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Accelerating the translation of research findings to clinical practice: insights from phantom limb pain clinical trials

K. Pacheco-Barrios[1], PS. de Melo[1], K. Vasquez-Avila[1], A. Cardenas-Rojas[1], P Gonzalez-Mego[1], A. Marduy[1], J. Parente[1], I. Rebello-Sanchez[1], P. Cortez[1], M. Whalen[1], L. Castelo-Branco[1], F. Fregni[1]

[1]Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States.

**Corresponding authors: Felipe Fregni, Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Boston, USA. Email: fregni.felipe@mgh.harvard.edu*

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Phantom limb pain (PLP) is defined as a painful sensation in an amputated limb or pain that follows partial or complete deafferentation. It belongs to a group of neuropathic pain syndromes, and its treatment is challenging and often refractory to many modalities, causing significant burden and suffering. The prevalence of PLP after amputation ranges between 60-80% (Limakatso et al., 2020). In some cases, the pain might decrease with time and even fade away, but studies have shown that even after two years, a majority of the patients still present pain, and only a small percentage have reported a decrease in intensity of pain (Erlenwein et al., 2021). To date, there is no guidelines for the treatment of PLP and most therapies have low levels of evidence. Possible treatments include the use of pharmacotherapy including opioids, antidepressants, neuroleptics, muscle relaxants and anticonvulsants (Flor, 2002), a variety of surgical procedures (Nikolajsen & Christensen, 2015), nerve blocks, local anesthesia, transcutaneous electrical nerve stimulation (TENS)(Kern et al., 2012), acupuncture, psychological interventions, physiotherapy, and mind-body techniques such as hypnosis(Bamford, 2006; Moura et al., 2012).

Conventional treatments used for PLP, such as pharmacologic agents, have pertinent limitations. The use of pharmacologic agents for controlling pain is associated with several side effects and can become unsustainable in the long term (Els et al., 2017). Opioids are not recommended but are widely used drugs for chronic pain being associated with constipation, fatigue, dizziness, nausea, vomiting, physical dependence, addiction, and others (Hoots et al., 2018). In addition, these drugs worsen central sensitization thus leading to longer and more intense neuropathic pain (Braulio et al., 2018; Kim et al., 2014). Beside opioids, antidepressants and antiepileptic drugs are recommended and used medications but they can lead to sedation, dizziness, nausea, and vomiting (Quintero, 2017). So far, studies that reported an effect of such interventions are inconclusive and have low quality, reporting a small effect of these drugs on pain, function, mood, sleep, quality of life, treatment satisfaction (Alviar et al., 2016).

The heterogeneous and partially effective treatment approaches for PLP can be explained by the lack of understanding of its pathophysiology. Current evidence suggests that PLP is driven by maladaptive cortical plasticity, mainly in the sensorimotor areas (Duarte et al., 2020; Gunduz et al., 2020; Pacheco-Barrios, Pinto, et al., 2020). It has been reported that this cortical reorganization is associated with higher PLP levels, thus converting it into a potential treatment target. Paradoxically, the most common treatments (opioids, antidepressants, and antiepileptic drugs) do not address PLP underlying pathophysiology directly.

Targeting maladaptive neuroplasticity

Some therapies, such as motor cortex stimulation (Pacheco-Barrios, Meng, et al., 2020) and somatosensory representation techniques of the phantom limb (Cuenca-Martínez et al., 2021; Thieme et al., 2016), are promising options since they are safer and low-cost, and can potentially revert the maladaptive plasticity associated to PLP.

Motor cortex stimulation

Considering phantom limb pain (PLP) is a hard-to-treat condition that is usually refractory to common therapies, noninvasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) targeting the primary motor cortex (M1) have recently gained traction as a possible alternative therapy for this condition (Collins et al., 2018; Pacheco-Barrios, Meng, et al., 2020). The rationale behind stimulating M1 for PLP is based on the sensory-motor cortical rearrangement and lower cortical inhibition that occurs after amputation (Nardone et al., 2019; Raffin et al., 2016). So far, clinical trials using tDCS and rTMS for PLP have shown promising results, reflecting clinically significant changes in pain scales (Pacheco-Barrios, Meng, et al., 2020). **Table 1** summarizes the current evidence for NIBS targeting M1 and their results.

