Model Simulations Challenge Reductionist Research Approaches

to Studying Chronic Low Back Pain

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 OPEN ACCESS

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BACKGROUND: Traditionally, low back pain (LBP) is studied using a reductionist approach, in which the factors contributing to the clinical presentation of LBP are studied in isolation to identify the primary pathology or condition linked to LBP. We argue that reductionism may not be suitable for studying LBP, considering the complex, multifactorial nature of this condition.

OBJECTIVES: To quantify the likelihood of successfully subclassifying patients with LBP and effectively targeting treatment based on a single dominant factor contributing to LBP.

METHODS: Both analytical and numerical simulations (Monte Carlo) of 1 million patients with LBP were performed. Several factors contributing to LBP were randomly assigned to each individual. The following outcome measures were computed, as a function of the number of factors: the percentage of individuals who could be subclassified by identifying a single factor exceeding a certain threshold, and the average reduction in LBP when treatment eliminates the largest contributing factor versus a multimodal treatment that eliminates a number of the randomly selected factors.

RESULTS: With an increasing number of factors, the probability of subclassifying an individual to a subgroup based on a single factor tends toward zero. A multimodal treatment arbitrarily addressing any 2 or more factors was more effective than diagnosing and treating a single factor that maximally contributed to LBP.

CONCLUSION: Results suggest that reductionism is not appropriate for subclassifying patients with LBP or for targeting treatment. The use of reductionist approaches may explain some of the challenges when creating LBP classification systems and designing effective treatment interventions. J Orthop Sports Phys Ther 2019;49(6):477-481. Epub 15 May 2019. doi:10.2519/jospt.2019.8791.

KEYWORDS: Monte Carlo simulation; classification; randomized clinical trials; risk factors; subgrouping

From the FULL TEXT Article:

Background

Lw back pain (LBP) is a multifactorial problem associated with many biological, psychological, and social factors. [8, 21, 28, 30] In most cases, the exact causes underlying LBP are unknown; hence, the term nonspecific LBP is often used. This nonspecificity makes selecting the appropriate treatment challenging for clinicians. Therefore, much of the current research efforts are directed toward identifying specific causal factors underlying the clinical presentation of LBP or toward subclassifying patients with specific characteristics (a collection of factors that determine the nature of an individ­ual’s LBP) to formulate the appropriate intervention strategies addressing these specific factors (hereafter referred to as “factors contributing to LBP”). This ap­proach is based on the rationale that when more is known about the etiology of LBP, the treatment can be more specific in addressing the factors contributing to LBP and result in better outcomes. Subse­quently, randomized clinical trials (RCTs) are conducted to evaluate whether such matching between factors contributing to LBP and treatment leads to improved outcomes compared to other treatments, standard care, or sham treatment.

The above-outlined strategy in LBP research is termed a reductionist ap­proach in the parlance of systems sci­ence. [1] In the reductionist approach, the system is broken down into smaller parts to isolate and study them compre­hensively. The reductionist approach is well suited for containable diseases, such as local infection. However, reduction­ism is less helpful when the problem is multifactorial and where interactions between biological subsystems exist. [1] These features make the behavior of a complex system difficult to predict, even when the behavior of its parts is well defined. [1] For example, studying motor control in patients with LBP is a reductionist approach that evaluates the pathomechanics of neuromuscular control in isolation from other biologi­cal, psychological, and social factors to identify the primary pathology or condi­tion linked to LBP. A natural extension of this approach is the development of intervention strategies attempting to correct those pathomechanics. [27]

Reductionism is not inherently wrong, as it allows for the identification of parts of the system (eg, factors associated with LBP) and has been useful for establish­ing factors associated with patient pre­sentations (phenotypes), an important part of patient care. The problem lies in the assumption that information about individual parts is sufficient to explain the behavior of the entire system. In the example of studying motor control using a reductionist approach, the assumption is that other biological, psychological, and social factors have minimal or no influence on motor control. Perhaps in some patients this may be the case, but the evidence suggests that motor control interventions are not superior to other interventions in the management of pa­tients with LBP, [27] which raises questions about other factors and interactions involved.

In contrast to reductionism, a systems approach takes the entire system into consideration when describing its be­havior and identifying interdependence between its subsystems. [1] Attempts to­ward such an approach have been made with conceptual, structural equation, or collaborative modeling to account for a number of factors contributing to LBP simultaneously. [5, 6, 9, 18, 25] Yet, research in LBP lags substantially behind systems biology, which rapidly progressed in re­cent years with its effective application of systems science. [4, 14] There is a critical lack of knowledge regarding the number of factors and their interactions needed to adequately represent LBP, which in turn, limits the ability to target them through treatment modalities. As spine research evolves, the trend points to­ward more complexity, with more sub­systems and their interactions requiring consideration. [6, 11]

There have been more than 1000 RCTs published evaluating various inter­ventions for LBP, such as manual thera­py, massage, acupuncture, dry needling, physical therapy, and specific exercise.15 Unfortunately, this literature collectively shows low to moderate effects and prac­tically no differences between various in­terventions.3 More importantly, to date, “no classification system is supported by sufficient evidence to recommend im­plementation into clinical practice.” [2, 7, 13] Even a triage based on various clinical prediction rules has not led to better outcomes. [13] One possible explanation for the lack of success in documenting large positive treatment outcomes could be the reductionist approach, typically applied in LBP research, whereby uni­modal intervention strategies targeting the dominant factor believed to be con­tributing to LBP are compared and stud­ied in RCTs. While this approach has its place in research, considering the ex­treme biological complexity of the spine system, the multifactorial nature of LBP, and interactions among these factors, [21, 30] an approach that addresses these issues simultaneously is needed to advance LBP research and the development of more effective intervention strategies.

