5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 3

EAN/PNS: Novel approach in the treatment of neuropathy (Level3)

Novel advances in the treatment of pain in neuropathies

Claudia Sommer
Würzburg, Germany

Email: sommer@uni-wuerzburg.de

Uniklinikum Würzburg

Novel advances in the treatment of pain in neuropathies

Claudia Sommer

Neurologische Klinik und Poliklinik

Conflicts of interest

- Educational talks and/or consulting for Pfizer, Lilly, Astellas
- Participation in clinical trials for Air Liquide, Biogen, Novartis, Vertex

Painful neuropathies

Painful neuropathies

- Diabetic NP
- Alcoholic NP
- Vasculitic NP
- GBS, CIDP
- HIV-Neuropathy
- Amyloidosis (ATTR, AL)
- Myeloma, paraneoplastic, POEMS
- Toxic NP
  - Chemotherapy
  - Other toxins (thallium)

- Chronic axonal idiopathic NP
- Small fiber neuropathy
  - Fabry disease
  - Channelopathies
- Mononeuropathies
  - Entrapment
  - Postoperative
  - Traumatic
- Plexopathies

Painful neuropathies: Study Würzburg (350 pts)

Neuropathy	painful	painless
SFN	42	15
CIAP	31	17
DNP	6	7
CIDP	41	48
NSVN	14	9
SVN	7	2
PIAN	10	9
CMT	8	7

Some surprises ?

- Painless SFN
  - Pain<3, no need for medication
  - Fabry disease without pain
- Painful CMT

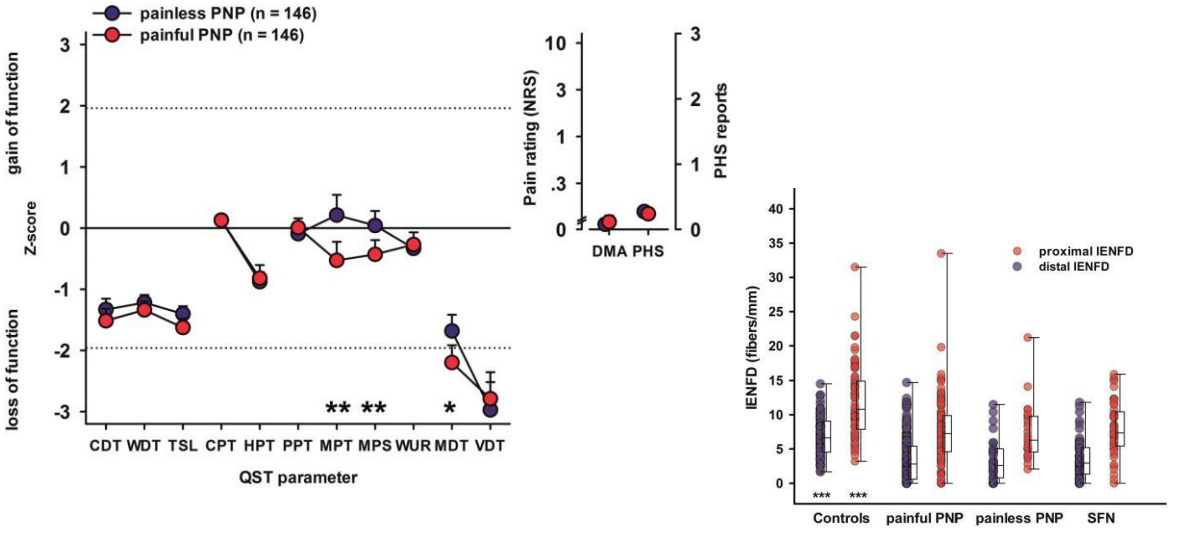
Journal of the Peripheral Nervous System 17:422–425 (2012)

CASE REPORT

Myelin protein zero Arg36Gly mutation with very late onset and rapidly progressive painful neuropathy

Patrizia Dacci[1], Franco Taroni[2], Eleonora Dalla Bella[1], Micaela Milani[2], Davide Pareyson[3], Michela Morbin[4], and Giuseppe Lauria[1]

Quantitative sensory testing and IENFD



Üçeyler et al. Pain 2018;159:1867-76.

NP pain treatment: State of the art

Antidepressants
- Tricyclics
- NSRI

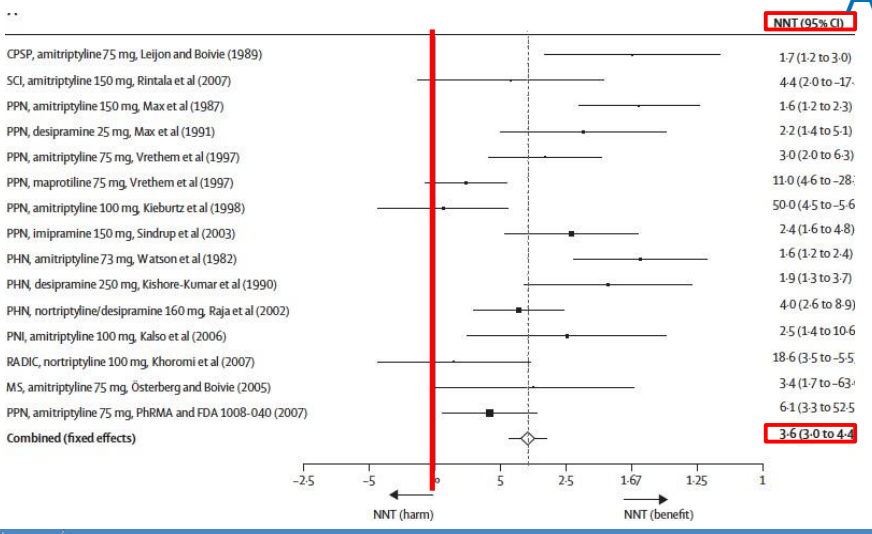
Anticonvulsants
- Ca-channel drugs
- Na-channel drugs

Opioids
- Weak opioids with additional characteristics
- Strong opioids

Local Treatment
- Lidocaine
- Capsaicin
- Botulinum toxin ?

