Experimental treatments for Peripheral Neuropathy 2019

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Peripheral vs. Central Nervous System

we include neuromuscular junction and muscles

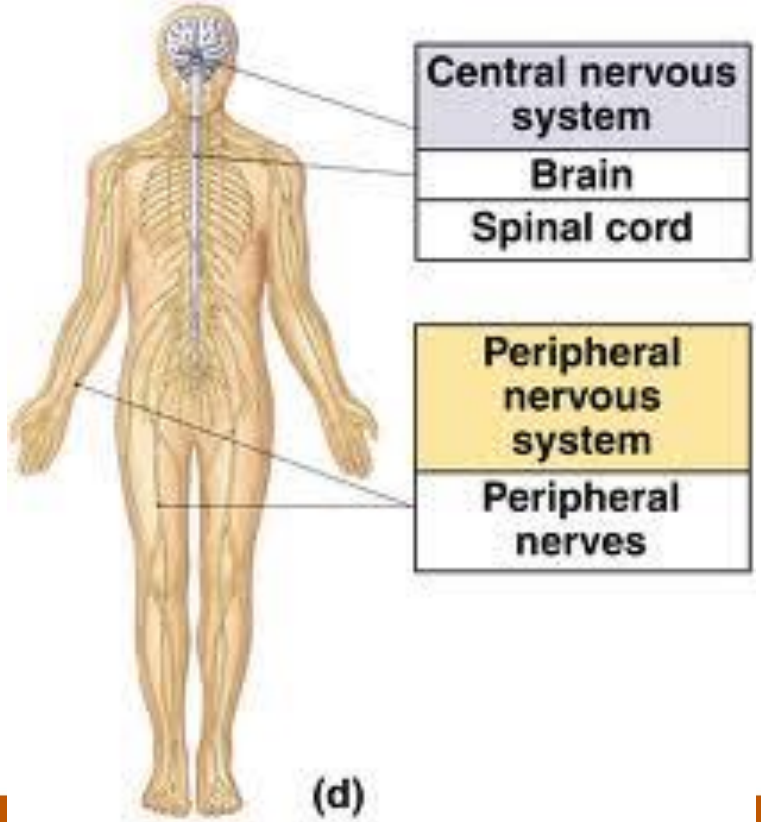

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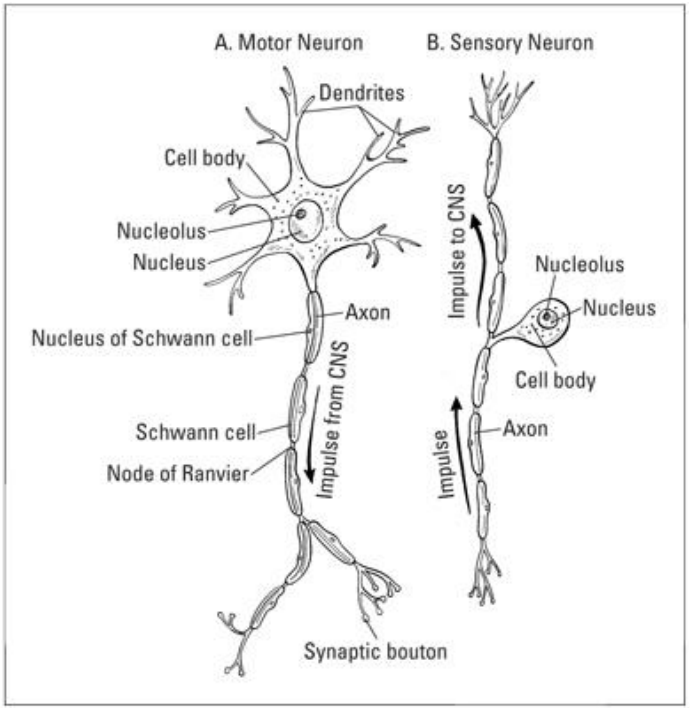
Diagram of motor and sensory nerves



Sensory and Motor Nerves

- Motor Nerves
  - From spinal cord to muscle thru neuromuscular junction

- Sensory Nerves
  - Large fiber sensation
    - Vibration
    - Proprioception
    - Pressure
  - Small fiber sensation
    - Temperature
    - Pain

Potential Causes of Neuropathy

- Diabetes
- Hereditary (CMT)
- Toxic
- Drug effect
- Vasculitis
- Sjogren's disease
- Rheumatoid arthritis
- CIDP
- Leprosy
- Multiple Myeloma
- Traumatic
- Compression
- Lupus
- Vitamin deficiency
- Paraneoplastic
- …….. ……. ……

