Spooky Action at a Distance: Neuromodulation, Physiologic Distress Keck School of Signals, and Limb Preservation Medicine of USC Ahmed Sami Raihane, BS¹, Gabriela Morales Deusch², Charles Liu MD,PhD³, Bijan Najafi, David G. Armstrong⁵

Background:

Rising Prevalence

- 537 million people globally have diabetes; projected to reach 643 million by 2030
- 38.4 million Americans affected; 97.6 million are prediabetic.
- Higher burden in underserved populations (e.g., American Indian, Black, Alaskan Native adults).

Health & Economic Impact:

- \$237 billion in direct diabetes costs (2017); ~33% related to lower extremity complications
- Diabetes linked to kidney disease, heart failure, stroke, infections, and chronic limb-threatening ischemia (CLTI).

Diabetic Foot Ulcers (DFUs) & CLTI:

- DFUs affect ~25% of diabetics; ~20% lead to amputation
- CLTI carries high risk of limb loss, often within 2 weeks if untreated
- Standard wound healing rates remain low (10– 33% at 12 weeks).

Innovation:

- Current therapies often inadequate for advanced wounds and ischemia.
- Emerging technologies aim to stimulate physiologic repair **remotely**:
 - Neuromodulation (e.g., 10-kHz spinal cord stimulation)
 - Peripheral focused ultrasound (pFUS) Splenic stimulation
 - Remote ischemic conditioning (RIC)
- Tibial transverse transport (TTT) & lateral tibial periosteum distraction (LTPD)

• These therapies share a **central** goal: → Driving systemic physiologic effects from a distant site to promote local healing

Acknowledgments: Founded in 1889, the University of New Mexico Pueblo, Navajo, and Apache since time immemorial, have deep connections to the land and have made significant contributions to the broader community relationship statewide. We honor the land throughout the generations and also acknowledge our committed to Indigenous peoples. We gratefully recognize our history. **Contact Information of Presenting Author:** araihane@salud.unm.edu

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Neuromodulation Techniques:

- painful diabetic neuropathy patients.

Remote Ischemic Conditioning (RIC):

• Protocols involving cycles of limb occlusion and reperfusion using blood pressure cuffs were examined. oxide production, leading to accelerated wound healing in diabetic foot ulcers.

Surgical Innovations:

- timelines, and improvements in limb function.
- Laser capture microdissection and protein analysis in animal models were reviewed to understand the activated during TTT.



Methods:

Studies on spinal cord stimulation (SCS) using 10-kHz devices for diabetic peripheral neuropathy (DPN) were reviewed, focusing on randomized controlled trials (RCTs) that evaluated pain relief, neurological function, and peripheral blood flow improvements. Data were extracted from trials involving refractory

• Peripheral focused ultrasound (pFUS) therapies were analyzed, emphasizing their mechanisms in activating anti-inflammatory pathways and enhancing angiogenesis, particularly through spleen-targeted interventions.

Specific attention was given to studies measuring upregulation of anti-inflammatory cytokines and nitric

• Case studies and clinical trials on tibial transverse transport (TTT) and lateral tibial periosteum distraction (LTPD) were assessed. Parameters included perioperative imaging for vascular changes, wound healing

molecular pathways, such as Orai1/STIM1-mediated nitric oxide release and osteopontin-driven angiogenesis,



Results and Conclusions:

SCHOOL OF MEDICINE

DEPARTMENT OF SURGERY

Neuromodulation Therapies:

- 10-kHz SCS showed a 79% success rate in achieving over 50% pain relief within three months of treatment. Patients also reported improvements in sensation and reduced reliance on pharmacological pain management.
- Peripheral focused ultrasound (pFUS) demonstrated accelerated healing in preclinical and clinical trials. Wound size reductions in diabetic ulcer models were 75% faster than control groups, with significant decreases in pro-inflammatory cytokines like TNF- α and IL-6.

Remote Ischemic Conditioning:

• Healing rates for diabetic foot ulcers improved by 41% compared to standard care in randomized trials. Significant increases in nitric oxide levels and antiinflammatory cytokines were observed, correlating with enhanced microvascular blood flow.

Surgical Interventions:

- TTT resulted in a 100% wound healing rate within three months in both arterial and non-arterial stenosis groups, with higher blood flow rates and visible angiogenesis in treated limbs.
- LTPD offered pain relief and improved limb functionality in cases refractory to traditional vascular treatments, with anklebrachial indices improving from 0.5 to 0.9 in clinical case studies.

Focused Ultrasound:

• Preclinical studies using splenic stimulation for burn wound care indicated wound closure 13 days faster than controls. Human trials suggested reduced inflammation and improved pain scores in participants receiving focused ultrasound interventions.