous recovery is more common than with paclitaxel	Cryotherapy[1,2] Exercise[3] Ganglioside-monosialic acid (GM-1)[4]	Venlafaxine[5] (with cisplatin) Duloxetine[5] (with cisplatin) Pregabalin[6]

[1]*Breast Cancer Res Treat* 2013; 142:109-118,
[2]*Ann* Oncol 2020; 31:131-136
Crit Rev Oncol Hematol 2012; 82: 51-77
[3]*Support Care Cancer.* 2018 April ; 26(4): 1019–1028.
[4]*J Natl Cancer Inst* 2020; 112:55-62
[5]*Cancer Chemother Pharmacol* 2018; 82:787-79
Raffa et al, eds. *Chemotherapy-Induced Neuropathic Pain*. Boca Raton, F: CRC Press, 2013.
[6]Clinical Drug Investigation (2020) 40:249–257

Vinca Alkaloids: Vincristine

Mechanism	Risk Factors	Clinical Features	Time Course	Px	Tx
Interfere with axonal microtubules; impairs axonal transport Large/small fiber neuropathy	Cumulative Dose >4 mg/m^2 (30-50 mg)	**Sensorimotor neuropathy** Decrease/loss of DTR (ankle reflexes)	• CIPN typically occurs within the 1st 3 months • Reversible once therapy is stopped • Median time to resolution after discontinuation is 3 months • Possible coasting effect in 1st month after discontinuation in 30% of patients	Exercise[1]	Topical BAK[2]?
		Sensory (hypoesthesia, dysesthesia, paresthesias) • Distal, lower extremities			
		One-third have autonomic dysfunction (orthostatic hypotension, bladder dysfunction, colicky abdominal pain, constipation, impotence)			
	Cumulative Dose >8 mg/m^2	Motor weakness or gait impairment			

Hale KE. Toxicities of Chemotherapy. In: Hall JB, Schmidt GA, Kress JP. eds. *Principles of Critical Care, 4e*. McGraw-Hill

[1]*Support Care Cancer.* 2018 April ; 26(4): 1019–1028.
[2]Support Care Cancer . 2011 June ; 19(6): 833–841
Crit Rev Oncol Hematol 2012; 82: 51-77

Proteasome Inhibitor: Bortezomib

Mechanism	Risk Factors	Clinical Features	Time Course	Px	Tx
Small fiber axonal neuropathy Mechanism largely unknown (immune system mediated, effect on DRG, mitochondrial damage)	Cumulative dose: 26 mg/m2 Intravenous administration > subcutaneous Recurrent disease (multiple myeloma) Multiple myeloma-associated neuropathy Twice weekly administration > once-weekly	Primarily sensory neuropathy (but may be mixed sensorimotor): • Distal painful paresthesias • Distal loss of sensation • Reduced reflexes and proprioception • Occasional distal muscle weakness in lower extremities Occasional autonomic symptoms: constipation, orthostasis	Resolution 3-4 months after discontinuation (in some cases, may have persistence of painful neuropathy)		Topical menthol[1-2]?

Ann Neurol . 2017 June ; 81(6): 772–781. *Crit Rev Oncol Hematol* 2012; 82: 51-77

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Raffa et al, eds. *Chemotherapy-Induced Neuropathic Pain*. Boca Raton, F: CRC Press, 2013.

[1]*Support Care Cancer* 2011;19: S158 (suppl2; abstr 263)
[2]*Ann Oncol 2012;* 23; ix513 (suppl9; abstr)

Hale KE. Toxicities of Chemotherapy. In: Hall JB, Schmidt GA, Kress JP. eds. *Principles of Critical Care, 4e*. McGraw-Hill;

Epotilones: Ixabepilone and Eribulin

Mechanism	Risk Factors	Clinical Features	Time Course	Px	Tx
Mechanism of chronic neurotoxicity similar to paciltaxel	Dose-dependent	Primarily sensory neuropathy • Distal painful paresthesias • Distal loss of sensation Less common: motor neuropathy Rare: autonomic neuropathy	Usually improves after discontinuation		

Raffa et al, eds. *Chemotherapy-Induced Neuropathic Pain*. Boca Raton, F: CRC Press, 2013.

Crit Rev Oncol Hematol 2012; 82: 51-77

Ann Neurol . 2017 June ; 81(6): 772–781.

