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Caractéristiques cliniques des neuropathies chimio-induites

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Généralités

- Toxicité neurologique périphérique la plus fréquente
- Impact significatif sur la qualité de vie des patients (avec des symptômes chroniques observés dans 40% des cas)
- Impact possible sur la dose de traitement administré aux patients
- Principaux agents de chimiothérapie responsables de neuropathie périphérique: taxanes (paclitaxel), vinca alkaloids (vincristine), platinum derivatives, epothilones (ixabepilone), halichondrin B analogues (eribulin), proteasome inhibitors (bortezomib), Imids (thalidomide).

- Facteurs de risque liés au traitement:

- la classe d'agent de chimiothérapie
- la dose reçue par cycle
- le schéma d'administration
- la dose cumulée
- la durée de perfusion

- Facteurs de risque liés au patient:

- neuropathie pré-existante, relié au diabète, alcool, carence folates/vit B12, neuropathie héréditaires sensori-motrice (Charcot Marie Tooth)
- neuropathie paranéoplasique

SNPs

- en cours d'évaluation
- liés à la précocité et à la sévérité de la neuropathie
- étude de gènes impliqués dans le métabolisme des agents de chimiothérapie et le contrôle du cycle cellulaire

Table 1. Studies on the genes with or without significant correlations with incidence and/or severity of platinum-induced peripheral neurotoxicity

Target gene		Relevance to platinum agents	SNP/deletion	With association		Without association	
				Studies	Patients	Studies	Patients
ABC	*ABCB1*	Drug transporters (membrane efflux proteins)	rs2032582			4 [65–68]	1,591
	ABCC1		rs2074087	1 [69]	144		
			rs35587			1 [69]	144
	ABCC2		rs1885301	1 [69]	144		
			rs2273697			1 [69]	144
			rs3740066	1 [69]	144		
			rs4148396	1 [69]	144		
			rs717620	1 [69]	144		
	ABCG2		rs2622604			1 [69]	144
			rs3114018	1 [70]	181	1 [70]	206
ACYP2			rs843748	2 [71]*	343		
AGXT		Detoxification enzyme	rs34116584	1 [72]	135	3 [69, 73, 74]	518
			rs4426527	1 [72]	135	3 [69, 73, 77]	570
			N/A del74bp			1 [69]	144
BTG4			rs4936453	2 [71]	343		
CAMK2N1			rs12023000	2 [71]	343		
CCNH		Cell cycle progression	rs2230641	2 [70]	206	1 [70]	181
COMT		Detoxification enzyme	rs4646316			1 [76]	66
DLEU7			rs797519	2 [71]	343		
ERCC	*ERCC1*	DNA repair mechanisms	rs11615	2 [74, 75]	169	15 [67, 68, 71, 77–88]	3,242
			rs3212986			1 [71]	247
	ERCC2		rs13181			1 [71]	247
			rs179983			1 [71]	247
			rs1052559			1 [88]	63
FAIM2			rs17140129	2 [71]	343		
			rs692471	2 [71]	343		
FOXC1			rs2358	2 [71]	343		
GST	*GSTM1*	Detoxification enzymes	N/A deletion	1 [88]	63	9 [69, 75, 78, 85, 86, 88–91]	1,472
	GSTM3		N/A deletion	1 [84]		1 [92]	107
	GSTP1		rs1695	9 [68, 74, 77, 80, 85, 88–90, 93]	1,408	15 [67, 71, 72, 75, 78, 81, 83, 84, 86, 87, 91, 94–97]	2,747
			rs947894			1 [69]	144
			rs1138272			1 [69]	144
			rs6591256			1 [76]	66
	GSTT1		Deletion			2 [88, 92]	170
ITG	*ITGA1*	Cell adhesion and cell surface-mediated signaling	rs830884	2 [71]	343		
	ITGB3		rs5918	1 [92]	55		
SCNA	*SCN1A*	Voltage-gated sodium channels	rs2298771			1 [71]	247
	SCN2A		rs17183814			1 [88]	62
	SCN4A		rs2302237	1 [20]	200		
	SCN5A		rs6746030			1 [20]	200
	SCN10A		rs1263292	1 [20]	200		
	SCN10A		rs6800541			1 [20]	200
TACI			rs10486003	2 [71]	343		
TPMT		Detoxification enzyme	rs4380755			1 [76]	66
			rs5008493			1 [76]	66
XRCC1		DNA repair mechanism	rs25487	1 [73]	292	1 [71]	247