NeuPSIG Guideline: Tricyclic antidepressants

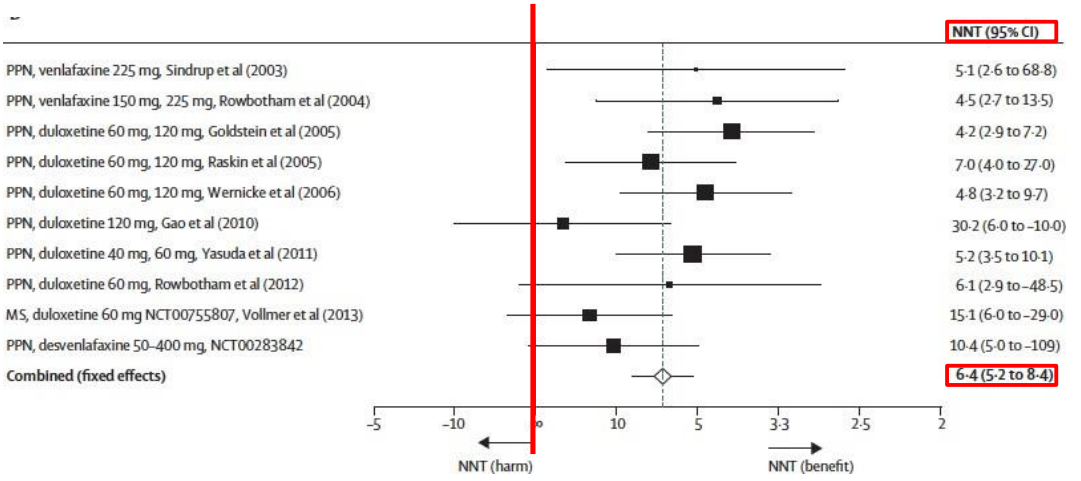
Amitriptyline



Finnerup et al. Lancet Neurol 2015;14:162-73.

NeuPSIG Guideline: NSRI

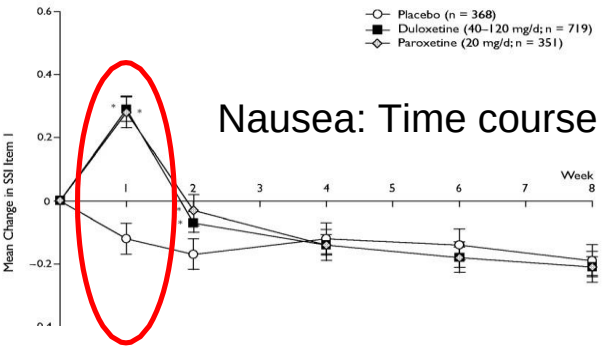
Duloxetine



Finnerup et al. Lancet Neurol 2015;14:162-73.

Duloxetine side effects

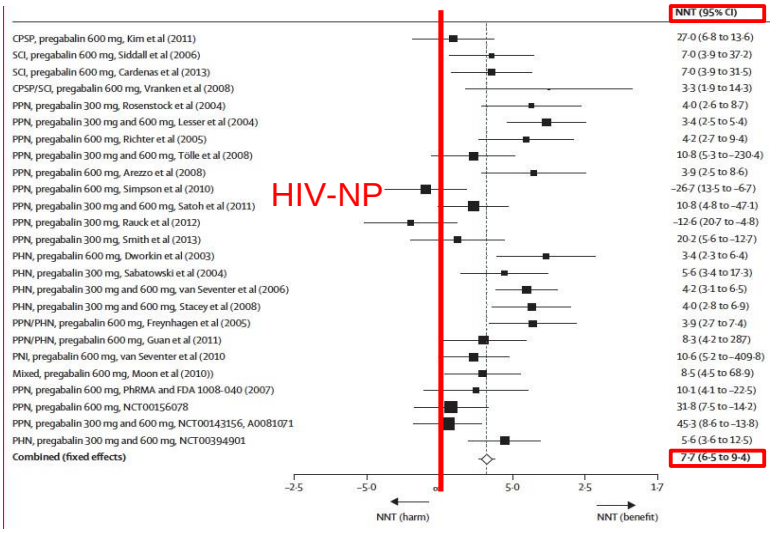
- Nausea/vomiting in 20%



- Prevent with antiemetic:
- Metoclopramide 50 mg, sulpirid 5 mg

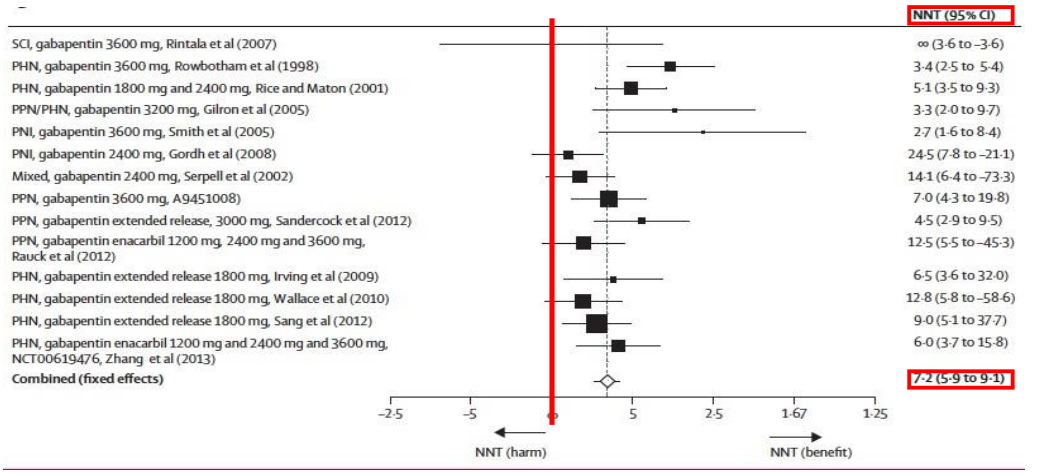
Greist et al. Clin Ther 2004;26:1446-55.

NeuPSIG Guideline: Pregabalin



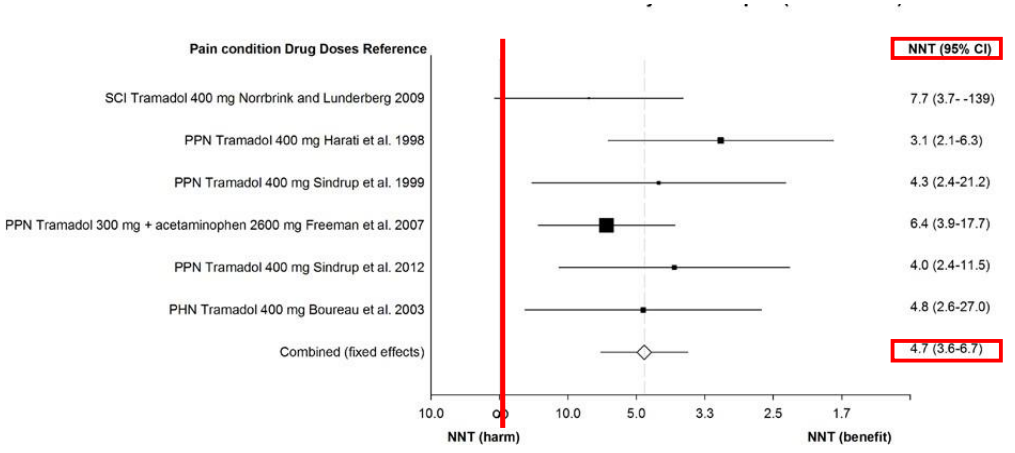
Finnerup et al. Lancet Neurol 2015;14:162-73.