Hale KE. Toxicities of Chemotherapy. In: Hall JB, Schmidt GA, Kress JP. eds. *Principles of Critical Care, 4e*. McGraw-Hill; Accessed August 19, 2020. https://accessmedicine.mhmedical.com/content.aspx?bookid=1340&sectionid=8003708

Immunomodulator: Thalidomide

Mechanism	Risk Factors	Clinical Features	Time Course	Px	Tx
Anti-angiogenesis Mechanism of CIPN is unknown	25-1600 mg/m^2 (dose-dependence uncertain) Multiple myeloma-associated neuropathy	Sensory Neuropathy • Painless hand/feet paresthesias • Reduced sensation to light touch • Loss of DTRs 30-40% weakness/tremor (motor neuropathy) Autonomic (constipation) manifestations are rare	Early onset (1-2 months) with higher doses Later onset (8-12 months) with lower doses Slow recovery and incomplete		Topical BAK[1]?

Neurology. 2007;69(6):573

J Clin Oncol. 2006;24(27):4507

Raffa et al, eds. *Chemotherapy-Induced Neuropathic Pain*. Boca Raton, F: CRC Press, 2013.

[1]Support Care Cancer . 2011 June ; 19(6): 833–841

Crit Rev Oncol Hematol 2012; 82: 51-77

Ann Neurol . 2017 June ; 81(6): 772–781.

Hale KE. Toxicities of Chemotherapy. In: Hall JB, Schmidt GA, Kress JP. eds. *Principles of Critical Care, 4e*. McGraw-Hill; Accessed August 19, 2020. https://accessmedicine.mhmedical.com/content.aspx?bookid=1340&sectionid=8003708

CIPN PREVENTION: Non-Pharmacological

Intervention	ASCO CIPN Guideline 2014		ASCO CIPN Guideline Update July 2020	
			Recommendation	Evidence since 2014
Acupuncture (during treatment with taxanes)			**No recommendation**	1 (-) RCT
Cryotherapy (frozen gloves or socks during primarily taxane infusion)			**No recommendation** ("available data support that [these interventions], in part, prevent CIPN symptoms and are reasonably safe')	1 (+) RCT 1 (-/+) RCT 3 (-) RCT → high withdrawal rate due to discomfort
Cryo-compression (cyclic pressure 5-15 mmHg during paclitaxel infusion)				1 (+) RCT
Compression (tight surgical glove during paclitaxel infusion)				1 (+) RCT
Exercise (6-8 week supervised and unsupervised programs during variety of chemo regimens)				2 (+) RCT

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J Clin Oncol 2014; 32:1941-1967.

J Clin Oncol 2020 Jul 14 DOI https://doi.org/10.1200/JCO.20.01399

CIPN TREATMENT: Non-Pharmacological

Intervention	ASCO CIPN Guideline 2014		ASCO CIPN Guideline Update July 2020	
			Recommendation	Evidence since 2014
Acupuncture (variety of chemo regimens)			**No recommendation** ("Note: While recent preliminary evidence suggests a potential for benefit from exercise, acupuncture, and scrambler therapy, larger sample–sized definitive studies are needed to confirm efficacy and clarify risks.")	3 (+) RCTs
Electro-acupuncture (variety of chemo regimens)				1 (-) RCT
Scrambler Therapy (electrocutaneous treatment for variety of chemo regimens)				1 (+) RCT 1 (-) RCT
Exercise (home-based program during paclitaxel and carboplatin or oxaliplatin)				2 (+) RCT

Non-Pharm Interventions Not Included

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J Clin Oncol 2014; 32:1941-1967.

J Clin Oncol 2020 Jul 14 DOI https://doi.org/10.1200/JCO.20.01399

Cryotherapy and Compression Therapy

Exercise Interventions and CIPN

Prevention

- Exercise for Cancer Patients (EXCAP©)
  - 6 week, unsupervised, low to moderate intensity aerobics, at home program
  - Progressive walking program
    - Increase steps by 5-20% each week
  - Progressive resistance exercise
    - Varying resistance bands and exercises
- Exercise reduced CIPN symptoms:
  - Hot/cold in feet/hands (p=0.045)
  - Numbness/tingling (p=0.06)
- Neuropathy still developed but less than the control group
- Other studies suggest stabilisation of symptoms

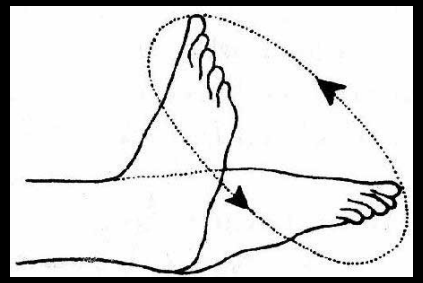
Support Care Cancer. 2018 April ; 26(4): 1019–1028.

