



NEUROPATI OG NEUROPATISKE SMERTER HOS KRÆFTOVERLEVERE

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Ca. 400.000 danskere lever i dag med eller efter en kræftsygdom

Over 50 % af alle kræftpatienter oplever en eller flere senfølger

Neuropati herunder neuropatisk smerte er en af de hyppigste

Hyppigste generelle problemer:
Depression, **smarter**, træthed (fatigue)

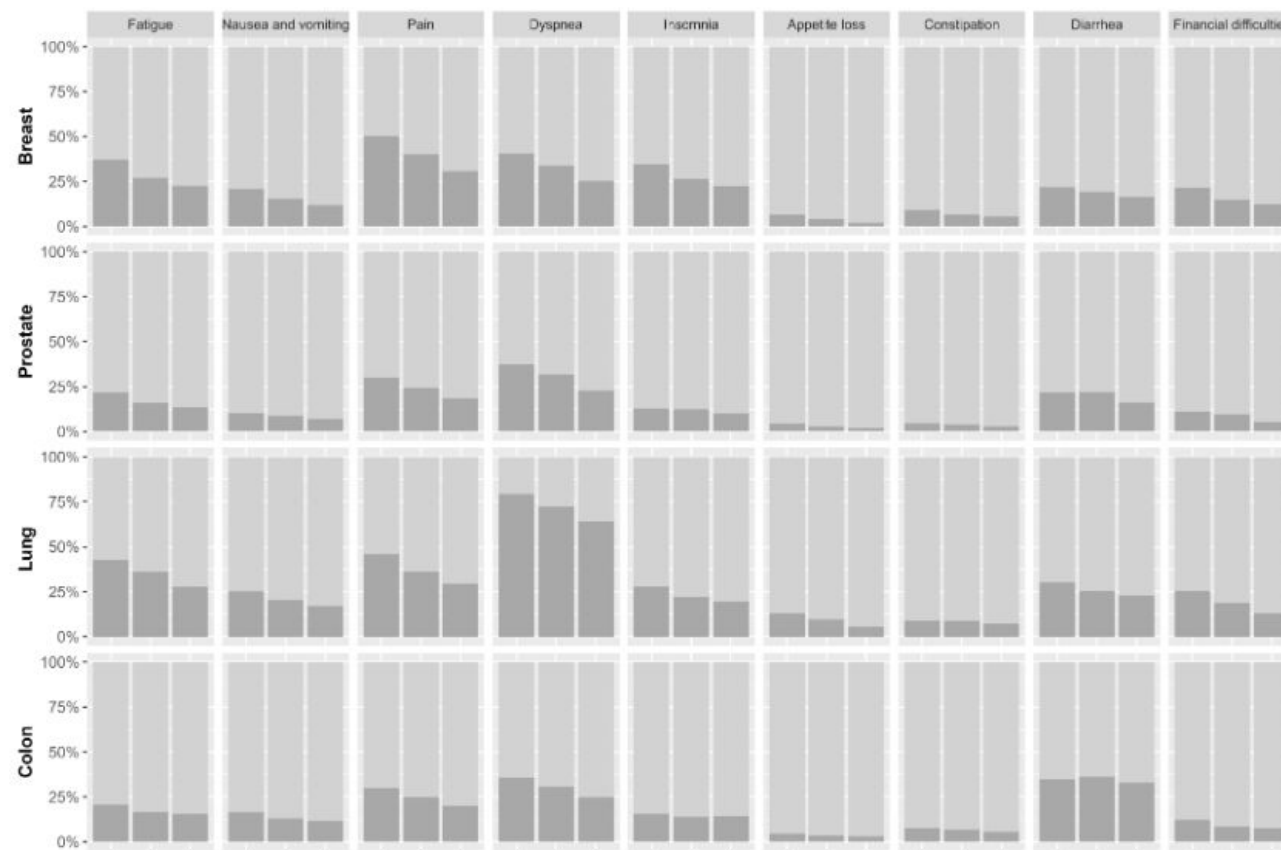


Kjær et al. 2017
<https://www.sst.dk/da/Udgivelser/2017/Vidensopsamling-paa-senfoelger-efter-kraeft-hos-voksne>



Ny undersøgelse

- Spørgeskemaundersøgelse bland 28.000 kræftoverlevende i Danmark
- 2-12 år efter deres kræftbehandling (bryst, prostata, tarm og lunge)



► Cancer Med. 2023 Oct;12(19):20150-20162. doi: 10.1002/cam4.6596. Epub 2023 Sep 29.

Social inequality in cancer survivorship: Educational differences in health-related quality of life among 27,857 cancer survivors in Denmark

Anne Katrine Graudal Levinsen¹, Trille Kristina Kjaer¹, Lau Caspar Thygesen², Thomas Maltesen³, Erik Jakobsen⁴, Ismail Gögenur⁵, Michael Borre⁷, Peer Christiansen⁸, Robert Zachariae⁸, Peter Christensen¹⁰, Søren Laurberg¹⁰, Peter de Nully Brown¹¹, Lisbet Rosenkrantz Hölmich¹², Christoffer Johansen¹³, Susanne K Kjaer¹⁴, Lonneke van de Poll-Franse¹⁶, Lena Saltbaek¹, Susanne Oksbjerg Dalton¹

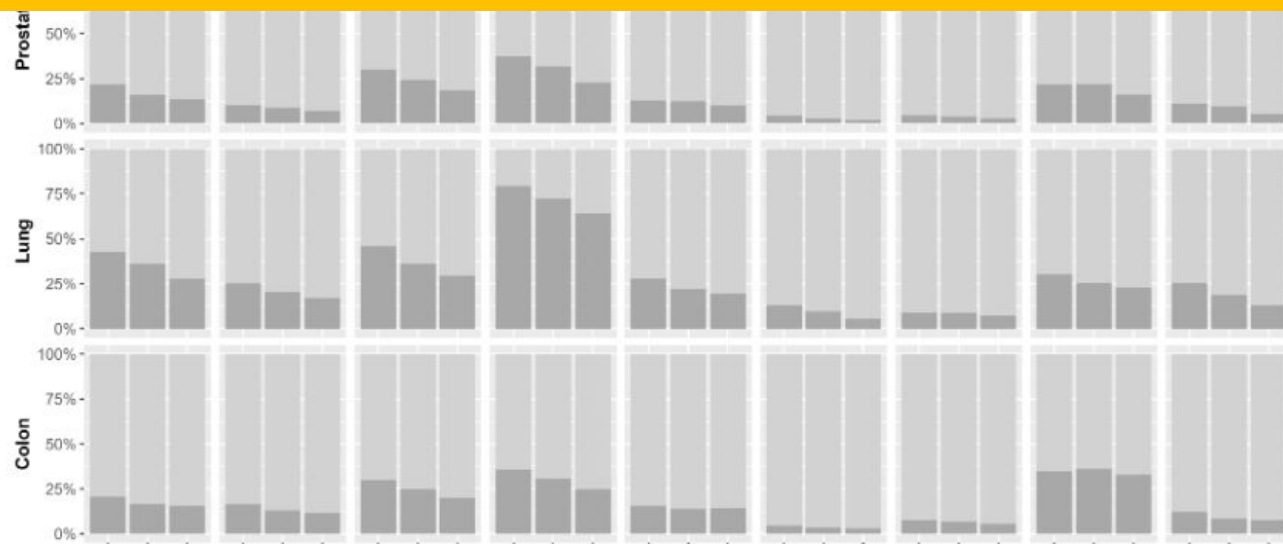


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En ud af tre har smerter



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Social inequality in cancer survivorship: Educational differences in health-related quality of life among 27,857 cancer survivors in Denmark

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Susanne

59 årig kvinde som har haft CML i 20 år

Behandlet med forskellige TKI'er over årene – både standard behandling og protokolleret behandling

Diabetes – formentlig som konsekvens af behandling

Neurogene smerter i fødderne – værst aften og nat. Har fjernet sengegærdet i fodenden. Sover uden dyne på fødderne. Vågner 4-5 gange hver nat hvor det føles som knive, der jages op i fødder og ben

Tilbudt behandling med gabapentin i hæmatologisk regi men har takket nej

Er Susanne en senfølgepatient/kræftoverlever??





René Descartes (1596 – 1650)



Tony Matelli, Fucked, 2005



Definitioner

- Nociceptive smerter

Smerter som skyldes vævsskade

- **Definition af neuropatisk smerte**

"Pain caused by a lesion or disease of the somatosensory nervous system."

Schaumburg et al. Disorder of peripheral nerves 1986

Inddeling

- Mononeuropati
 - Afficerer enkelte nerver. Fx: kompression, iskæmi, traume
- **Polyneuropati**
 - Afficerer multiple nerver symmetrisk



Frida Kahlo





Klassifikation

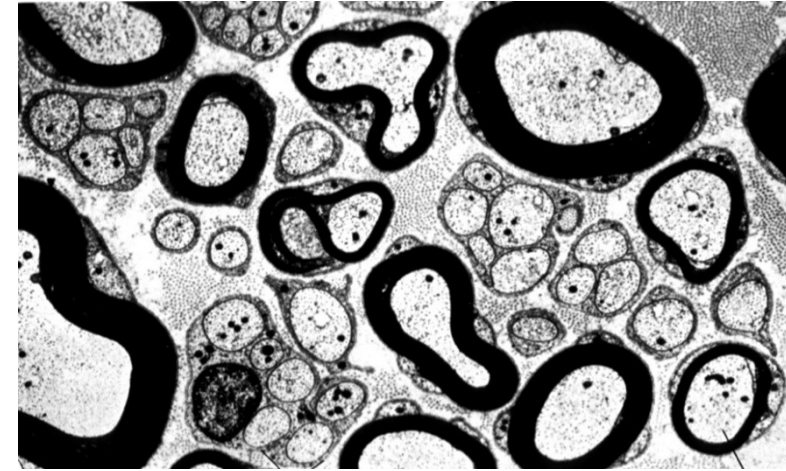
Stor-fiber neuropati

- Tykke myelinbeklædte sensoriske nervefibre
- Symptomer: følelsesløshed, sovende fornemmelse
- Tegn: tab af vibrationssans og proprioception

Små-fiber neuropati

- Små nervefibre
- Symptomer: smerte/følelsesløshed
- Tegn: tab af smerte og temperatur sensation

Blandet stor- og småfiber neuropati





- Småfiber-neuropatier:
 - Heterogen gruppe
 - Kan skyldes mange forskellige ting bl.a.
 - Kemoterapi
 - Statiner
 - Diabetes
 - B-12 mangel
 - Forskellige virussygdomme
 - **Ca. 50 % idiopatiske**

Panel 2: Causes of small fibre neuropathy

Metabolic causes

- Diabetes, impaired glucose tolerance, and rapid glycaemic control in the setting of chronic hyperglycaemia (treatment-induced neuropathy of diabetes)
- Hypothyroidism
- Hypertriglyceridaemia
- Uraemia

Vitamin deficiency

- Vitamin B12

Neurotoxic exposure or vitamin intoxication

- Alcohol
- Antiretroviral agents
- Chemotherapeutic agents
- Organic solvents
- Pyridoxine B6 intoxication
- Statins
- Anecdotal cases: antiarrhythmic drugs (flecainide), antibiotics (metronidazole, nitrofurantoin, linezolid, ciprofloxacin), ingestion of *Clostridium botulinum* toxin, heavy metals (thallium, lead), and tumour necrosis factor α inhibitors

Infections

- Hepatitis C virus
- HIV
- Influenza
- Leprosy
- Severe sepsis, septic shock, and critical illness
- Anecdotal cases: Epstein-Barr virus, herpes simplex infection, mycoplasma pneumoniae, rubella, syphilis, vaccination for rabies, varicella or Lyme disease, and hepatitis B virus