NeuPSIG Guideline: Gabapentin



Finnerup et al. Lancet Neurol 2015;14:162-73.

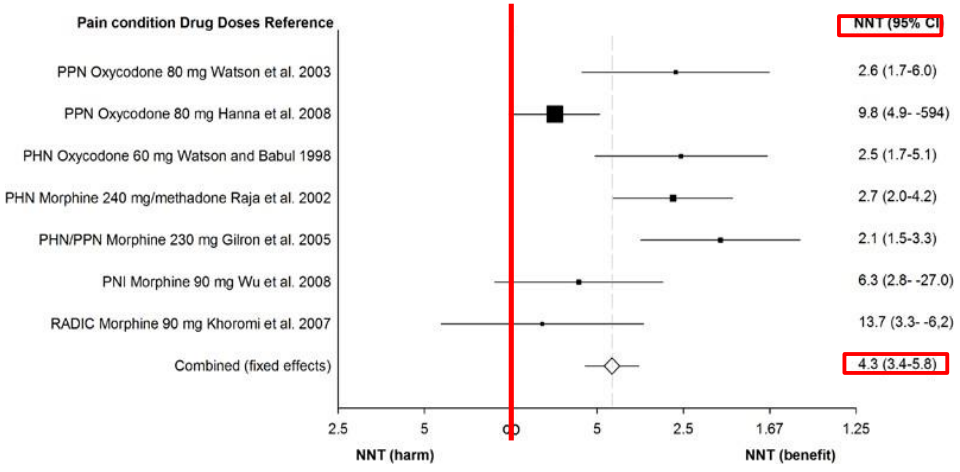
NeuPSIG Guideline: Tramadol



Finnerup et al. Lancet Neurol 2015;14:162-73.

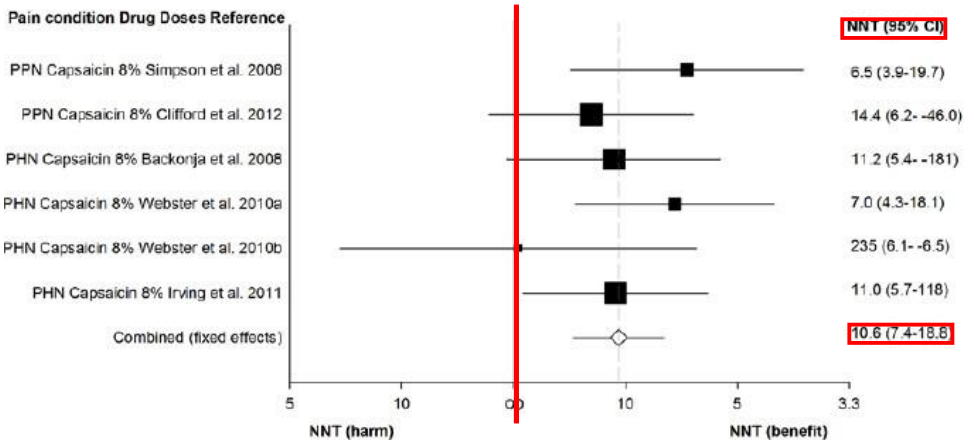
NeuPSIG Guideline: Opioids

Oxycodone, Morphin



Finnerup et al. Lancet Neurol 2015;14:162-73.

High dose capsaicin (8% patch)



Finnerup et al. Lancet Neurol 2015;14:162-73.

Qutenza in diabetic neuropathy

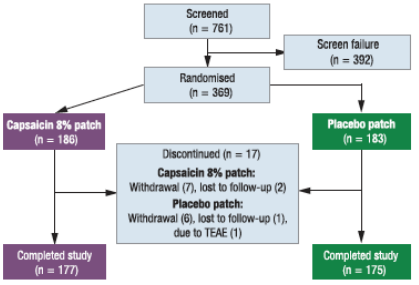
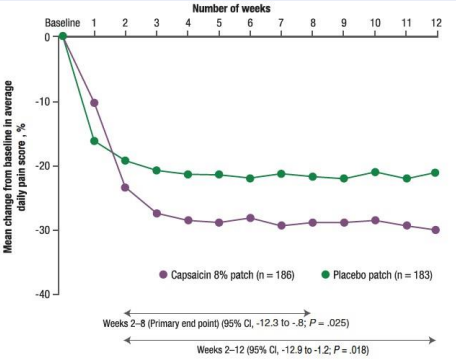
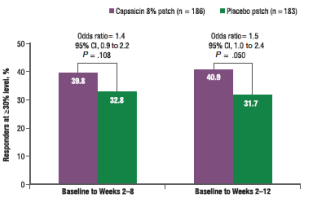


Figure 2. Patient flow.





Simpson et al., J Pain 2017;18:42-53

Botulinum toxin

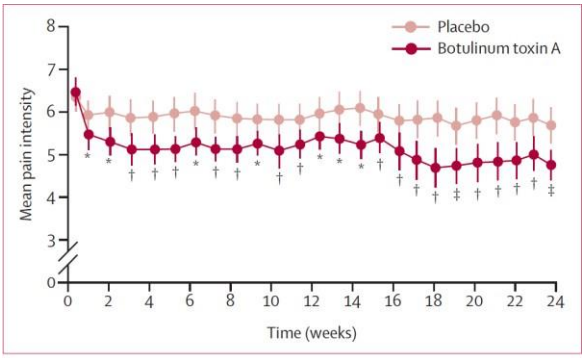


***Figure 2*: Effects of botulinum toxin A and placebo on the primary endpoint**
Bars are SE. p values are for the difference between botulinum toxin A and placebo at each timepoint. *p<0·05. †p<0·01. ‡p<0·001.

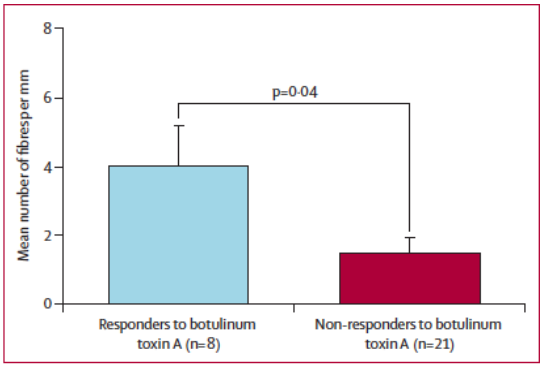


***Figure 3*: Intra-epidermal nerve fibre density at baseline**
Bars are SD.

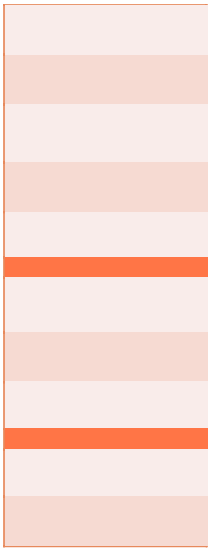
Attal et al. Lancet Neurol 2016;15:555-65.