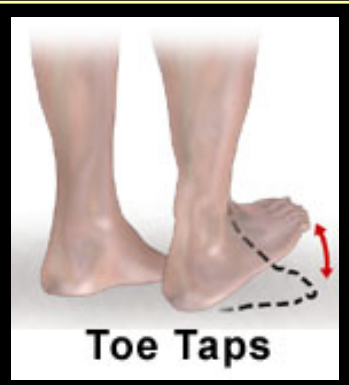
Exercise Interventions and CIPN

Treatment

10-week home-based muscle strengthening and balancing exercises

Lying Down Exercises (7 minutes)	Sitting Exercises (13 minutes)	Standing Exercises (10 minutes)
1. Ankle motion 2. Hip abduction 3. Straight leg raise	4. Digit abduction/adduction 5. Wrist motion 6. Elbow flexion and extension 7. Knee flexion and extension 8. Toe tapping	9. One legged stand 10. Toe stand 11. Hip extension 12. Tandem forward walking





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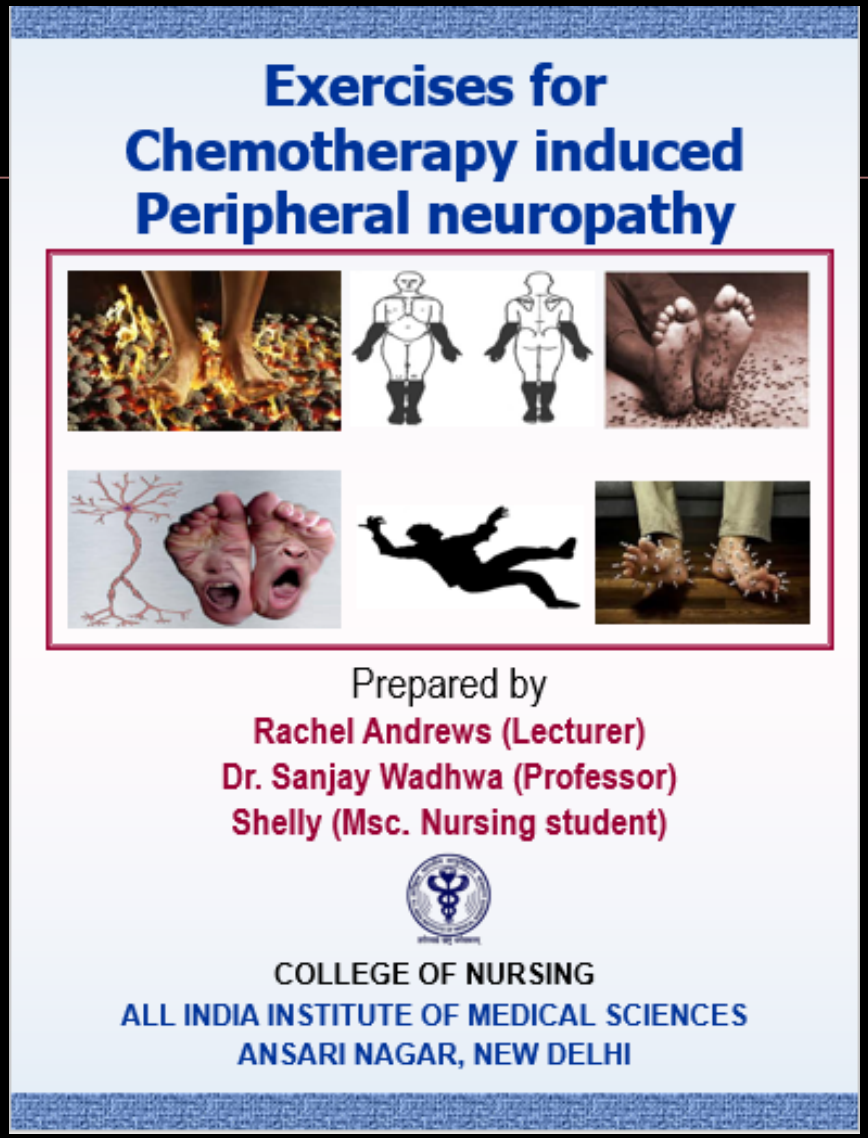
Cancer Nurs 2020; 43(4): 269-280.

Exercise Booklet for CIPN

Digital Content from *Cancer Nursing*

- http://links.lww.com/CN/A20



Cancer Nurs 2020; 43(4): 269-280.

CIPN PREVENTION: Pharmacological

Intervention	ASCO CIPN Guideline 2014		ASCO CIPN Guideline Update July 2020	
	Recommendation	Evidence	Recommendation	Evidence since 2014
Amifostine (with platinum, taxane, and combination agents)	**Should NOT offer** (variable benefit, adverse effects)	4 (+) RCTs 2 (-) RCT	**Should NOT offer**	**No new evidence since 2014 guideline**
CaMg Infusion (with oxaliplatin infusion)	**Should NOT offer** (no benefit; some concern for reduced anti-tumor effect)	1 (+) RCT 1 (-) RCT 3 terminated early; no benefit seen	**Should NOT offer** (no benefit)	1 (-) meta-analysis of 5 RCTS 1 (-) RCT
Metformin (500 mg TID with 12 cycles of oxaliplatin)	Not included in 2014 guideline		**Should NOT offer** (small sample size)	1 (+) RCT
Minocycline (100 mg BID ± 200 mg on day 1)	Not included in 2014 guideline		**Should NOT offer** (no benefit)	2 (-) RCTs (oxaliplatin, paclitaxel)
Nimodipine (90 mg/d with cisplatin tx)	**Should NOT offer** (worse outcomes)	1 (-) RCT→ N/V and worsened neuropathy	**Should NOT offer**	**No new evidence since 2014 guideline**

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J Clin Oncol 2014; 32:1941-1967.