Immunological causes

- Autoimmune autonomic ganglionopathy
- Coeliac disease
- Guillain-Barré syndrome, monoclonal gammopathies, and primary amyloidosis (immunoglobulin light chain associated)
- Paraneoplastic syndrome
- Sarcoidosis
- Scleroderma
- Sjögren's syndrome
- Systemic lupus erythematosus
- Vasculitis

Hereditary causes

- Familial amyloid polyneuropathy (transthyretin amyloidosis)
- Hereditary sensory and autonomic neuropathies
- Fabry disease
- Mutations in COL6A5 and genes encoding voltage-gated sodium channels
- Pompe's disease

Idiopathic small fibre neuropathy



Symptomer

Positive symptomer

- Sensoriske:
 - Smerte, prikken, stikken, kløe
- Motoriske:
 - Krampe, tremor, fasciculationer

Negative symptomer

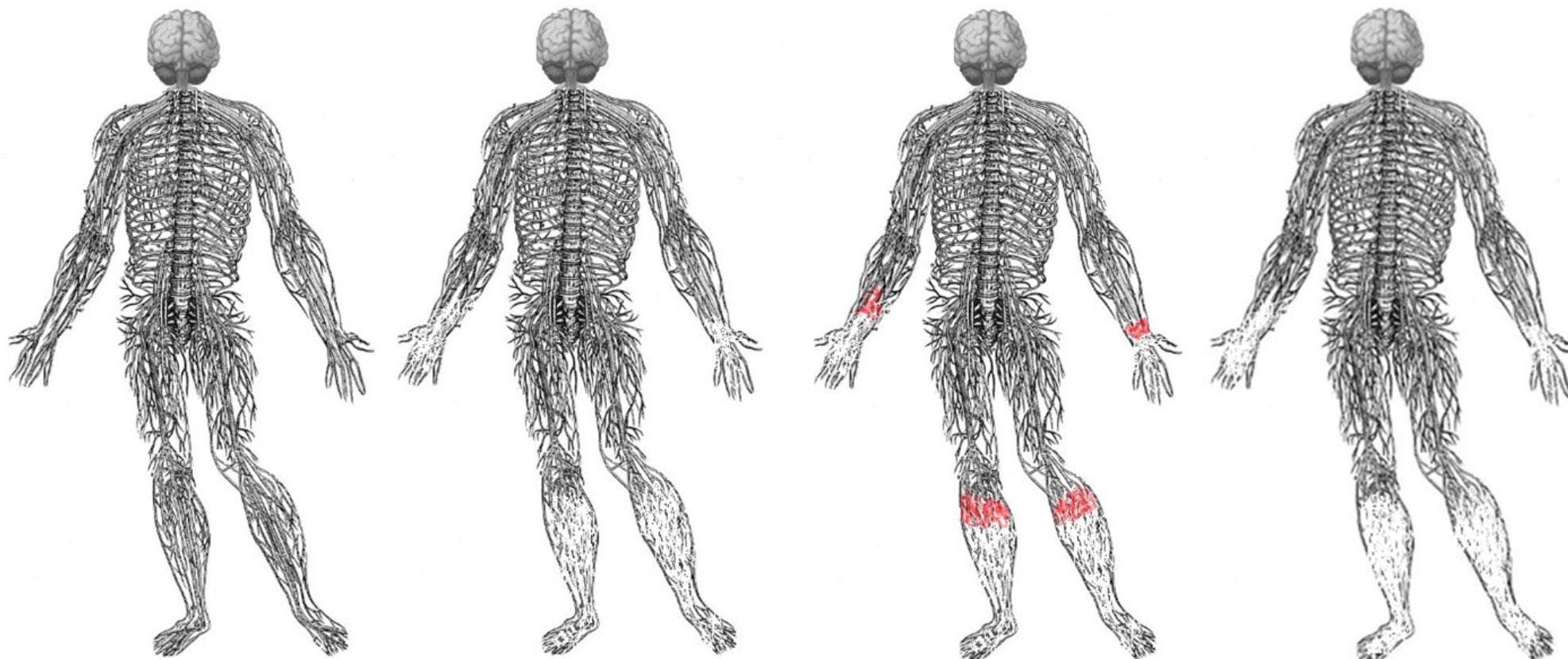
- Sensoriske:
 - Følelsesløshed, gangproblemer
- Motoriske:
 - Nedsat kraft, dropfod, tyngdefornemmelse
- Tab af reflekser



Symptomer – hvordan vil I beskrive dem?



Symptomer – hvordan udvikler de sig?





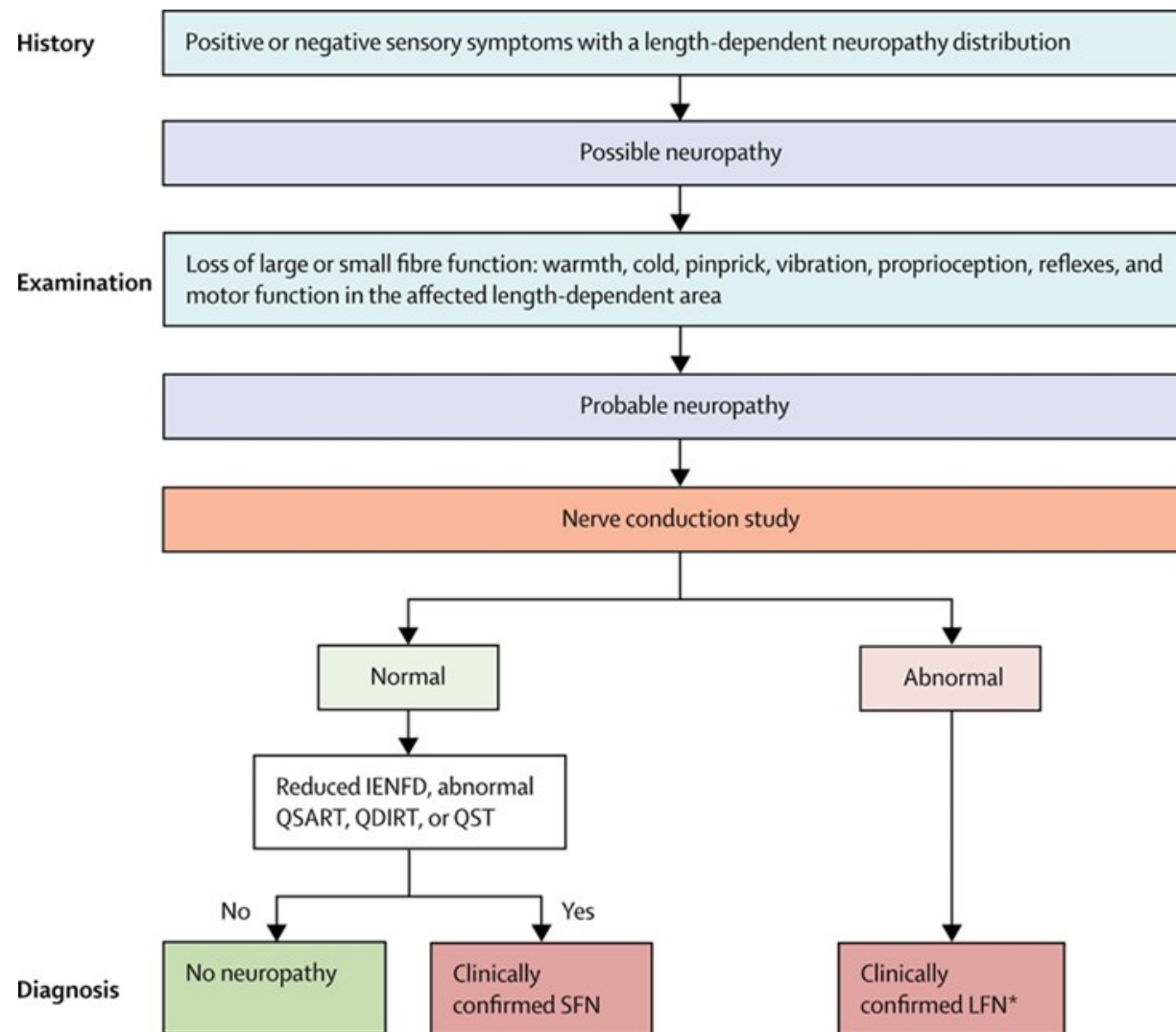
Symptomer

- Smerter og abnorme sanseoplevelser i samme område!?
- Spontane (stimulus-uafhængige) smerter
- Evokerede (stimulus-afhængige) smerter
- Debut umiddelbart eller latenstid i op til nogle måneder
- **Kan forværres af kulde, træthed, sygdom, stress**