Symptômes cliniques

- globalement similaire d'un agent à l'autre
- atteinte principalement sensitive avec une distribution gants et chaussettes, et:

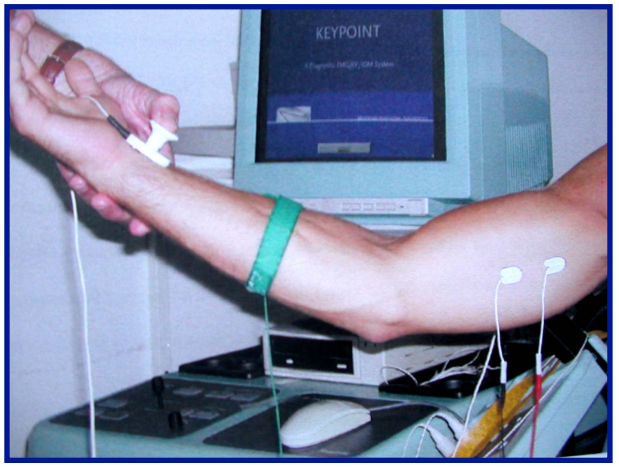
  - un engourdissement pouvant être responsable d'une difficulté à la réalisation des gestes fins et de troubles de l'équilibre

  - des paresthésies, des douleurs neuropathiques à type de picotement, brûlures, décharges électriques
- atteinte motrice possible avec déficit moteur, crampes
- atteinte dysautomique possible avec hypotension, troubles du rythme cardiaque, troubles sphinctériens
- atteinte des nerfs crâniens possible

Cotation du déficit moteur

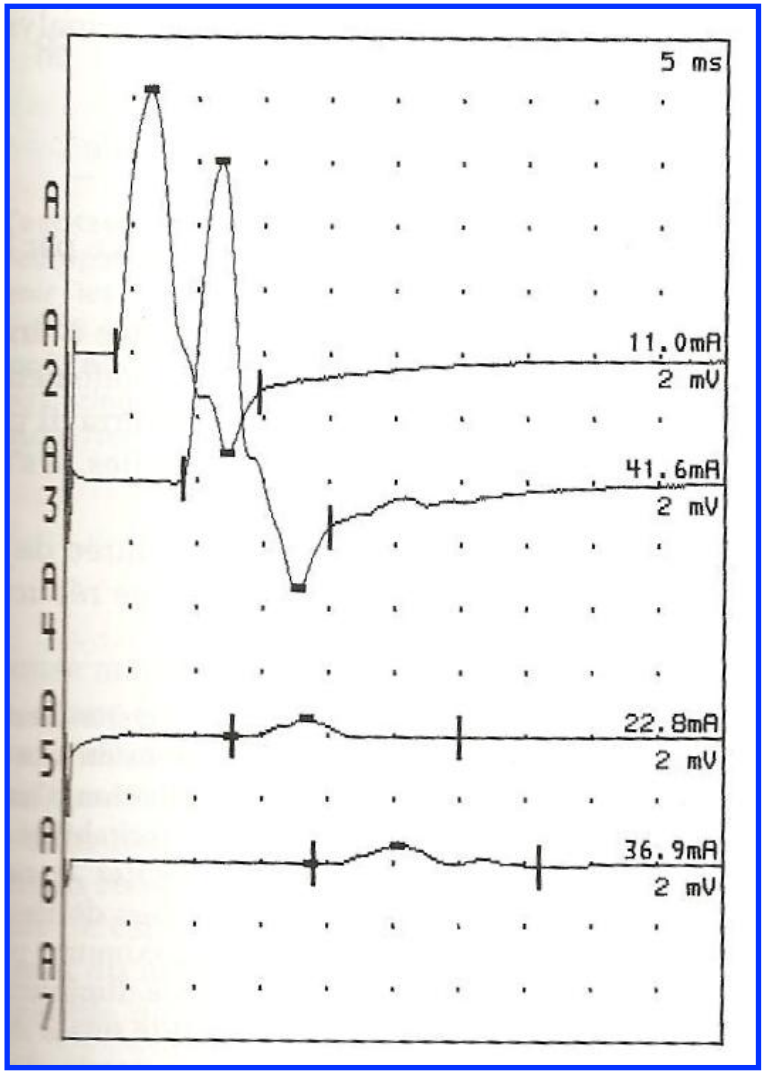
0 : absence de contraction volontaire
1 : contraction faible sans déplacement
2 : déplacement possible si l' action de la pesanteur est compensée
3 : déplacement possible
4 : déplacement possible contre la pesanteur et contre résistance
5 : force musculaire normale