Studies investigating repetitive TMS and tDCS as therapies for PLP have conveyed conflicting results regarding its effectiveness towards pain alleviation. While some rTMS studies report improvement in both active and sham groups after a 5-session protocol, but no difference between groups, others with longer protocols report clinically significant pain reduction in the active groups compared to sham (Ahmed et al., 2011; Irlbacher et al., 2006; Malavera et al., 2016). Whereas studies assessing the use of tDCS report more consistent and significant, short-term improvements in pain symptoms, which are attributable to increased excitability in M1 (Bolognini et al., 2013; Bolognini et al., 2015; Kikkert et al., 2019). This improvement suggests that individuals with PLP do have maladaptive cortical plasticity because of their pain, and therefore can

Table 1. Evidence on motor cortex stimulation for managing PLP.

Study (year)	Design	Sample size	NIBS type	Number of sessions	Main outcome and results
Irlbacher (2006) (Irlbacher et al., 2006)	cross-over	27	5 HZ and 10Hz rTMS on M1	5	- VAS A significant effect of the time of measurement ($p < 0.02$) but not of the form of therapy ($p < 0.09$) could be demonstrated. The interaction of the two main factors was also not significant ($p < 0.8$).
Bolognini (2013) (Bolognini et al., 2013)	parallel	8	tDCS on M1	1	-VAS. - The ANOVA showed a significant effect for the VAS for PLP (Friedman $v2 = 15.99$, $P < .01$), with a significant difference between pre-tDCS and post-tDCS evaluations only for the anodal tDCS of M1 (pre-tDCS = 2.6 cm vs post tDCS = 0.8 cm, $P < 0.02$).
Bolognini (2015) (Bolognini et al., 2015)	cross-over	8	tDCS on M1	5	- VAS. - With respect to PLP intensity, the rmANOVA showed a significant effect of the tDCS week ($F1,7 = 6.64$, $p = 0.04$, $p\eta 2 = 0.49$), showing a significant difference between Sham tDCS (-9%) and Active tDCS (-28%, $p = 0.04$)

Malavera (2016) (Malavera et al., 2016)	parallel	54	rTMS on M1	10	- VAS - −53.38±53.12% vs −22.93±57.16%; mean between-group difference=30.44%, 95%CI 0.30, 60.58; p=0.03
Kikkert (2019) (Kikkert et al., 2019)	cross-over	17	tDCS on M1/S1 of the missing hand	1	- Short pain questionnaire (SPQ - This resulted in a significant difference in PLP modulation between the intervention and sham conditions immediately following stimulation (Wilcoxon Z = −2.73, p = 0.006, r = −0.73)
Gunduz, Pacheco-Barrios, Pinto (2021) (Gunduz et al., 2021)	factorial	112	tDCS on M1		-VAS - analyzed the main effects separately and we found a statistically significant main effect of tDCS on PLP (beta coefficient = −0.99, P = .04) when comparing active versus sham tDCS, controlling by PLP-PLS index and PLPPLS category

benefit from brain stimulation techniques (Bolognini et al., 2013). However, the short-term effects of neuromodulation on M1 suggest that these techniques could benefit from additive therapies such as sensorimotor therapies like motor representation techniques (Gunduz et al., 2021). Currently our group is evaluating and refining the possible synergistic effects of tDCS over M1 and motor imagery for PLP alleviation.

Mirror therapy

Mirror Therapy (MT) is a type of movement representation technique that has been suggested as a therapeutical approach for treating limb pain and motor disabilities (Thieme et al., 2016). MT specifically uses the mirror's reflection of a non-affected limb to provide visual feedback of normal pain-free movement to the affected limb, therefore the subject feels performing the movement through imagination (Wang et al., 2021). It was fist applied in amputees to relieve pain in the phantom limb and several studies have been published since then (Barbin et al., 2016; Wang et al., 2021). Pooled analyses are, however, conflicting. Thieme et al. performed a meta-analysis showing an inconclusive effect of MT in reducing pain on phantom limb (Thieme et al., 2016), while a recent meta-analysis showed reasonable evidence for its analgesic effect in the same population (Thieme et al., 2016). The unsettled evidence might be related to the different sorts of control interventions used in RCTs, leading to heterogeneous findings (Thieme et al., 2012). We currently question not only the need, but the value of mirror feedback in inducing analgesic effects on PLP – beyond the effects of components of motor imagery and limb movement provided by movement representation techniques in general.

