

Methodological challenges in measuring pain and how to overcome them

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Abstract

This paper discusses some of the main methodological challenges involved in carrying out research on pain, especially pain experienced by people with multiple sclerosis (MS). It starts by arguing the most common challenges in pain related research methodology, which will form the framework of this article. Within this framework, the issues include pain definition, the self-reported nature of pain, the complex and multidimensional nature of pain, confounders, study design, and other methodological challenges faced by researchers in using assessment tools and scales. Presenting a universal framework for pain measurement, suggesting appropriate study design, and using comprehensive assessment and appropriate statistical method to analyze the collected data will be the main solutions for those challenges that are discussing at the end of this paper. Finally, paper will end with a conclusion of study's implications and significance.

Keywords: Methodological challenges, Pain assessment, Multiple sclerosis, Disability, Structure equation modeling

Introduction

Pain is a common health problem such that 29% of Canadians in the general population report significant chronic pain (1). The field of pain research is becoming increasingly important. Pain is commonly measured in inpatient and outpatient settings, and is managed to some extent by most health care professionals. Therefore, it is not surprising that there should be an extensive amount of attention concerning the research on pain. Dealing with pain presents unique challenges. In 1995, the American Pain Society (APS) set out guidelines indicating that a first step in improving the treatment of pain is its adequate measurement. Pain cannot be relieved unless pain has been correctly assessed (2), and similarly pain cannot be correctly measured without appropriate study design. Presentation of

collected data and interpretation of results using appropriate statistical methods are also important parts of the most quality assessment process that need to be taken into consideration when study on pain. Understanding of the complex nature and interactive mechanisms underlying pain symptom and its related factors has the potential to enhance pain management.

The purpose of this paper is to provide an overview of the main aspects of existing challenges inherent in measuring pain and discuss proposed approaches to dealing with those challenges.

Challenges

Pain definition

Pain definition is not as straightforward as it might first appear (3). The International

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Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (4). Pain is often perceived as mysterious symptom that varies in quality, duration, severity, and location (5). Therefore, there is always an issue about which dimension of pain can be considered as the best illustration of pain. For example, pain can be described in terms of its intensity (i.e. how much pain), its quality (e.g. if it is burning, aching, dull, sharp, etc.), its duration (i.e. how long pain lasts), or its distribution (6, 7). Most of the studies on pain, however, either have not provided a definition for pain experience, or vary considerably on pain definition, with some requiring a specific pain duration or severity, and others not specifying the criteria used to determine the presence of pain (8).

In addition, many of studies on pain have not distinguish acute pain from chronic pain, nor provided similar definitions for what constitutes being classified as having chronic or acute pain (9). This causes variation in the results of the different studies. For example, in one community-based study, 44% of 442 persons with MS were categorized as having chronic pain (10). This prevalence rate was lower than many other studies of pain in MS because the definition used for including participants as having chronic pain in this study was more restrictive than many other studies. In this study it was required that respondents define their pain as both persistent and bothersome for a 3-month time period, while other studies have assessed pain prevalence in shorter time (11).

Moreover, although persons may experience many forms of pain with multiple etiologies, type of pain and the way pain is classified are not well recognized in many studies (9). For example, some studies include any type of pain, while others exclude certain types of

pain from consideration, such as headache, or visceral pain (5). Uncertainty about the extent of the pain type makes it difficult to determine whether symptoms are more consistent with one condition or multiple conditions (12). For instance, it is important to note that the overlapping symptomatology between headache and musculoskeletal pain, or other symptoms increase the occurrence of a second pain.

Dissimilar points of view regarding a patient's pain related outcomes and inappropriate definition of pain across studies provide different results of pain and so limit comparison across studies (13).

Pain as a patient reported outcome

Pain is a personal experience with subjective properties that cannot be measured directly (14). Pain is often assessed using self-reported outcome measures to collect meaningful information about perceptions an individual may have about their pain experience over some specified period of time (15). This means that when dealing with the patient in pain, the guiding principle should be, “pain is whatever the experiencing person says it is, existing whenever the experiencing person says it does” (16).

