Spinal cord injury (SCI) disrupts the communication pathway between the brain and the nerves that control muscles to produce movement, typically leaving the planning, coordination and effector centers above and below the injury functional. One promising avenue of research is focused on creating new pathways for signal transmission between the brain and the rest of the body.

Researchers at Mayo Clinic's campus in Rochester, Minnesota, are exploring the use of electronic devices that can wirelessly transmit signals from the brain to the intact spinal cord circuitry below the injury. In this novel approach, injured nerves are bypassed with electronics. Although this field of research is in its early stages, the prospects are intriguing.

Worldwide, several different stimulation modalities for activating muscle have been tested in both animal models and humans, including transcutaneous stimulation, percutaneous stimulation, intramuscular stimulation and peripheral nerve stimulation; however, none of these techniques has experienced widespread clinical translation.

Mayo researchers are currently exploring the therapeutic use of electrical stimulation within the spinal cord, termed intraspinal microstimulation (ISMS), as a means to provide neuromuscular activation to restore function in paralyzed limbs. ISMS involves the implantation of stimulating electrodes within the ventral gray matter of the spinal cord to activate motor circuitry.

"Over the past 15 years, multiple studies have demonstrated that ISMS can successfully and safely evoke coordinated limb movement and weight bearing in rodent and feline models, while overcoming some of the limitations, such as the rapid onset of muscle fatigue during stimulation, that accompany conventional stimulation techniques," explains Mayo Clinic neurosurgeon Kendall H. Lee, M.D., Ph.D.

Dr. Lee is the director of the Mayo research team and co-author of a recent publication in the Journal of Neurosurgery. That article outlines a study establishing proof of principle for wireless control of ISMS to evoke controlled motor function in a rodent model of complete spinal cord injury. Results from that study indicated that wireless ISMS was capable of evoking controlled and sustained activation of ankle, knee and hip muscles in 90 percent of spinalized rats.

But Dr. Lee and colleagues are careful to point out that a great deal more research must occur before ISMS technology can be used outside of a controlled laboratory environment to improve quality of life for people with SCI. Small animal models are not optimal for determining the clinical efficacy and safety of spinal stimulation techniques for functional restoration of movement.

To address these and other issues, Mayo Clinic researchers recently created a protocol, published in PLOS One, using a large animal (porcine) model to allow standardized development, testing and optimization of novel clinical strategies for restoring motor function following SCI. Development of this larger animal model for testing ISMS technology will also help reduce variations in surgical
procedure, targeting and electrode implantation techniques that could affect therapeutic outcomes and make it difficult to compare results derived from multiple studies.

“We tested this protocol using both epidural and intraspinal stimulation in a porcine model of spinal cord injury, but the protocol is suitable for the development of other novel therapeutic strategies,” says J. Luis Lujan, Ph.D., an assistant professor of biomedical engineering and neurosurgery and a member of Dr. Lee’s team.

This protocol is helping to characterize spinal circuits vital for selective activation of motor neuron pools, which Mayo researchers hope will expedite the development and validation of high-precision therapeutic targeting strategies and stimulation technologies for optimal restoration of motor function in humans.

Continued refinement of the electronic devices used is another necessary advance required before ISMS or similar technologies can be used in the clinical setting. In a review article published in Frontiers in Neuroscience, Mayo researchers note that the next generation of neuroprosthetic systems must be fully implantable, multichannel stimulators capable of real-time processing and integration of both command signals from the brain and sensor-based feedback from the environment.

“Although clinical restoration of functional movement via ISMS remains a distant goal, we are hopeful that these recent advances will ultimately improve quality of life for people with SCI,” says Peter J. Grahn, a Ph.D. candidate within Dr. Lee’s laboratory.

For more information


Treating Cancer-Related Pain: Exploring the Efficacy of Physical Medicine Modalities

Effective treatment of cancer-related pain is essential if patients are to maintain their mobility and independence. In many cases, cancer-related pain is caused by one or more of the following: direct tumor invasion, maladaptive changes due to cancer treatment or local tumor effects, exacerbation of pre-existing musculoskeletal pain, and hypertonicity and spasm related to any of the above.

Finding effective treatments that are not associated with unwanted side effects can be challenging. It’s been well-established that opiates and other medications commonly prescribed to alleviate cancer pain may cause a decrease in blood pressure, confusion, constipation and other significant side effects, especially in older patients.

Mayo Clinic physiatrist Andrea L. Cheville, M.D., asserts that basic rehabilitation medicine pain management techniques should be integrated into the care plan for cancer patients who experience pain. Dr. Cheville is a professor of physical medicine and rehabilitation, and she serves as the Department of Physical Medicine and Rehabilitation’s research chair and chief of the Cancer Rehabilitation and Lymphedema Program at Mayo Clinic’s campus in Minnesota.

“Rehabilitation medicine and physical modalities-based strategies offer a range of pain management options that may serve as beneficial adjuncts to the conventional systemic and interventional analgesic strategies used to control cancer-related pain,” says Dr. Cheville.

Dr. Cheville acknowledges the fact that many traditional rehabilitation medicine strategies have not been thoroughly evaluated in the scientific literature as cancer pain management tools. In an article published in the Journal of Clinical Oncology, Dr. Cheville and colleagues outline four basic categories of physical medicine modalities available to manage pain (Table) and review the scientific literature.

