Editorial Comment

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Patients with shoulder pain referred to specialist care; treatment, predictors of pain and disability, emotional distress, main symptoms and sick-leave: a cohort study with a 6-months follow-up

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Background

In the last issue of the Scandinavian Journal of Pain, Engebretsen et al. [1] describe a cohort of patients with subacromial shoulder pain referred to a clinic specializing in complex shoulder problems – the Department of Physical Medicine and Rehabilitation, Ullevaal, Oslo University. At baseline, demographic data were collected as well as data to develop a modified psychological profile plus clinical data related to shoulder pathology. The primary aim was to attempt to use all this data to be able to predict pain and disability at six month's follow-up. A majority of the subjects were assigned to different treatment paradigms after the initial evaluation – 44% to physiotherapy in the Ullevaal specialist clinic and 38% to physiotherapy in primary care. Of the 71% that returned questionnaires at the six month's follow-up, the mean change (improvement) in the shoulder pain and disability (SPADI) score was 10.5/100 points with only 29% showing more than the least detectable difference. Was this a clinically important improvement? There was also a statistical improvement in pain at rest and with activity. However, there were no improvements in psychological variables. Fourteen subjects took fewer pain medications. More importantly for this discussion, there were no differences in all variables between those treated in the specialized clinic and those referred for physiotherapy in primary care. Perhaps the fact that those selected for care in the clinic were slightly worse – longer duration of pain, more emotional distress, and more failures in previous treatment – could account for this. The researchers' final conclusion, based on the intent of the study, was that low education, higher initial pain levels and more severe initial disability were predictors for higher levels of pain and disability at follow-up after treatment.

Why were there poor outcomes in the clinic?

It appears that the study team was a little perplexed by the poor effects of physiotherapy treatment in their specialty clinic. In a previous study with two protocols, one testing extracorporeal shock wave treatment (rESWT) plus physiotherapy vs. sham rESWT plus physiotherapy, the second examining the correlation between MRI findings and outcome of the therapies, subjects had a much better response to physiotherapy than the cohort in the present study [2, 3]. In the study examined here, the Ullevaal team therefore added an analysis to compare the outcomes of the present study with the other two studies and found that the controlled trial had much better outcomes.

For me, this is the most interesting aspect of the present study. Why should shoulder pain subjects with similar phenotypes enrolled basically in the same physiotherapy programme, have dissimilar outcomes? Why did those in the present study have poorer effects from physiotherapy in a specialized clinic than those having what one could assume to be less structured physiotherapy in primary care?

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Clinical trials versus the "real world"

To take a step back, it is interesting to look at an entirely different area to demonstrate the difference in outcome between clinical trials and the same therapy in the real world. The gold standard for clinical trials comes from clinical pharmacology research and that is a randomized, double blind, placebo controlled trial (RCT) [4]. Successful clinical trials have been performed and they have succeeded in bringing several new therapies to the market. But do these new therapies perform as effectively in the real world where we work as clinicians? Often, the results are disappointing but rarely have the reasons for failure been analyzed. It is unusual for therapies from successful clinical trials to be compared to effects in the clinic using controlled observational studies. One study, RELIEF (Real Life), previously published in this journal, did look at a large cohort of patients with neuropathic pain treated in various clinics in Canada over a year and despite the use of many proven and unproven drugs singly and in various combinations, there was little effect [5]. The disappointing effects of myriad drugs for neuropathic pain were no better than NSAIDs. Why?

Natural history of disease

There are several theories to account for why clinical trials may differ from observational trials. One theory is that over a longer time span, the natural history of the disease with gradual improvement will be stronger than the effects of study medication and this phenomenon can bias clinical trials [6]. This was not so with RELIEF since no improvement was seen and obviously this phenomenon does not apply in the Engebretsen study in this issue of SJPain. Perhaps the long duration of the pain problems in both studies led to a stable "steady state" and thus there was no improvement with "tincture of time".

Regression to the mean

A second theory is that improvements can be due to "regression to the mean". The data show that meeting patients when they are having more symptoms is not the same as random testing and that random testing will show lower levels of pain and other symptoms than when meeting the patients during flairs of their symptoms [7]. This could possibly mask a mild treatment effect and be the primary reason for a positive effect of treatment that is unrelated to the type of treatment. This could have masked some of the effects in RELIEF but surely would not have been very dramatic. Since the recruitment was based on referral and not "flairs" and little improvement was seen, regression to the mean is not an element in the Engebretsen et al. trial.