Examens complémentaires



- EMG: vitesse de conduction nerveuse, évaluation du potentiel d'action, détection à l'aiguille
- atteinte démyélinisante: ralentissement des VC, augmentation des latences distales
- atteinte axonale: diminution amplitude des potentiels
- atteinte des petites fibres ou atteinte ganglion spinal dorsal: EMG non contributif

- Biopsies de nerf ou de muscle rarement indiqué



A1: Stim médian gauche au poignet
A2: Stim médian gauche au coude
A3: stim médian droit au poignet
A4: stim médian droit au coude

tracé normal

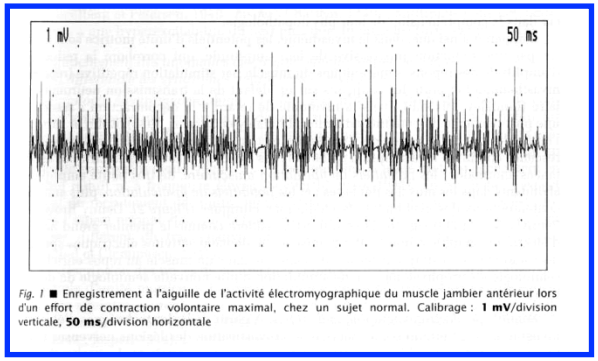


Fig. 1 ■ Enregistrement à l'aiguille de l'activité électromyographique du muscle jambier antérieur lors d'un effort de contraction volontaire maximal, chez un sujet normal. Calibrage : **1 mV**/division verticale, **50 ms**/division horizontale

tracé neurogène

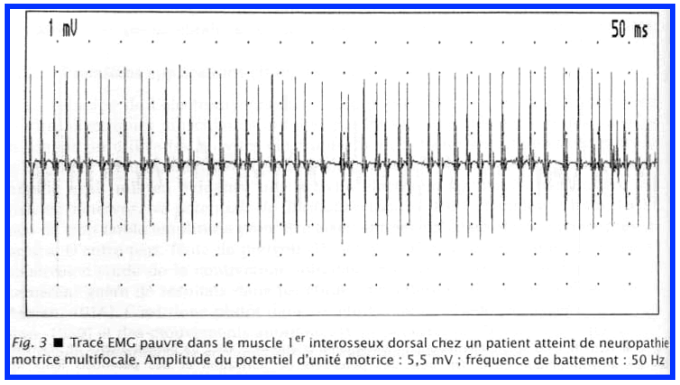


Fig. 3 ■ Tracé EMG pauvre dans le muscle 1er interosseux dorsal chez un patient atteint de neuropathie motrice multifocale. Amplitude du potentiel d'unité motrice : 5,5 mV ; fréquence de battement : 50 Hz

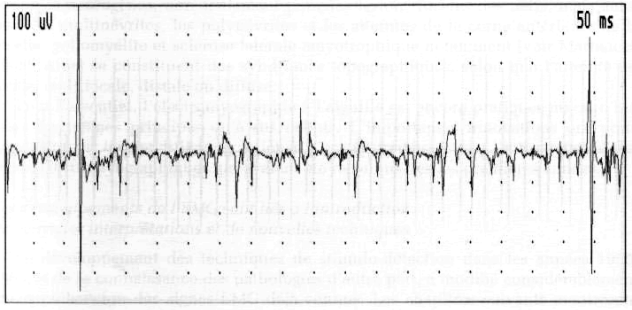


Fig. 2 ■ Activité EMG spontanée dans un muscle jambier antérieur chez un patient atteint de sclérose latérale amyotrophique (SLA). On note des potentiels de fibrillation et des potentiels lents de dénervation, de petite amplitude, ainsi que deux potentiels de fasciculation de plus grande amplitude

Echelles utilisées pour l'évaluation des neuropathies

Table 1
Commonly used assessment tools for CIPN.

