TITLE: Disentangling contextual effects from musculoskeletal treatments

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When a patient receives a treatment for a musculoskeletal pain condition, the outcome they experience (total effect) is made up of the specific treatment effect and non-specific effects that may include natural history, regression to the mean, and contextual effects[1]. Understanding the specific effect of the treatment is important for research consumers; patients, clinicians and policy makers, as some treatments have harms or costs that could outweigh any positive specific effects. In this article we 1) discuss challenges in identifying and removing contextual effects in pragmatic trials, 2) introduce a way to isolate contextual effects of treatments using causal mediation analysis, and 3) highlight the importance of explicitly defining the contextual effect we want to estimate or control.

Disentangling treatment effects

Randomised controlled trials (RCTs) are used to disentangle effects associated with natural history and regression to the mean from the total effect of a treatment on a given outcome, and placebo controls are used to disentangle these effects *plus* contextual effects. By comparing the average outcome under the treatment and placebo groups, the specific effect of the treatment, that is the effect of the treatment without the non-specific (contextual and non-contextual effects) can be estimated (Figure 1).

Insert Figure 1. Here

Complex interventions that are made up of several interacting components are commonly used to manage musculoskeletal pain conditions. RCTs of complex interventions for musculoskeletal pain rarely use placebo controls. In a recent systematic review of physiotherapy interventions for low back pain only 79 RCTs out of 2215 (4%) used a placebo control[2]. Placebos of complex interventions are not straightforward to design[3] and there may not be consensus, even among experts, on what constitutes an appropriate placebo for a given complex intervention[4]. For RCTs of complex interventions it is more common to use pragmatic designs to estimate the difference between treatment and usual care/no treatment group. Pragmatic trials test the effectiveness of treatments in real world settings and in theory increase the applicability of the findings to clinical settings[5]. In

pragmatic trials, effects associated with regression to the mean and natural history are removed, but contextual effects remain. Consumers of evidence are therefore left wondering how much of the effect of the complex intervention is attributable to the specific effect of the treatment.

Isolating specific effects of treatments in pragmatic trials

A novel type of treatment effect, the "natural direct effect", can be used to represent the specific effect of a treatment in a pragmatic trial[6]. A natural direct effect is just like a standard treatment effect from an RCT, but it partitions out the treatment effect that goes through a defined variable on the causal pathway. So to isolate the specific effects of a treatment, one would first define and measure a variable that represents a contextual effect (such as the patient and therapist beliefs and behaviours, the patient-therapist relationship, or the non-specific clinical procedures and clinical environment in which the treatment is provided[7,8]). Then the effect that goes through that contextual variable can be partitioned out using causal mediation analysis[9].

Although this approach requires stronger assumptions than the placebo controlled trial[10], it offers several advantages. First it forces the investigator to be specific about the contextual effect that is being partitioned out. This is not common practice in placebo controlled trials[11]. Second, it allows the investigator to answer the question of "what would the treatment effect be if the contextual effect was set at the natural value it would take under the control (or intervention)?". This is advantageous because it allows the specific effect of treatment to be estimated in isolation of the contextual effect. Finally, the benefits of a pragmatic trial can be maintained, thereby allowing the estimation of specific treatment effects under more realistic conditions. The trade-off of these benefits to the degree of robustness of the natural direct effect, and the challenges in measuring and estimating contextual effects should be weighed.

Applying mediation analysis to isolate specific treatment effects

In the Back Skills Training Trial (n=701), Lamb et al[12]. showed that a 6-week group cognitive behavioural intervention for people with low back pain reduced disability more than best practice

advice alone (total treatment effect = 1.3 [95% confidence interval (CI), 0.6 to 2.1] points on the 24 point Roland Morris Disability Questionnaire at 12 months). This pragmatic, multicentre RCT, recruited adults with troublesome subacute or chronic low-back pain from 56 general practices in England. We used causal mediation analysis[13] to determine the size of the specific treatment effect when the mediator, patient satisfaction (contextual effect mechanism), was set to be the value it would take (naturally) under the control intervention (Figure 2). Our complete-case mediation analysis (n=426), indicated that 5% of the treatment effect was mediated by patient satisfaction (natural indirect effect = 0.1, [95% CI, -0.1 to 0.2]) (Table 1). The natural direct effect suggests that the majority of the total effect worked through the specific effects of the intervention and possibly other contextual effects unrelated to patient satisfaction (natural direct effect = 1.1 [95% CI, 0.1 to 2.2] (Table 1).

Insert Figure 2. Here

Insert Table 1. Here

Researchers should consider embedding mediation analyses into RCTs so that research consumers can better understand the specific and non-specific effects of treatments. Contextual effect mechanisms should be explicitly defined and measured. A greater understanding of specific effects of treatment will help guide the implementation of effective treatments into clinical practice, and ultimately improve outcomes for people with musculoskeletal pain.

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Effect	What the effect represents	Estimate (mean difference, 95% confidence interval)
Total effect	The entire effect of the intervention (including specific and contextual effects)	1.2 (0.2 to 2.3)
Natural direct effect	The specific effect of the intervention without the contextual effect through patient satisfaction	1.1 (0.1 to 2.2)
Natural indirect effect	The effect of the intervention that goes through patient satisfaction	0.1 (-0.1 to 0.2)
Proportion mediated	The proportion of the total effect that is explained by the natural indirect effect	5% (-10% to 33%)

Table 1. Effect decomposition for the total treatment effect of cognitive behavioural treatment on disability (measured 12 months post-randomisation) with patient satisfaction (measured 3 months post-randomisation) as the contextual effect mechanism.