Title: Are small effects for back pain interventions really surprising?

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Background:

There is reasonably strong evidence that some physical therapy interventions such as exercise and manual therapy are effective (compared to minimal or no intervention) for patients with low back pain (LBP); however, the effect sizes are typically small.[6] Many clinicians argue this evidence is at odds with their daily clinical experience, which begs the question 'why the disparity'? There are several reasons that likely contribute to small effects in clinical trials of LBP and other musculoskeletal conditions. In this viewpoint we will look at which of these reasons are beyond our control as clinicians and simply need to be acknowledged and understood, and which reasons might provide insights into improving the design of future clinical trials of LBP and ultimately deliver better care to our patients.

Many patients with back pain have a favourable natural prognosis:

There is strong evidence that the prognosis of many patients presenting to primary care with LBP is favorable regardless of treatment. A systematic review of the prognosis of acute duration LBP found that on average patients' pain scores (on a 0-100 scale) reduced from 52 when they presented for care, to 23 at 6 weeks, and only 6 out of 100 at one year.[2] Even patients who presented with persistent LBP improved markedly with average pain intensity dropping from 51/100 to 33/100 over the first 6 weeks.[2]

Clinical trials compare the outcomes of patients allocated to treatment or control groups. As many patients with LBP have a favorable prognosis, then even if the

control group gets minimal or no treatment, the evidence is strong that on average they will show substantial improvement, especially if the study sample includes patients with acute LBP. In this situation where the control group on average recovers well, it is very difficult or even impossible for a treatment to demonstrate significant benefits over the control. It is common (although often not appropriate) for clinical trials to consider the benefit from treatment to be 'clinically important' if the difference between the outcome score for the treatment and control groups is greater than a 'minimal clinically important change' score. For the outcome of LBP intensity minimal clinically important change is frequently reported to be approximately 20 points on a 100 point scale.[7] If the average pain intensity outcome score of the control group is similar or lower than the minimal clinically important change score (e.g. 15 points on 100 point scale) then it is virtually impossible for the treatment to meet this criteria, regardless of how efficacious the intervention actually is.

So how should we respond to the favorable natural prognosis of acute LBP in particular? Firstly we need to question the usefulness of conducting further physical therapy trials in unselected acute LBP populations. Guidelines recommend simple care for people presenting with acute LBP with an option for a review after 1-2 weeks.[5] One option is to design trials which only include patients who do not improve markedly over the first 1-2 weeks with simple care. Another option is to only include patients whose baseline presentation suggests their prognosis is less favorable, using existing prognostic tools.[4] Importantly this is not taking away a physical therapist's role but rather changing the role to align with their increasingly

common role as primary care clinicians. Patients with a favorable prognosis still need good advice and reassurance and the opportunity for a review to ensure they are progressing well. Until physical therapists are willing to embrace the critical role of simple care and review when appropriate, the profession cannot optimize their role as a first contact health care provider managing LBP and other musculoskeletal conditions. Clinical trials of physical therapy interventions in patients who are not improving well with simple care, or have a less favorable prognosis, would appear more clinically important and also have a greater chance of showing larger treatment effects. Investigating longer-term outcomes, at least as the primary outcome in patients with acute LBP also needs careful thought, given the favorable natural clinical course over longer periods of most patients with LBP.

Using patient reported outcomes:

As a researcher or clinician it is frustrating to see a patient who reports marked improvement only to see the failure of the outcome measure to capture this during data collection. A limitation of most currently used outcome measures is that these tools are unidimensional, whereas recovery is multidimensional. These tools often don't capture many domains of what physical therapists offer their patients. For example, after 3 sessions of physical therapy a patient may have only improved slightly with respect to pain intensity or disability (measured with Oswestry Disability Index); however, they may now be more confident to manage their back, be more physically active and less worried about their back pain. Most treatments patients receive are complex, consisting of numerous active ingredients that target multiple

factors such as pain, function, interference with leisure activities and work/daily routine, while also seeking to address patients' pain-related concerns and level of understanding about their condition. Further, although generic health-related quality of life measures such as the EQ-5D and SF-36 are available these are not focused on back specific treatment targets, and unsurprisingly show lower sensitivity to change than back-specific outcome measures. A challenge for future research is therefore to develop multidimensional measures that are sensitive to change for patients with LBP and include domains which patients with LBP have prioritized as being particularly important and relevant to their experience.