	Assessment tool	Test format	Description of test
Physician-based assessments [5] [29] [30] [32]	NCI-CTCAE v4	Physician-based assessment	–Neuropathy graded on scale 1–4 –Focus on inhibition of ADLS –Critiqued for lack of sensitivity c/w patient reports
	WHO scale	Physician-based assessment	–Neuropathy graded on scale 1–4 –Focus on inhibition of ADLS
	Ajani scale	Physician-based format	–Neuropathy grade associated with morbidity range that provides guidance on future therapy –Focus on difficulty with ambulation as measure of functional capacity
	Total neuropathy Scale	Physician-based assessment	–Evaluation of autonomic sx, vibration perception, neurophysiological exam
Patient-based assessments [31] [34] [35] [36] [37]	FACT/GOG-Ntx	11-Item subscale of FACT/GOG	–Positive findings correlate to NCI-CTC grade ≥ 1 –Critiques for evaluation of astereognosis and ototoxicity [61] –4-Item neurosensory can be used alone, highly reflective of CIPN
	EORTC QLQ-CIPN20	20-Item subscale of EORTC QLQ	–Combined assessment of QoL and CIPN –Highly correlated with NCI-CTC
	PNQ	2-Item questionnaire	–Specific focus on symptoms of CIPN –If symptom present, assessed for its interference with specific daily activities –Weak correlation with FACT/GOG-Ntx and NCI-CTC [61]
	CINQ	Questions presence of symptoms in upper and lower extremities and face	–If symptoms present, patient asked to rate degree of bother and effect on daily activities –Highly correlated with FACT/GOG-Ntx

CTCAE V4.0

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.					

Caractéristiques des principaux agents de chimiothérapie responsables de neuropathies

Drug	Incidence of CIPN by CTC grade	Threshold of cumulative dose	Clinical features	Outcome
Docetaxel	all grade: 11-64% grade 3-4: 1.6-7%	400-600 mg/m2	axonal sensory neuropathy motor neuropathy reported in less than 5% optic neuropathy associated lymphedema with scleroderma-like lesion and associated nerve entrapment	34% of grade 0-I neuropathy 1 to 3 years after treatment discontinuation, with 15% reporting a significant impact on quality of life
Paclitaxel	all grade: 59-87% grade 3-4: 7-33%	200 mg/m2	axonal sensory neuropathy acute neuropathy (paclitaxel acute pain syndrome) associated myalgia, myopathy, arthralgia	All grade CIPN in 41% of the patients 3 years after treatment discontinuation
Ixabepilone	6-71%	>120-160 mg/m2	axonal sensory neuropathy	Poorly defined
Nab-paclitaxel	all grade: 51.0% grade 3-4: 12.4%	Unclear	axonal sensory neuropathy	Poorly defined
Cabazitaxol	all grade: 27.8% grade 3-4: 1.1%	Unclear	axonal sensory neuropathy	Poorly defined
Eribulin	all grade 14-44% grade 3-4: 3-27%	dose cumulative unknown	axonal sensori-motor neuropathy autonomic neuropathy	Resolution of symptoms within 12 months
Oxaliplatin	all grade: 20-50% grade 3-4: 10-20%	800 mg/m2	axonal sensory neuropathy acute neuropathy reported in 85-95% of the cases with cold triggered paresthesia and dyesthesiae in the throat, mouth, face and hands, motor symptoms such as cramps, jaw spasms L'hermitte's syndrome	Coasting Resolution of symptoms in 80% in 6-8 months, but clinically significant symptoms observed 2 to 11 years after treatment discontinuation
Cisplatin	all grade: 20% grade 3-4: 0.001%	300-400 mg/m2	axonal sensory neuropathy L'hermitte's syndrome irreversible hearing loss in 19-77% of the cases permanent tinnitus in 19%-42% of the cases taste and smell disorders, Raynaud syndrome	Coasting Asymptomatic or symptomatic neuropathy can be observed 15 years after completion of treatment in 38% and 28%

Particularités des neuropathies au taxanes

- docetaxel: régime 3 semaines est responsable de plus de neuropathies que le régime hebdomadaire (Rivera 2015)

- paclitaxel: perfusions courtes augmentent le risque de neurotoxicité (Park 2013), intérêt d'un régime 3 semaines vs. 1 semaine discuté pour la gestion de la neurotoxicité (Park 2013)

- mécanisme: stabilisation des microtubules, interférence avec le transport axonal, dysfonction mitochondriale, modification de l'excitabilité membranaire