Study volunteer phenotype 1

A third possible explanation is that for many clinical trials, the study population is "ideal". Volunteers in most studies, especially phase 1, 2, and 3 pharmacological studies, must not have comorbidities that could confound the outcome. They must have a clear phenotype appropriate as a target for the supposed effects of the drug or other therapy based on preclinical data and/or a hypothesis. Patients in the clinic come with a lot of baggage and very few would be suitable for clinical trials using the RCT paradigm. Clinical trials where pain is the primary outcome variable, whether based on medications, physiotherapy, surgery, spinal cord stimulation, or chiropractic, focus primarily on the "bio" of what is universally accepted as a biopsychosocial problem. Most clinical trials exclude those who have significant psychosocial problems. However, those are the patients whom we usually meet in clinical practice. Clearly, this was not the case in the Engebretsen et al. studies since they did not have specific exclusion criteria that would rule out serious psychosocial problems and wished to address psychosocial variables in their analysis.

Study volunteer phenotype 2

A fourth theory is that subjects in the majority of studies do come with an inherent bias. They must sign a consent and therefore are motivated to help. This motivation to help makes participants more suggestible to the positive effects of any treatment and could be part of the difference between the present study and the other two Engebretsen et al. studies [8]. Motivation could wane with infrequent contact as in the present study where subjects had only 3–5 physiotherapy (PT) sessions over the first weeks and then had no contact until follow-up by mail at six months. Many had lost interest as reflected in the 70% return of questionnaires at six months. And it is possible that the 30% who didn't respond had poorer outcomes and did not want to report the failure of treatment. In the rESWT study, one-on-one therapy with the physiotherapist was conducted weekly with rESWT for four weeks and then twice weekly

for eight weeks. This not only encouraged compliance with therapy but also had a much stronger motivating effect than with the present study's infrequent contact.

The placebo effect

A final consideration is the placebo effect [9, 10]. The concepts of bias and motivation referred to in the above paragraphs are a part of the placebo effect. In the rESWT studies, another treatment paradigm, a sham control, was used and the equipment needed for the rESWT sham therapy alone could have a strong placebo effect similar to the placebo effect of surgery [11]. 53% of those who had sham rESWT thought that they actually had the therapy. Thus, rESWT adjunctive therapy, sham or not, had a strong placebo effect additive to the other considerations in placebo.

Suggestions for the future

The placebo effect of hands-on treatment is very powerful. Surgical trials exemplify this as undergoing surgery is very hands-on. In the orthopedic world, both with shoulder [12] and knee surgery [13], sham surgery showed that long-held beliefs of the benefits of surgery and the focus on the "bio" were shown to be wrong. What is badly needed, not only in pain research, but in many other areas with other primary outcomes, are more RCTs and RCTs that include studies and subjects that focus not only on the "bio" but also on the "psychosocial". Those studies are more complicated. Most pharmacological pain studies now must include psychosocial parameters as secondary outcomes [14] but in other areas, they are often lacking.

A further suggestion for pain studies, especially pharmacological, is to include a phase 4 trial before new medications are approved and released. This would be a clinical study in the real world where subjects are randomly included from pain clinics where exclusion related to biopsychosocial variables is not an option. All comers. The selection bias of motivation would also be there but most patients coming to pain clinics are willing to try any new therapy. There should also be a category of patients that is exclusively those who have failed three or more approved medications since these are often the very patients that try the newest treatment on the market. In this group, the newest treatment usually fails. This type of research should be used also for all therapies for chronic pain – neuromodulation, physiotherapy, both active and passive, surgery, chiropractic, etc., not just for drug studies. These "phase 4" studies would more accurately identify the phenotypes that respond to treatment, a current focus in the literature [15]. It would also identify the phenotype of non-responders to various forms of treatment, equally important so as not to waste time and money spent in the hope rather than the belief that a certain new therapy would be helpful. I doubt that drug companies or those developing new techniques for neurostimulation or back surgery would fund such studies since they would limit the populations that would use new treatments and limit their profits.

Conclusion

Finally, Engebretsen et al. should be complimented on taking their research a step further. They were willing to question why physiotherapy in a specialized clinic was not helpful and not better than physiotherapy in the community. Rather than just reporting that treatment for subacromial pain was not successful they compared the results to what they thought was similar treatment of the same problem in a much more structured protocol. The study reported here was closer to clinical treatment in the real world and was not very successful. This revelation should prompt clinicians from several disciplines to be skeptical of new therapies from selective patient populations. Life in the real world is not always the same as life in a controlled but often biased clinical study.

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