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Associations of treatment effects between follow-up times and between outcome domains in interventions for somatoform disorders: review of three Cochrane reviews.

Running head:
Outcome domains and measures for somatoform disorders

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ABSTRACT

Background

Interventions for somatoform disorders typically address a range of outcomes. We aimed to examine treatment effects across outcome domains and specifically assess the association, at study level, between short and long term treatment effects and between treatment effects in different outcome domains.

Methods

We used data from recent systematic reviews of interventions for somatoform disorders to address three questions: We described outcome domains and measures by compiling forest plots of standardised mean difference. We examined the association of changes in outcome between short and long-term and between different outcome domains by non-parametric correlation.

Results

We analysed data from 47 studies across four outcome domains: physical symptoms, health-related quality of life, depression and anxiety. Short-term and long-term treatment effects within each outcome domain were broadly similar and were correlated. Reported reduction in physical symptoms was correlated with reductions in depression (ρ = 0.73, p=0.002) and anxiety (0.70, p<0.001) and increase in quality of life (0.54, p=0.03).
Conclusion

Short term changes in outcome measures are correlated with longer term changes; outcome changes are correlated across domains independently of the type of treatment.

Keywords

Somatoform; Medically Unexplained Symptoms; Outcome Measures; Interventions; Systematic Review
Background

Somatoform disorders, including medically unexplained symptoms, are characterised by patients experiencing physical symptoms which cannot be fully explained by organic disease, in multiple body systems, and in a way which impairs quality of life and / or increases healthcare use [1]. A number of intervention approaches have been evaluated in randomised controlled trials, and in turn the findings of these trials have been synthesised in systematic reviews of pharmacotherapy[2], psychological interventions[3] and enhanced medical consultations[4].

While future interventions and trials are being developed there is a need to ascertain the best outcome measures to use in trials and other evaluations [5-7]. Such outcome measures should be validated, accurate and responsive to therapy [8]. They should also be of importance to patients [7] and should persist over time. The choice of outcome measures has consequences for sample size calculation [9](and thus the feasibility and cost of trials) as well as for external validity with clinicians and patients. The first step of such a process is typically a review of systematic reviews of trials to examine current and past practice [8].

We aimed to conduct a review of three recent Cochrane reviews to address the following objectives in relation to trials of interventions for somatoform disorders or medically unexplained symptoms. : (1) To describe, in one place, which outcome domains (e.g. physical symptoms, depression) were reported and
which measures were used? (2) To examine the relationship between short-term and long-term treatment effects within outcome domains (3) To examine the association between treatment effects in one outcome domain and treatment effects in another.

**Methods**

**Overview of methods**

We aimed to use outcome data which had already been extracted, quality-assessed and summarised for meta-analysis from recent Cochrane reviews of interventions for MUS / somatoform disorders. In comparing data across reviews, we took the perspective that for any given outcome measure, the effect of a study on that outcome would depend on many factors relating to the intervention, patients, and setting. Prior reading of the reviews showed that there was a high level of conceptual and contextual heterogeneity across the studies. Additionally, we recognised that in some instances the type of intervention might also influence the choice of measure (for instance studies of antidepressant drugs typically include the Hamilton Depression Rating Scale).

We thus aimed to synthesise data in a way which allowed us to visualise patterns of response across a diverse range of interventions [12,13], while stopping short of conducting formal statistical meta-analysis to produce summary effects with magnitude and precision.

**Data sources**

We extracted data from three systematic reviews of interventions for somatoform disorders[2-4]. These had all been published in the preceding three
years and related to pharmacological, psychological, and enhanced primary care interventions. All three reviews reported outcomes as standardised mean difference (SMD)\[14\] between allocation groups at short (up to 3 months) and longer term (nearest to one year) follow-up.

We included data from studies which compared active treatment with an inactive control condition (placebo, usual care, waiting list) and from studies which compared two active treatments. Where a single active treatment was compared with a control condition we extracted SMDs of the active treatment relative to the control. Where two active treatments were compared we could not make a priori assumptions about which treatment should be more effective, so recorded SMDs as favouring the more effective treatment.

**Data extraction and categorisation**

We extracted data from tables in two ways. One reviewer (SC) extracted data from studies listed in the reviews manually, another reviewer (CB) electronically extracted data from the statistical data tables of the reviews from the Cochrane Collaboration website. Any discrepancies were sought out and resolved by reference to the original studies.

We sorted individual outcomes into five outcome domains: physical symptoms, health-related quality of life, depression, anxiety, and health anxiety. Where quality of life measures were reported at both summary and subscale levels (e.g. SF-36 physical component summary and physical functioning), we took the most inclusive (highest level) measure. While some studies used a quality of life
subscale as a measure of physical symptoms, we chose to exclude these from the physical symptoms domain as they do not specify number or impact of symptoms which are integral to the concept of somatoform disorders.

