Commentary

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More than "just do it"—fear-based exposure for complex regional pain syndrome

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Complex regional pain syndrome (CRPS) is difficult to treat, no matter what your treatment approach. Of the 25 pharmacological, interventionist, exercise, and alternative therapy approaches that have been systematically reviewed, only a few have any promise and even those "*may*" be helpful.[32] Clinical guidelines reflect this underwhelming situation—recommendations to promote function, to include "physiotherapy" (whatever that might be[6]), and to act early are common, but so too are recommendations that reflect the expert panels' expertise rather than published data. This is understandable when the level of evidence is so low, but it presents a clinical conundrum—should we indeed "turn people with CRPS away?"[4]

Fortunately, the situation is not quite that dismal—there are promising developments. One such development is presented in an article in this issue by den Hollander et al.[8] Their randomized controlled trial compared "Exposure in vivo" to a "Treatment as usual" approach. Exposure was the better of the 2, and most patients had clinically important symptomatic and functional gains. There is much to like about this study—the authors check treatment fidelity and consider potentially powerful factors such as perceived credibility of the intervention and patient expectations, which were similar between treatments, and clinician expectations, which were not. That clinician expectations were much higher for Exposure is arguably worthy of more attention than den Hollander et al. give it—Gracely et al.'s[12] elegant study in which dentists' expectations of the probability that they were delivering an active drug markedly modulated pain relief induced by an inactive one, surely provides evidence enough that it matters. den Hollander et al.'s use of a Reliable Change Index,[19] which accounts for variability of the measurement tool and allows confident conclusions about the proportion of participants who make clinically important gains, is also commendable and showed that *most* patients in the Exposure group improved and *most* patients in the Treatment as usual group did not.

That Exposure was clearly better than Treatment as usual could of course be due to how bad Treatment as usual was. Indeed, their selection of the control treatment is intriguing. It was based on a previous clinical trial[33] and focussed on "extinguishing the source of ongoing pain by rest (locally), connective tissue massage, transcutaneous electric nerve stimulation and…practicing compensatory activities." However, treatment guidelines have emphasized time-contingent rather than pain-contingent active intervention for almost 2 decades,[35] and updates consolidate the focus on function not pain relief.[13,36] That the control treatment may still reflect common clinical practice is disturbing; that it was based on a treatment that seemed effective in clinical trials[33] but was more or less useless in real life provides an important reminder that effects vary when apparently efficacious treatments are implemented in "real-world scenarios" characterized by competing conceptual paradigms, variable clinician expectations, and logistical and administrative barriers (eg, see Refs. 14,20).

Aside from the research team's preliminary case series a decade ago,[7] others have taken a pain exposure approach to CRPS. Over a decade ago, rumors spread of a "Ms Shinka" and her "Macedonian method" of treating CRPS. She focussed solely on getting the patient to regain use of the affected extremity, with little or no regard for the pain evoked by attempts to do so. A group of open-minded Dutch clinicians visited "the guru" and subsequently embarked on testing the approach. They established the safety of this "Pain exposure physical therapy" (PEPT) and observed improvements in pain and disability.[37] They developed a protocol for a randomized controlled trial comparing PEPT to care based on the Utrecht-based Institute for Healthcare Improvement (CBO) CRPS guidelines[1] and ultimately undertook the trial.[3] They did everything "by the book" and deserve great credit for doing so, but the results of PEPT seemed underwhelming—the intention to treat analysis showed similar outcomes in the 2 groups. Closer appraisal, however, was more promising: of the 28 participants allocated to the CBO Guidelines group, only 17 actually participated and the "per protocol" analysis (as distinct from the intention to treat analysis) showed significant and clinically important differences between the groups on several outcomes.

The Exposure approach tested by den Hollander et al.[7] corroborates the promise of the PEPT but it also has some important differences. Aside from being much more intensive (approximately 17 hours vs approximately 3 hours), the Exposure approach targets patients with high fear, is directed by a fear-based hierarchy of activities (something PEPT specifically avoids), and is centered on the creation of "expectancy violations." Critical to that approach is ascertaining a patient's personal theory of their pain—what biological mechanisms are causing it—and gleaning specific hypotheses that the patient may have about their pain. The clinician's task then is to formulate alternative hypotheses that are grounded in current pain science knowledge. Treatment seems to involve a progression of "behavioural experiments" that serve to falsify the patient's hypotheses and support the alternative. One can see clear similarities between this approach and approaches that center around "Explaining

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pain" (EP), which is the utilization of a range of educational and conceptual change strategies to shift a patient's understanding of the biological processes that underpin their pain.[27] Although EP has level 1 supportive evidence,[27] an ongoing (although arguably achievable[24]) challenge for EP is the requirement that the clinician has a high-level knowledge of modern pain science and high-level expertise in teaching the patient. Treatments are only as good as the clinician's ability to deliver them, and this is as important a consideration for Exposure as it seems to be for EP.

