From Competitive Technologies Inc:

Non-invasive relief from chemotherapy-induced peripheral neuropathy (CIPN)

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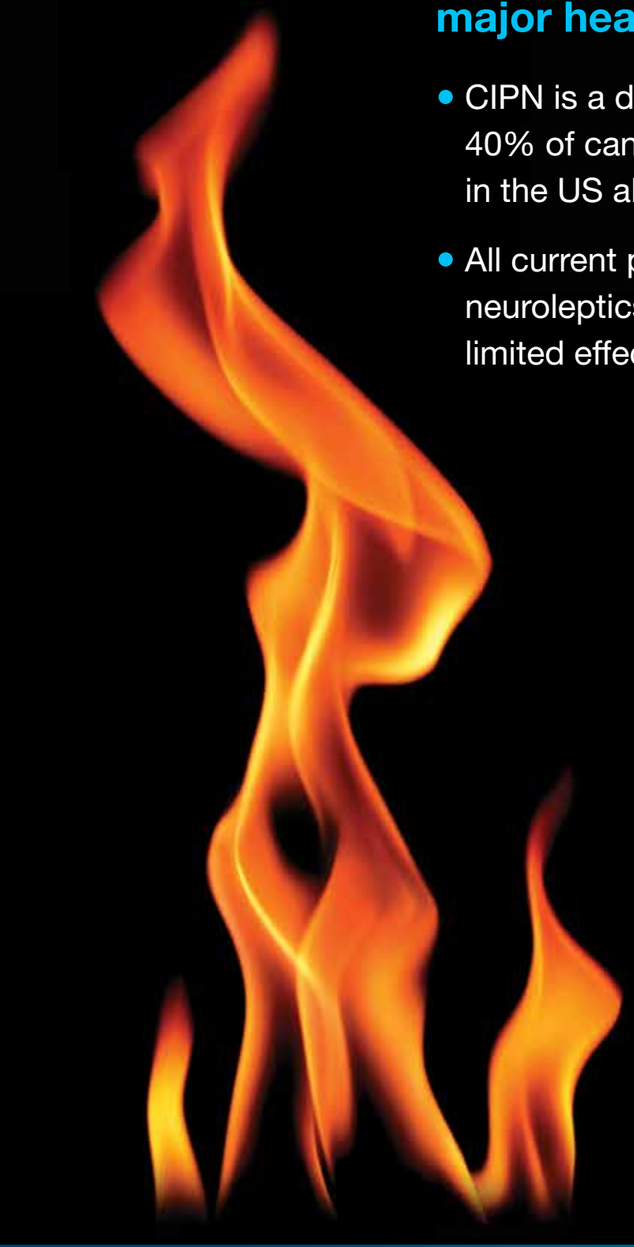
CALMARE: A bold advance in pain therapy

CIPN is a major health issue worldwide

- CIPN is a debilitating side effect for 30% to 40% of cancer patients—an estimated 4 million in the US alone.[1]
- All current pharmacotherapies (eg, opioids, neuroleptics) have side effects and show limited effectiveness.[2]



1. Smith, p. 884.
2. Smith, p. 884; Coyne, p. 360.

The CALMARE® Pain Device delivers neurocutaneous electrostimulation

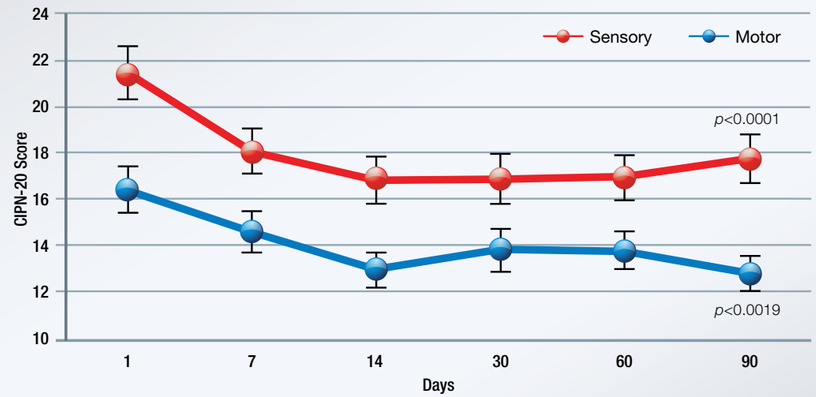
- A non-invasive, non-addictive alternative to drug therapy
- In clinical trials, shown to dramatically reduce pain in refractory CIPN—with no toxicity
- FDA 510(k)-cleared in 2009