Between group differences and within group changes

Whereas between-group differences in outcomes are typically reported as being small, many trials compare one intervention to another intervention so between-group differences represent the *difference in effectiveness* of one approach compared to another; rather than simply the *effectiveness* of the intervention. While this may seem relatively obvious it is commonly misunderstood or reported incorrectly in trial publications. For example there is strong evidence that most trials comparing different types of exercise for chronic LBP find little or no difference in effect.[3] However, this does not mean that the different exercise types had little or no effect, but just that the effects between the different types were similar on average. Trials commonly compare a treatment to standard care or minimal care and few trials compare one treatment to no treatment. It is difficult to compare one treatment for LBP to a no treatment control because there is evidence some

treatments are effective, thus randomising patients to no treatment is often not ethical or practical. Only randomized trials comparing a treatment to non-treatment group are really designed to assess the total effect of a treatment. Even placebo controlled trials are designed to test particular components of a treatment. Often in studies of multimodal treatments used by physical therapists, the placebo treatment includes some active elements such as reassurance.

Treatment effects are the average effect in the population

Most randomized controlled trials involving patients with LBP compare pain and disability outcomes between groups, often at key time points. Importantly this is a comparison of the *average score* (or change) for the outcome across all people in the groups. It is widely accepted that patients with LBP are heterogeneous in many regards and that back pain is a complex multifactorial condition. While it would be ideal if one single, simple intervention was highly effective across this heterogeneous population, this does not seem likely given our understanding of LBP and neither is this approach supported by the clinical trial evidence of thousands of trials that have investigated mostly unidimensional interventions in patients with non-specific LBP.

This problem of heterogeneity has been known for quite a while and identifying groups of patients who are more homogenous and respond best to particular interventions has been identified as the number one priority in back pain research.[1] Unfortunately these trials need to be very large and are expensive to conduct. As a result, few have been conducted, and little evidence is currently available to inform whether better matching of patients to interventions can increase effect sizes.[8,9]

Some promising findings exist and replication studies are under way to assess the generalisability of these early findings. A related but different approach to this problem of heterogeneity is to develop more multidimensional treatment approaches that address a range of potential contributors to LBP and can be tailored to an individual patient's needs. Interestingly this is what many clinicians report they do in clinical practice; however, few clinical trials have followed this approach possibly due to challenges in designing and interpreting the results of such trials.

Need for a better understanding of patient phenotypes and treatment mechanisms

Should it really be surprising that treatment effect sizes for LBP are small when the nociceptive source and causes for LBP remain poorly understood and there is no clear theoretical framework for how most interventions might work? A physical therapist may take for granted that exercise should help LBP (and it does a little on average), but what is the biological rationale or mechanism for this? We debate and investigate the best type of exercise; however, without a strong understanding of the underlying causes (phenotypes) and hypothesised treatment targets it is difficult to empirically test who an intervention might work best for or how it might be working. Arguably there is a need to stop doing more clinical trials in a condition we don't really understand using interventions that we don't have a strong rational for and put more effort into better understanding the different causes and types of patients with LBP and the mechanisms of the interventions available. If this was achieved, some existing treatments may be found to produce larger effects when

targeted to the right patients. Other treatments may be discarded as they have no logical basis, and new more effective treatments may also be developed.

The recent interest in bacterial infection (Modic changes) as a potential cause of LBP in some people is an example of how important it is to investigate both the causes of LBP and the mechanisms by which treatments work. The identification of a phenotype of LBP (e.g. due to likely bacterial infection) results in a more homogenous group in whom a more logical treatment can be tested. If the treatment is shown to be more effective in those in this phenotype than those not in the phenotype, the phenotype is a moderator of treatment. It is also important to test or confirm if the treatment is working in the manner hypothesised (mediation analysis). In the example of using antibiotics for LBP, it would be important to test if the improvements in outcome are actually due to reduction in bacterial infection or due to some other mechanism such as reduction in inflammation.

We suggest that future research needs to focus on firstly, developing a better understanding about the causes and phenotypes (clinically important subgroups) of LBP and secondly, testing if treatments are working in the manner hypothesised to have a greater chance of identifying more effective interventions for LBP.

Summary

The widely reported small effects of physical therapy interventions for LBP need to be understood and interpreted in the context of the natural course of LBP and the inherent limitations of clinical trials especially in complex health conditions. The findings should motivate the profession to reconsider its role as a primary health care professional, with much more to offer than highly effective interventions. Researchers should be challenged to better understand the causes of LBP and the mechanisms by which treatments work so more effective and individualised treatments can be developed in the future.

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