How does Exposure compare? Although den Hollander compared Exposure to what seems an outdated control intervention, the reliable change data are very promising indeed. The long-term effects seem to be better than the short-term effects, which, interestingly, is also the case for Graded Motor Imagery[5,26]—another treatment that prioritizes the patient gaining a sound understanding of contemporary pain science—and indeed for EP itself.[15] The effect sizes for Exposure are at least as good and mostly better than previously published data, regardless of the modality or setting of treatment.[32] These are clearly exciting developments that beg the question "Where to next?" Contemporary pain theories that emphasize the protective utility of pain (see Refs. 23,27,31 for relevant reviews) would predict that even patients who seem to be "low fear" should respond to an approach based on violated expectations. That mediation analysis on the PEPT data suggests that change in fear does not mediate improvements in pain and function,[2] suggest that change in fear itself may not be critical (although whether this is also the case for Exposure remains to be seen)—it would seem sensible to test Exposure for low fear patients too. There is compelling evidence that chronic CRPS is associated with a wide range of perceptual and sensory processing deficits[11,16–18,21,25,28–30,34] and sensorimotor cortical reorganization[9,10]—it would be valuable to identify whether Exposure affected any of these problems, whether or not any such changes mediated symptomatic or functional improvements, and whether such deficits modulate the effect of Exposure. Finally, there are clear commonalities between Exposure and other treatments for CRPS, for example Graded Motor Imagery,[22] but there are also clear differences in targeted mechanisms and method of delivery. Combining treatments may offer super additive effects, which might bring us close to effects that excite patients, rather than the effects that just excite clinical scientists.

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References

[1] Barnhoorn KJ, Oostendorp RA, van Dongen RT, Klomp FP, Samwel H, van der Wilt GJ, Adang E, Groenewoud H, van de Meent H, Frolke JP. The effectiveness and cost evaluation of pain exposure physical therapy and conventional therapy in patients with complex regional pain syndrome type 1. Rationale and design of a randomized controlled trial. BMC Musculoskelet Disord 2012;13:58.
[2] Barnhoorn KJ, Staal JB, van Dongen RT, Frolke JP, Klomp FP, van de Meent H, Samwel H, Nijhuis-van der Sanden MW. Are pain-related fears mediators for reducing disability and pain in patients with complex regional pain syndrome type 1? An explorative analysis on pain exposure physical therapy. PLoS One 2014;10:e0123008.
[3] Barnhoorn KJ, van de Meent H, van Dongen RT, Klomp FP, Groenewoud H, Samwel H, Nijhuis-van der Sanden MW, Frolke JP, Staal JB. Pain exposure physical therapy (PEPT) compared to conventional treatment in complex regional pain syndrome type 1: a randomised controlled trial. BMJ Open 2015;5:e008283.
[4] Bowering JK. Should we turn people with CRPS away? Available at: bodyinmind.org. Accessed June 8, 2016.
[5] Bowering KJ, O'Connell NE, Tabor A, Catley MJ, Leake HB, Moseley GL, Stanton TR. The effects of graded motor imagery and its components on chronic pain: a systematic review and meta-analysis. J Pain 2013;14:3–13.
[6] Daly AE, Bialocerkowski AE. Does evidence support physiotherapy management of adult Complex Regional Pain Syndrome Type One? A systematic review. Eur J Pain 2009;13:339–53.
[7] de Jong JR, Vlaeyen JWS, Onghena P, Cuypers C, Hollander Md, Ruijgrok J. Reduction of pain-related fear in complex regional pain syndrome type I: the application of graded exposure in vivo. PAIN 2005; 116:264–75.
[8] den Hollander M, Goossens M, de Jong J, Ruijgrok J, Oosterhof J, Onghena P, Smeets R, Vlaeyen J. Expose or protect? A randomized controlled trial of exposure in vivo versus pain-contingent treatment as usual in patients with Complex Regional Pain Syndrome Type 1. PAIN 2016;157:2318–29.
[9] Di Pietro F, McAuley JH, Parkitny L, Lotze M, Wand BM, Moseley GL, Stanton TR. Primary motor cortex function in complex regional pain syndrome: a systematic review and meta-analysis. J Pain 2013;14: 1270–88.
[10] Di Pietro F, McAuley JH, Parkitny L, Lotze M, Wand BM, Moseley GL, Stanton TR. Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. J Pain 2013;14: 1001–18.
[11] Forderreuther S, Sailer U, Straube A. Impaired self-perception of the hand in complex regional pain syndrome (CRPS). PAIN 2004;110:756–61.
[12] Gracely RH, Dubner R, Deeter WR, Wolskee PJ. Clinicians' expectations influence placebo analgesia. Lancet 1985;1:43.
[13] Harden RN, Oaklander AL, Burton AW, Perez RS, Richardson K, Swan M, Barthel J, Costa B, Graciosa JR, Bruehl S. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. Pain Med 2013;14:180–229.
[14] Johnson S, Hall J, Barnett S, Draper M, Derbyshire G, Haynes L, Rooney C, Cameron H, Moseley GL, de C Williams AC, McCabe C, Goebel A. Using graded motor imagery for complex regional pain syndrome in clinical practice: failure to improve pain. Eur J Pain 2012;16:550–61.
[15] Lee H, McAuley J, Hubscher M, Kamper S, Traeger AC, Moseley GL. Does changing pain-related knowledge reduce pain and improve function through changes in catastrophizing? PAIN 2016;157:922–30.
[16] Lewis JS, Kersten P, McCabe CS, McPherson KM, Blake DR. Body perception disturbance: a contribution to pain in complex regional pain syndrome (CRPS). PAIN 2007;133:111–9.
[17] Lewis JS, Kersten P, McPherson KM, Taylor GJ, Harris N, McCabe CS, Blake DR. Wherever is my arm? Impaired upper limb position accuracy in complex regional pain syndrome. PAIN 2010;149:463–9.
[18] McCabe CS, Cohen H, Hall J, Lewis J, Rodham K, Harris N. Somatosensory conflicts in complex regional pain syndrome type 1 and fibromyalgia syndrome. Curr Rheumatol Rep 2009;11:461–5.
[19] Morley S, Dowzer C. Manual for the leeds reliable change indicator: simple Excel applications for the analysis of individual patient and group data. University of Leeds, Leeds, United Kingdom; 2014.
[20] Moseley G. Rehabilitation of complex regional pain syndrome. In: Mogil J. editor. Refresher course syllabus, 13th World Congress on Pain. Montreal, IASP Press, 2012.
[21] Moseley GL. Distorted body image in complex regional pain syndrome. Neurology 2005;65:773.
[22] Moseley G, Butler D, Beames T, Giles T. The graded motor imagery handbook. Adelaide: NOI group publishing, 2012.
[23] Moseley G, Lotze M. Theoretical considerations for chronic pain rehabilitation. Phys Ther 2015;95:1316–20.
[24] Moseley GL. Unravelling the barriers to reconceptualisation of the problem in chronic pain: the actual and perceived ability of patients and health professionals to understand the neurophysiology. J Pain 2003;4: 184–9.
[25] Moseley GL. Why do people with complex regional pain syndrome take longer to recognize their affected hand? Neurology 2004;62:2182–6.
[26] Moseley GL. Graded motor imagery for pathologic pain—a randomized controlled trial. Neurology 2006;67:2129–34.