Particularités des neuropathies aux sels de platine

- phénomène de *coasting*: aggravation des symptômes après arrêt de l'administration du traitement
- augmentation de l'incidence des neuropathies induites par le cisplatine avec doses élevées par perfusion (Park 2013)
- augmentation de la durée de la perfusion d'oxaliplatine et l'utilisation de régimes hebdomadaires pourrait réduire la toxicité de l'oxaliplatine (Park 2013)
- carboplatine est le sel de platine le moins neurotoxique

- mécanisme: accumulation dans le ganglion spinal dorsal, action sur canaux sodium dépendants au niveau axonal

Particularités des neuropathies des autres chimiothérapies

- Vinca-alkaloids: vincristine et vindésine responsables de plus de neuropathies que vinblastine, vinorelbine et vinflunine; vincristine liposomale: moins de neuropathie (Grisold 2012)

- Bortezomib: neuropathie axonale sensitive; moins de toxicité observe avec carfilzomib (Park 2013, Grisold 2012).

- Thalidomide: neuropathie sensitive dose-dépendente; moins de toxicité observée avec lenalidomide, pomalidomide, nouveaux imids

Prévention des neuropathies chimio-induites

- Pas de traitement standard selon les recommandations de l'ASCO

- pas d'intérêt: acide lipoïque, nimodipine, gabapentine, lamotrigine, acetyl l-carnitine, venlafaxine, and BNP7787
- résultats variables: amifostine, glutathion, infusions of calcium and magnesium, vitamine E
- intérêt possible: N-Acetylcysteine, carbamazepine and oxcarbazepine, Xaliprodenis (a 5-hydroxytryptamine 1A agonist), Goshajinkigan (Kampo medicine), erythropoietin, PFT-μ, omega-3 fatty acids supplements, topical gel containing baclofen, amitriptyline, nortriptyline and ketamine, combination Vitamin B12/B6, combination Vitamin D and low polyamine diet.

- Intérêt d'une activité physique (Mols 2015)
- port de gants et chaussettes réfrigérants pourraient réduire le risque de neurotoxicité (Eckhoff 2013)

Table 2
Pharmacologic Agents Tested for Prevention of CIPN [15].

	Pharmacologic agent	Neurotoxic chemotherapy	Limitations of studies/agents
Limited benefit	Amifostine	Platinum and taxane, (specifically carboplatin/paclitaxel)	–Benefits not consistent across studies –Significant toxicity from agent: nausea, vomiting, lightheadedness* –Some reports of associated dermatologic, cardiovascular and neurologic toxicity*
	Glutamine	Oxaliplatin	–Small sample size –Unblinded study –Lack of placebo-control
	Glutathione	Platinum	–Small sample sizes –Inconsistent results across studies
	Oxcarbazepine	Oxaliplatin	–Small sample size –Lack of placebo-control
	Venlafaxine	Oxaliplatin	–Small study size –Results not reproduced
No proven benefit or harmful	Acetyl-L-carnitine	Platinum	Worsening of CIPN
	Amitriptyline	Vinca alkaloids, platinum or Taxanes	Drug associated toxicities
	Calcium and magnesium	Oxaliplatin	Convincingly negative large phase 3 study
	Diethyldithiocarbamate (DDTC)	Platinum	–Increased toxicity and early treatment dc in treatment arm –Lower cumulative cisplatin doses
	Glutathione	Specifically for Paclitaxel/carboplatin	Convincingly negative study
	Nimodipine	Cisplatin	Worse outcomes in active arm
	Org 2766	Cisplatin or vinca alkaloids	–Multiple studies with negative results –Possible worse outcome for active arm
	Retinoic acid	Cisplatin + paclitaxel	Drug toxicity
	Recombinant human leukemia inhibitory factor (rhuLIF)	Paclitaxel + cisplatin	Worse neuropathy endpoints in active therapy arm
	Vitamin E	Taxane or platinum	Convincingly negative studies

* Due to significant side effect profile, ASCO guideline recommend against use although some studies showed benefit.