To illustrate, Brodie et al. randomized 80 subjects to either mirror therapy or a control condition (i.e., no mirror feedback), and results depicted similar analgesic effects between both groups (Brodie et al., 2007). Similarly, Rothgangel et al. found no significant differences in pain reduction between traditional MT and sensorimotor exercises on a PLP sample of 75 subjects (Rothgangel et al., 2018). In a recent factorial trial published by our group, 112 subjects were randomized to different levels of tDCS and mirror therapy (active M1 tDCS or sham tDCS and active mirror therapy or covered mirror therapy) (Gunduz et al., 2021). MT and its control differed only by the presence of mirror feedback, but both groups performed the same sensorimotor tasks. We did not find synergistic effects of tDCS combined with MT, but active tDCS had a significant main effect in comparison to sham tDCS, while mirror therapy and its control conveyed similar results (beta coefficient: 0.71, P = 0.16). We hypothesize that this phenomenon was secondary to a real effect induced by both active and covered mirror therapy whether than due to high placebo responses, since their effect sizes (0.81 – 1.22) were notably larger than

placebo responses on previous PLP trials (varying from 0.38 to 0.53)(Hsiao et al., 2012; Nikolajsen et al., 2006; Pacheco-Barrios, Meng, et al., 2020). Notably, we also performed secondary analysis on phantom limb sensations and found a statistically significant pain reduction favoring covered MT group (beta coefficient = -1.01, P = 0.03).

It might be that the visual feedback not only is negligible to induce analgesia but may jeopardize the engagement in somatosensory training. Both M1 tDCS and movement representation techniques are expected to engage similar neurophysiological circuits to treat pain, and therefore there has been an attempt to couple MT with neuromodulation techniques in clinical research. The aforementioned body of facts has led us to believe that somatosensory training without mirror visual feedback can be a better fit for M1 tDCS on PLP and a turning point to yield significant and larger effect sizes.

The process of translating research findings into clinical practice

Unfortunately, the "bench to bedside" translation of neuroplasticity-targeted therapies for PLP remains a challenge. The process in which research evidence is created, disseminated and applied in clinical practice is known as knowledge translation (Curtis et al., 2017). This process is a key part of a bigger one called knowledge-to-action cycle (Graham et al., 2006), which shows different steps, divided in three phases, for the transfer of knowledge from pre-clinical environments to the general population. In this cycle (**Figure 1**), the first phase consists of the evidence generation, generally starting from pre-clinical laboratories and then moving through the three phases of clinical trials. These steps assure the gain of knowledge on safety and efficacy. Moreover, those interventions with great profile under controlled conditions, need to be explored in real-world settings to test their effectiveness and impact on terms of cost in the health systems. At this stage of evidence generation, pragmatic trials and cost-effectiveness studies are needed.

The second phase is the synthesis of the available evidence, especially confirmatory trials (phase III), pragmatic trials, and economic studies. This can be accomplished using several tools such as systematic reviews and clinical practice guidelines, which allow easy access and updated information to clinicians (Curtis et al., 2017). Nonetheless, a rigorous analysis of