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Two Focuses for Treatment of neuropathy

- Treatment for the underlying cause of the neuropathy itself

- Treatment for the symptoms (usually pain or weakness)

Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations (PAIN-CONTRoLS)

STUDY DESIGN/METHODS

- Prospective randomized comparative effectiveness adaptive design study

- 30+ sites will be participating in this study (15 proposed in grant)
- Patients with Likert type pain score of at least 4 will be enrolled
- Patient will be randomized to one of the 4 drug options
- They will then be written a prescription for the drug at the study dose
  - Nortriptyline 75 mg (25 mg for 1 week, then 50 mg HS for 1 week, then 75 mg HS)
  - Duloxetine 60 mg (20 mg for 1 week, then 40 mg for 1 week, then 60 mg daily)
  - Pregabalin 300 mg (100 mg for 1 week then 100 BID for 1 week, then 100mg tid)
  - Mexiletine 600 mg (200 mg HS for 1 week, then 200 mg BID for 1 week, then 200 mg TID)

pcori ANNUAL MEETING | OCT. 31–NOV. 2, 2018 WASHINGTON, DC

Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations (PAIN-CONTRoLS)

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Background

Cryptogenic sensory polyneuropathy (CSPN) is a common, progressive neuropathy associated with significant pain. Research that encourages engaging patients in determining clinical trial outcomes relevant to their lived experience holds the potential of more meaningful comparative effectiveness research. CSPN patients can inform the study question, data collection strategies and measurement tool selection.

Objectives

- Determine which of four commonly prescribed medications is most effective and best tolerated
- Maintain continuous patient engagement to ensure their preferred outcomes inform the design and analysis of findings

Methods

- Prospective randomized open label comparative effectiveness trial using a Bayesian adaptive design (including response adaptive randomization)
- Decisions were made to continue or stop the trial at prespecified interim analyses using data from baseline, weeks 4, 8 and 12
- Primary outcome was utility function (composite of efficacy and quits)
- Patients agreed with the investigator-selected choice of the PROMIS pain interference measure and suggested two additional PROMIS measures – fatigue and sleep interference
- Secondary endpoints: SF-12, PROMIS pain interference,

Results

Forty-eight U.S. sites recruited 402 patients with CSPN who were randomized to nortriptyline (n=134), duloxetine (n=126), pregabalin (n=73), and mexiletine (n=69).

TABLE 1: Primary outcome (Utility Function) by drug	Nortriptyline n=134	Duloxetine n=126	Pregabalin n=73	Mexiletine n=69
Utility	0.81	0.80	0.69	0.58
[95% Bayesian Credible Interval (BCI)]	[0.69, 0.93]	[0.68, 0.92]	[0.55, 0.84]	[0.42, 0.75]
Probability Treatment is Best	0.52	0.43	0.05	0.00
Week 12 Outcome, [95% BCI]				
Efficacious and Non-Quit	0.25 [0.18, 0.33]	0.23 [0.16, 0.31]	0.15 [0.08, 0.24]	0.20 [0.12, 0.31]
Non-Efficacious & Non- Quit	0.36 [0.29, 0.45]	0.40 [0.31, 0.48]	0.42 [0.31, 0.54]	0.22 [0.13, 0.32]
Quit	0.38 [0.30, 0.46]	0.37 [0.29, 0.46]	0.42 [0.31, 0.54]	0.58 [0.45, 0.69]

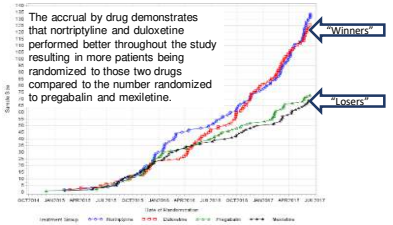
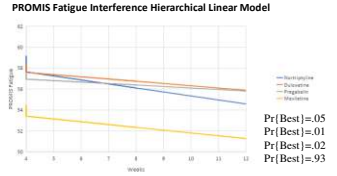