A big deal of research in patient reported outcome is that self-reported ratings are affected by situational factors such as memory distortion, momentary mood states, and personal characteristics (17). Pain scores can be easily exaggerated or minimized by the person completing them (18). Patients with mental illness and cognitive impairments may have some limitations in insight about their pain experiences (19). The willingness of patients to report pain could also contribute as it may be expected that not all patients are able or willing to provide correct estimations of their pain perception (20).

In addition, given that self-reported measures are affected by emotion, it is reasonable to hypothesize that self-reported assessment may be especially challenging in individuals with pain who experience

variety of emotional symptoms such as anxiety and depression (21). For example, it has been realized that participants who are happy, more likely report positive information in their ratings, while participants may rate their pain more severe while they are sad (22), depressed (23), or anxious (24).

Like all questionnaires, the way the instrument is administered can have an effect on the final score as well. For example, if a patient is asked to fill out the form in front of other people in a clinical setting, social expectations might report an inaccurate response (22).

Further, although self-reporting put the patients at the center of their own assessment (25), and can be considered as the most reliable indicator of the patient's pain (26), recall bias due to memory distortion, and response shift may limit the reliability of patients' self-report data and bias the results of the study (27).

Recall bias

Recall bias can happen when outcomes are measured using self-reported tools, and when subjects are required to recall past events. It has been found that respondents may not be able to exactly remember their pain severity, frequency, or duration over a past period of time (18). This bias may be more serious in neurological health conditions such as MS population as cognition impairments, such as memory and concentration problems, are frequent in people with MS (28). Another methodological concern in recall bias is the appropriate time during which to conduct data collection in order to achieve a balance between maximizing the accurate recall of events and minimizing any potential distress to the respondent (29).

Response shift

In studies that participants should fill out the questionnaires by themselves, response shift may occur by subjects' misunderstanding of questions or

redefinition of the construct (30). The difference between true change and the observed change can be considered an overall measure of response shift (31). If response shift is not taken into account, values may be incorrectly interpreted (32). Sprangers and Schwartz have distinguished three types of response shift (31) including recalibration, a change in the respondent's internal standards of measurement, reprioritization, a change in the respondent's values, and reconceptualization, a redefinition of the target construct (34-36). As an example of recalibration, persons with MS may rate a back pain as 7/10 on a 0 to 10 numeric rating scale, later acquire a headache, which is much more painful, so next time if they want to rate their back pain, they realize that the earlier back pain was probably only a 3/10 (34). As an example of reprioritization, an individual originally values pain over spasticity and muscle weakness. After a relapse period and fear of activity limitation, this person may find physical function is now more important concept to him than pain (34). With regards to reconceptualization, persons might give different answers about their pain on self reported measures over time, not because their pain has changed, but because they might have changed their conception on pain, for example, they may feel that important aspects contributing to their life is activity, but following a MS diagnosis, they may now feel that pain is more important contributors to their life (34).

Pain as a multidimensional health outcome

The official definition of pain endorsed by the International Association for the Study of Pain emphasizes that pain is a complex symptom (4). It has been found that responses to pain in different patients are unique; different people may experience different pain expressions from the same stimulus (37), so it can be inferred that the strength and unpleasantness of pain is, neither simply nor directly, related solely to

the nature and extent of tissue damage (38). Therefore, the correct understanding of pain requires both an understanding of the nociceptive system, and control of the many other factors that modify pain perceptions (39).

The primary limitation of previous studies is the consideration of a relatively limited range of possible intermediate variables that might account for the relationship between pain and other related factors. Previous studies have generally looked at pain as a unidimensional health outcome, and have focused on either a single specific symptom or a single dimension of pain. However, it is important to understand that pain should not be considered and measured as a unitary concept, because it has been shown to have both distinct mental and physical components (40).