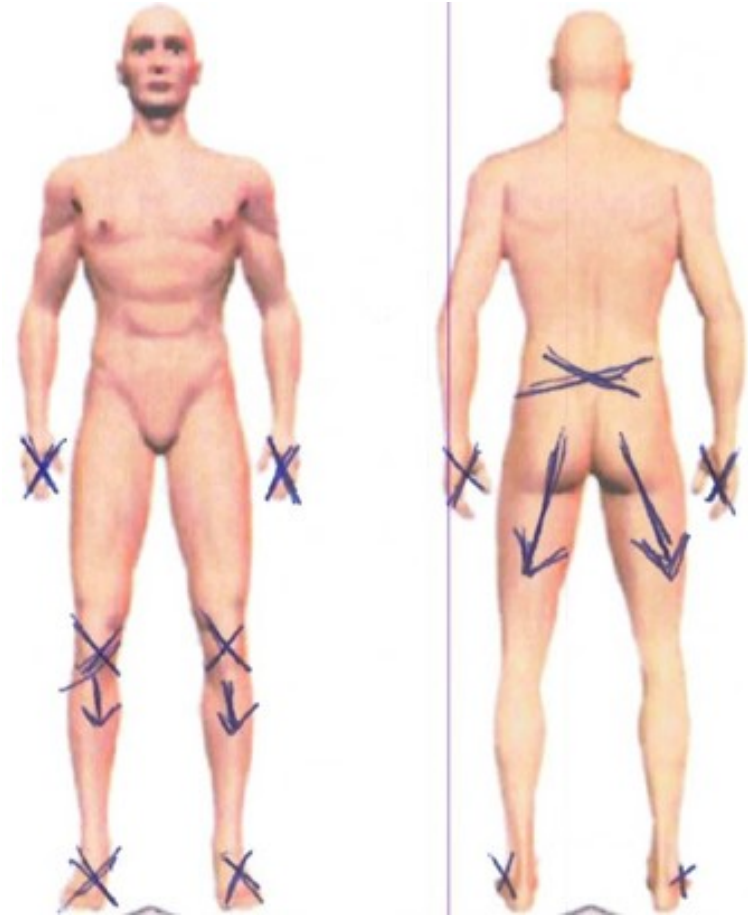
Diagnose

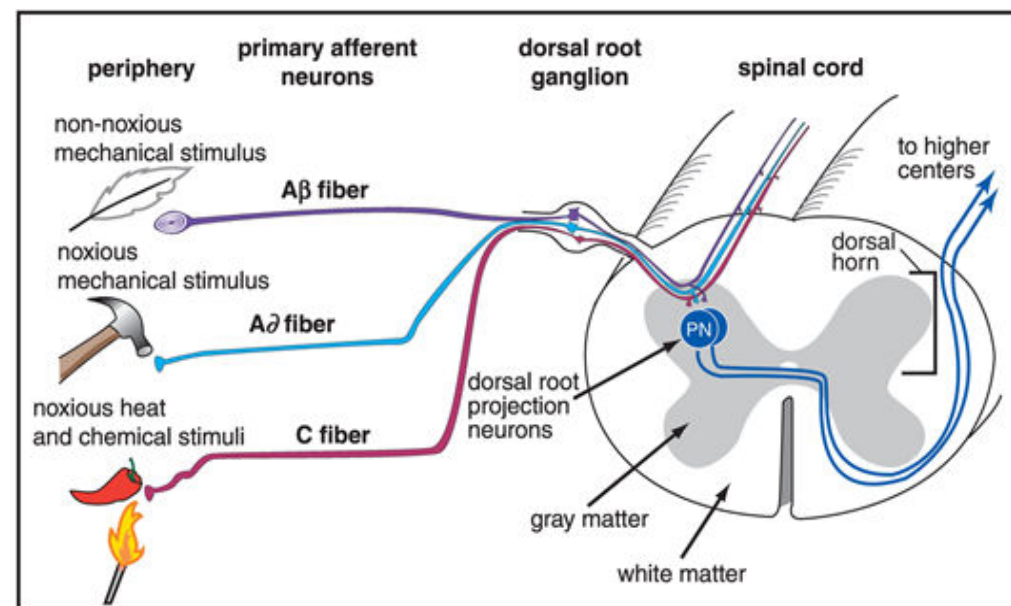
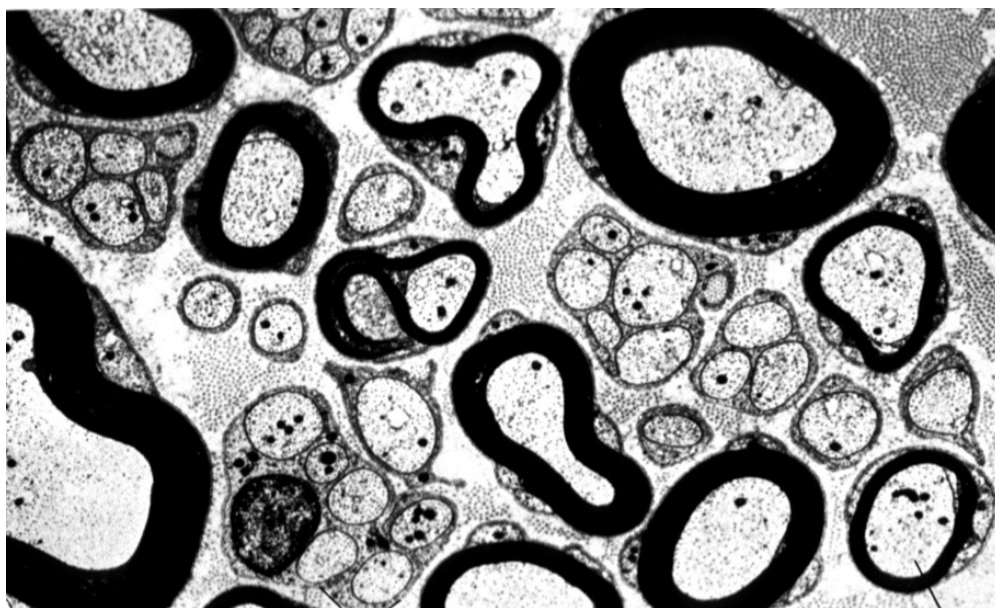




Diagnose

- **Anamnese** (nerveskade/sygdom/debut)
- Spørgeskemaer
- Smerteintensitet
 - Visuel analog skala (VAS), numerisk rating skala (NRS) osv.
- Smertekarakter
 - Spørgeskemaer som beskriver smertens sensoriske kvalitet, affektive kvalitet osv.
- Smerteindtegning

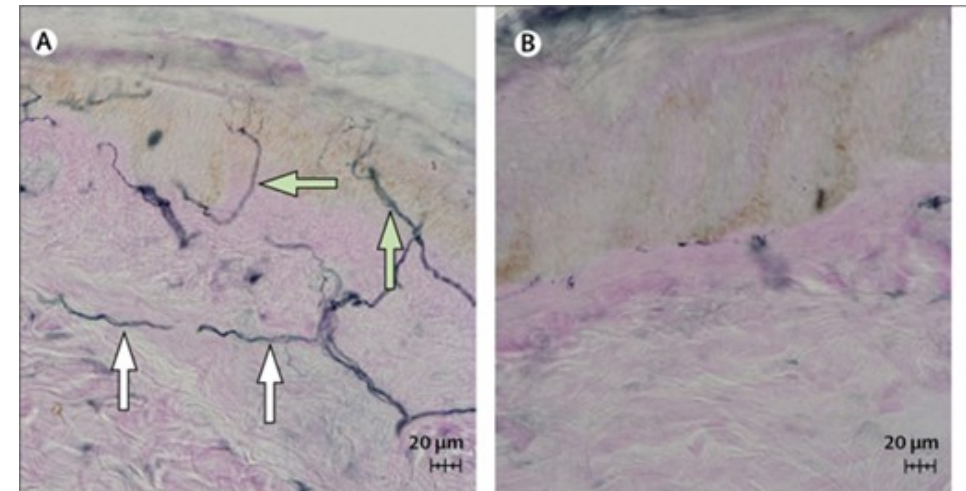
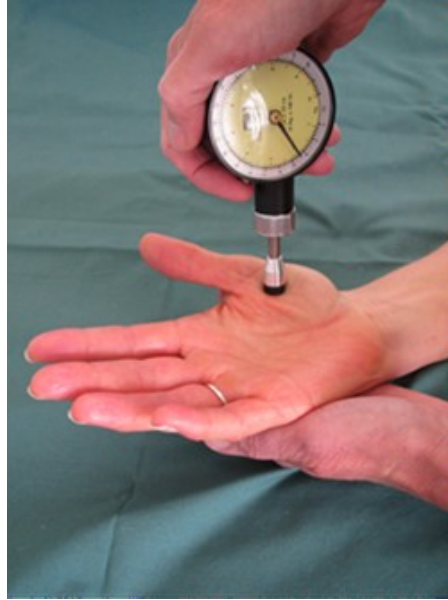
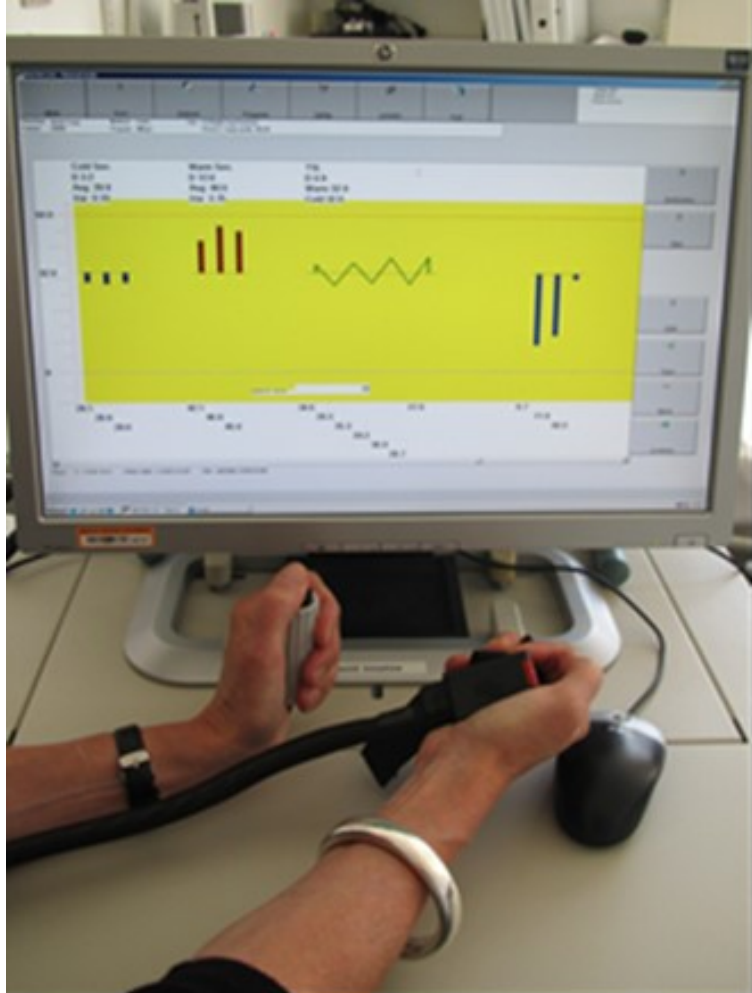




Fiber type	Properties	Velocity (m/sec)	Function	Perception
Aβ (large)	Myelinated	30–70	Touch Pressure Vibration	Touch /Sharp Well localized
Aδ (small)	Myelinated	5–30	Pain (pinprick) Temperature (cold threshold)	Sharp Well localized
C (small)	Unmyelinated	≤1	Pain (Temperature/ pressure/ chemical)	Dull Poorly localized Persistent



Diagnose

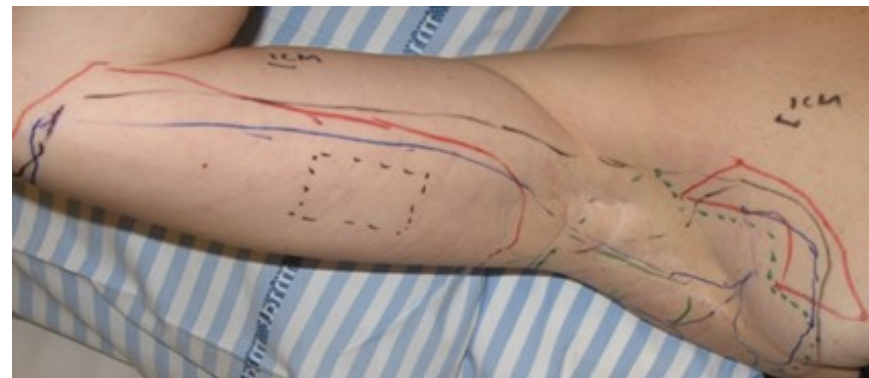
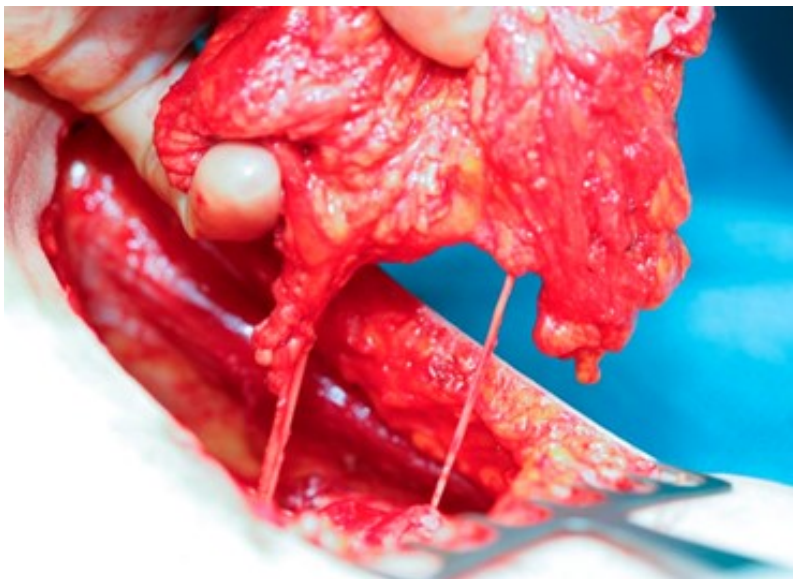




Neuropati og smerter hos kræftpatienter

- Kirurgi
 - Primær tumor eller metastaser
 - Fjernelse af lymfeknuder
- Strålebehandling
- Kemoterapi
- Anden onkologisk behandling