TABLE 2: Adverse Events (* = patient selected)	Nortriptyline	Duloxetine	Pregabalin	Mexiletine	Total
Number of patients	134	126	73	69	402
With no adverse events	59 (44.0)	67 (53.2)	44 (60.3)	42 (60.9)	212 (52.7)
With one or more adverse events	75 (56.0)	59 (46.8)	29 (39.7)	27 (39.1)	190 (47.3)
With one or more serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most Common Adverse Events					
Dry Mouth	27	3	1	3	34
Drowsiness/Sleepiness*	16	7	8	3	34
Nausea	3	11	1	6	21
Insomnia*	5	12	1	2	20
Fatigue*	7	8	3	1	19
Bloating/Constipation	10	3	1	2	16
Dizziness	7	4	1	3	15



Discussion

This is the first comparative effectiveness study using four drugs with different mechanism of action for patients with CSPN. Both nortriptyline and duloxetine performed best when combined efficacy and quit rates are considered. Duloxetine had the best combined efficacy and quit rates (removing drop outs), but still did not meet our predefined definition of a "winner." Finally, mexiletine was the least tolerated (due to gastrointestinal side effects) and had a high number of dropouts, but if the drug could be taken for 12 weeks, it had the best profile for reducing pain and fatigue outcomes.

In this real world study, many variables determine whether or not a drug is a winner or loser in helping reduce neuropathic pain. These factors go beyond whether or not the drug reduces pain but also the drug's side effects, if the patients insurance company will pay for the drug, the out-of-pocket cost of the drug and other factors. Side effects in particular predict duration of using a medication. Capturing side effects was informed by patients' preferences and quantified using PROMIS measures they selected.

Clinical Trials.gov (clinicaltrials.gov)

- 263 trials that are recruiting or plan to recruit soon in the US

- 48 trials that are advertising in Texas

Chemotherapy Induced Peripheral Neuropathy (CIPN)

- Chemotherapy induced peripheral neuropathy (CIPN) is a common side effect of many forms of chemotherapy having a negative impact on the quality of life for cancer survivors due to numbness, decreased sensation, pain (of various intensities in the extremities), gait/balance problems, and difficulty with fine motor skills of the hands and fingers. **To date, there are no preventive modalities to mitigate CIPN development**.When CIPN becomes intolerable, optimal doses of chemotherapy have to be reduced or discontinued, which may affect a patient's overall survival.
- **Intraneural facilitation (INF) is a technique developed by physical therapists at Loma Linda University after careful study of the structure, pathophysiology and biomechanics of peripheral nerves.** The focus of INF is restoration of circulation to an ischemic nerve. INF has been offered to subjects receiving treatment at LLUCC with anecdotal success. The purpose of this study is to evaluate INF as a treatment modality under the rigor of scientific inquiry to determine its effectiveness as a viable treatment option for breast cancer patients with CIPN.

Chemotherapy Induced Peripheral Neuropathy

- Dextromethorphan
- Candesartan for patients with non-Hodgkins' lymphoma
- N-acetyl cysteine supplements
- **Effectiveness Assessment of Riluzole in the Prevention of Oxaliplatin-induced Peripheral Neuropathy. (RILUZOX-01)**
- Yoga for Painful Chemotherapy-Induced **Peripheral Neuropathy**: A Pilot, Randomized-Controlled Study
- Whole Exome Sequencing in Finding Causative Variants in Germline DNA Samples From Patients With **Peripheral Neuropathy** Receiving Paclitaxel for Breast Cancer

Cannabinoids (CBD oil) for Taxane Induced Peripheral Neuropathy

- The investigators' goal is to study the efficacy of cannabinoids as a potential treatment for TIPN. Volunteers with a diagnosis of breast cancer and chemotherapy-induced peripheral neuropathy, secondary to treatment with paclitaxel or docetaxel, will be enrolled. This study involves the administration of cannabinoids in different strength capsules.

Botulinum Toxin A for the Treatment of Chemotherapy Induced Peripheral Neuropathy