J Clin Oncol 2020 Jul 14 DOI https://doi.org/10.1200/JCO.20.01399

CIPN PREVENTION: Pharmacological

Intervention	ASCO 2014 Recommendation	ASCO 2020 Recommendation
Acetyl-l-carnitine (ALC)	**Should NOT offer** (inconclusive evidence)	**DISCOURAGE** (significantly worse CIPN)
Diethyldithio-carbamate (DDTC)	**Should NOT offer** (no benefit, toxicity)	**Unchanged; No new evidence**
Glutathione for paclitaxel/carboplatin	**Should NOT offer** (RCT "convincingly" negative)	**Unchanged; No new evidence**
Glutathione for cisplatin or oxaliplatin	**No recommendation** (inconclusive; 5 out of 6 small trials suggested benefit)	**Not discussed**
Org 2766	**Should NOT offer** (2 large RCT negative)	**Unchanged; No new evidence**
Retinoic Acid	**Should NOT offer** (1 small RCT, some benefit)	**Unchanged; No new evidence**
rhuLIF	**Should NOT offer** (worse outcomes)	**Unchanged; No new evidence**
Vitamin E	**Should NOT offer** (3 small RCTs positive, large RCT "convincingly" negative)	**Should NOT offer** (1 negative meta-analysis of 6 studies; 1 negative small RCT)
N-acetylcysteine	**No recommendation** (inconclusive,1 small RCT)	**Unchanged; No new evidence**
Glutamate	**No recommendation** (inconclusive, 2 small RCTs with some benefit)	**Unchanged; No new evidence**
Goshajinkigan (GJG)	**No recommendation** (inconclusive,1 small RCT with some benefit)	**Should NOT offer** (1 negative meta-analysis of 5 studies)
Omega-3-fatty acids	**No recommendation** (inconclusive,1 small RCT with some benefit)	**Unchanged; No new evidence**

CIPN PREVENTION: *NEW* Agents in 2020 ASCO Update

Intervention*	Recommendation	Evidence
Alpha-lipoic acid (600 mg TID while on platinum treatment)	**Recommendation not provided**	1 (-) RCT (high dropout rate, not tolerated, and does not prevent neuropathy)
Calmangafodipir (5 min infusion prior to oxaliplatin)	**Should NOT offer** (phase III trials ongoing)	1 (+) RCT (phase II trial)
L-carnosine (oral 500 mg daily during treatment with oxaliplatin)	**Should NOT offer** (additional data needed)	1 (+) RCT (no placebo control, not double blinded)
Ganglioside-monosialic acid (GM-1) (100 mg IV daily; 80 mg IV day prior to chemo through day 2)	**No recommendation** *("seemed to be effective in preventing taxane-induced peripheral neuropathy in Chinese populations, but this should be confirmed in a large trial in a different ethnic group")*	2 (+) RCTs (oxaliplatin study lacked placebo; taxane study showed peculiar finding of complete reversal of CIPN 3 months after tx in placebo arm)
Vitamin B complex (1 capsule BID during oxaliplatin or vincristine treatment)	**Should NOT offer** (additional data needed)	1 (-) RCT (primary endpoint negative; decreased patient perceived CIPN)

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J Clin Oncol 2020 Jul 14 DOI https://doi.org/10.1200/JCO.20.01399