Traitement des neuropathies chimio-induites

- Détection de la neuropathie avant l'installation de symptômes sévères

- Identification d'autres causes

- Arrêt de l'agent toxique responsable pour les grades ≥ 3 de toxicité

- Approches pharmaceutiques:

- intérêt éventuel de la duloxetine (cf diapo suivante)

- intérêt discuté de la gabapentine ou pregabaline: phase III randomisée en double aveugle, contre-placebo avec crossover évaluant la gabapentine négatif (Rao 2007), essai négatif pour lamotrigine

- peu d'intérêt à utiliser la venlafaxine (Gallagher 2015), pas d'intérêt de l'imipramine (Hearn 2014)

- autres options: tricycliques, amitriptyline locale, inhibiteurs recapture sérotonine et norépinéphrine, opïoides, anesthésiques locaux, perfusion de lidocaïne

- dextromethorphan en cours d'évaluation (NCT02271893)

- Approches non pharmaceutiques: acupuncture, scrambler (électro-analgésie), neurostimulation, massage et kinésithérapie

Table 3
Selected pharmacologic agents evaluated for treatment of CIPN [15].

Pharmacologic agent	Neurotoxic chemotherapy	Recommendation
Acetyl-L-carnitine		Not recommended — prevention trial a/w increased CIPN
Duloxetine	Taxane or platinum	Recommended — positive trial for oxaliplatin or paclitaxel neuropathy
Gabapentin	Vinca alkaloids, platinum, or taxanes	Not recommended — negative trial, but effective in other forms of neuropathy
Lamotrigine	Vinca alkaloids, platinum, or taxanes	Not recommended — negative trial
Nortriptyline/amitriptyline	Vinca alkaloids, platinum (cisplatin), or taxanes	Not recommended — small trials, not powered but favor treatment arms
Topical (amitriptyline, ketamine, ± baclofen)	Vinca alkaloids, platinum, taxanes, or thalidomide	Not recommended — suggestion of improvement in active treatment arm, but not statistically significant

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

A Randomized Clinical Trial

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Herbert Pang, PhD
Constance Cirrincione, MS
Stewart Fleishman, MD
Electra D. Paskett, PhD
Tim Ahles, PhD
Linda R. Bressler, PharmD
Camilo E. Fadul, MD
Chetaye Knox, BS
Nguyet Le-Lindqwister, MD
Paul B. Gilman, MD
Charles L. Shapiro, MD
for the Alliance for Clinical Trials in Oncology

Importance There are no known effective treatments for painful chemotherapy-induced peripheral neuropathy.

Objective To determine the effect of duloxetine, 60 mg daily, on average pain severity.

Design, Setting, and Patients Randomized, double-blind, placebo-controlled crossover trial at 8 National Cancer Institute (NCI)–funded cooperative research networks that enrolled 231 patients who were 25 years or older being treated at community and academic settings between April 2008 and March 2011. Study follow-up was completed July 2012. Stratified by chemotherapeutic drug and comorbid pain risk, patients were randomized to receive either duloxetine followed by placebo or placebo followed by duloxetine. Eligibility required that patients have grade 1 or higher sensory neuropathy according to the NCI Common Terminology Criteria for Adverse Events and at least 4 on a scale of 0 to 10, representing average chemotherapy-induced pain, after paclitaxel, other taxane, or oxaliplatin treatment.

Interventions The initial treatment consisted of taking 1 capsule daily of either 30 mg of duloxetine or placebo for the first week and 2 capsules of either 30 mg of duloxetine or placebo daily for 4 additional weeks.

Main Outcome Measures The primary hypothesis was that duloxetine would be more effective than placebo in decreasing chemotherapy-induced peripheral neuropathic pain. Pain severity was assessed using the Brief Pain Inventory-Short Form "average pain" item with 0 representing no pain and 10 representing as bad as can be imagined.

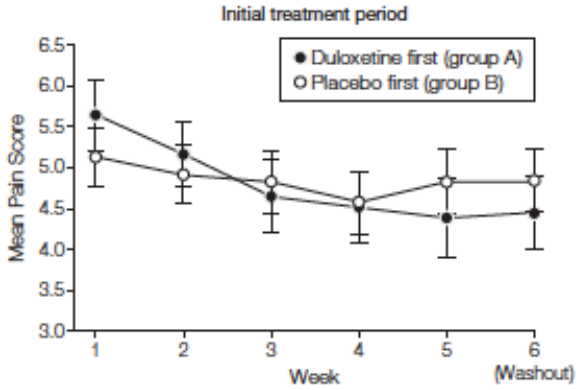
Results Individuals receiving duloxetine as their initial 5-week treatment reported a mean decrease in average pain of 1.06 (95% CI, 0.72-1.40) vs 0.34 (95% CI, 0.01-0.66) among those who received placebo ($P = .003$; effect size, 0.513). The observed mean difference in the average pain score between duloxetine and placebo was 0.73 (95% CI, 0.26-1.20). Fifty-nine percent of those initially receiving duloxetine vs 38% of those initially receiving placebo reported decreased pain of any amount.