**Description and visualization**

For each outcome domain we summarized the number of studies by review, separating short term and long term treatment effects. We plotted these using forest plots in which each study's SMD was displayed with 95% confidence intervals. We grouped individual studies by the outcome measure used and plotted values in ascending order of magnitude within the outcome measure group. For each point we indicated the review from which it was taken by the symbol for the point value. As each outcome domain contained different numbers of outcome measures, some of which were only used once, we adopted a pragmatic approach to grouping small numbers of individual items together in “other measures” categories. We did not carry out meta-analysis either to generate summary measures of treatment effect or to provide statistical estimation of heterogeneity because of the contextual heterogeneity of populations, interventions and measures.

**Relationship of short term to long-term outcomes within study domains**

We examined the relationship between short and long term treatment effects in the subset of studies which reported both short and long term effects, by constructing scatter plots of short term vs. long term outcomes and calculating the Spearman non-parametric correlation coefficient. We expected that short and long term outcomes should be correlated, but wished to examine the
relationship between the two in order to inform the way that short term measures (such as from a pilot trial) might be used to guide longer term measures (in a definitive study).

**Association of treatment effects between outcome domains**

We examined the correlation between SMDs for pairs of outcome domains, where these were both reported in the same study, by constructing scatter plots and calculating the Spearman correlation coefficient. For the scatter plots, we used plotting symbols to distinguish points from different reviews and showed the best fitting regression line for all studies and for the non-pharmacological studies. As there were relatively few studies from each review, we did not calculate correlations separately. As the number of studies reporting long-term data was relatively small, we only used short term outcome data for this correlation analysis.

**Sensitivity analysis**

We identified a number of studies in the review of pharmacotherapy which compared two active drug treatments. We included them in the forest plots of treatment effects but used a different symbol to identify them from the others in the same review. None of these studies reported long term treatment effects. We conducted a sensitivity analysis of the association of treatment effects between domains with them excluded.
Results

Outcome domains and measures

The three reviews contained tabulated data from a total of 47 studies (Kleinstauber [2] 23, van Dessel [3] 18, Rosendal [4] 6). They reported data on 172 outcomes across the five outcome domains. Table 1 summarises the distribution of these outcomes by review, outcome domain and the timing of the outcome in relation to treatment as either short term (typically post-treatment) or long term. A more extensive table in which these are broken down by measure used at individual study level is in Appendix 1.

There were several outcome measures (instruments) used for physical symptoms (9), depression (9) and anxiety (6). There were fewer measures for quality of life (most studies used one of the SF- family of instruments). Health anxiety was reported for only four studies, all with one of the forms of the Whitely index. Because of this, we excluded it from further analysis and reporting. Most studies used existing and well-validated measures such as the Hamilton rating scales [15], the Symptoms Checklist [16], Beck inventories [17] or scales from the Personal Health Questionnaire [18]. Only 10/172 outcomes used either unspecified (5) or idiosyncratic (5) outcome measures; a further two used a visual analog scale for one of the outcomes.
Differences in reported treatment effects by domain and measure

Figure 1 shows the treatment effects of each study, expressed as standardized mean difference (SMD), for short term or post-treatment outcomes. Similar plots for long-term outcomes are in appendix 2.

Only 19 studies (40%) reported long term outcomes. None of the pharmacological studies reported long term outcomes. One study reported long term outcomes but no short term outcomes. Short and long-term treatment effects were correlated for all outcome domains: physical symptoms (rho = 0.78, p<0.01); depression (rho = 0.79, p<0.01); anxiety (rho =0.94, p=0.02); quality of life (rho = 0.85, p<0.01). Scatter plots of these associations are shown in figure 2. For these studies which reported both short and long term outcomes, the median (IQR) SMD at the two points was for physical symptoms -0.23 (-0.51 to 0.13) and -0.20 (-0.37 to -0.03), 16 studies; for quality of life +0.16 (0.08 to 0.25) and +0.16 (0.10 to 0.27), 11 studies; and for depression -0.05 (-0.25 to 0.07) and -0.09 (-0.20 to 0.09), 15 studies. Only 6 studies reported short and long-term outcomes for anxiety (median SMD 0.22 and 0.09 respectively).

Correlation between treatment effects in pairs of outcome domains

The plots in figure 3 demonstrate the correlation of treatment effects between domains. The correlations shown between SMD for physical symptoms and SMD for depression, anxiety and quality of life at the study level were all statistically significant: Spearman rho = 0.73 (p<0.01); 0.70 (p<0.01) and -0.54 (p=0.03)
respectively. Unsurprisingly, there was also a strong correlation between SMD for anxiety and SMD for depression (rho = 0.83, p<0.01). In the sensitivity analysis which excluded studies comparing two active treatments, correlations between SMD for physical symptoms and SMD for depression, anxiety and quality of life at the study level were all similar: Spearman rho = 0.71, 0.73 and -0.54 respectively.