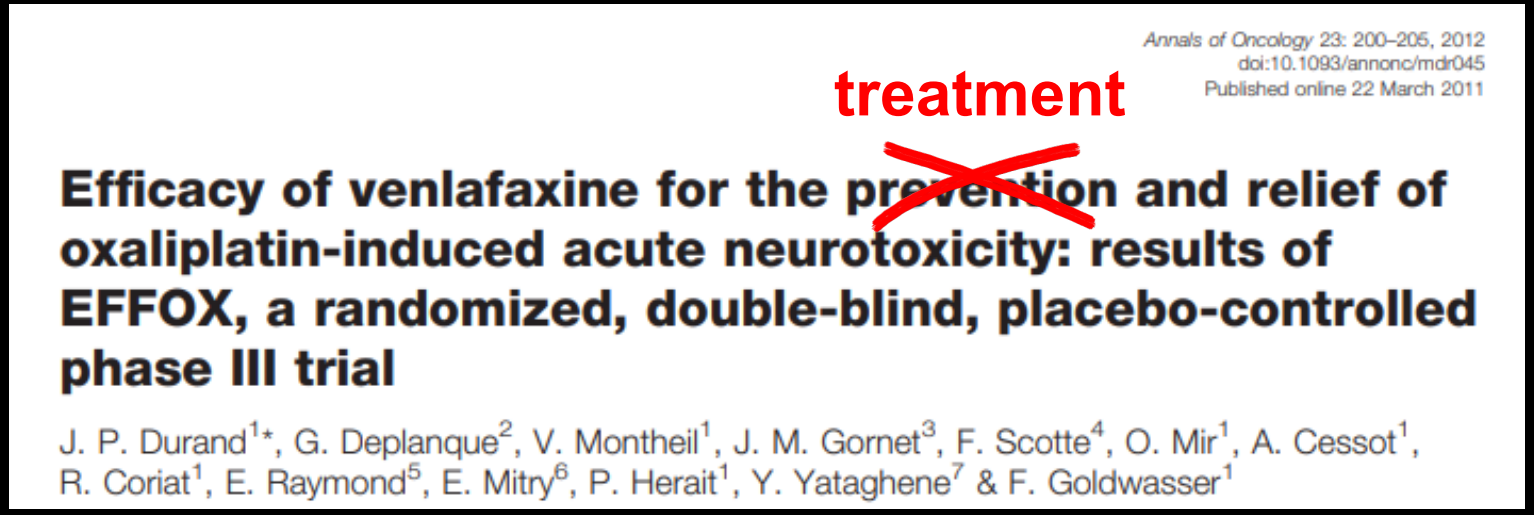
CIPN PREVENTION : Antidepressants/Anticonvulsants

Intervention	ASCO CIPN Guideline 2014		ASCO CIPN Guideline Update 2020	
	Recommendation	Evidence	Recommendation	Evidence since 2014
Venlafaxine (with oxaliplatin treatment)	**Not recommended for routine use** (insufficient evidence, potential utility)	1 (+) RCT (50 mg IR 1 h prior to oxaliplatin and 37.5 mg ER BID from day 2 to 11)	**Should NOT offer** (study in 2014 guideline illustrated *treatment role* not prevention)	1 (-) RCT (37.5 mg ER BID continuous with initiation of oxaliplatin)
Amitripytline (25 mg/d up to 100 mg/d with vinca, taxane, or platinum chemo)	**Should NOT offer** (no benefit)	1 (-) RCT	**Should NOT offer**	**No new evidence since 2014 guideline**
Carbamazepine (200 mg/d with titration to target concentrations during oxaliplatin treatment)	**No recommendation**	1 (-) RCT→study underpowered		
Oxcarbazepine (150 mg/d up to 1200 mg/d during oxaliplatin tx)	**No recommendation**	1 (+) RCT→small sample size; lacked placebo control		

PAINWEEK

J Clin Oncol 2014; 32:1941-1967.

J Clin Oncol 2020 Jul 14 DOI https://doi.org/10.1200/JCO.20.01399



Annals of Oncology 23: 200–205, 2012
doi:10.1093/annonc/mdr045
Published online 22 March 2011

treatment

Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial

J. P. Durand[1]*, G. Deplanque[2], V. Montheil[1], J. M. Gornet[3], F. Scotte[4], O. Mir[1], A. Cessot[1], R. Coriat[1], E. Raymond[5], E. Mitry[6], P. Herait[1], Y. Yataghene[7] & F. Goldwasser[1]

Eligibility

- Patients reporting acute neurotoxicity *after* oxaliplatin administration

Baseline Characteristics

- Median cycles: 4.5
- Mean cumulative dose: 709.8 mg

Results

- ≥ 50% relief of acute neuropathy: 68.8% vs 26.3% in placebo (p=0.02)
- Secondary endpoint: less grade 3 toxicity 3 months after completion of chemo 0% vs 33.3% (p =0.03)

Annals of Oncology 2012; 23: 200–205

CIPN PREVENTION: Anticonvulsants, cont. and Cannabinoids

Intervention	ASCO CIPN Guideline 2014		ASCO CIPN Guideline Update July 2020	
	Recommendation	Evidence	Recommendation	Evidence since 2014
Pregabalin (75 mg BID or preemptive use before/after chemo)	Not included in 2014 guideline		**Should NOT offer** (no benefit)	1 (-) RCT (paclitaxel) 2 (-) RCT (oxaliplatin)
Gabapentin (300 mg TID)	Not included in 2014 guideline		**Should NOT offer** (small sample size)	1 (+) RCT (paclitaxel)
Cannabinoids	Not included in 2014 guideline		**Should NOT offer** (lack of studies)	Not applicable

J Clin Oncol 2014; 32:1941-1967.