Conclusion and Relevance Among patients with painful chemotherapy-induced peripheral neuropathy, the use of duloxetine compared with placebo for 5 weeks resulted in a greater reduction in pain.

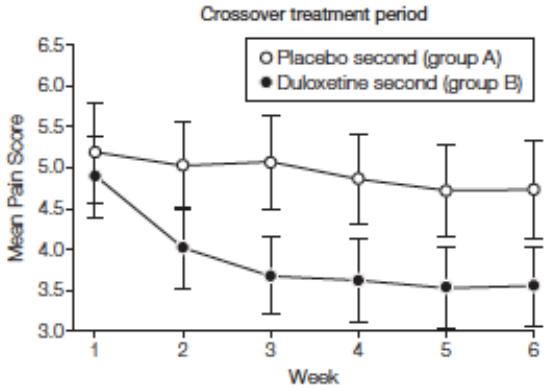
Trial Registration clinicaltrials.gov Identifier: NCT00489411

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

Figure 2. Duloxetine and Placebo Effects on Average Pain Severity During the Initial and Crossover Treatment Periods



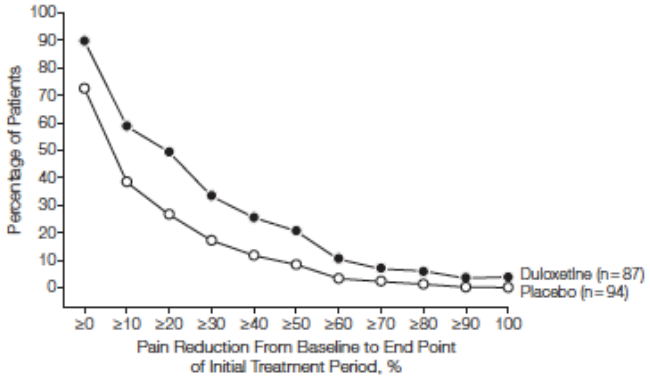
No. patients						
Duloxetine first (group A)	87	86	86	87	85	87
Placebo first (group B)	94	92	91	91	91	94



No. patients						
Placebo second (group A)	67	65	65	66	63	67
Duloxetine second (group B)	74	68	71	69	66	74

The mean average pain score was measured on the first day of each week in the initial and crossover treatments periods. Day 1 of the first week begins the initial treatment period. Day 1 of week 6 begins the washout period when patients received 1 capsule of duloxetine or placebo. Patients took no drug during week 7. Error bars represent 95% CIs.

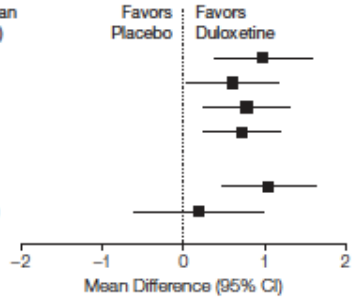
Figure 3. Percent Decrease in Pain Score Due to Duloxetine vs Placebo



The plot shows the proportion of patients achieving various levels of pain reduction at the completion of the initial treatment period.

Figure 4. Comparison of the Mean Differences in Average Pain Scores Across Duloxetine Chronic Pain Studies

Source	No. of Patients	Mean Difference in Mean Pain Scores (95% CI)
Goldstein et al,[13] 2005	176	0.98 (0.37 to 1.60)
Russell et al,[30] 2008	294	0.60 (0.05 to 1.16)
Chappell et al,[26] 2011	225	0.79 (0.26 to 1.32)
Current study	181	0.73 (0.26 to 1.20)
Neurotoxic agents, current study		
Platinums	106	1.06 (0.48 to 1.63)
Taxanes	75	0.19 (–0.61 to 0.98)



Duloxetine was compared against placebo in studies involving patients with diabetic neuropathy, Goldstein et al; fibromyalgia, Russell et al; osteoarthritis, Chappell et al; and chemotherapy-induced peripheral neuropathy, the current study, including a breakdown by neurotoxic agent that patients in the current study took.

Articles à lire

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