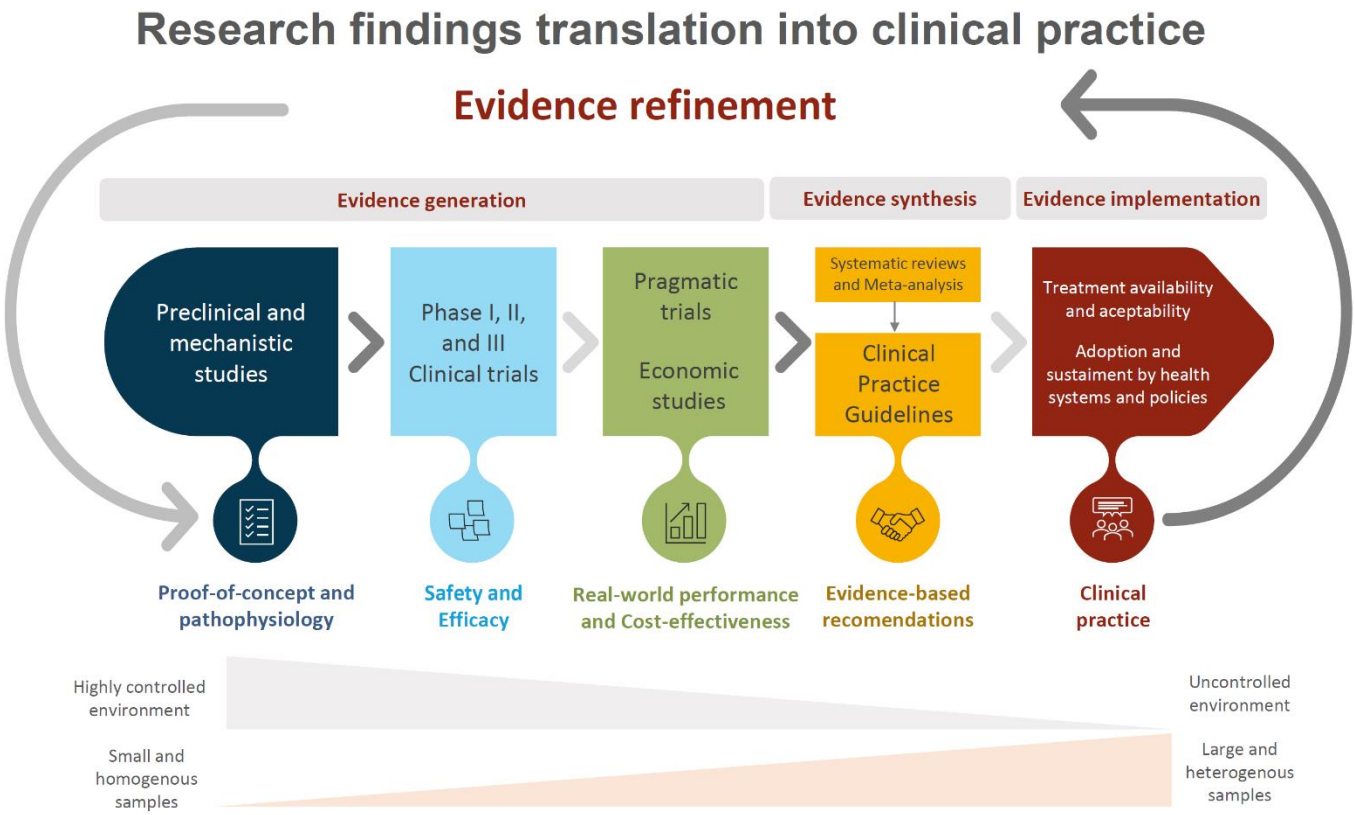

Figure 1. Clinical research translation process

the available data must be done. The third phase, known as the action cycle or implementation phase, consist of the steps needed for that evidence to be applied in the clinical field, such as adapting the knowledge to the local context, assessing the possible barriers for knowledge usage, selecting and implementing the interventions, and monitoring the knowledge use among others (Curtis et al., 2017; Graham et al., 2006). It is important to highlight the cyclic nature of the knowledge translation process, meaning results from advanced stages can inform prior steps and re-start the cycle, a process known as evidence refinement.

In order to move from the evidence generation and synthesis phases to the implementation stage several regulatory issues must be cleared by proper institutions in each country. In the US, the highest authority is the Food and Drug Administration (FDA), and they must give their approval.

According to the FDA, for an intervention to be able to be offered in the U.S it must have been reviewed by the FDA's Center for Drug Evaluation and Research (CDER). It must pass through all the research phases (preclinical and clinical) and show that its benefits outweigh "it's known and potential risks for the intended population" (Ciociola et al., 2014).

However, the fact that an intervention is approved by the FDA does not necessarily mean that it will be available for the general population. Other factors come into play: the amount of resources, the training, clinician behavior, the cost, the entity that will cover the expenses, among others (Lalu et al., 2020). Many insurances will not cover the expenses of these new treatments and therefore handicap this process (Lalu et al., 2020). That is why it is important for researchers even in the first stages of research to plan for the long term, in other words, explore interventions that may be useful, with long lasting effects and that are cost-effective (Curtis et al., 2017). In the case of PLP, one of the therapies mentioned before was the non-invasive brain stimulation, which presents itself as a safe, effective and cheap alternative for this population (Pacheco-Barrios, Meng, et al., 2020; Zaghi et al., 2009).

The next step: designing a pragmatic trial

Over 30 Randomized Clinical Trials on tDCS in chronic pain conditions have been published according to a recent evidence-based guideline reporting a level B of evidence for the use of anodal M1 tDCS stimulation for neuropathic pain (Fregni et al., 2021). These studies include strict inclusion and exclusion criteria resulting in a relatively homogeneous study population with a small sample size (from 18 to 132 participants), and the application of the treatments is restricted to a controlled laboratory setting with highly trained researchers. Therefore, most clinical trials of tDCS do not represent the complexity of patients in a general population, and may overestimate treatment efficacy and our understanding on responders to this therapy (Wexler, 2016).