In a trial of 39 patients

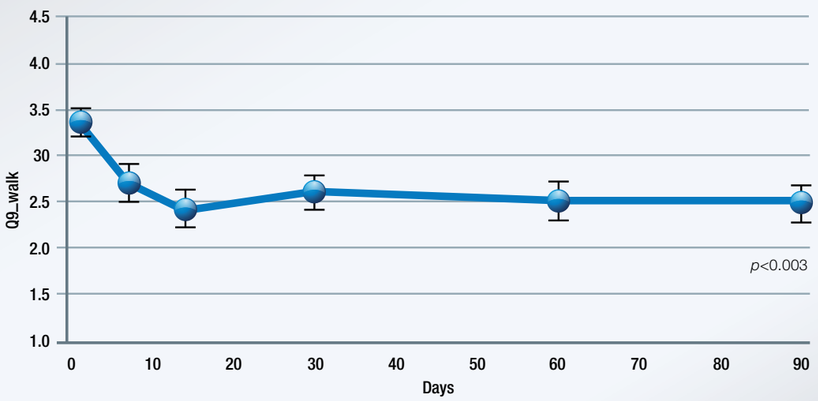
CALMARE therapy significantly reduced CIPN pain[3]

- **Purpose:** to evaluate chronic and acute pain relief, and to evaluate the effect of that relief on quality of life
- In a single-arm US trial, patients received 10 consecutive 45-min treatments daily over a 2-week period.
- N=39 (m 16, f 23), mean age 56.5
- Treatments occurred over an 18-mo period, avg 9.3 days each.
- Cause of pain: CIPN (n=33), post-mastectomy (n=3), postherpetic neuralgia (n=2), radiation-related (n=1)
- Clinically and statistically significant improvements were seen in average, least, and worst pain measures.
- "Pain-now" scores were reduced from 6.6 (before treatment) to 4.5 (after 14 days), 4.6 (after 1 mo), 4.8 (after 2 mo), 4.6 (after 3 mo), $p<0.001$.
- No adverse effects were observed.
- Across-the-board improvements were noted in all components of the Brief Pain Inventory (BPI) "interference with normal life" scale (eg, mood, sleep, ability to walk).
- **Conclusion:** CALMARE therapy appeared to relieve cancer-associated chronic neuropathic pain and provided sustained improvements in many indicators of quality of life.

Effect of CALMARE therapy on CIPN-20 motor and sensory scores



A typical result from Brief Pain Inventory (BPI): "How much did pain interfere with your ability to walk?"



3. Coyne, pp. 359-360, 363.

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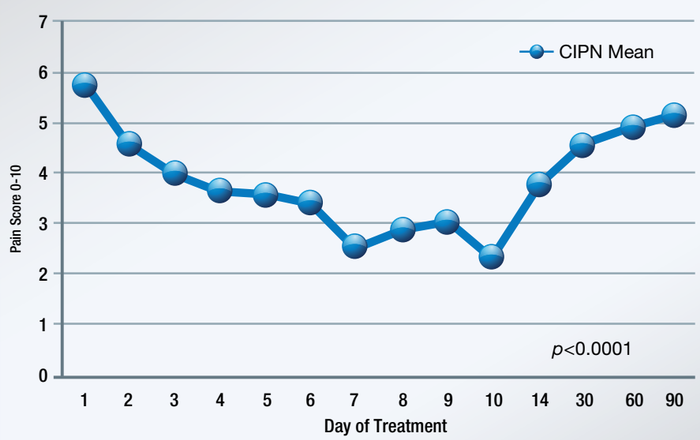
Results were similar in earlier pilot study (Massey Cancer Center, Virginia Commonwealth University)[4]

- **Objective:** To evaluate the impact of CALMARE electrostimulation therapy on pain associated with CIPN in 18 patients (m 4, f 14) of which 16 were evaluable
- Patients (mean age 58.6) received 1 hour of CALMARE therapy daily for 10 days.
- **Results:**
  - —20% reduction in numeric pain scores (15 of 16 patients)
  - —Pain-now scores fell 59% from 5.81+1.11 before treatment to 2.38+1.82.
  - —Complete disappearance of pain in 4 patients
  - —Some responses were durable without maintenance.
  - —No toxicity was seen.
- **Conclusion:** CALMARE therapy appeared to dramatically reduce pain in a small cohort of refractory CIPN patients without toxicity.