NNTs

Finnerup et al. Lancet Neurol 2015;14:162-73.

Recommendations

	Total daily dose and dose regimen	Recommendations
Strong recommendations for use		
Gapabentin	1200–3600 mg, in three divided doses	First line
Gabapentin extended release or enacarbil	1200–3600 mg, in two divided doses	First line
Pregabalin	300–600 mg, in two divided doses	First line
Serotonin-noradrenaline reuptake inhibitors duloxetine or venlafaxine*	60–120 mg, once a day (duloxetine); 150–225 mg, once a day (venlafaxine extended release)	First line
Tricyclic antidepressants	25–150 mg, once a day or in two divided doses	First line†
Weak recommendations for use		
Capsaicin 8% patches	One to four patches to the painful area for 30-60 min every 3 months	Second line (peripheral neuropathic pain)‡
Lidocaine patches	One to three patches to the region of pain once a day for up to 12 h	Second line (peripheral neuropathic pain)
Tramadol	200–400 mg, in two (tramadol extended release) or three divided doses	Second line
Botulinum toxin A (subcutaneously)	50–200 units to the painful area every 3 months	Third line; specialist use (peripheral neuropathic pain)
Strong opioids	Individual titration	Third line§



First line

Second line

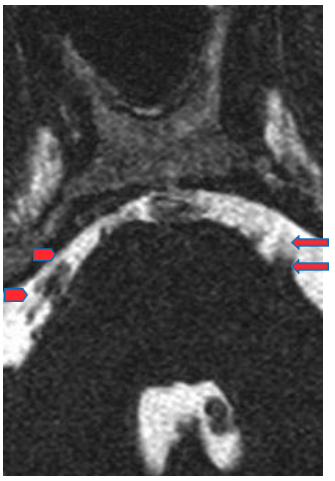
Third line

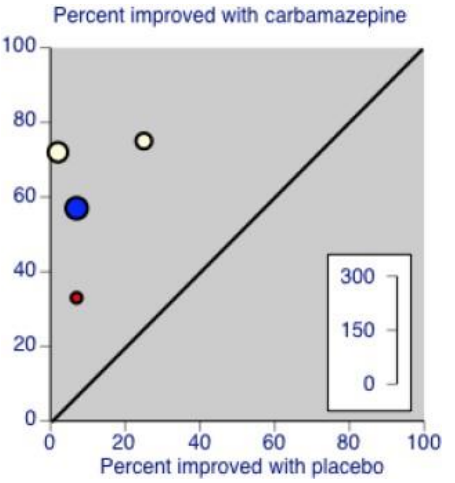
Finnerup et al. Lancet Neurol 2015;14:162-73.

Treatment of the individual patient – how to chose ?

- Licencing status/availability of the drug
- Diagnosis / symptoms
- Side effect profile
- Interaction profile
- Convenience
- Your own experience
- Patient‘s preference

Special cases: Trigeminal neuralgia





Wiffen et al. Cochrane Database Syst Rev 2014;4:CD005451.

Trigeminal neuralgia

Effects	Treatment
Likely to be beneficial	
Systematic reviews, randomised controlled trials, or the best alternative source of information have shown some effectiveness, although this has not been fully established; benefits are likely to be greater than harms	Carbamazepine
	Oxcarbazepine*
	Baclofen (in people with multiple sclerosis who develop trigeminal neuralgia)*
Trade off between benefits and harms	
Clinicians and patients should weigh up beneficial and harmful effects according to individual circumstances and priorities	Microvascular decompression*
	Non-percutaneous destructive neurosurgical techniques (stereotactic radiosurgery)*
	Percutaneous destructive neurosurgical techniques (radiofrequency thermocoagulation, glycerol rhizolysis, and balloon compression)*
Unknown effectiveness	
Data are currently insufficient or of inadequate quality	Lamotrigine
	Gabapentin

Clinical practice

- Add low dose of PGB to CBZ, if effect is not sufficient
- Do not wait too long with surgery

Zakrzewskaet al. BMJ 2015;350:h1238.

Opioids in chronic neuropathic pain ?

NATURE REVIEWS | NEUROLOGY

2017

NEWS & VIEWS

PERIPHERAL NEUROPATHIES

Long-term opioid therapy in neuropathy: benefit or harm?

Claudia Sommer

who received long-term opioid treatment was higher than among patients who received short-term treatment, even after correcting for other influences, such as comorbidities.

One could argue that the patients who received the long-term prescriptions were more-severely affected at baseline, with more-severe pain and more comorbidities. Pain severity was not documented in the regi-

who receive long-term opioid prescriptions are worse off

Opioids in chronic neuropathic pain ?

JAMA Neurology | Original Investigation

Association of Long-term Opioid Therapy With Functional Status, Adverse Outcomes, and Mortality Among Patients With Polyneuropathy

E. Matthew Hoffman, DO, PhD; James C. Watson, MD; Jennifer St Sauver, PhD; Nathan P. Staff, MD, PhD; Christopher J. Klein, MD

CONCLUSIONS AND RELEVANCE Polyneuropathy increased the likelihood of long-term opioid therapy. Chronic pain itself cannot be ruled out as a source of worsened functional status among patients receiving long-term opioid therapy. However, long-term opioid therapy did not improve functional status but rather was associated with a higher risk of subsequent opioid dependency and overdose.

Monotherapy or combinations?

- Monotherapy first
- Stop inefficient drug (exceptions)
- Increase dose if moderate effect
- If increase is not tolerated:
  - Combine with drug with different mode of action
- Indications for early combination treatment (GCP)
  - Very different pain types
  - Low tolerance
  - Local and systemic combinations

NP pain treatment: What is new?

Cannabinoids and neuropathic pain

Annals of Internal Medicine

REVIEW

The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms

A Systematic Review

Shannon M. Nugent, PhD; Benjamin J. Morasco, PhD; Maya E. O'Neil, PhD; Michele Freeman, MPH; Allison Low, BA; Karli Kondo, PhD; Camille Elven, MD; Bernadette Zakher, MBBS; Makalapua Motu'apuaka, BA; Robin Paynter, MLIS; and Devan Kansagara, MD, MCR

Nugent et al. Ann Intern Med 2017;167:319-31.