The next step in expanding our knowledge on the application of neuromodulatory techniques to treat PLP and to accelerate its translation to clinical practice (**Figure 1**) is the design of pragmatic trials. These pragmatic studies, unlike the "classical" randomized clinical trials focus on demonstrating efficacy of a specific therapy in a hermetic and controlled scenario, are focused on assessing the effectiveness of one or more therapies in scenarios closer to clinical practice in the real world (Hohenschurz-Schmidt et al., 2021). One interesting example of a pragmatic clinical trial is the "stepped-wedge" design, in which all participants start as the control group and clusters of subjects are randomized to the order in which they will receive one or more interventions (Ellenberg, 2018). Pragmatic trials can offer the possibility to generalize results to a broader population and capture key outcomes relevant to patients and physicians including overall survival, functional status, and costs. They are also useful for policy makers as they look at comparative effectiveness of interventions and, eventually, cost-effectiveness analyses (Maclure, 2009).

Thus, as we proceed through the PLP knowledge translation and face new research and clinical practice demands, the framework summarized in this editorial can help guide us on how best to improve the translation of clinical research into clinical practice and reduce the substantial discovery-delivery gap.

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REFERENCES

Ahmed, M. A., Mohamed, S. A., & Sayed, D. (2011). Long-term antalgic effects of repetitive transcranial magnetic stimulation of motor cortex and serum beta-endorphin in patients with phantom pain. Neurological research, 33(9), 953-958.

Alviar, M. J. M., Hale, T., & Lim-Dungca, M. (2016). Pharmacologic interventions for treating phantom limb pain. Cochrane Database of Systematic Reviews(10).

Bamford, C. (2006). A multifaceted approach to the treatment of phantom limb pain using hypnosis. Contemporary Hypnosis, 23(3), 115-126.

Barbin, J., Seetha, V., Casillas, J.-M., Paysant, J., & Perennou, D. (2016). The effects of mirror therapy on pain and motor control of phantom limb in amputees: a systematic review. Annals of physical and rehabilitation medicine, 59(4), 270-275.

Bolognini, N., Olgiati, E., Maravita, A., Ferraro, F., & Fregni, F. (2013). Motor and parietal cortex stimulation for phantom limb pain and sensations. PAIN®, 154(8), 1274-1280.

Bolognini, N., Spandri, V., Ferraro, F., Salmaggi, A., Molinari, A. C. L., Fregni, F., & Maravita, A. (2015). Immediate and sustained effects of 5-day transcranial direct current stimulation of the motor cortex in phantom limb pain. The Journal of Pain, 16(7), 657-665.

Braulio, G., Passos, S. C., Leite, F., Schwertner, A., Stefani, L. C., Palmer, A. C. S., . . . Caumo, W. (2018). Effects of Transcranial Direct Current Stimulation Block Remifentanil-Induced Hyperalgesia: A Randomized, Double-Blind Clinical Trial. Front Pharmacol, 9, 94. https://doi.org/10.3389/fphar.2018.00094

Brodie, E. E., Whyte, A., & Niven, C. A. (2007). Analgesia through the looking-glass? A randomized controlled trial investigating the effect of viewing a 'virtual'limb upon phantom limb pain, sensation and movement. European journal of pain, 11(4), 428-436.

Ciociola, A. A., Cohen, L. B., Kulkarni, P., Kefalas, C., Buchman, A., Burke, C., . . . Fang, J. (2014). How drugs are developed and approved by the FDA: current process and future directions. Official journal of the American College of Gastroenterology| ACG, 109(5), 620-623.

Collins, K. L., Russell, H. G., Schumacher, P. J., Robinson-Freeman, K. E., O'Conor, E. C., Gibney, K. D., . . . Tsao, J. W. (2018). A review of current theories and treatments for phantom limb pain. The Journal of clinical investigation, 128(6), 2168-2176.

Cuenca-Martínez, F., Reina-Varona, Á., Castillo-García, J., La Touche, R., Angulo-Díaz-Parreño, S., & Suso-Martí, L. (2021). Pain relief by movement representation strategies: An umbrella and mapping review with meta-meta-analysis of motor imagery, action observation and mirror therapy. European journal of pain.