Kirurgi og strålebehandling

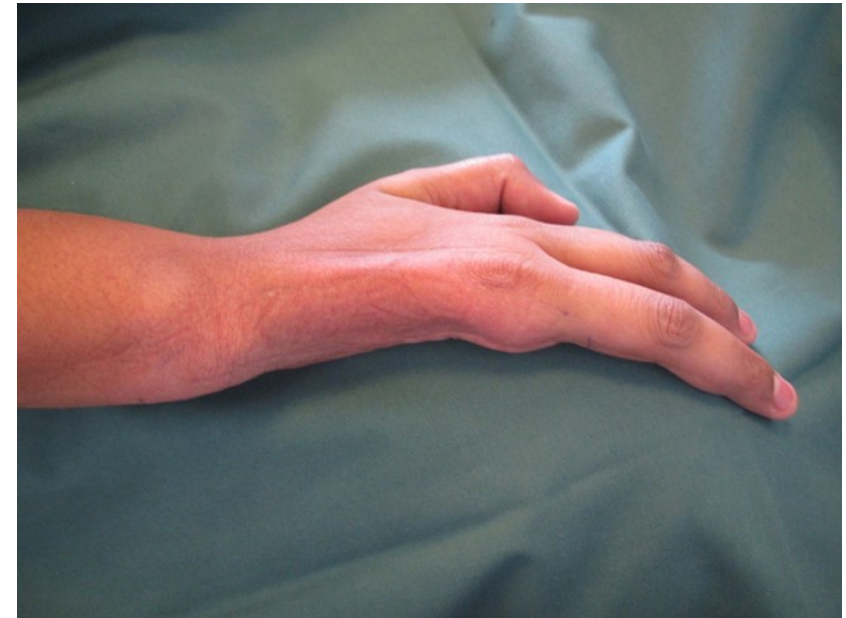


Billeder fra Smerteklinikken, AUH
Lymfødembillede fra Vestergaard R et al. Kirurgisk
behandling af lymfødem. Ugeskrift for læger
2018;180:V11160788



Kirurgi og strålebehandling

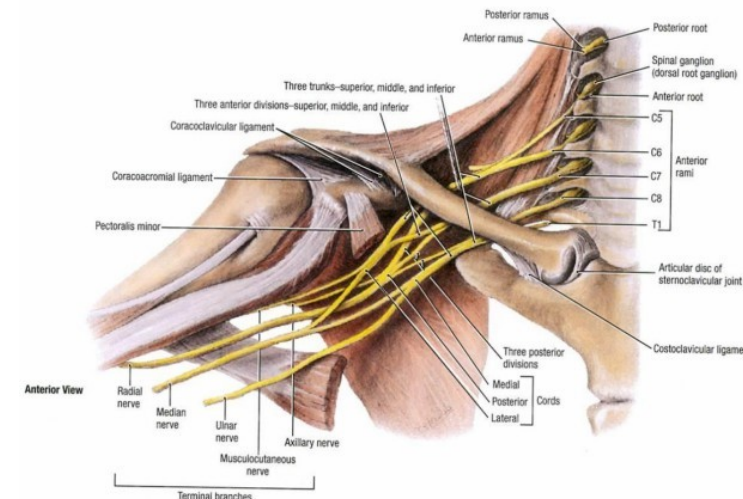
- 25 årig kvinde med synovialt sarkom i højre hypotenar region
- Behandlet med amputation af 4. og 5. stråle samt strålebehandling
- Fantomsmerter, dysæstesi og hyperalgesi
- Bivirkninger til sekundære analgetika
- Ønske om graviditet
- Effekt af Versatis®
- Forsøg med Qutenza®





Kirurgi og strålebehandling

- 59 årig mand opereret for lungecancer i 2017. Non-radikalitet hvorfor der gives adj. strålebehandling mod plexus cervikalis/brachialis.
- 2019 recidiv hvor patienten behandles med kemoterapi og senere immunterapi.
- Aktuelt recidivfri.
- Henvises til Klinik for senfølger pga. smerter svt. skulder/overarm
- Er i behandling med paracetamol depot i maximal dosis samt NSAID i høj dosis med lidt effekt.





Kemoterapi-induceret neuropati



<https://www.sundhed.dk/borger/patienthaandbogen/kraeft/sygdomme/behandlingsmetoder/kemoterapi/>



Kemoterapi-induceret neuropati

- Velkendt alvorlig komplikation til både den **pallierende** og **adjuverende** kræftbehandling
- Stort problem i den kliniske hverdag
- Tiltagende problem, idet der er flere langtidsoverlevende efter kræft
- Påvirker livskvaliteten
- Manglende viden om patogenese
- Manglende effektiv forebyggelse og behandling



Kemoterapi-induceret neuropati

- Platinderivater
 - Cisplatin
 - Carboplatin
 - Oxaliplatin
- Taxaner
 - Paclitaxel
 - Docetaxel
 - Cabazitaxel
 - Nab-paclitaxel
- Vinkaalkaloider
 - Vincristin
 - Vinblastin
 - Vinorelbin
 - Vinflunin
- Checkpoint inhibitorer bl.a.
 - Nivolumab
 - Pembrolizumab

> [Front Oncol.](#) 2022 Mar 15;12:824511. doi: 10.3389/fonc.2022.824511. eCollection 2022.

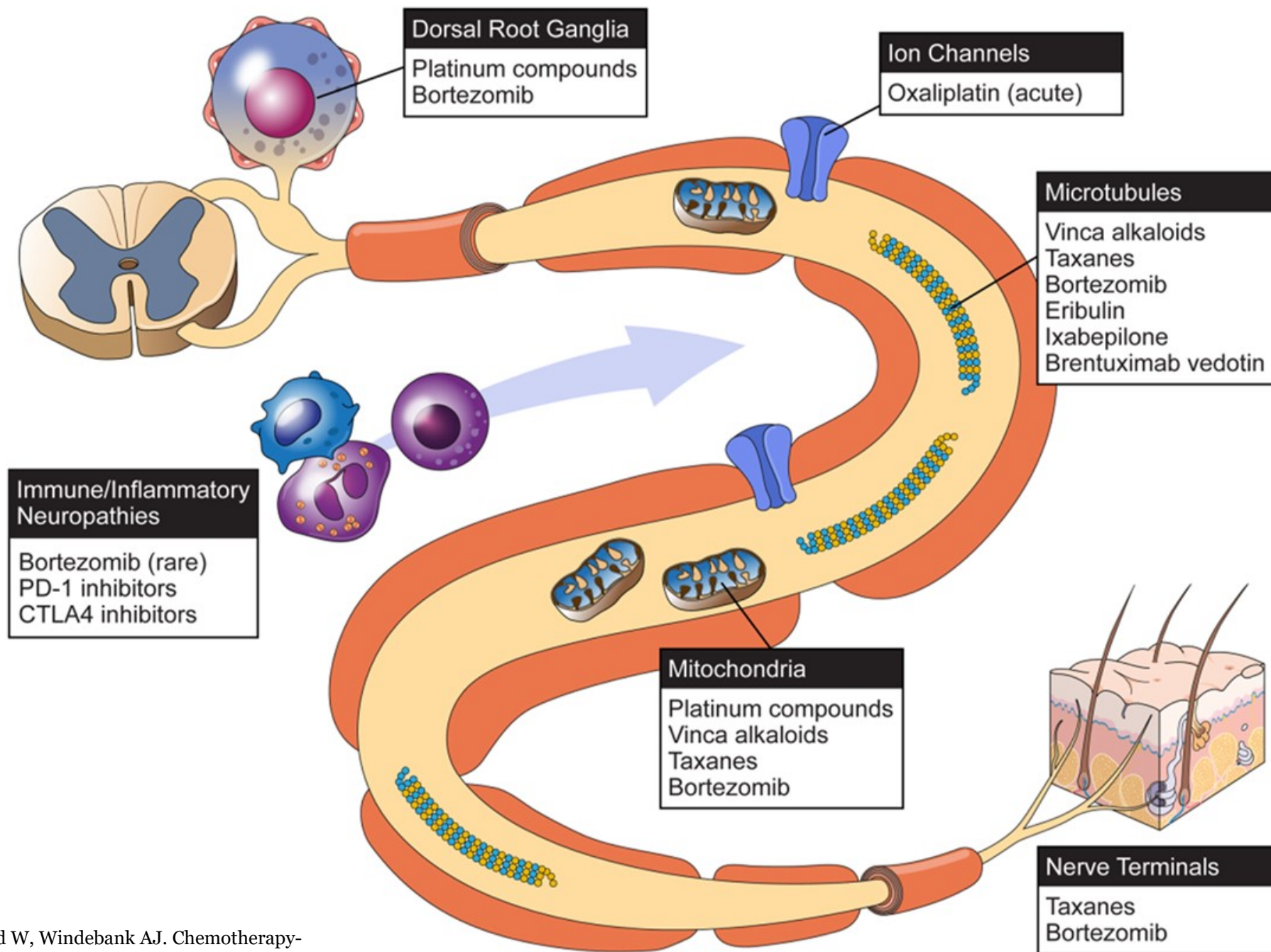
Neurological Manifestations Related to Immune Checkpoint Inhibitors: Reverse Translational Research by Using the European Real-World Safety Data

Rosanna Ruggiero ^{1 2}, Barbara Stelitano ^{1 2}, Federica Fraenza ^{1 2}, Gabriella di Mauro ^{1 2}, Cristina Scavone ^{1 2}, Liberata Sportiello ^{1 2}, Concetta Rafaniello ^{1 2}, Raffaella Di Napoli ¹, Romano Danesi ³, Marzia Del Re ³, Francesco Rossi ^{1 2}, Annalisa Capuano ^{1 2}

Affiliations + expand

PMID: 35372076 PMCID: PMC8964934 DOI: 10.3389/fonc.2022.824511

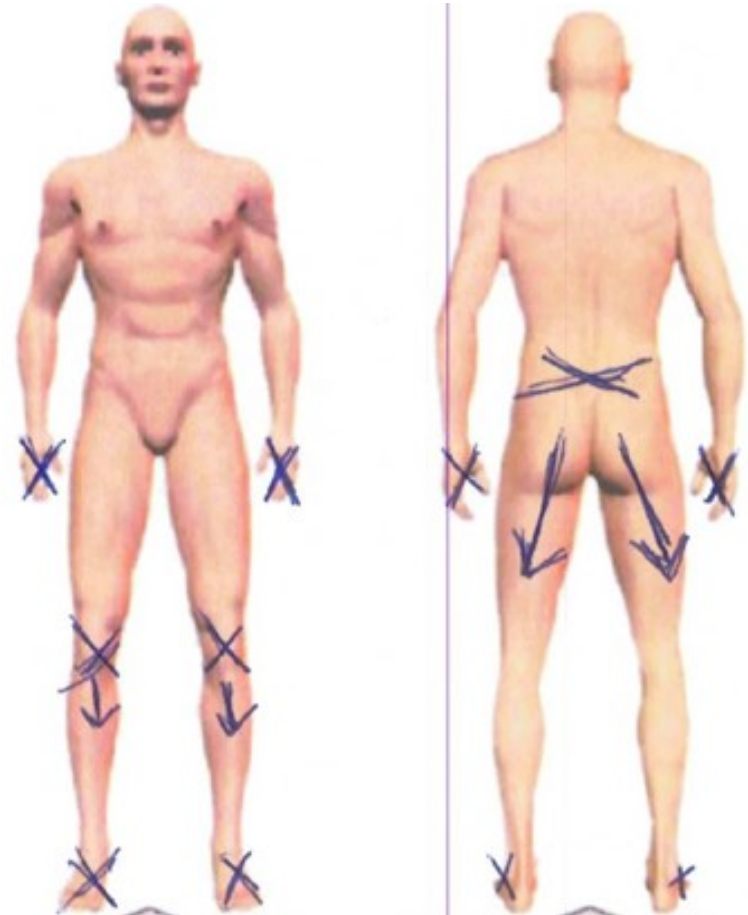
[Free PMC article](#)





Kemoterapi-induceret neuropati

- Perifer – starter længst væk fra hjernen
- Bilateral – mærkes lige meget på begge sider
- Paræstesi – nedsat følesans
- Dysæstesi – abnorm ubehagelig følelse
- Smerter
- Motoriske forstyrrelser



Ventzel L, Jensen AB, Jensen AR, Jensen TS, Finnerup NB. Chemotherapy-induced pain and neuropathy: a prospective study in patients treated with adjuvant oxaliplatin or docetaxel. *Pain*. 2016 Mar;157(3):560-568.