With pharmacotherapy positioned as the dominant tool for treating cancer-related pain, Dr. Cheville notes that many of the simpler and side-effect-neutral treatments that are overlooked may be particularly beneficial to patients with movement-associated pain. These include the use of heat and cold, desensitization, and the use of
Examining the Role of Tricyclic Antidepressants in Osteoporotic Fractures

Osteoporotic fractures can cause severe disability and death, especially in older adults. Although multiple researchers have sought to establish an association between treatment with tricyclic antidepressants (TCAs) and increased fracture risk, much of the research performed to date has yielded conflicting results, making it difficult to draw conclusions about the role of TCAs in osteoporotic fractures.

To address this issue, a team of Mayo Clinic researchers conducted a comprehensive meta-analysis, published in the Journal of Bone and Mineral Research, that examines the association between TCA treatment and risk of fracture. Wenchun Qu, M.D., M.S., Ph.D., from the Department of Physical Medicine and Rehabilitation at Mayo Clinic’s campus in Minnesota, and a research biostatistician at Mayo Clinic’s campus in Arizona, quantitatively assessed all available qualified studies that have examined the effect of TCAs on fracture risk to gather more accurate and precise information about this effect.

“We hypothesized that TCA treatment would be associated with an increased risk of fractures,” says Dr. Qu. “We also examined whether the effect varied by sex, study design, anatomical site of fracture, dose, exposure duration, geographic location, or adjustment for bone mineral density (BMD) or depression.”

Findings

From a list of more than 1,500 studies involving human participants, use of TCA as exposure, and BMD or fracture as outcome, Dr. Qu’s team identified 12 eligible studies — five cohort studies and seven case-control studies. No related randomized controlled trials were found. From this meta-analysis, Mayo researchers found that the relative risk of fracture was increased by 45 percent in TCA users compared with non-TCA users.

This moderate, but clinically relevant increase in fracture risk was consistent in multiple sensitivity analyses and in subgroup analyses. After Dr. Qu and colleagues adjusted for possible publication bias, the increased risk associated with TCA treatment (RR, 1.36; 95 percent CI, 1.24-1.50; p < 0.001) remained moderate and clinically important, although slightly weaker.

“These findings strongly suggest that TCA use is associated with an increased risk of fractures,” says Dr. Qu. “But the underlying mechanism for the association between TCA use and fractures remains unclear.”

Dr. Qu says that it’s important to remember that both bone loss and a higher propensity to fall contribute to increased fracture risk. The fact that antidepressant use has been linked with increased falls risk among the elderly may also explain their association between TCA use and fractures.

Table. Rehabilitation and Physical Modalities Used to Manage Pain

- 1. Modalities that modulate nociception, including topical heat, short wave diathermy, cold, transcutaneous nerve stimulation and interferential current therapy
- 2. Modalities that stabilize or unload painful structures, including compensatory strategies and adaptive devices and orthotics
- 3. Modalities that influence local physiological processes that indirectly influence nociception, including laser and light therapy and manual lymphatic drainage
- 4. Modalities that reduce pain arising from muscles and connective tissues, including corticosteroid injections, trigger-point injections and dry needling, massage, therapeutic exercise, and manipulation

gait aids and assistive devices to reduce the load on painful joints and limbs.

“Although they have not been explicitly tested in cancer patients, many of these modalities are patient controlled, are free of adverse effects and have been validated for use with other diagnoses,” explains Dr. Cheville. “Common sense and extensive experience help argue persuasively for their clinical effectiveness in cancer patients.”
TCAs can cause decreased blood pressure, increased heart rate (especially during the initial phase of treatment), increased body sway and decreased postural balance. All of these reported and potentially adverse effects can increase the potential for fractures caused by falls.

Mayo researchers had several other findings that also strongly suggest that TCAs may increase the propensity for falling rather than causing bone loss:

• Adjusting for bone mineral density (BMD) did not decrease the estimates, which suggests that TCA use may increase fracture risk independent of BMD reduction.
• While increased fracture risk was associated with current TCA use, it was not associated with past use. This suggests that the effect of TCAs is to increase falls instead of affecting skeletal strength.
• The incidence of hip fractures, which are typically linked to falls, was greater than the incidence of other types of fractures.
• The increased fracture risk was much higher among patients who underwent a shorter duration of TCA treatment (< six weeks) than among patients who underwent extended treatment (≥ six weeks).
• Even low-dose TCAs (less than 0.5 defined daily dose) were associated with an increased fracture risk.

Study limitations

Dr. Qu acknowledges several study limitations, including the absence of a multivariate meta-regression analysis to further investigate the sources of heterogeneity presented, due to the small number of studies included; the inability to assess risks of falling, because few individual studies accounted for falls; and the limited use of claims data, which may lack information on nutrients, physical functioning, cognition or other potential confounders.

Conclusions

The increased fracture risk associated with TCAs is moderate and independent of depression and BMD. Because this increased risk may have a substantial clinical impact, physicians prescribing even low-dose TCAs should monitor fall risk in patients, especially during the initial treatment period, and consider offering fall prevention education, especially for older patients.

For more information