**Discussion**

**Summary of main findings**

When we compared the outcomes of trials across a wide range of interventions for, and populations with, somatoform disorders, we found correlations both between short and long term outcomes and between different outcome domains. This association appeared to be independent of the treatment type.

**Strengths and limitations**

A key strength of this study is that the data had already undergone careful selection, assessment of study quality and preparation for synthesis by the authors of the original reviews. The study took as an underlying rationale, the idea, compatible with a critical realist scientific approach, that consistent processes may underpin observed data across a wide range of contexts [12,13]. While the data were too heterogeneous to conduct a network meta-analysis we used non-parametric statistics to examine patterns across studies. Nevertheless, the heterogeneity of the studies is a limitation. In particular, the review of pharmacotherapy included several studies focusing on chronic pain in treatment naïve patients which showed large treatment effects, mostly using the same
measure (Hamilton rating scale), however as these studies generally only reported short term outcomes for one domain, their inclusion or exclusion did not influence the correlations reported here. We considered extending the review by including data from reviews of specific functional somatic syndromes such as fibromyalgia which has well developed and validated syndrome-specific outcome measures [19]. We chose not to include these because such measures typically include multiple domains such as symptoms, functional impairment and emotional / psychological factors. The outcome measures reported here reflect those reported in the systematic reviews, and does not include others which were more difficult to compare across studies (e.g. health service use or costs).

**Relationship to other studies**

In comparing measures of treatment effects within and between outcome domains for a heterogeneous set of studies, this project takes an original approach which is neither a network meta-analysis [10] nor a multi-system review [11]. Rather it takes an approach which, while quantitative, has parallels with the qualitative approach taken in realist evaluation [13]: the emphasis is on common processes across contexts [12] rather than restriction of analysis to tightly defined contexts. Our findings of strong correlations at the study level between diverse outcomes (physical symptoms, anxiety and depression) suggests that despite working through diverse mechanisms (e.g. antidepressant drugs, behavioural interventions focused on symptoms) interventions appear to produce common outcomes. It is possible that similar associations across outcome domains would be seen in other conditions, such as arthritis, but we are not aware of research comparing them.
Implications

In planning evaluation of future interventions, researchers need to consider which domains and measures to use as primary and secondary study outcomes [8,9]. At first glance, the different outcomes studied may appear to be similar, however a closer look at the studies shows three things of importance. First, short term treatment effects appear to be sustained to longer term outcomes, at least for physical symptoms and quality of life. This is important as developmental and pilot studies of interventions may have limited follow-up. While sustained benefit from interventions requires testing, short term effects can reasonably be used to plan sample size calculations. Second, treatment effects in one domain are correlated with effects in others, suggesting non-specific treatment effects across different intervention types. Third, most treatment effects are small. With median SMD of 0.2-0.3 these are at the lower limits of clinical usefulness. It is not clear whether this modest effect represents a limitation of the interventions or of the outcome measures. Approaches to outcome measurement such as responder analysis [20] which examine individual responses within a study population may be informative in this regard.

Further work is needed to develop a core outcome measure set for trials of interventions. While for specific functional syndromes, there is a good case for using a composite outcome measure which covers many domains (e.g. the fibromyalgia impact questionnaire [19]), the alternative for heterogeneous
populations of patients with somatoform disorders may be a suite of measures covering a range of domains. [21]

**Conclusion**

Trials of interventions for somatoform disorders across differing interventions and study populations show broadly similar distributions of treatment effects in each of the major outcome domains. Importantly, short term treatment effects are correlated with longer term effects in all major treatment domains and effects in one domain are correlated with effects in others.
References


Table 1 Distribution of outcomes reported by domain, review and timing in relation to treatment

<table>
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<tr>
<th></th>
<th>Kleinstauber</th>
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<td><strong>49</strong></td>
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<td><strong>20</strong></td>
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</table>
Figure 1 Forest plots of short term treatment effects by measurement instrument within outcome domain

Names in the legend refer to the first author of the respective reviews. Kleinstauber(a) refers to studies from the review of pharmacotherapy which compared two drugs.
Abbreviations: BDI, Beck Depression Inventory; HAD, Hospital Anxiety & Depression Scale; HAM, Hamilton Depression / Anxiety Rating Scale; PHQ, Personal Health Questionnaire; SCL, Johns Hopkins Symptoms Checklist; SOM, Screening for Somatoform Symptoms; SFI, Medical Outcomes Study Short Form-6, 12 or 36
Figure 2 Comparison of short term and long term SMDs for studies, by outcome domain
Figure 3 Relationship between treatment effects in different outcome domains by study and review.