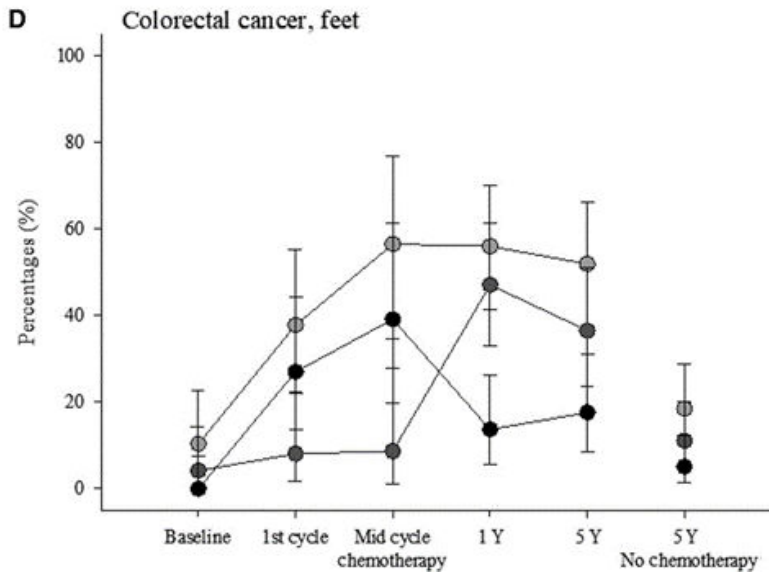
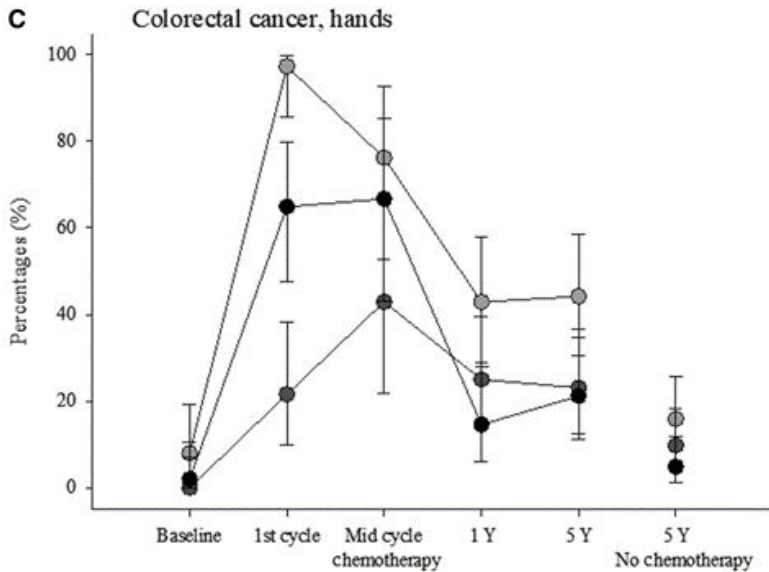
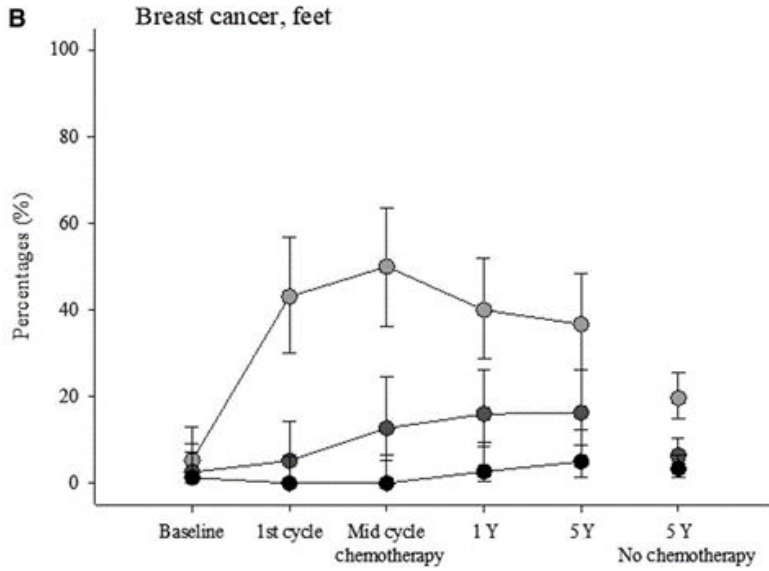
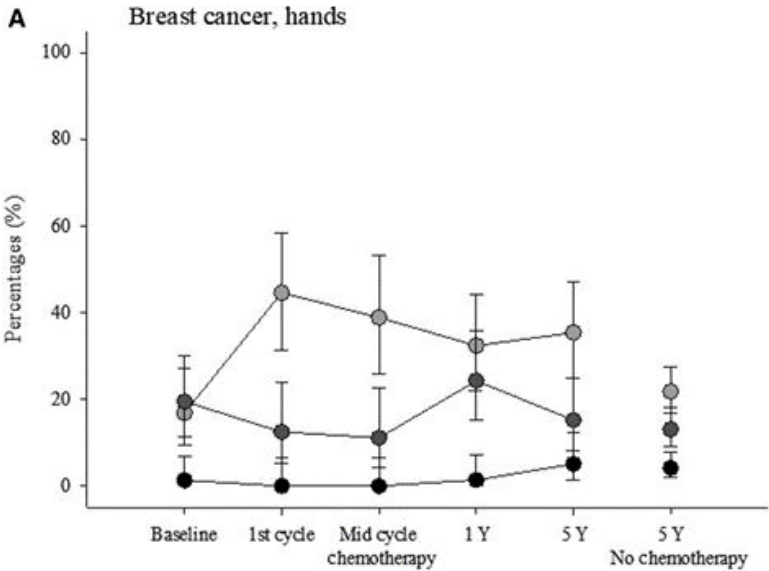
Long-term symptoms of polyneuropathy in breast and colorectal cancer patients treated with and without adjuvant chemotherapy

Kristine Bennedsgaard¹ | Lise Ventzel^{1,2} | Andreas C. Themistocleous^{3,4} |
David L. Bennett³ | Anders B. Jensen² | Anni R. Jensen² | Niels T. Andersen⁵ |
Troels S. Jensen^{1,6} | Hatice Tankisi⁷ | Nanna B. Finnerup^{1,6}

Light gray circle: tingling

Dark gray circle: numbness

Black circle: burning pain
when touching something cold





Oxaliplatin

	Colorectal cancer	
	Chemotherapy (n = 52)	No chemotherapy (n = 83)**
Polyneuropathy		
Tingling or numbness in feet, % (CI 95%)	57.7% (43.2-71.3)	23.5% (14.8-34.2)
MNSIq ≥ 4 , % (CI 95%)	19.2% (9.6-32.5)	9.6% (4.3-18.1)
Neuropathic pain		
Pain in both feet and DN4 ≥ 3 , % (CI 95%)	21.2% (11.1-34.7)	2.4% (0.3-8.4)

ORIGINAL RESEARCH

Cancer Medicine WILEY

Long-term symptoms of polyneuropathy in breast and colorectal cancer patients treated with and without adjuvant chemotherapy

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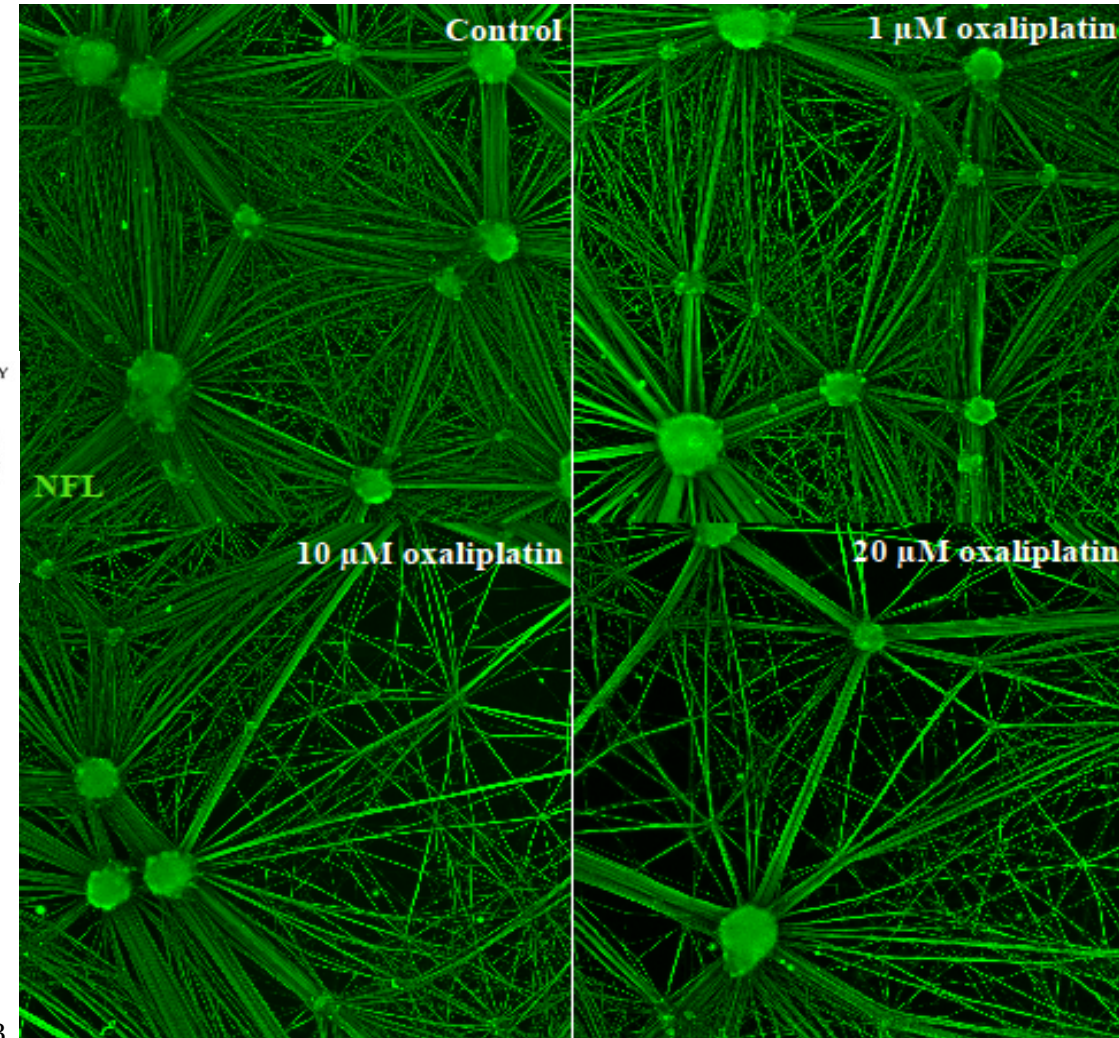
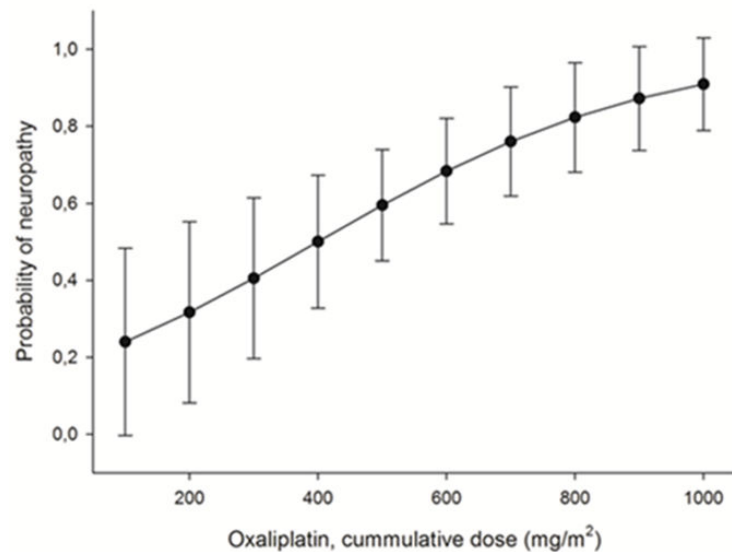