- Botox for treatment of chronic pain

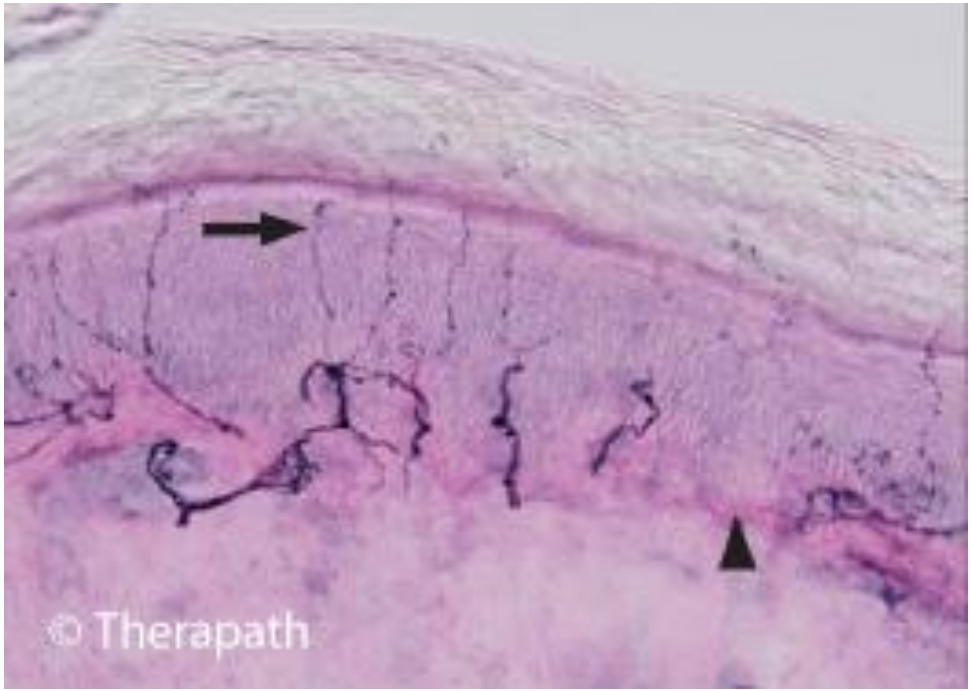
Investigation of Plastic Changes in the CNS Associated With Peripheral Neuropathy

- Recent neuroimaging literature on neuropathy suggests that chronic pain is characterized by learning-related and memory-related plastic changes of the central nervous system (CNS) with concomitant maladaptive changes in body perception

Exercise (is really being looked at)

- **Small studies show that exercise significantly reduces pain and neuropathic symptoms and it increases intraepidermal nerve fiber branching**

Intraepidermal nerve fiber density



Metabolic Syndrome

- Abdominal obesity*
- Hypertension*
- Insulin resistance
- High triglycerides

- Long term inactivity is ‘proinflammatory’
- IPN is more common in metabolic syndrome

Benefits of Exercise

- Increases cutaneous reinnervation capacity (intraepidermal nerve fiber density is increased)
- Improved BMI
- Improved glucose tolerance
- Decreased blood triglycerides

ADAPT trial
Activity for Diabetic Polyneuropathy

- **Type 2 diabetes (T2D) affects over 8% of Americans, and half will develop peripheral neuropathy**, a progressive injury to the very longest nerves of the body. Our previous research has found that neuropathy can be detected early in its course and followed by examining nerves that reach to the skin using a small punch biopsy. These cutaneous nerves can be injured by high blood glucose, obesity and high triglycerides, but have the potential to regrow in response to treatments that improve these metabolic conditions. **The proposed study will randomize participants with mild to moderate diabetic peripheral neuropathy to receive either generic annual counseling or an integrated program of moderate supervised exercise and actigraphy based anti sedentariness counseling.**

Walk your dogs!

And if you don’t have a dog, walk anyway!

A Causative Role for Amylin in Diabetic Peripheral Neuropathy

1. Individuals with Type-2 diabetes commonly develop peripheral neuropathy.
2. Increased production of the hormone amylin occurs in individuals who have Type-2 diabetes.
3. Aggregations of amylin was found in the peripheral vasculature of rats that overexpressed human amylin.

- Skin biopsy from volar forearm and RBC samples are processed for Amylin deposition
- Amylin measures may be a surrogate for microvascular disease and may serve as metrics of disease severity.

Treatment of Pain in Cryptogenic Sensory Painful Neuropathy (CSPN)

- **The TopCSPN trial** is a double blinded randomized placebo controlled study of oral topiramate as a potential disease modifying therapy for cryptogenic sensory peripheral neuropathy (CSPN)
- **Acupuncture treatment**
- **Essential oils**