Cannabinoids and neuropathic pain

Table 1. Characteristics and Findings of RCTs on Cannabis Extracts for Treating Chronic Pain*

Trial: Author, Year (Reference)	Pain Type	N	Intervention Formulation; Dosage; Study Design	Duration
Abrams et al, 2007 (33)	Neuropathic sensory, HIV-associated	55	Smoked THC, 4%; 1 cigarette/d (0.9 g)	12 d
Berman et al, 2004 (30)	Neuropathic brachial plexus avulsion	48	Nabiximols (THC oromucosal spray); ≤48 sprays/d; crossover	2 wk (no washout)
Ellis et al, 2009 (31)	Neuropathic sensory, HIV-associated	34	Smoked THC, started at 4% and adjusted as necessary; 4 smoking sessions/d; crossover	5 d (2-wk washout)
Lynch et al, 2014 (24)	Neuropathic chemotherapy-induced	18	Nabiximols; ≤12 sprays/d	4 wk (2-wk washout)
Notcutt et al, 2004 (43)	Mostly neuropathic; 47% MS	34	Sublingual spray delivering 2.5-mg THC, 2.5-mg CBD, or 2.5 mg each; 1 to 8 sprays/d	8 wk
Nurmikko et al, 2007 (35)	Neuropathic pain with allodynia	125	Nabiximols; ≤48 sprays/d	5 wk
Selvarajah et al, 2010 (26)	Neuropathic diabetic peripheral	30	Nabiximols; maximum unclear	12 wk
Serpell et al, 2014 (27)	Neuropathic peripheral with allodynia	246	Nabiximols; ≤24 sprays/d	15 wk
Wallace et al, 2015 (36)	Neuropathic diabetic peripheral	16	Vaporized THC, 7%, 4%, or 1%; 4 h observation at each dose; crossover	4 h (2-wk washout)
Ware et al, 2010 (39)	Neuropathic, postsurgical or posttraumatic	23	Smoked THC, 2.5%, 6%, or 9.4%; crossover	5 d (9-d washout)
Wilsey et al, 2008 (28)	Neuropathic	38	Smoked THC, 3.5% or 7%; 9 puffs; crossover	6 h (3- to 21-d washout)
Wilsey et al, 2013 (40)	Neuropathic, peripheral	39	Vaporized THC, 1.29% or 3.53%; 4 puffs at 1 h after baseline, 4 to 8 puffs at 3 h; crossover	6 h (3- to 7-d washout)
Wilsey et al, 2016 (47)	Neuropathic, spinal cord injury	42	Vaporized THC, 2.9% or 6.7%; 400 mg using Foltin Puff Procedure at 8 to 12 puffs over 240 min, adaptable dose design	8 h

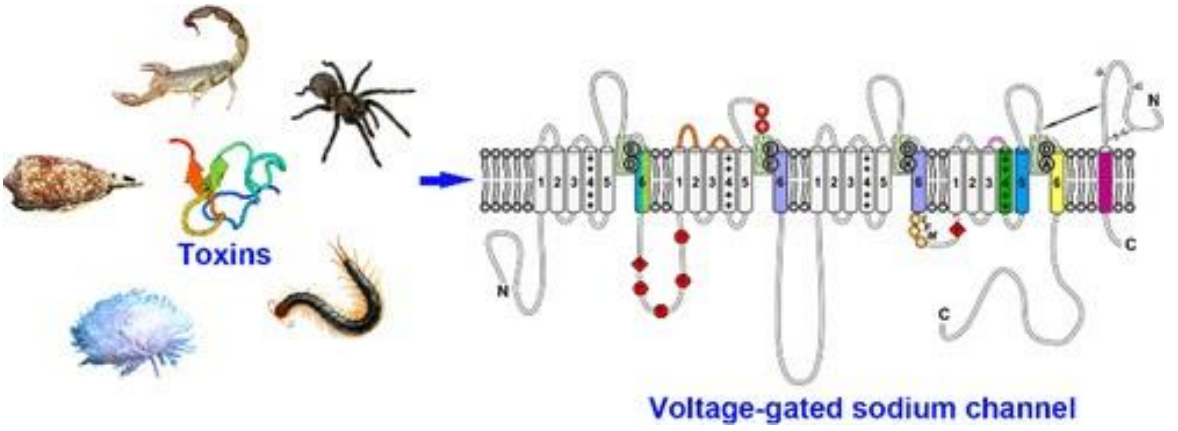
Nugent et al. Ann Intern Med 2017;167:319-31.

Cannabinoids and neuropathic pain

- Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain.
- Among general populations, limited evidence suggests that cannabis is associated with an increased risk for adverse mental health effects.

Nugent et al. Ann Intern Med 2017;167:319-31.

Nociceptor-selective Na-channel blockers



Wu et al. ACS Chem Neurosci 2018;9:187-97

ORIGINAL ARTICLE

OPEN

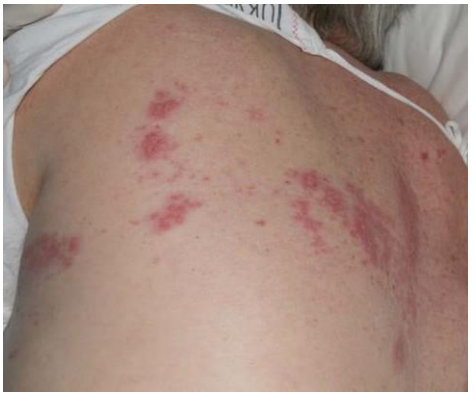
Safety and Efficacy of a Topical Sodium Channel Inhibitor (TV-45070) in Patients With Postherpetic Neuralgia (PHN)

A Randomized, Controlled, Proof-of-Concept, Crossover Study, With a Subgroup Analysis of the Nav1.7 R1150W Genotype

Nicola Price, BSc(hons), Rostam Namdari, PhD,* Judith Neville, PhD,* Katie J.W. Proctor, MSc,* Samer Kaber, MD,† Jeffery Vest, PhD,† Michael Fetell, MD,‡ Richard Malamut, MD,‡ Robin P. Sherrington, PhD,* Simon N. Pimstone, MB, ChB, PhD,*§ and Yigal P. Goldberg, MB, ChB, PhD**

Uniklinikum Würzburg

Topical Nav1.7 blockade



- Application of an ointment with TV-45070
- 7,5 µl/cm^2, up to 400 cm^2
- (60, 120, 180 or 240 mg 2x/day