TABLE 2 Proportion of Patients with Symptoms of Polyneuropathy and Neuropathic Pain

	Breast cancer					
	Chemotherapy (n = 80)*	No chemotherapy (n = 249)**	OR (CI 95%)	P value	aOR(CI 95%) ^a	aP value
Polyneuropathy						
Tingling or numbness in feet, % (CI 9%)	38.8% (28.1-50.3)	20.2% (15.3-25.8)	2.5 (1.4-4.3)	.001	3.2 (1.6-6.4)	.001
MNSIq ≥4, % (CI 95%)	17.7% (10.0-27.9)	11.8% (8.1-16.6)	1.6 (0.8-3.2)	.18	2.0 (0.8-3.3)	.10
Neuropathic pain						
Pain in both feet and DN4 ≥3, % (CI 95%)	13.8% (7.1-23.3)	2.4% (0.9-5.2)	6.7 (2.4-18.7)	<.001	6.2 (1.8-21.9)	.006
	Colorectal cancer					
	Chemotherapy (n = 52)	No chemotherapy (n = 83)**	OR (CI 95%)	P value	aOR (ci 95%) ^b	aP value
Polyneuropathy						
Tingling or numbness in feet, % (CI 95%)	57.7% (43.2-71.3)	23.5% (14.8-34.2)	4.4 (2.10-9.45)	<.001	4.8 (2.2-10.4)	<.001
MNSIq ≥4, % (CI 95%)	19.2% (9.6-32.5)	9.6% (4.3-18.1)	2.2 (0.81-6.09)	.12	2.2 (0.80-6.0)	.11
Neuropathic pain						
Pain in both feet and DN4 ≥3, % (CI 95%)	21.2% (11.1-34.7)	2.4% (0.3-8.4)	10.7 (2.3 –51.4)	.003	11.4 (2.4-54.4)	.002

ORIGINAL RESEARCH

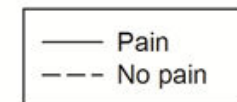
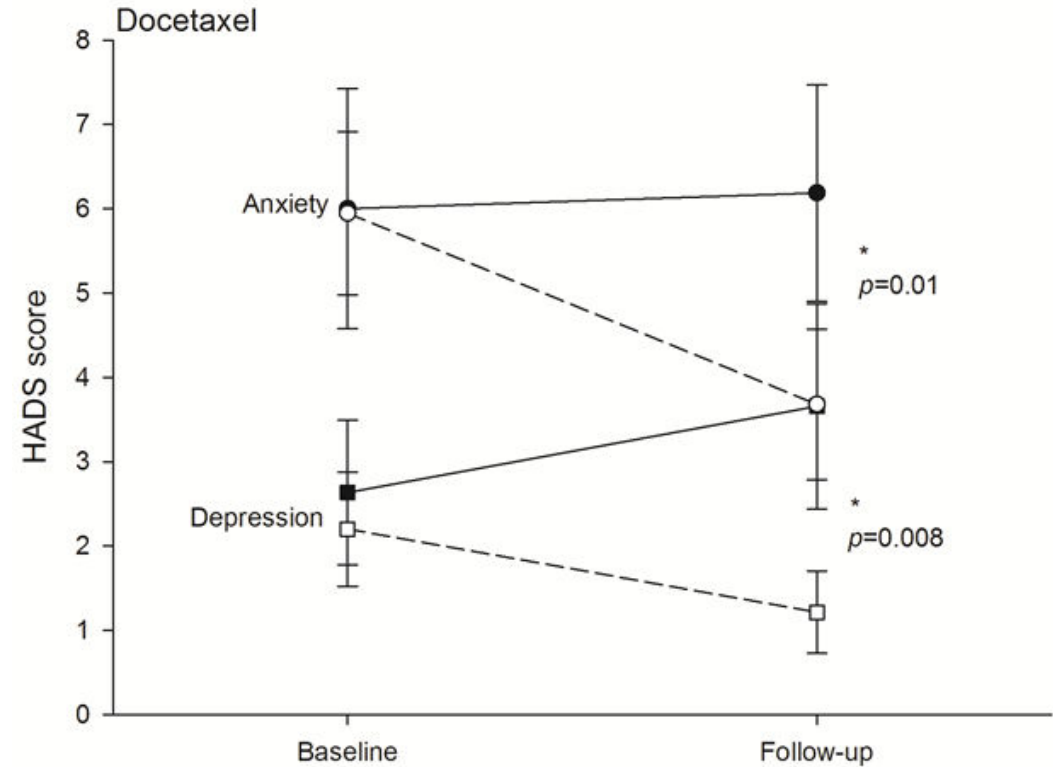
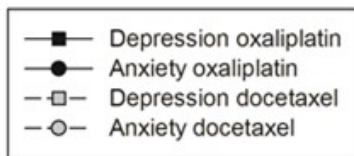
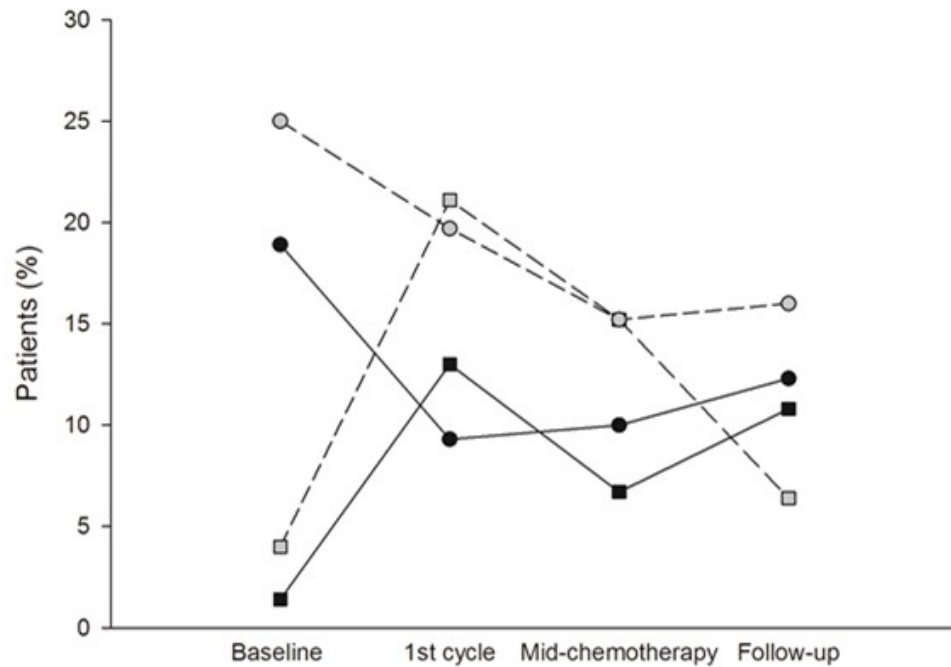
ORIGINAL RESEARCH

Long-term symptoms of polyneuropathy in breast and colorectal cancer patients treated with and without adjuvant chemotherapy

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Angst og depression

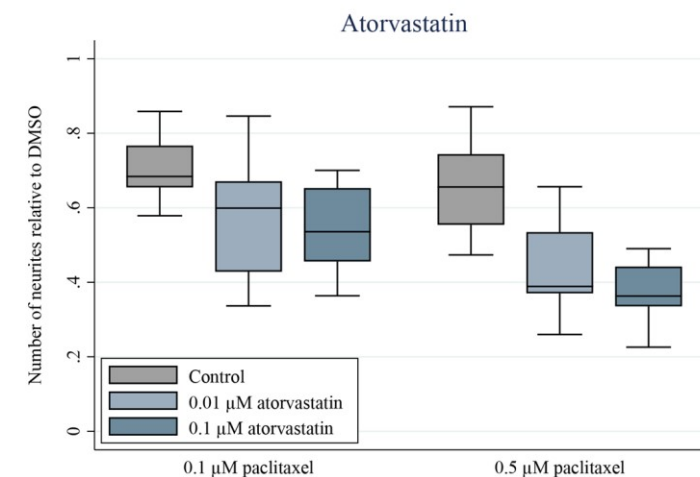
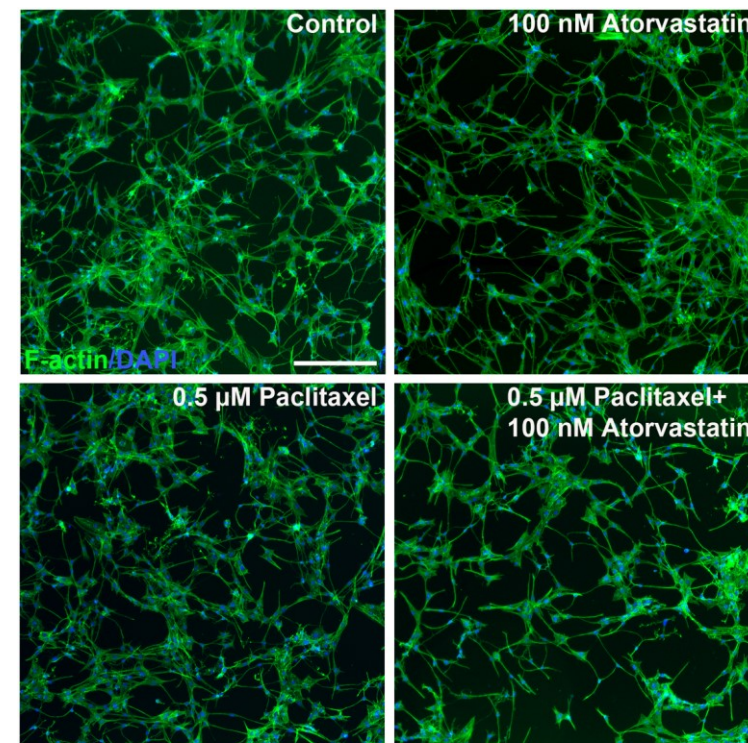


Ventzel L, Jensen AB, Jensen AR, Jensen TS, Finnerup NB. Chemotherapy-induced pain and neuropathy: a prospective study in patients treated with adjuvant oxaliplatin or docetaxel. *Pain*. 2016 Mar;157(3):560-568.



Er nogen i højere risiko end andre?