Curtis, K., Fry, M., Shaban, R. Z., & Considine, J. (2017). Translating research findings to clinical nursing practice. Journal of clinical nursing, 26(5-6), 862-872.

Duarte, D., Bauer, C. C. C., Pinto, C. B., Velez, F. G. S., Estudillo-Guerra, M. A., Pacheco-Barrios, K., . . . Fregni, F. (2020). Cortical plasticity in phantom limb pain: A fMRI study on the neural correlates of behavioral clinical manifestations. Psychiatry Research: Neuroimaging, 304, 111151.

Ellenberg, S. S. (2018). The stepped-wedge clinical trial: evaluation by rolling deployment. Jama, 319(6), 607-608.

Els, C., Jackson, T. D., Kunyk, D., Lappi, V. G., Sonnenberg, B., Hagtvedt, R., . . . Straube, S. (2017). Adverse events associated with medium-and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews(10).

Erlenwein, J., Diers, M., Ernst, J., Schulz, F., & Petzke, F. (2021). Clinical updates on phantom limb pain. Pain Reports, 6(1).

Flor, H. (2002). Phantom-limb pain: characteristics, causes, and treatment. The Lancet Neurology, 1(3), 182-189.

Fregni, F., El-Hagrassy, M. M., Pacheco-Barrios, K., Carvalho, S., Leite, J., Simis, M., . . . Venkatasubramanian, G. (2021). Evidence-Based Guidelines and Secondary Meta-Analysis for the Use of Transcranial Direct Current Stimulation in Neurological and Psychiatric Disorders. International Journal of Neuropsychopharmacology, 24(4), 256-313.

Graham, I. D., Logan, J., Harrison, M. B., Straus, S. E., Tetroe, J., Caswell, W., & Robinson, N. (2006). Lost in knowledge translation: time for a map? Journal of continuing education in the health professions, 26(1), 13-24.

Gunduz, M. E., Pacheco-Barrios, K., Bonin Pinto, C., Duarte, D., Vélez, F. G. S., Gianlorenco, A. C. L., . . . Battistella, L. R. (2021). Effects of Combined and Alone Transcranial Motor Cortex Stimulation and Mirror Therapy in Phantom Limb Pain: A Randomized Factorial Trial. Neurorehabilitation and Neural Repair, 15459683211017509.

Gunduz, M. E., Pinto, C. B., Saleh Velez, F. G., Duarte, D., Pacheco-Barrios, K., Lopes, F., & Fregni, F. (2020). Motor cortex reorganization in limb amputation: a systematic review of TMS motor mapping studies. Frontiers in neuroscience, 14, 314.

Hohenschurz-Schmidt, D., Kleykamp, B. A., Draper-Rodi, J., Vollert, J., Chan, J., Ferguson, M., . . . Turk, D. C. (2021). Pragmatic trials of pain therapies: a systematic review of methods. Pain.

Hoots, B. E., Xu, L., Kariisa, M., Wilson, N. O., Rudd, R. A., Scholl, L., . . . Seth, P. (2018). 2018 Annual surveillance report of drug-related risks and outcomes--United States.

Hsiao, A.-F., York, R., Hsiao, I., Hansen, E., Hays, R. D., Ives, J., & Coulter, I. D. (2012). A randomized controlled study to evaluate the efficacy of noninvasive limb cover for chronic phantom limb pain among veteran amputees. Archives of physical medicine and rehabilitation, 93(4), 617-622.

Irlbacher, K., Kuhnert, J., Röricht, S., Meyer, B. U., & Brandt, S. A. (2006). Central and peripheral deafferent pain: therapy with repetitive transcranial magnetic stimulation. Der Nervenarzt, 77(10), 1196-1198.

Kern, U., Busch, V., Müller, R., Kohl, M., & Birklein, F. (2012). Phantom limb pain in daily practice—still a lot of work to do! Pain Medicine, 13(12), 1611-1626.

Kikkert, S., Mezue, M., O'Shea, J., Henderson Slater, D., Johansen-Berg, H., Tracey, I., & Makin, T. R. (2019). Neural basis of induced phantom limb pain relief. Annals of neurology, 85(1), 59-73.

