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Systematic review

Identifying potential moderators for response to treatment in low back pain: A systematic review

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Abstract

Background Identifying which patients with non-specific low back pain are likely to gain the greatest benefit from different treatments is an important research priority. Few studies are large enough to produce data on sub-group effects from different treatments. Data from existing large studies may help identify potential moderators to use in future individual patient data meta-analyses.

Objective To systematically review papers of therapist delivered interventions for low back pain to identify potential moderators to inform an individual patient data meta-analysis.

Data sources We searched MEDLINE, EMBASE, Web of Science and Citation Index and Cochrane Register of Controlled Trials (CENTRALhttp://www.cochrane.org/editorial-and-publishing-policy-resource/cochrane-central-register-controlled-trials-central) for relevant papers.

Data extraction and data synthesis We screened for randomised controlled trials with ≥500 or more participants, and cohort studies of ≥1000 or more participants. We examined all publications related to these studies for any reported moderator analyses. Two reviewers independently did risk of bias assessment of main results and quality assessment of any moderator analyses.

Results We included four randomised trials ($n = 7208$). Potential moderators with strong evidence ($p < 0.05$) in one or more studies were age, employment status and type, back pain status, narcotic medication use, treatment expectations and education. Potential moderators with weaker evidence ($0.05 < p \leq 0.20$) included gender, psychological distress, pain/disability and quality of life.

Conclusion There are insufficient robust data on moderators to be useful in clinical practice. This review has identified some important potential moderators of treatment effect worthy of testing in future confirmatory analyses.

Keywords: Low back pain; Back pain; Randomised controlled trial; Cohort; Prospective studies

Background

Low back pain (LBP) is very common and has a large personal and societal cost [1]. Most LBP is classified as non-specific LBP (NSLBP) which affects one-third of the population each year [2]. There is good evidence to show that several treatment approaches are effective, and that some of these are cost-effective [2]. The effect sizes are of similar magnitude for different approaches [3–6]. However, the mean effect size from these treatments is, at best, small to moderate and may be short lived. Typically, the mean effect sizes, on current outcome measures, are substantially smaller than the minimally detectable change for an individual. Thus, most of the patients who receive a particular treatment will not gain a noticeable additional benefit from treatment [7]. At a population level, we have useful data on the management of LBP. What is not clear is how we can use these data to maximise the treatment benefit for the individual patient, or to identify those who will respond to different treatment and target treatment accordingly. Identifying which patients are

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likely to gain the greatest benefit from different treatments for LBP is an identified research priority [8] and was one of the key recommendations for future research in UK National Institute for Health and Clinical Excellence (NICE) back pain guidelines [9].

In clinical practice, to try to maximise treatment benefit, subgrouping is used for patients with LBP despite lack of evidence that results vary between subgroups [10]. NICE considers identification of subgroups as an important part in their decision making on whether the technology is clinically effective or cost-effective [4]. In order to develop such subgroups a clear understanding of the potential moderators of treatment is required.

Many studies have examined predictors of outcome from LBP [11–13]. These do not, however, identify moderators; those factors indicating who is likely to gain largest benefit from a particular treatment. Mediators, measured during treatment, identify potential mechanisms that have an interactive effect on outcome [14]. This review solely focuses on moderators of treatment response; factors measured prior to randomisation that affect whether an individual has a greater, or lesser benefit from treatment [15]. Identification of potential effect modifiers needs sufficient statistical power to detect an interaction between the moderators and treatment [16].

Any RCT designed to test effects in subgroups will need to be several times larger than nearly all existing RCTs. Most trials simply compare the effects of two interventions with one primary outcome measure. More complex designs testing multiple baseline measures, and multiple interventions, would be implausibly large. However, many participants are now included in RCTs, in some cases testing similar interventions and most using very similar outcome measures. Combining data from these trials could provide a more cost-effective way of exploring and testing for moderator effects without the expense of a large costly and time consuming trial.

Aims & objectives

The aim of this systematic review was to inform hypothesis development for an individual patient data meta-analysis for moderators of therapist delivered interventions in RCTs. Therefore the question being addressed was are there subgroups of patients with low back pain, receiving therapist delivered interventions that do better or worse?

To achieve this our objectives were:

- To search the relevant literature in the field.
- To screen the literature based on predefined inclusion criteria.
- To extract data and quality assess the literature.
- To highlight the potential moderators from the literature to apply to an individual patient data meta-analysis.

Methods

Eligibility criteria

The following inclusion criteria was pre specified:

(a) RCTs with sample size of ≥500, non-RCTs and observational studies with sample size ≥1000 published in English language; see below for justification of the 500 cut-off.
(b) Participants aged 18 years or more with history of NSLBP of any duration.
(c) Therapist delivered interventions for LBP examining the effect of patient preference and expectations, and individual predictors.
(d) Primary and secondary analysis papers of RCTs seeking to identify predictors of response to treatment using a 'priori' and 'post hoc' subgroups and those looking for interaction between baseline variable and treatment.

We only included studies of people with NSLBP. We excluded studies with no comparison between two treatment groups and studies that did not report effect sizes for treatment by using moderator interactions.

Information sources

We searched MEDLINE (1948 to September 2011), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, EMBASE (1974 to September 2011), Web of Science and Citation Index and Cochrane Controlled Trial Registered (CENTRAL) databases for relevant papers. The searches were updated in May 2013 then again in July 2014.

Search criteria

Preliminary searches were carried out by using search terms such as 'low back pain' combined with keywords like 'subgroup', 'effect modifier' and 'moderator'. However this only yielded publications that had terms 'subgroup' in the title/abstract only, missing out publications that had the term 'subgroup' in the main text. We therefore re-ran searches using keywords ('trial') for RCTs and ('Observational', 'Cohort', 'Prospective studies') for non-RCTs or observational studies separately and then combining them with terms 'low back pain' (see Supplementary file 1). Hand searching and screening of included studies were carried out for additional studies.

Study selection and data extraction

Two authors (TG & DE) scanned titles and abstracts based on the pre-specified inclusion criteria. Data extraction was carried out by two reviewers (TG & DE) independently, using a standardised data extraction form. A third reviewer (MU) was available to consult if there were discrepancies.