Uniklinikum Würzburg

Nav 1.7 blocker TV-45070

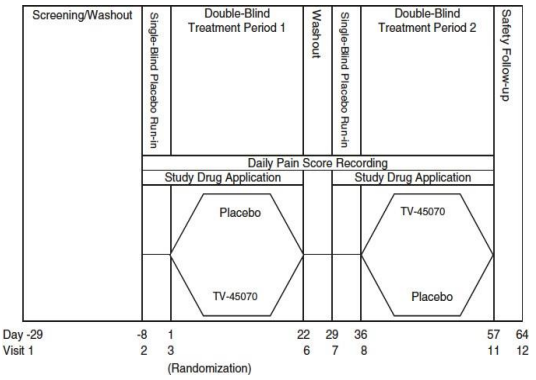


TABLE 5. Proportion of Patients Achieving at Least 30% or 50% Pain Improvements—Efficacy Evaluable Population

Timepoint Criteria	(n [%]) Placebo (N = 57)	TV-45070 (N = 57)	P
Week 1	N' = 54	N' = 54	
Mean improvement from baseline ≥ 30%	8 (14.8)	13 (24.1)	0.2266
Mean improvement from baseline ≥ 50%	5 (9.3)	6 (11.1)	1.0000
Week 2	N' = 55	N' = 55	
Mean improvement from baseline ≥ 30%	11 (20.0)	18 (32.7)	0.0923
Mean improvement from baseline ≥ 50%	5 (9.1)	11 (20.0)	0.0703
Week 3	N' = 52	N' = 52	
Mean improvement from baseline ≥ 30%	12 (23.1)	21 (40.4)	0.0636
Mean improvement from baseline ≥ 50%	6 (11.5)	15 (28.8)	0.0039
Week 3 with LOCF	N' = 56	N' = 56	
Mean improvement from baseline ≥ 30%	13 (23.2)	22 (39.3)	0.0784
Mean improvement from baseline ≥ 50%	6 (10.7)	15 (26.8)	0.0039
Overall	N' = 56	N' = 56	
Mean improvement from baseline ≥ 30%	9 (16.1)	19 (33.9)	0.0213
Mean improvement from baseline ≥ 50%	5 (8.9)	9 (16.1)	0.2188

Overall improvement ≥ 30%

P<0.002

Price et al. Clin J Pain 2017;33:310-8.

Nav 1.7 blocker

TABLE 6. R1150W Mutation Status and Response to TV-45070

Treatment Response	No. Patients (n [%]) R1150W Heterozygotes (N = 8)	Wild Type (N = 37)
TV-45070		
≥ 30% reduction in pain	5 (62.5)	13 (35.1)
≥ 50% reduction in pain	3 (37.5)	9 (24.3)
Placebo		
≥ 30% reduction in pain	1 (12.5)	8 (21.6)
≥ 50% reduction in pain	1 (12.5)	3 (8.1)

- More patients with >30% pain reduction if they have a R1150W polymorphism than with wild type
- Less placebo response with R1150W polymorphism

Price et al. Clin J Pain 2017;33:310-8.

Nav 1.7 blocker in trigeminal neuralgia

Safety and efficacy of a Nav1.7 selective sodium channel blocker in patients with trigeminal neuralgia: a double-blind, placebo-controlled, randomised withdrawal phase 2a trial

- 67 patients
- BIIB074 3x 150 mg for 28 days
- Open label run-in
- Outcome: Time to treatment failure

Zakrzewska et al. Lancet Neurol 2017;16:291-300

Nav 1.7 blocker in trigeminal neuralgia

Time to treatment failure

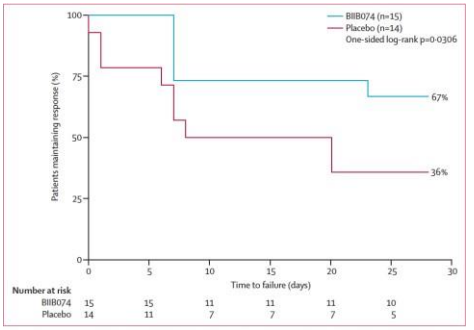
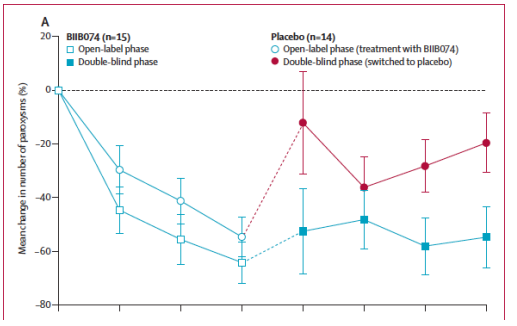


Figure 2: Kaplan-Meier analysis of time to treatment failure in the double-blind phase in the modified intention-to-treat population

Mean change in number of pain attacks



Zakrzewska et al. Lancet Neurol 2017;16:291-300

Nav 1.7 blocker (BIIB074) follow-up trial

Biogen

A Phase 2 Placebo-Controlled, Double-Blind, Randomized Withdrawal Study to Evaluate the Efficacy and Safety of BIIB074 in Subjects With Idiopathic Small Fibre Neuropathy or Diabetes Mellitus with Confirmed Small Fibre Neuropathy

Study is recruiting

Other Nav blockers (Nav 1.8)

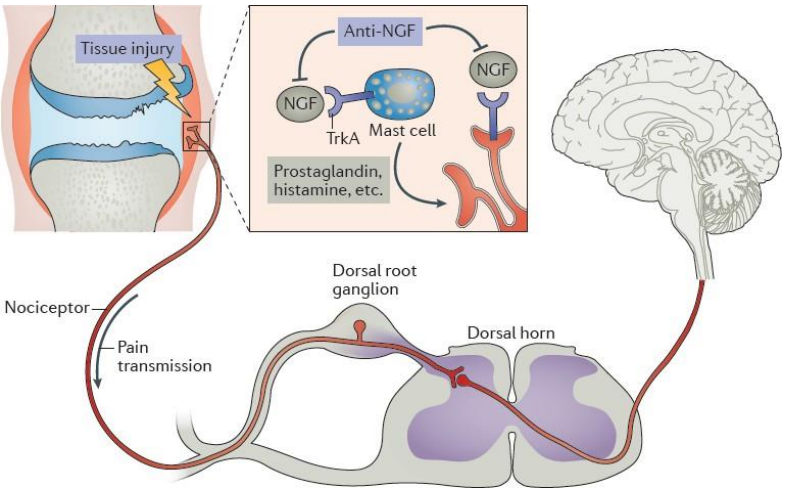
Vertex-Pharmaceuticals

A Phase 2, Randomized, Double-blind, Placebo-controlled, 6-Week, Parallel-design Study of the Efficacy and Safety of VX-150 in Treating Subjects With Pain Caused by Small Fiber Neuropathy

Study is completed

- The study met its primary endpoint and showed that treatment with VX-150 demonstrated statistically significant and clinically meaningful pain reduction

Nerve growth factor (NGF)