Kim, S. H., Stoicea, N., Soghomonyan, S., & Bergese, S. D. (2014). Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: systematic review [Review]. Frontiers in Pharmacology, 5(108). https://doi.org/10.3389/fphar.2014.00108

Lalu, M. M., Montroy, J., Begley, C. G., Bubela, T., Hunniford, V., Ripsman, D., . . . Moher, D. (2020). Identifying and understanding factors that affect the translation of therapies from the laboratory to patients: a study protocol. F1000Research, 9.

Limakatso, K., Bedwell, G. J., Madden, V. J., & Parker, R. (2020). The prevalence and risk factors for phantom limb pain in people with amputations: A systematic review and meta-analysis. PloS one, 15(10), e0240431.

Maclure, M. (2009). Explaining pragmatic trials to pragmatic policy-makers. Cmaj, 180(10), 1001-1003.

Malavera, A., Silva, F. A., Fregni, F., Carrillo, S., & Garcia, R. G. (2016). Repetitive transcranial magnetic stimulation for phantom limb pain in land mine victims: a double-blinded, randomized, sham-controlled trial. The Journal of Pain, 17(8), 911-918.

Moura, V. L., Faurot, K. R., Gaylord, S. A., Mann, J. D., Sill, M., Lynch, C., & Lee, M. Y. (2012). Mind-body interventions for treatment of phantom limb pain in persons with amputation. American Journal of Physical Medicine & Rehabilitation, 91(8), 701.

Nardone, R., Versace, V., Sebastianelli, L., Brigo, F., Christova, M., Scarano, G. I., . . . Sellner, J. (2019). Transcranial magnetic stimulation in subjects with phantom pain and non-painful phantom sensations: a systematic review. Brain research bulletin, 148, 1-9.

Nikolajsen, L., & Christensen, K. F. (2015). Phantom limb pain. Nerves and Nerve Injuries, 23-34.

Nikolajsen, L., Finnerup, N. B., Kramp, S., Vimtrup, A.-S., Keller, J., & Jensen, T. S. (2006). A randomized study of the effects of gabapentin on postamputation pain. The Journal of the American Society of Anesthesiologists, 105(5), 1008-1015.

Pacheco-Barrios, K., Meng, X., & Fregni, F. (2020). Neuromodulation techniques in phantom limb pain: A systematic review and meta-analysis. Pain Medicine, 21(10), 2310-2322.

Pacheco-Barrios, K., Pinto, C. B., Velez, F. G. S., Duarte, D., Gunduz, M. E., Simis, M., . . . Guidetti, M. (2020). Structural and functional motor cortex asymmetry in unilateral lower limb amputation with phantom limb pain. Clinical Neurophysiology, 131(10), 2375-2382.

Quintero, G. C. (2017). Review about gabapentin misuse, interactions, contraindications and side effects. Journal of experimental pharmacology, 9, 13.

Raffin, E., Richard, N., Giraux, P., & Reilly, K. T. (2016). Primary motor cortex changes after amputation correlate with phantom limb pain and the ability to move the phantom limb. Neuroimage, 130, 134-144.

Rothgangel, A., Braun, S., Winkens, B., Beurskens, A., & Smeets, R. (2018). Traditional and augmented reality mirror therapy for patients with chronic phantom limb pain (PACT study): results of a three-group, multicentre single-blind randomized controlled trial. Clinical Rehabilitation, 32(12), 1591-1608.

Thieme, H., Mehrholz, J., Pohl, M., Behrens, J., & Dohle, C. (2012). Mirror therapy for improving motor function after stroke. Cochrane Database of Systematic Reviews(3).

Thieme, H., Morkisch, N., Rietz, C., Dohle, C., & Borgetto, B. (2016). The efficacy of movement representation techniques for treatment of limb pain—a systematic review and meta-analysis. The Journal of Pain, 17(2), 167-180.

Wang, F., Zhang, R., Zhang, J., Li, D., Wang, Y., Yang, Y.-H., & Wei, Q. (2021). Effects of mirror therapy on phantom limb sensation and phantom limb pain in amputees: A systematic review and meta-analysis of randomized controlled trials. Clinical Rehabilitation, 35(12), 1710-1721.

Wexler, A. (2016). A pragmatic analysis of the regulation of consumer transcranial direct current stimulation (TDCS) devices in the United States. Journal of Law and the Biosciences, 2(3), 669-696.

Zaghi, S., Heine, N., & Fregni, F. (2009). Brain stimulation for the treatment of pain: a review of costs, clinical effects, and mechanisms of treatment for three different central neuromodulatory approaches. Journal of pain management, 2(3), 339.