CMT 1A Hereditary Neuropathy

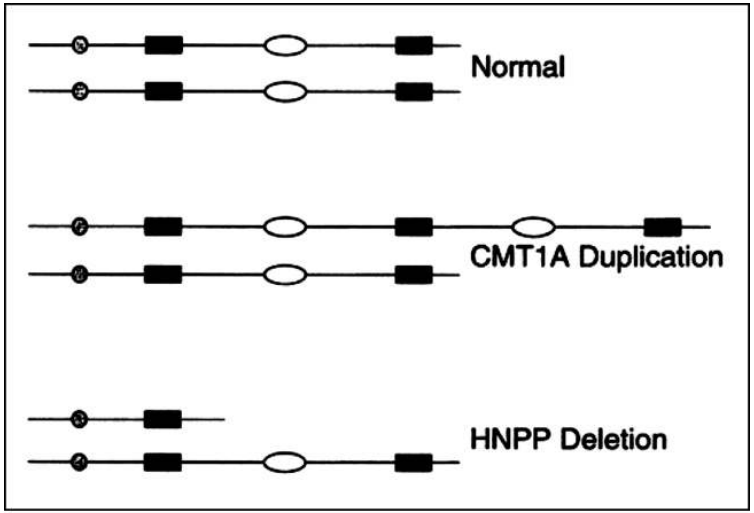


Figure-3: Structure of CMT1A duplication and HNPP deletion. Chromosome 17 homologues are depicted with filled circle representing the centromere, filled rectangles corresponding to the flanking CMT1A-REP repeat, and the open oval depicting the PMP22 gene. The chromosome 17p short arm is not drawn to scale and the 1.5 Mb tandem duplication and 1.5 Mb deletion are not visible by conventional clinical cytogenetics techniques.

PXT3003 for CMT1A to improve disability

- PXT3003 is a rational design, fixed combination of low-dose (RS) **baclofen**, **naltrexone hydrochloride and D-sorbitol**. The use of PXT3003 in a multicenter, randomised, placebo controlled phase II study (CLN-PXT3003-01) was well-tolerated and safe in patients with CMT1A for the three dose-levels investigated (Attarian et al., 2014). The intermediate and high dose of PXT3003 demonstrated an improvement of disability in this patient population.
- PXT3003, is a fixed dose combination of (RS)-baclofen, naltrexone hydrochloride and D-sorbitol selected via a Systems Biology approach and developed by Pharnext, **with the aim to lower toxic PMP22 gene over-expression in CMT1A.** On September 18th 2017, the PXT3003 dose 2 was prematurely discontinued, due to an unexpected investigational medicinal product quality event (failed month 18 stability testing). The independent data safety monitoring committee did not identify any safety concern on September 5th 2017. All patients randomised to dose 2 were requested to undergo the end of study visit, and were offered to enter the extension study (CLN-PXT3003-03)

Phase I/IIa Trial of scAAV1.tMCK.NTF3 for Treatment of CMT1A
Ohio State

- This clinical trial is an **open-label, one-time injection** ascending dose study in which scAAV1.tMCK.NTF3 will be administered by intramuscular injections into muscles in both legs in CMT1A subjects with PMP22 gene duplication. Cohort 1 will include three subjects ages 18 to 35 years receiving (2e12 vg/kg), and Cohort 2 will include six subjects ages 15 to 35 years old receiving (6e12 vg/kg)

- Not enrolling yet

CMT treatment: Nationwide Children's Hospital and Ohio State University

- Schwann cells — found in the peripheral nervous system — normally form the myelin (fatty layer) sheath around peripheral nerves, which provides electrical insulation and improves signal conductance in these nerves.
- **In CMT1A, the gene that provides the instructions for making peripheral myelin protein-22 (PMP-22) is duplicated, leading to the overproduction of abnormal myelin by Schwann cells and disease-related symptoms** such as weakness, muscle atrophy, and loss of sensation.
- NT-3 belongs to the nerve growth factor family, meaning it contributes to the growth and survival of neuronal cells in both the central and peripheral nervous systems.