Lane et al., Nat Rev Rheumatol 2017;13:76-8

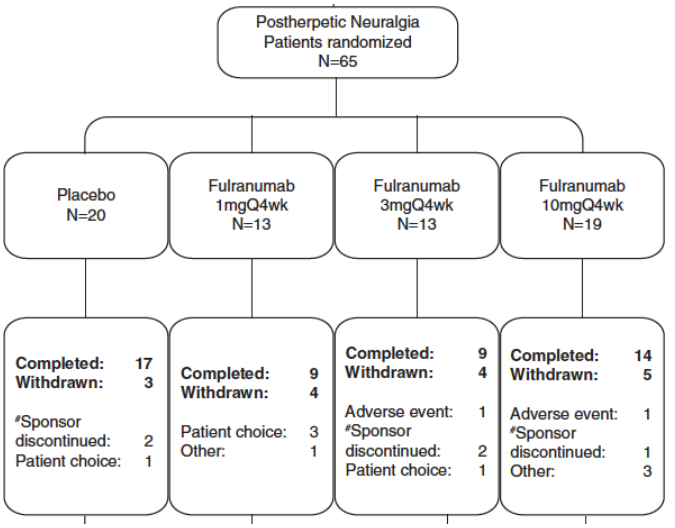
NGF inhibitors

Fulranumab in Patients With Pain Associated With Postherpetic Neuralgia and Postraumatic Neuropathy

Efficacy, Safety, and Tolerability Results From a Randomized, Double-blind, Placebo-controlled, Phase-2 Study

Hao Wang, PhD, Gary Romano, MD, PhD,† Margaret Fedgchin, PharmD,† Lucille Russell, MD,† Panna Sanga, MD,† Kathleen M. Kelly, MD,† Mary Ellen Frustaci, MAS,† and John Thipphawong, MD†*

Fulranumab



- Low patient number
- Negative
- Trials continue

Wang et al. Clin J Pain 2017;33:99-108.

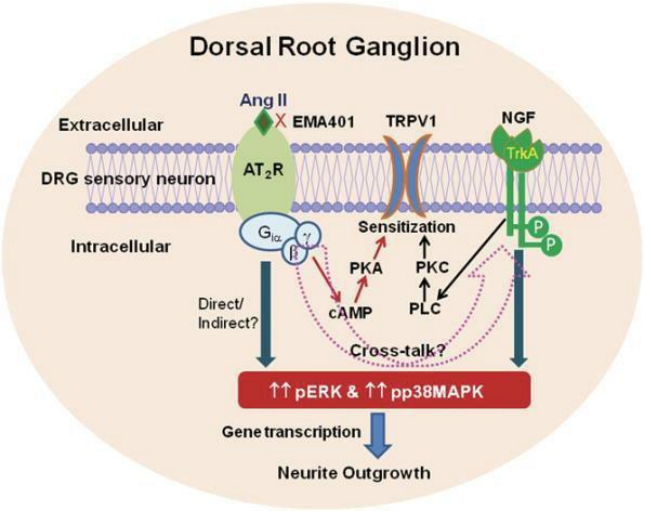
EMA401 in PHN

EMA401, an orally administered highly selective angiotensin II type 2 receptor antagonist, as a novel treatment for postherpetic neuralgia: a randomised, double-blind, placebo-controlled phase 2 clinical trial

*Andrew S C Rice, Robert H Dworkin, Tom D McCarthy, Praveen Anand, Chas Bountra, Philip I McCloud, Julie Hill, Gary Cutter, Geoff Kitson, Nuket Desem, Milton Raff, for the EMA401-003 study group**

Rice et al. Lancet 2014;383:1637-47.

How should an ATII-R2 antagonist work like ?



- Only in the periphery
- Blocks input of TRPV1-and TrkA-receptors
- Potentially pro-regenerative

Smith et al, Pain. 2016 Feb;157 Suppl 1:S33-41

EMA401 in PHN

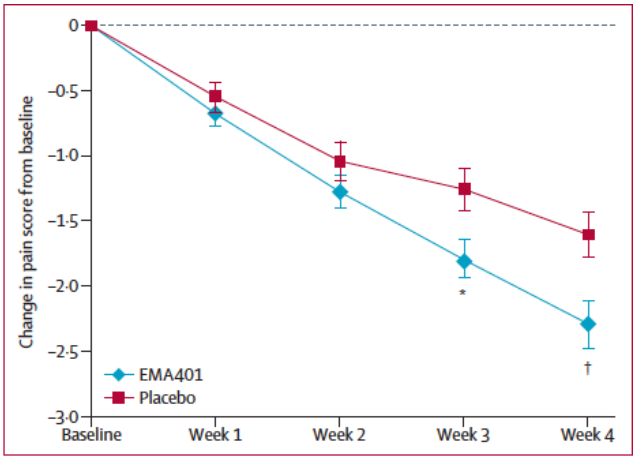
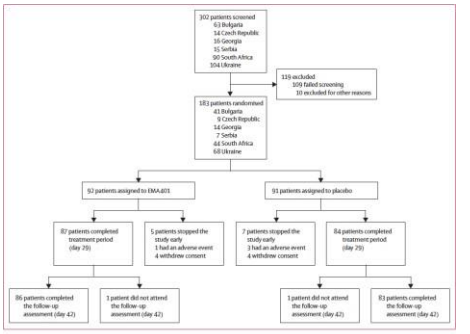


Figure 2: Timecourse of mean change in pain intensity from baseline by week of treatment



Rice et al. Lancet 2014;383:1637-47.

EMA401

Novartis

A double-blind, placebo-controlled, randomized dose ranging trial to determine the safety and efficacy of three dose levels of EMA401 in patients with post-herpetic neuralgia

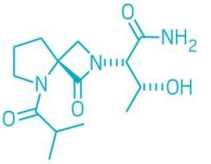
EMPADINE
Studie für Erwachsene mit schmerzhafter diabetischer Neuropathie

Discontinued due to side effect in a monkey

NDMA inhibitors

- **NYX-2925** is a novel, oral, small-molecule NMDA receptor modulator in development for the treatment of chronic pain.
- NYX-2925 is currently being evaluated in multiple Phase 2 studies in patients with fibromyalgia and painful diabetic peripheral neuropathy

Apyntix company website



NYX-2925

NDMA inhibitors

- April 2019, Phase 2 study in patients with painful DPN, demonstrating robust analgesic activity in patients with advanced (more chronic) DPN.
- June 2019, positive data from a Phase 2 study of NYX-2925 in patients with fibromyalgia, demonstrating significant effects on both biomarkers and patient-reported outcomes.
- In the second half of 2019, we expect to initiate a larger 12-week Phase 2 study in patients with fibromyalgia which will evaluate patient-reported outcomes as the primary endpoint.