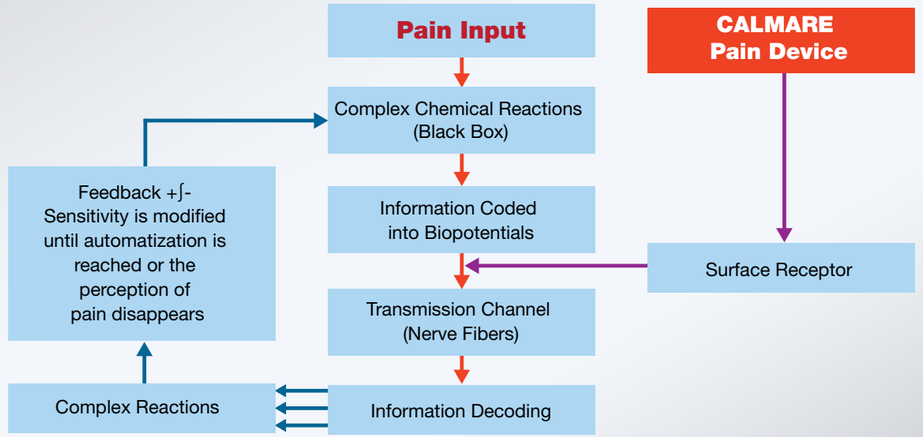
Duration of effect of CALMARE therapy on pain scores: pain relief over time.



4. Smith, pp. 883, 888-889.

CALMARE—A well-established rationale for nerve-based pain therapy

Mechanisms of pain and CALMARE therapy



- The CALMARE device was designed for cutaneous electrostimulation based on proprietary hardware and software designed to reduce pain.
- CALMARE therapy seeks to relieve pain by providing “no-pain” information via cutaneous nerves to block the effect of pain information. The “no-pain” signal becomes the dominant signal received by the brain.
- Unlike conventional electro-analgesia, the theory behind CALMARE is not to inhibit pain transmission (through A-beta fiber excitation), but to substitute pain information with synthetic “no-pain” information.
- The CALMARE device can synthesize 16 types of nerve action potentials (similar to endogenous action), string them into sequences, and directly stimulate peripheral nerves.
- Because CALMARE waveforms are wider than conventional systems, they are able to stimulate C-fibers (instead of only A-beta fibers).
- The complex mechanism by which nerve stimulation reduces pain is not completely understood, but includes raising the pain threshold at the spinal cord, and reducing amplified or recruited impulses from damaged nerve.
- Unlike transcutaneous electrical nerve stimulation (TENS), CALMARE therapy uses various stimulation types to mimic natural nerve impulses.

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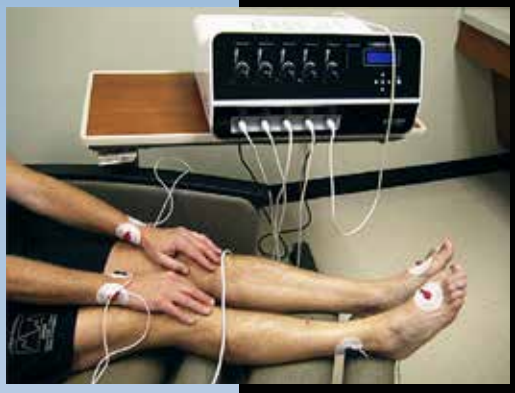
The patient experience with CALMARE therapy



- The patient visits the practice for 10 to 12 consecutive daily treatments.
- Each daily session may last from 30 to 60 minutes.
- While the electrodes bracket the pain area, they are never placed directly on it.
- Intensity of stimulation current is very low, with peaks below 5.5 mA.
- Patient sensation (pressure, itching, or other "bee-sting" sensation directly beneath the electrodes) is followed by instantaneous analgesia.
- After initial treatments, pain will re-emerge at lesser intensity, and duration of relief will be prolonged.
- Booster treatments are administered if and when needed.
- CALMARE therapy is contraindicated within 4 weeks after celiac plexus block or other neurolytic pain control treatment.
- **Other contraindications:** Contraindicated in cancer patients on pain pump: severe arrhythmia or cardiac ischemia within 6 months; wounds or skin irritation at electrode attachment site; history of epilepsy, brain damage, or symptomatic brain metastases; vena cava, aneurysm clips, coronary or other vascular stents; implanted device (eg, stimulator); pacemaker or implantable defibrillator; latex allergy; pregnant or nursing

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References: 1. Coyne PJ, Wan W, Dodson P, Swainey C, Smith TJ. A trial of Scrambler therapy in the treatment of cancer pain syndromes and chronic chemotherapy-induced peripheral neuropathy. *J Pain Palliative Care Pharmacother.* 2013: 27:359-364. **2.** Smith TJ, Coyne PJ, Parker GL, Dodson P, Ramakrishnan V. Pilot trial of a patient-specific cutaneous electrostimulation device (MC5-A Calmare®) for chemotherapy-induced peripheral neuropathy. *J Pain Symptom Manage*. 2010:40;883-891.

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