[27] Moseley GL, Butler DS. 15 Years of explaining pain—the past, present and future. J Pain 2015;16:807–13.
[28] Moseley GL, Gallace A, Di Pietro F, Spence C, Iannetti GD. Limb-specific autonomic dysfunction in complex regional pain syndrome modulated by wearing prism glasses. PAIN 2013;154:2463–8.
[29] Moseley GL, Gallace A, Iannetti GD. Spatially defined modulation of skin temperature and hand ownership of both hands in patients with unilateral complex regional pain syndrome. Brain 2012;135(pt 12):3676–86.
[30] Moseley GL, Gallace A, Spence C. Space-based, but not arm-based, shift in tactile processing in complex regional pain syndrome and its relationship to cooling of the affected limb. Brain 2009;132(pt 11):3142–51.
[31] Moseley GL, Vlaeyen JW. Beyond nociception: the imprecision hypothesis of chronic pain. PAIN 2015;156:35–8.
[32] O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome. Cochrane Database Syst Rev 2013; CD009416.
[33] Oerlemans HM, Oostendorp RA, de Boo T, Goris RJ. Pain and reduced mobility in complex regional pain syndrome I: outcome of a prospective randomised controlled clinical trial of adjuvant physical therapy versus occupational therapy. PAIN 1999;83:77–83.
[34] Reid E, Wallwork SB, Harvie D, Chalmers KJ, Gallace A, Spence C, Moseley GL. A new kind of spatial inattention associated with chronic limb pain? Ann Neurol 2016;79:701–4.
[35] Stanton-Hicks M, Baron R, Boas R, Gordh T, Harden N, Hendler N. Complex regional pain syndromes: guidelines for therapy. Clin J Pain 1998;14:155–66.
[36] Stanton-Hicks MD, Burton AW, Bruehl SP, Carr DB, Harden RN, Hassenbusch SJ, Lubenow TR, Oakley JC, Racz GB, Raj PP, Rauck RL, Rezai AR. An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. Pain Pract 2002;2:1–16.
[37] van de Meent H, Oerlemans M, Bruggeman A, Klomp F, van Dongen R, Oostendorp R, Frolke JP. Safety of "pain exposure" physical therapy in patients with complex regional pain syndrome type 1. PAIN 2011;152:1431–8.