J Clin Oncol 2020 Jul 14 DOI https://doi.org/10.1200/JCO.20.01399

CIPN TREATMENT (≥1 month of CIPN): Pharmacological

Intervention	ASCO CIPN Guideline 2014		ASCO CIPN Guideline Update 2020	
	Recommendation	Evidence	Recommendation	Evidence since 2014
Duloxetine (*with or after* completion of platinum agents and taxanes)	**MAY offer** (recommended based on large, positive phase III trial)	1 (+) RCT (duloxetine 30 mg daily x 1 week, then 60 mg daily x 4 weeks)	**MAY offer** ("Additional data…further support the utility of duloxetine for treating established painful CIPN")	2 (+) RCTs (30 mg daily; 20 mg daily x 1 week, then 40 mg daily x 3 weeks)
Venlafaxine (*with* platinum agents and taxanes)	**Not discussed**		**Not discussed**	1 (+) RCT (37.5 mg/d vs placebo)
Pregabalin (*with* paclitaxel or docetaxel)	**No recommendation** (inconclusive but "reasonable to try" given established efficacy for other neuropathic pains)	Not available for CIPN	**No recommendation** ("harder to support" prior endorsement from 2014)	1 (+) RCT (pregabalin 75 mg BID >duloxetine 30 mg BID)
Gabapentin (*with or after* completion of vinca alkaloids, platinum, taxanes)		1 (-) RCT (up to target dose of 2700 mg/day x 6 weeks)*		No new evidence

*with continuous use during a prevention trial, would expect *"to see a decrease in the severity of neuropathic symptoms if it was truly beneficial for treating established neuropathy."* -ASCO 2020 Update

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J Clin Oncol 2014; 32:1941-1967.

J Clin Oncol 2020 Jul 14 DOI https://doi.org/10.1200/JCO.20.01399

Effect of Duloxetine on Pain, Function, and Quality of Life Among Patients With Chemotherapy-Induced Painful Peripheral Neuropathy

A Randomized Clinical Trial *

*a randomized phase 3 double-blind, placebo controlled crossover trial (weeks 1-5 and weeks 8-12) using duloxetine 30 mg daily x 1 week, then 60 mg daily x 4 weeks

Eligibility

- Patients with ≥ grade 1 sensory pain and 4/10 on neuropathic pain scale for ≥ 3 months *after* completion of platinum (oxaliplatin, cisplatin) or taxane (paclitaxel, nab-paclitaxel, docetaxel) chemotherapy

Baseline Characteristics

- Majority of patients received oxaliplatin (59%); paclitaxel (40%)
- Majority of patients had GI malignancy (56%) or breast cancer (38%)

Results

- Initial duloxetine users vs initial placebo users:
  - ↓ **average pain score** on BPI-SF 1.06 vs 0.34 (p=0.003)
- RR of **30% pain reduction** = 1.96 (95% CI 1.15-3.35)
- RR of **50% pain reduction** = 2.43 (95% CI 1.11-5.30)

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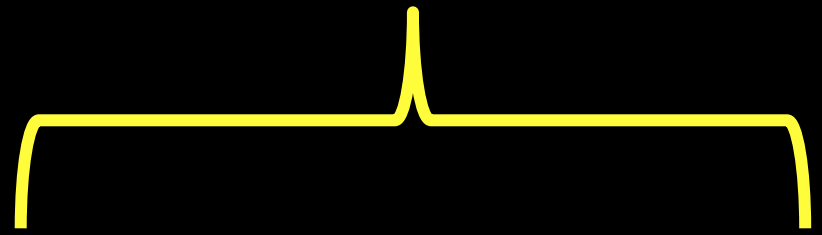
JAMA. 2013;309(13):1359-1367

Exploratory Subgroup Analysis



Oxaliplatin

- RR of **30% pain reduction** = 3.05 (95% CI 1.49-6.27)
- RR of **50% pain reduction** = 3.78 (95% CI 1.32-10.84)

Paclitaxel

- RR of **30% pain reduction** = 0.97 (95% CI 0.41-2.32)
- RR of **50% pain reduction** = 1.22 (95% CI 0.35-4.18)

Non-painful Symptoms

- Initial duloxetine users vs initial placebo users:
  - ↓ **numbness and tingling in feet** 41% vs 23%
  - No difference in hand numbness/tingling

JAMA. 2013;309(13):1359-1367

Duloxetine Going Head-to-Head

	Duloxetine vs Venlafaxine	Duloxetine vs Pregabalin
Who?	Any malignancy (majority breast cancer) Any chemotherapy (mostly platinum agents and taxanes)	Breast Cancer Patients Paclitaxel or Docetaxel
How?	Venlafaxine **37.5 mg daily** Duloxetine **30 mg daily** Placebo For 4 weeks	Duloxetine 30 mg daily x 1 week, then 30 mg BID x 5 weeks Pregabalin 75 mg daily, then 75 mg BID x 5 weeks

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Cancer Chemother Pharmacol 2018; 82:787-793,

Duloxetine vs Venlafaxine

What?