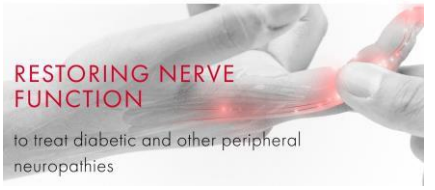
Apyntix company website

Disease modifying drugs

- Aren‘t there any drugs that do not only alleviate the pain, but make the neuropathy better?

Ricolinostat (ACY-1215)

- Ricolinostat (ACY-1215) is an oral, selective inhibitor of the microtubule modifying enzyme HDAC6 with first-in-class potential, currently positioned to enter Phase 2 clinical trials.
- Disease-modifying therapy that reverses nerve damage and reduces pain, numbness, and muscle weakness resulting from diabetes, chemotherapy, and Charcot–Marie–Tooth disease.
- Studied in myeloma and other cancers



Website Regenacy Pharmaceuticals

Ricolinostat (ACY-1215)

Study Description

Brief Summary:

This is a randomized, double-blind, parallel group clinical study of

Condition or disease
Diabetic Neuropathic Pain

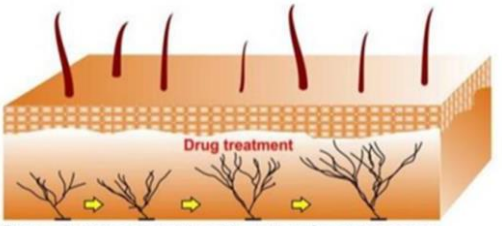
Go to

ate the safety and efficacy of ricolinostat for Diabetic Neuropathic Pain (DNP).

Intervention/treatment	Phase
Drug: ricolinostat	Phase 2
Drug: Placebo	

Clinicaltrials.gov

WST-057, a disease modifying drug?



Progressive neuronal growth and branching of axonal processes

WST-057	Location	2017	2018	2019
Preclinical Dev't Topical NCE	U.S.			
Phase 1	Australia			
Phase 2a	Canada, Europe, China, US			

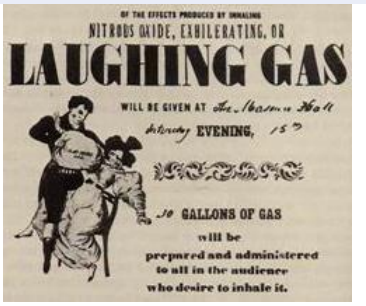
https://winsantor.com/

AP-325

- Small molecule developed for neuropathic pain and acute spinal cord injury.
- Belongs to the malononitrilamides (MNAs), originally developed as low molecular weight immunosuppressants.
- Targets receptors in the superficial dorsal horn of the spinal cord and in DRG.
- Reversibly inhibits dihydro-orotate dehydrogenase (DHODH), a key cellular enzyme involved in de novo pyrimidine synthesis.....central role of pyrimidine nucleotides in immune cell function and inflammation.

Compound	*Indication*	*Discovery*	*Preclinical development*	*Clinical Phase* I	II	III
AP-325	Neuropathic pain					
	Spinal cord injury					

Something different



In Operating Room:

- N_2O 50/70%: weak anesthetic
- adjuvant of general anesthesia

Outside Operating Romm

- N_2O/O_2 50%/50% (EMONO): analgesic, sedative, anxiolytic
- Short-term analgesia in painful procedures or condition of mild to moderate pain in adults and children >1 month
- Sedation during dental surgery
- Analgesia in obstetrics

Why should N_2O work in chronic pain?

N_2O is an NMDA-Antagonist

N_2O reduces phosphorylation of NR2B and neuroinflammation

Arq Neuropsiquiatr 2015;73(7):578-581

Chronic pain relief after the exposure of nitrous oxide during dental treatment: longitudinal retrospective study

Alívio da dor crônica após exposição ao óxido nitroso durante tratamento odontológico: estudo retrospectivo longitudinal

Francisco Moreira Mattos Júnior[1], Rafael Villanova Mattos[1], Manoel Jacobsen Teixeira[1], Silvia Regina Dowgan Tesseroli de Siqueira[2], Jose Tadeu Tesseroli de Siqueira[3]

N_2O work in neuropathic pain

Study Description Go to

Brief Summary:

To assess the effect of 3 consecutive days of one-hour administration of Nitrous Oxide/Oxygen 50%/50% (EMONO) versus placebo as Oxygen/Nitrogen 22%/78% (synthetic medical air), in add-on therapy to chronic analgesic treatments, on average pain intensity in patients with chronic peripheral neuropathic pain. A total of 250 randomised patients to be included in all the participating centres, i.e., 125 randomised patients in each of the 2 study groups treatments

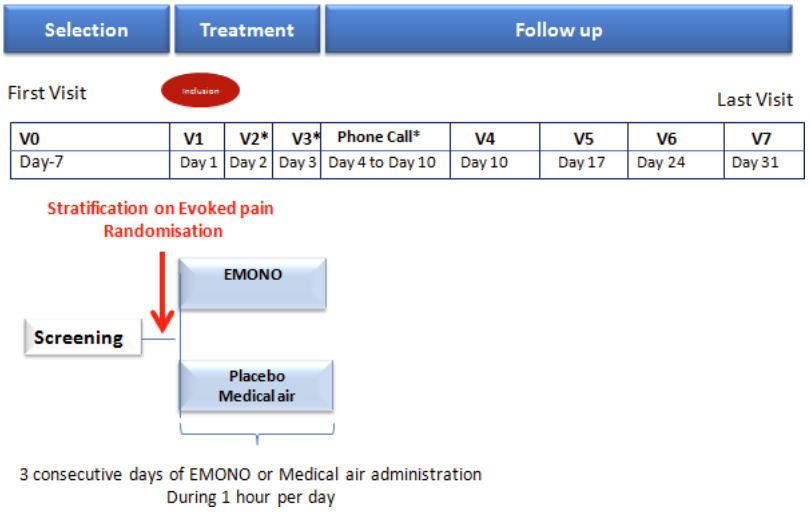
Condition or disease	Intervention/treatment	Phase
Neuralgia	Drug: Medical Air Drug: EMONO	Phase 2

ClinicalTrials.gov Identifier: NCT02957851

Recruitment Status : Completed
First Posted : November 8, 2016
Last Update Posted : September 21, 2018

Air Liquide

N_2O work in neuropathic pain



Air Liquide
Study completed

Summary Painful neuropathies

- State of the art treatment:
  - We have options, but not for everybody
  - Molecular phenotyping?
- Novel treatments
  - Botulinum toxin in localized neuropathic pain
  - Na_v 1.7- and Na_v 1.8 blockers
  - Anti-NGF: still open
  - N_2/O_2
  - NMDA-inhibitors
  - Ricolinostat