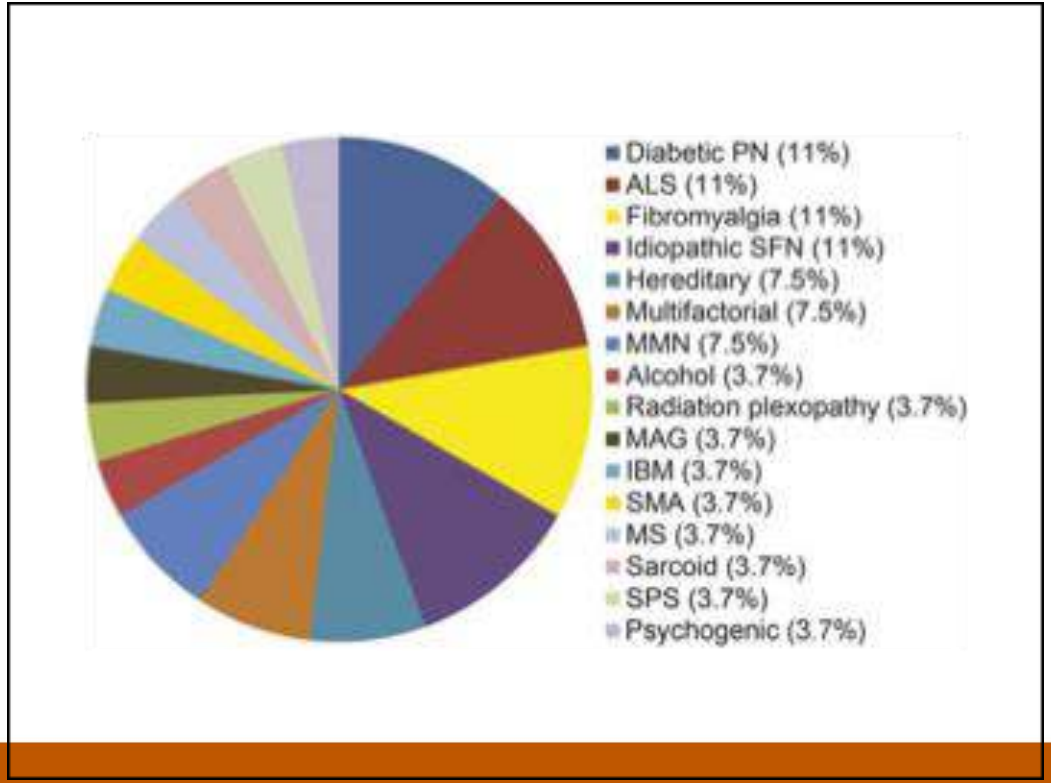
CMT genetic treatment (con't)

- Researchers previously found that an NT-3 gene construct — a lab-made piece of DNA to be introduced in a target organism — promoted nerve regeneration and sensory improvement in a mouse model of CMT1A.
- They also **dosed eight CMT1A patients with either a placebo or 150 micrograms/kg of NT-3 three times a week for six months**.
- **The four patients who received NT-3 tolerated the treatment well and had significant nerve regeneration compared with the placebo** group, which translated to better hand coordination and dexterity. However, due to the small sample size, further research is underway to ascertain potential benefits.

CIDP trials

- A Study to Assess the Efficacy, Safety and Tolerability of Rozanolixizumab in Subjects With Chronic Inflammatory Demyelinating Polyradiculoneuropathy (MyCIDPchoice)
- Continuation of Hizentra trial (20% SQ IVIG for subcutaneous infusion
- Stem cell transplant trial in progress

Dx’ed as CIDP, but not CIDP



Peripheral neuropathy trials in Texas

- Ongoing or recruiting
- 48 studies found
  - Massage therapy in cancer neuropathy
  - Neuromodulation for chemotherapy neuropathy
  - Topiramate for cryptogenic sensory neuropathy in metabolic syndrome
  - Preventative treatment of oxaliplatin induced PN in metastatic colon cancer
  - Omnitram safety and efficacy in treatment of diabetic neuropathy

The End

- Questions?

- Peripheral Neuropathy Registry
- Topiramate for Cryptogenic Sensory Peripheral Neuropathy in Metabolic Syndrome (CSPN) (TopCSPN)
- Activity for Diabetic Polyneuropathy (ADAPT)
- International GBS Outcome Study
- A Clinical Study of ANX005 and IVIG in Subjects With Guillain Barré Syndrome (GBS)
- A Study to Assess the Efficacy, Safety and Tolerability of Rozanolixizumab in Subjects With Chronic Inflammatory Demyelinating Polyradiculoneuropathy (MyCIDPchoice)
- Long-Term Tolerability and Safety of HYQVIA/HyQvia in CIDP
- Comparison of 10 kHz SCS Combined With CMM to CMM Alone in the Treatment of Neuropathic Limb Pain (SENZA-PDN)

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hATTR (amyloidosis) neuropathy treatment

- Vutrisiran vs. Patisiran

Assessing Long Term Safety and Tolerability of PXT3003 in Patients With Charcot-Marie-Tooth Disease Type 1A (KUMC)

Expanded Access Protocol of Patisiran for Patients With Hereditary ATTR Amyloidosis (hATTR