The goal of this study was to high­light the challenges of studying a complex condition using reductionist approaches. Specifically, using analytical and numerical simulations, we quanti­fied the likelihood of correctly identify­ing the dominant factor contributing to LBP and of effectively treating LBP by modifying such a dominant factor. The following 2 hypotheses were tested:

(1) when dealing with a large number of fac­tors contributing to LBP, it is not pos­sible to identify subgroups effectively based on the dominant factor; and

(2) on a population scale, providing a num­ber of treatments targeting any 2 or more factors is more effective than iden­tifying and treating a single factor that maximally contributes to LBP.

If these hypotheses are true, perhaps a different research method, based on a systems ap­proach,1 could lead to the development of more effective intervention strategies for LBP.

Methods

Figure 1

We performed both analytical and numerical simulations (Monte Carlo) of a large popu­lation (n = 1 million) with LBP. Factors contributing to LBP for each individual were uniformly distributed random vari­ates (U1, U2, U3, ... Uk) between 0 and 1. For each individual, each factor Ui was normalized by dividing it by the sum of k factors to create a fraction contribu­tion to LBP; ie, the total pain/disabil­ity effect of 1 is: (X1 + X2 + … + Xk) = 1 (Figure 1). For example, for 3 factors (k = 3), a person with LBP may have normal­ized factors such as X1 = 0.3, X2 = 0.1, and X3 = 0.6. This means that factor X1 contributes 30%, factor X2 contributes 10%, and factor X3 contributes 60% to the overall presentation of LBP, totaling 100%.

To test the 2 hypotheses, we cal­culated

(1) the percentage of individuals who could be subclassified by identifying a single normalized factor (Xi) exceed­ing a certain threshold θ (where θ = 0.2, 0.3, 0.4), and

(2) the average reduction in pain/disability when the largest fac­tor contributing to LBP is identified and eliminated with the targeted unimodal treatment, versus a number of treat­ments (multimodal treatment) elimi­nating a number of randomly selected factors.

The analytical derivation and calcula­tion of the hypothesized values are pre­sented in the APPENDIX (available at www.jospt.org). To validate these analytical calculations, a numerical model simula­tion (Monte Carlo) was performed twice (macro feature in Excel 2010; Microsoft Corporation, Redmond, WA) by seeding an array with 1 million random variables between 0 and 1 and calculating the val­ues derived analytically.

Results

Figure 2

Figure 3

The maximum differences be­tween any analytically derived val­ues and the 2 simulation results were 5.28 × 10–4 and 4.75 × 10–4. These small differences indicate excellent agree­ment between the 2 methods, validating the analytical approach.

With an increasing number of fac­tors, the probability of a single factor exceeding a certain threshold (Xi>θ) tends toward zero (Figure 2). In our model, this result represents the dimin­ishing likelihood of classifying an indi­vidual to a subgroup of patients with LBP based on a single factor reaching some set threshold of contribution to the overall LBP (Figure 2). Even with a low threshold of θ = 0.2 (accounting for 20% of LBP symptoms), less than 1% of the LBP population can be subclassified when the number of factors exceeds 11.

On average, in a multifactorial mod­el, the sum of any 2 or more factors is greater than the largest factor identified in each individual (Figure 3). This simula­tion result illustrates that a multimodal intervention addressing any 2 or more factors will likely be more effective in the population of patients with LBP than di­agnosing and treating a single dominant factor that maximally contributes to LBP in each individual.

Discussion

The results from our analytical and numerical simulations of a multifactorial presentation of LBP are consistent with the data reported in the literature. With respect to the first hypothesis, our results show that with an increasing number of factors con­tributing to LBP, there is a diminishing likelihood of classifying an individual to a subgroup of patients based on the dominant factor. This could explain why attempts to identify subgroups of patients who would respond more favorably to a particular treatment have not yet been successful or reproduced. [2, 7, 13, 22, 23] Our simulations suggest that such a result would be expected if LBP were a large multifactorial problem. Reductionist re­search approaches, focusing at most on a few dominant factors contributing to LBP, are not able to address the entire complexity of this condition or document meaningful impact of interventions tar­geting those dominant factors. This sce­nario can be further complicated if many different mechanisms and factors inter­act and overlap, rendering the presence of pure subgroups rare. [16]

Based on the number of existing baseline predictors and the variance in outcomes they explain, Mistry et al [19] concluded that it is unlikely we can iden­tify a single strong moderator of LBP treatment effects. None of the RCTs they reviewed were powered sufficiently to identify differential subgroup effects, and appropriately powered studies would be practically unrealistic. [19] To circumvent this problem, Patel et al [23] pooled data from 19 back pain trials that provided a data set of 9328 patients. Yet they, too, did not find any subgroups that would benefit from specific treatment, and, more importantly, they calculated that such an approach to identifying patients would not be cost-effective.