- Høj alder (Hershmann et al. JCO (2016))
- Diabetes (Hershmann et al. JCO (2016))
- Race (se figur)
- Høj BMI
- Neuropati forudgående
- Rygning
- Akut neuropati under behandling (oxaliplatin)
- Andet medicin - interaktion





Behandling

asco special articles

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update

Charles L. Loprinzi, MD¹; Christina Lacchetti, MHSc²; Jonathan Bleeker, MD³; Guido Cavaletti, MD, PhD⁴; Cynthia Chauhan, MSW⁵; Daniel L. Hertz, PharmD, PhD⁶; Mark R. Kelley, PhD⁷; Antoinette Lavino, BS Pharm, RPh⁸; Maryam B. Lustberg, MD⁹; Judith A. Paice, PhD, RN¹⁰; Bryan P. Schneider, MD¹¹; Ellen M. Lavoie Smith, RN, PhD⁶; Mary Lou Smith, JD, MBA¹²; Thomas J. Smith, MD¹³; Nina Wagner-Johnston, MD¹³; and Dawn L. Hershman, MD¹⁴

abstract

PURPOSE To update the ASCO guideline on the recommended prevention and treatment approaches in the management of chemotherapy-induced peripheral neuropathy (CIPN) in adult cancer survivors.

METHODS An Expert Panel conducted targeted systematic literature reviews to identify new studies.

RESULTS The search strategy identified 257 new references, which led to a full-text review of 87 manuscripts. A total of 3 systematic reviews, 2 with meta-analyses, and 28 primary trials for prevention of CIPN in addition to 14 primary trials related to treatment of established CIPN, are included in this update.

RECOMMENDATIONS The identified data reconfirmed that no agents are recommended for the prevention of CIPN. The use of acetyl-L-carnitine for the prevention of CIPN in patients with cancer should be discouraged.

Furthermore, clinicians should assess the appropriateness of dose delaying, dose reduction, substitutions, or stopping chemotherapy in patients who develop intolerable neuropathy and/or functional impairment.

Duloxetine is the only agent that has appropriate evidence to support its use for patients with established painful CIPN. Nonetheless, the amount of benefit from duloxetine is limited.

Additional information is available at www.asco.org/survivorship-guidelines.

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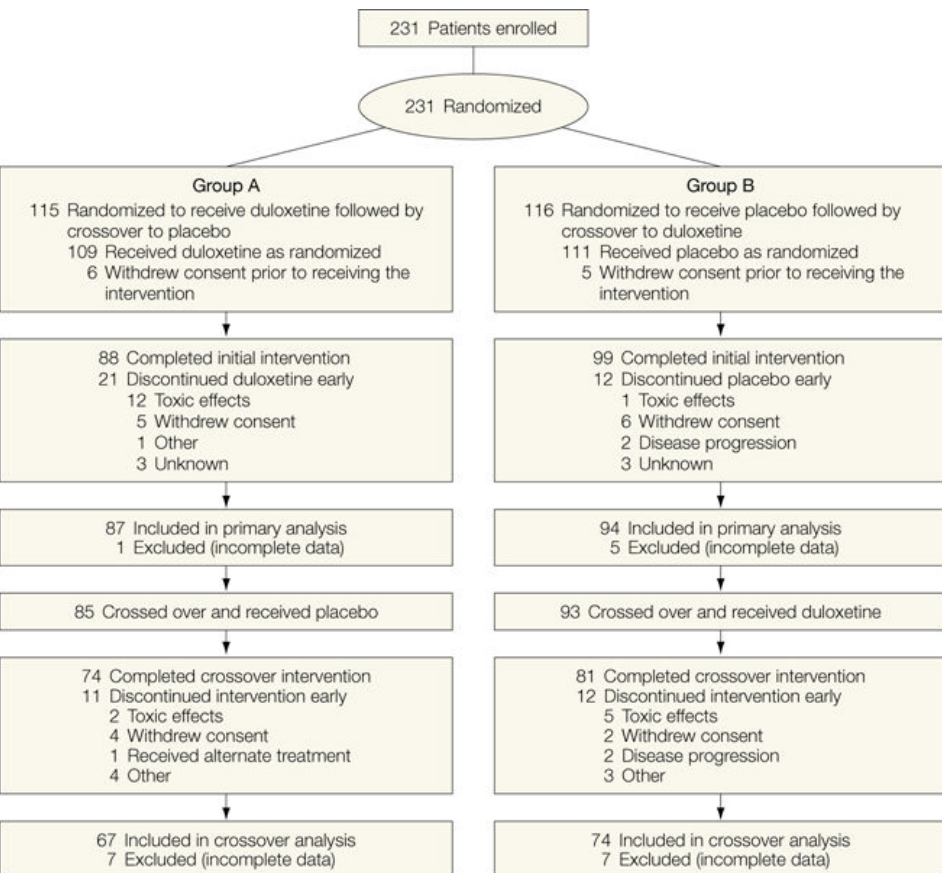
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KEYWORDS: the Great Recession; residential mobility; residential satisfaction; residential turnover; residential vacancy; residential vacancy duration; residential vacancy time; residential vacancy time to rent; residential vacancy time to sell; residential vacancy time to lease; residential vacancy time to purchase; residential vacancy time to rent; residential vacancy time to sell; residential vacancy time to lease; residential vacancy time to purchase

Search The search strategy identified 237 new references, which were a full-text review of 97 manuscripts, a total of 13 systematic reviews, 7 full-text analyses, and 28 primary trials for prevention of CYPH in addition to 14 primary trials added to treatment of established CYPH, are included in this update.

Stimulus is the only significant tax expenditure available to support the use for public use of commercial property (CPS). Nevertheless, the amount of benefit from stimulus is limited.

© 2006 Blackwell Publishing Ltd, *Journal of Internal Medicine* 260: 103–110



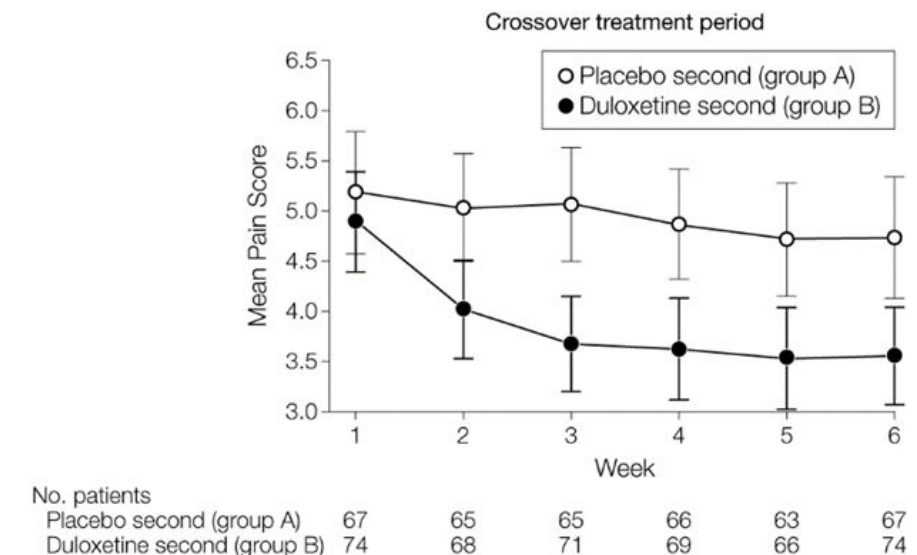
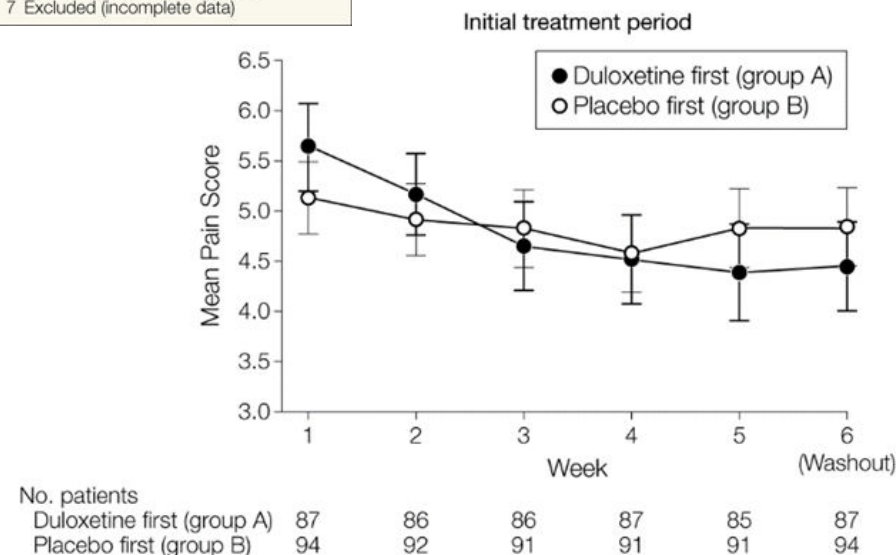
April 3, 2013

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

A Randomized Clinical Trial

Ellen M. Lavoie Smith, PhD; 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

- 30mg of duloxetine or placebo first week and 60 mg of duloxetine or placebo daily for 4 additional weeks
- Primary outcome: Brief Pain Inventory-Short Form (0-10)





Behandling af neuropatiske smerter

GRADE classification	Drugs	Recommendations
STRONG FOR	Gapabentin Gabapentin ER/enacarbil Pregabalin SNRIs duloxetine/venlafaxine TCAs	First-line First-line First-line First-line First-line
WEAK FOR	Capsaicin 8% patches Lidocaine patches Tramadol BTX- A (SC) Strong opioids	Second-line (PNP) Second-line (PNP) Second-line Third-line; specialist use (PNP) Third line
INCONCLUSIVE	Carbamazepine, Lacosamide, Lamotrigine, Oxcarbazepine, Topiramate, Zonisamide, SSRI antidepressants, NMDA antagonists, Tapentadol, Capsaicin cream, Topical clonidine	
WEAK AGAINST	Cannabinoids Valproate	
STRONG AGAINST	Levetiracetam Mexiletine	

Finnerup et al. Lancet Neurology 2015



Bivirkninger og compliance

Risiko for antikolinerg belastning

Amitriptylin er et middel med en meget stærk antikolinerg effekt. Opmærksomhed på den antikolinerge belastning - særligt hos ældre og ved kombination med andre antikolinerge midler. Se endvidere [Antikolinerge lægemidler, Sundhedsstyrelsen, juni 2019](#).