Both ↓ sensory and motor neuropathy vs PL at week 2 and 4

D > V ↓ sensory neuropathy at week 2 but V ↔ D at week 4

D > V ↓ motor neuropathy at week 2 and week 4

Both ↓ cranial neuropathy vs PL at week 4 but V ↔ D

HTN > with D at 4 weeks vs V

Cancer Chemother Pharmacol 2018; 82:787-79,

Duloxetine vs Pregabalin

CIPN at 6 weeks vs baseline decreased for both D and PR

At 3 weeks:

Paclitaxel group: D ↔ PR

Docetaxel group: CIPN ↓ PR > D

At 6 weeks for both taxane groups:

CIPN: ↓ PR > D

Clinical Drug Investigation (2020) 40:249–257

PAINWEEK

D: Duloxetine HTN: Hypertension PL: Placebo PR: Pregabalin V: Venlafaxine

CIPN TREATMENT (≥1 month of CIPN): Pharmacological

Intervention	ASCO CIPN Guideline 2014		ASCO CIPN Guideline Update 2020	
	Recommendation	Evidence	Recommendation	Evidence since 2014
Tricyclic Antidepressants (nortriptyline target dose of 100 mg/d *with or after* completion of cisplatin; amitriptyline target dose of 50 mg/d *with* ongoing use of vinca, platinum, or taxanes)	**No recommendation** (inconclusive but "reasonable to try" given established efficacy for other neuropathic pains; caution regarding toxicity in elderly)	2 (-) RCTs (small, 4-8 week, low-power phase III trials; some "numerical data favoring the active treatment arms")	**No recommendation** (lack of further evidence decreases the "tepid support" provided in the "initial ASCO CIPN guideline")	No new evidence since 2014 guideline
Lamotrigine (target dose 300 mg/d *with or after* completion vinca, platinum, or taxanes)	**Should NOT offer** (no benefit; negative CIPN trial and "data in non-CIPN neuropathy are not impressive.")	1 (-) RCT (10 weeks)	**Not discussed**	Not applicable
Nabiximols (THC:CBD 1:1 oromucosal spray *after* completion of paclitaxel, vincristine, or cisplatin; up to 12 sprays/day)	**Not discussed**	Not applicable	**No recommendation for "oral cannabinoids"** (low evidence quality)	1 (-) RCT (no difference among whole group at 4 weeks; in responder group trend toward significance)

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J Clin Oncol 2014; 32:1941-1967.

J Clin Oncol 2020 Jul 14 DOI https://doi.org/10.1200/JCO.20.01399

CIPN TREATMENT (≥1 month of CIPN): Topicals

Intervention	ASCO CIPN Guideline 2014		ASCO CIPN Guideline Update 2020	
	Recommendation	Evidence	Recommendation	Evidence since 2014
Compounded topical baclofen (10 mg), amitriptyline (40 mg), and ketamine (20 mg) (applied BID to hands or feet; used *with or after* vinca, platinum, taxanes or thalidomide)	**No recommendation** (inconclusive but "reasonable to try")	1 (+/-) RCT (decrease in motor neuropathy p=0.021; trend toward decrease in sensory neuropathy p=0.053; no change in autonomic neuropathy) Benefits in hands > feet	**No recommendation** (lack of further evidence and negative trial of topical amitriptyline/ketamine decreases the "tepid support" provided in the "initial ASCO CIPN guideline")	No new evidence since 2014 guideline
Topical amitriptyline 4% and ketamine 2% (applied BID *after* completion of various chemotherapies)	**Not discussed**	Not applicable		1 (-) RCT (however, taxane group did show significant benefit vs non-taxane group)
Topical 1% Menthol (applied BID *after* bortezomib, platinum, or taxane)	**Not discussed** (a potential "promising agent" needing further study)	2 (+) RCTs (phase II study; open-label)	**Not discussed**	Not applicable

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J Clin Oncol 2014; 32:1941-1967.