Our simulations are consistent with such findings. With only 12 factors con­tributing to LBP, only 0.5% of the LBP population could be subclassified based on a single factor and treated to achieve a minimal clinically important difference of a 20% reduction in pain [20] (θ = 0.2) (FIGURE 2). What if there were 21 factors,24 69 factors,8 or more6? Our simulation re­sults indicate that this percentage would be 10–6 and 10–36 for 21 and 69 factors, respectively. Even if such an RCT could be conducted, it would likely have little clinical relevance.

With respect to the second hypothesis, it appears that multidisciplinary (ie, mul­timodal) rehabilitation strategies consis­tently show better results when compared to any single approach. [12] Likewise, our simulations suggest that when dealing with a multifactorial problem, it is more effective to treat several factors than to try to diagnose and treat the single domi­nant factor that contributes the most to LBP in each individual. Perhaps future research efforts should focus on design­ing effective multimodal, integrative, and adaptive approaches to the management of LBP. [17] As the management of patients with LBP continues to progress toward personalized medicine, multimodal treat­ment sequence, timing, and interaction effects will need to be considered.

There are, however, instances in the literature where the combination of 2 treatment approaches (eg, physical ther­apy and cognitive behavioral therapy [29]) was not superior to a unimodal treatment (physical therapy). One possibility in this example is that a single treatment mo­dality (physical therapy) affected several factors contributing to LBP, [31] including those targeted by the cognitive behavior­al therapy. In our model, such a situation could be simulated by a comparison of a single treatment targeting several fac­tors contributing to LBP versus the same number of unimodal treatments target­ing a single factor. Both interventions would show the same effectiveness in such a comparison. Alternatively, in the above example, the psychological factors targeted by cognitive behavioral therapy might not have been important factors contributing to LBP in these patients.

Several assumptions determine the behavior of this model simulation. The assumption having probably the biggest effect on the results was that various fac­tors contributing to LBP are uniformly distributed across the population with LBP. That is, all factors have the same probability of being present in each in­dividual, and there is no factor occurring more frequently in the LBP population. If some factors were occurring more frequently, it would have been easier to identify a cluster of patients with these factors. We submit, however, that in real­ity the distribution of factors contribut­ing to LBP might be closer to uniform, because the studies thus far have failed to identify a dominant modifiable factor or subgroup of patients with LBP. [13] The simulated treatments were unrealistic because they completely eliminated the targeted factors contributing to LBP in every case. Most likely, the real treatment effects would have been much smaller, because interventions for LBP are not 100% effective, and not all individuals respond to them.

Another assumption that impacted the model results was that the model was unstructured (Figure 1). Such a mod­el assumes that each factor is indepen­dent and directly linked to LBP, which is unlikely to be the case. However, we purposefully chose such a model, given that it represents the common factorial analyses used in LBP research. The addi­tion of interactions between the factors, which could represent serial, parallel, and feedback connections, would make the model more complex, strengthen­ing the argument that reductionist ap­proaches are not appropriate to study the complex phenomena represented by such a model.

Conclusion

Research to identify the factors, or group of factors, that contribute to LBP and to understand the ef­ficacy of individual treatment interven­tions is necessary but not sufficient to address the LBP problem effectively. As demonstrated by our unstructured mul­tifactorial model of LBP, simply identi­fying components within the model and not the structure of the model (ie, the in­teractions between these components) is not likely to lead to robust classification or better treatment effects.

To advance LBP research, more so­phisticated modeling methods that con­sider the structure of the system being studied [9, 18] and possibly the dynamics of the system[1] (LBP symptoms and treat­ment effects are not static and change with time) are needed. Future research should involve a paradigm shift toward a systems approach, which allows for integration of knowledge in a more sys­tematic and effective way. [26] A systems approach has been specifically devel­oped to address complexity and success­fully implemented in engineering. Such an approach appears to be well suited for studying medical conditions that are multifactorial in nature. [1]

Key Points

FINDINGS: With an increasing number of factors contributing to low back pain (LBP), the probability of finding sub­groups of patients, based on a single fac­tor exceeding a certain threshold, tends toward zero. Arbitrarily applying treat­ments addressing any 2 or more factors was more effective in the simulated population of patients with LBP than diagnosing and treating a single factor that maximally contributed to LBP in each individual.

IMPLICATIONS: A reductionist approach aimed at identifying 1 or a few domi­nant factors contributing to LBP, or subclassifying patients based on those factors, will likely not result in the dis­covery of strong modifiers of treatment effects. The simulations suggest that multimodal management of LBP will likely be more effective than unimodal treatment.

CAUTION: The main assumptions influ­encing the specific numerical results were that factors contributing to LBP were uniformly distributed and that there were no interactions among them. While these assumptions affect the com­plexity of the modeled LBP problem, the simulation trends will likely hold for more complex models.

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