Tilstande der påvirkes af den antikolinergiske effekt

En række tilstande kan forværres pga. den antikolinerge effekt, bl.a.:

- Autonom neuropati
- GI-obstruktion (fx svær obstipation, risiko for ileus)
- Snævervinklet glaukom
- Hjertesvigt
- Myastenia gravis
- Prostatahyperplasi
- Tyrotoksikose

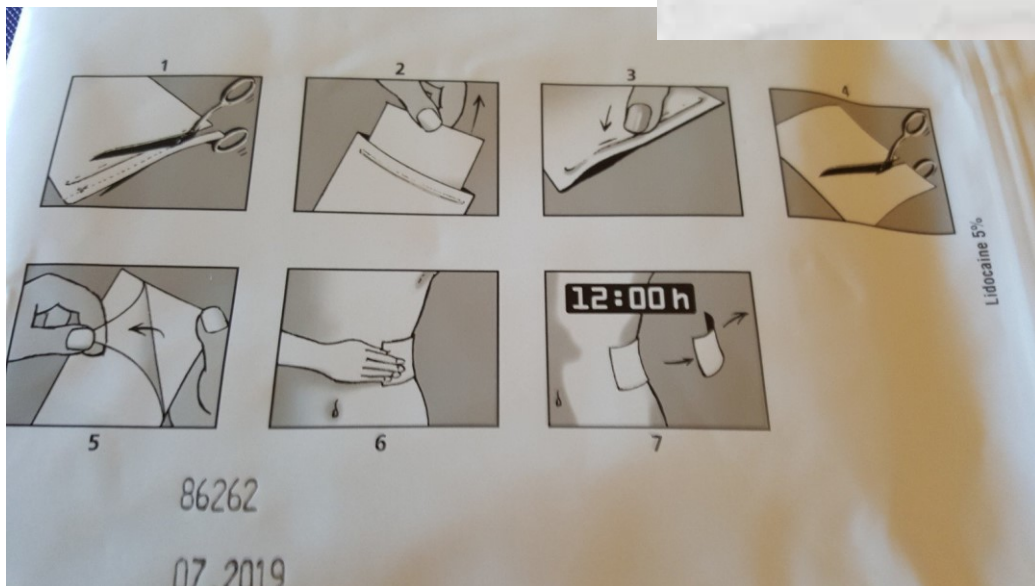


Topikal behandling

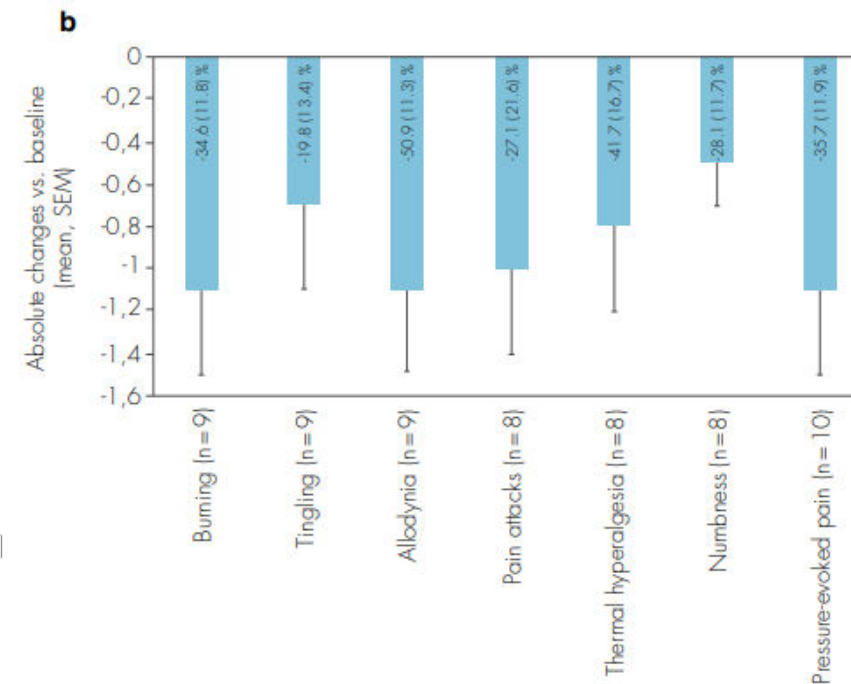
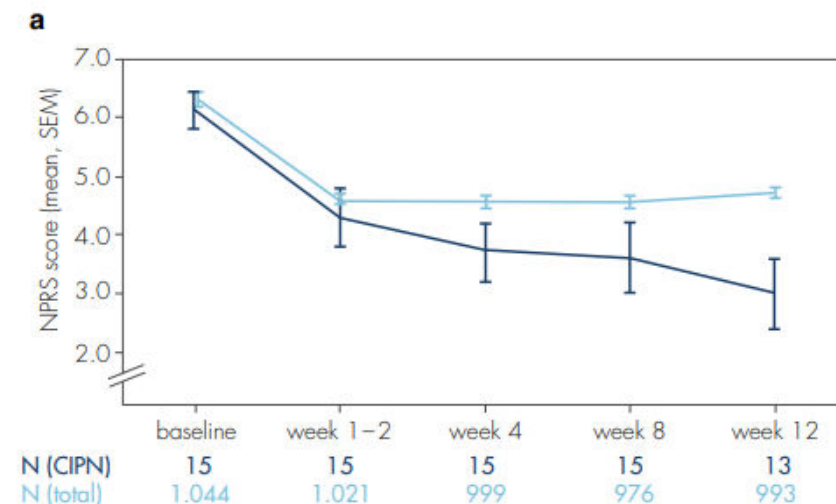
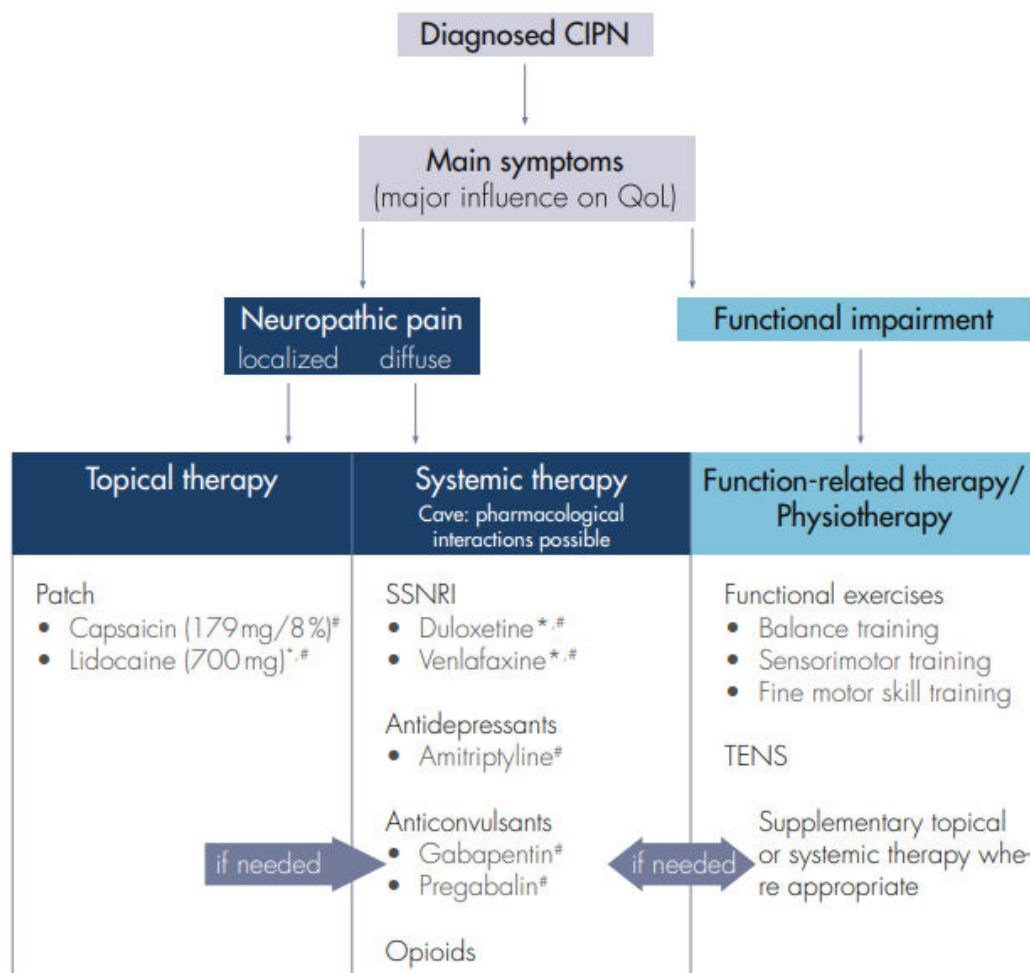
Case fra tidligere:

Effekt af Versatis®

Forsøg med Qutenza®



Topikal behandling



Review > Support Care Cancer. 2021 Aug;29(8):4223-4238. doi: 10.1007/s00520-021-06042-x.

Epub 2021 Feb 23.

Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer

Chemotherapy-induced peripheral neuropathy (CIPN): current therapies and topical treatment option with high-concentration capsaicin

Christian Mailhofner ¹, Ingo Diehl ², Hans Tesch ³, Tamara Quandt ⁴, Ralf Baron ⁵



Behandling af neuropati

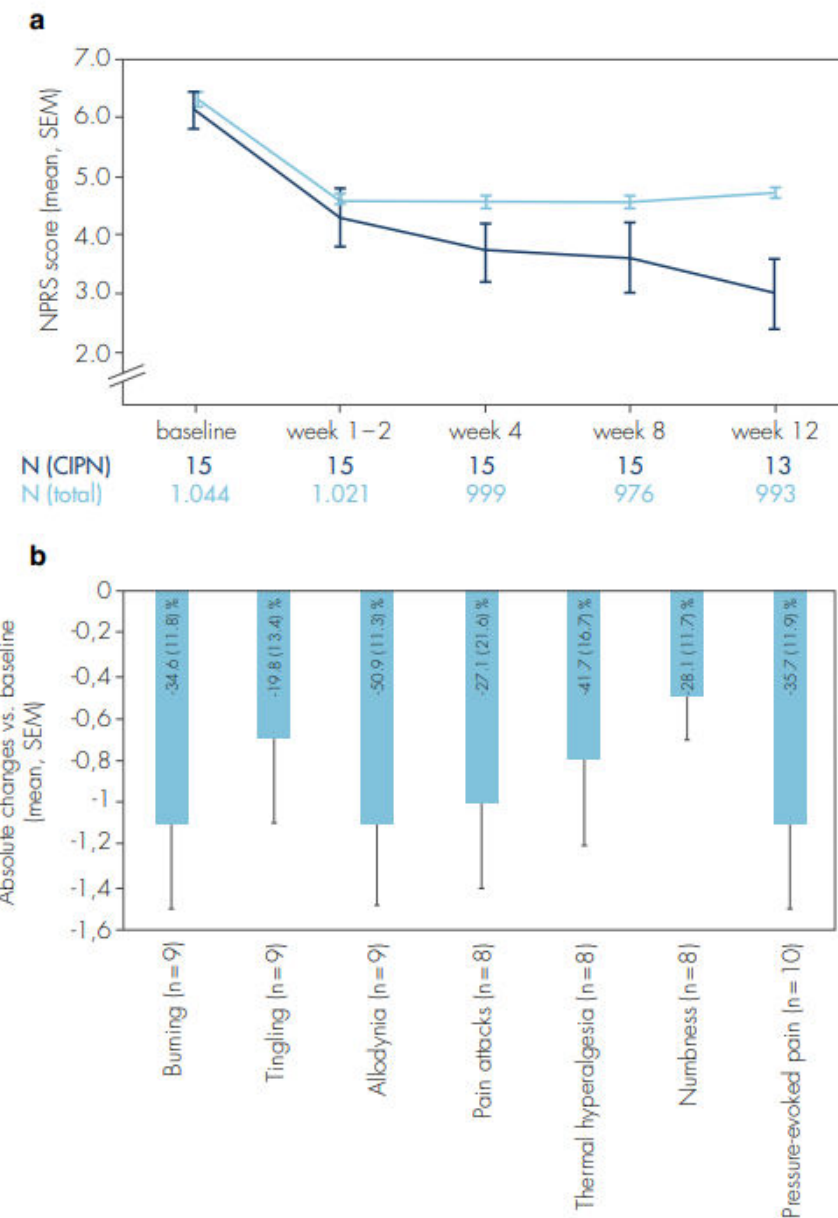
- Nedsat følesans (paræstesi) kan ikke behandles farmakologisk
- Dysæstesi kan forsøges behandlet som neuropatiske smerter
- Ved behandling af neuropatiske smerter henvises til NeuPSIG guidelines
- Husk at hjernen er plastisk
- Information og viden om nervesystemet og symptomerne er afgørende





Forskning på området

- Projekt omkring forebyggende behandling
- Biomarkører
- Topikal behandling?
- Cannabis?
- Cryoneurolyse





Spørgsmål?



Tony Matelli, Fucked, 2005