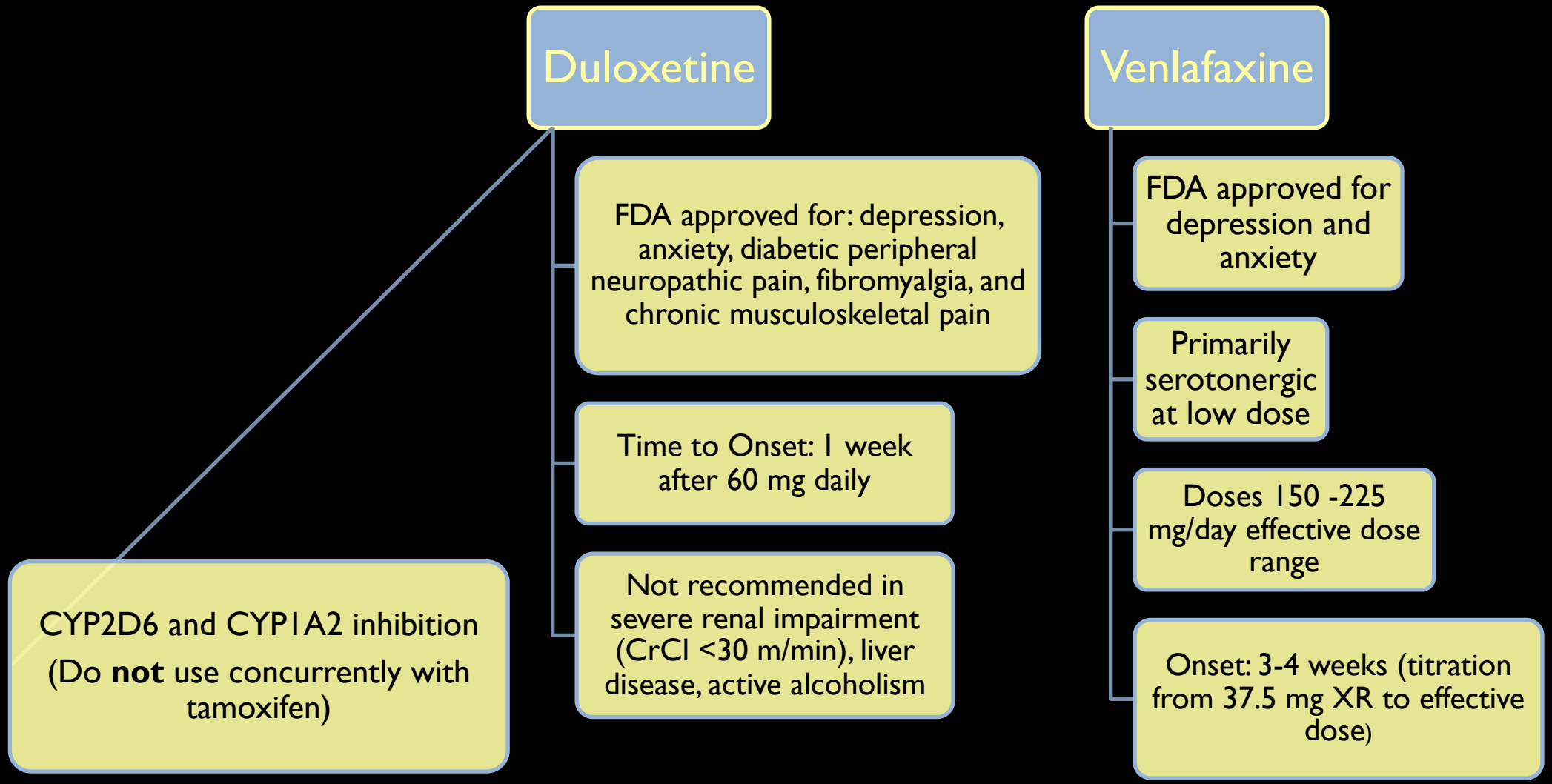
J Clin Oncol 2020 Jul 14 DOI https://doi.org/10.1200/JCO.20.01399

Duloxetine

"For treatment of established painful neuropathy, ***duloxetine remains the sole recommended treatment***. Along with the data demonstrating that duloxetine decreases CIPN pain, there is a suggestion from exploratory analyses that it also decreases nonpainful CIPN symptoms"

ASCO CIPN Guideline Update July 2020

J Clin Oncol 2020 Jul 14 DOI https://doi.org/10.1200/JCO.20.01399



Journal of Pain & Palliative Care Pharmacotherapy, 2020 DOI: 10.1080/15360288.2020.1734144

T.R. Deer et al, eds. *Treatment of Chronic Pain by Medical Approaches; the American Academy of Pain Medicine Textbook on Patient Management*

Conclusion

- CIPN continues to be a significant concern in cancer care (and in survivors)
- Mechanisms and thresholds for toxicity as well as clinical course differ among agents. Awareness of this may assist in early recognition and intervention.
- As a whole, there are limited prevention and treatment strategies.
- However, given the significant impact of CIPN on quality of life and even treatment/survival outcomes, rational use of pharmacotherapy and non-pharmacological interventions may be warranted (after discussion and assessment of risks versus benefits)