From the multidimensional view of pain analysis, pain is considered as a complex symptom with many intermediate variables (41). Intermediate variable means a variable in an interrelation pathway that may provide variation in the relationship between exposure and outcome (42). As it is often not clear whether such a variable is directly responsible for a symptom or whether it is an indirect provocation that causes certain processes linked with the symptom, it is called a mediator (43). In pain studies, this means that the effect of other variables on pain, or the effects of pain on other variables, may be mediated by other factors (41). The complexity of the relationship is based on the position that pain influences intermediate variables, and those intermediate variables influence pain. Individuals with MS have number of other ongoing symptoms, such as fatigue, mood disorders, and cognition dysfunction (44), with patterns of improvement that may differ widely among patients and affect their pain perception (45). It has been found that concurrent symptoms, in comparison to a single symptom, probably have a stronger effect on an outcome (46), because concurrent, interrelated symptoms can modify each other and increase the severity

of the symptom experience (47, 48). For instance, pain is considerably worse when one is fatigued (46), or depressed or anxious (40, 49). In particular, depression or anxiety, which naturally results from chronic pain, may also more increase risk of chronic pain (50, 9). Unfortunately, previous studies consider a relatively limited range of possible concurrent, interrelated symptoms might account for the relationship between pain and other related factors.

Pain assessment tools

There are several common types of pain self-reported measures such as Numerical Rating Scales (NRS), Visual Analogue Scales, McGill Pain Questionnaire (MPQ), and Brief Pain Inventory that have been used in MS population (9, 11). One of the challenges related to measurement tools is scales' heterogeneity and lack of unique standard measure to assess the same construct. This makes it difficult to compare the results across studies. For example, it is not possible that we compare the results of a study that used a 0 to 10 scale to measure pain with another that used a 0 to 5 scale. In addition, most of the time, rating scales developed for the general population are used in MS population, and this produce ceiling effect that is the scores of those individuals may fall at the bottom or the floor of a scale and the rating yields little useful information.

Moreover, most of the pain related instruments, such as NRS and VAS are unidimensional scales that are often used to assess only one dimension of pain which is more pain severity or intensity (51). However, there is huge evidence that pain has at least two dimensions, a sensory and an affective one (52, 53). Thus, unidimensional pain scales might be inadequate, since it is hard to know which dimension of pain the patient is rating and how he/she understands the different dimensions to rate. It can also be expected that lack of adequate education on pain, adequate knowledge of operation, and

practical procedure for assessment of pain in therapists involved in providing the assessment and treatment, continues to be a problem for pain appropriate measurement (54).

Another problem with pain related measures is that data of these tools are often analyzed as continuous data, and many assume that scales used to assess pain are linear metricscales and their values are numerical; however, most measures of pain-related patient-reported outcomes are comprised of ordinal rating scales. An ordinal scale orders the response options, for instance pain severity, but unlike interval scales, it does not define the magnitude of the interval between categories (55). For example, when an individual rates his pain on a scale of 0 to 10, a rating of 4 should not imply twice as much pain as a rating of 2. In addition, the spacing between response options in ordinal scales is not necessarily equal (55). For example, on a 0-10 VAS, change in pain intensity from 8 to 6 might not be considered of similar magnitude of 5 to 3. This issue should be considered while interpreting the results of the studies.

Confounders

Confounding is a special type of bias when the effect of the factor under consideration is confused with effects of other factors not directly relevant to the study purpose (56). Due to complexity and multidimensionality nature of pain, there are many variables that can be considered as cofounders while study on pain (9, 10). For example, a large number of patient characteristics, such as personality factors, previous life experiences, and cultural factors, may become important covariates to evaluate the validity of MS pain (9, 10). It has also been shown that demographic variables, such as age and gender, factors related to the heterogeneity and complexity of the disease itself, such as duration of illness, and disease subtypes, and developmental issues, such as illness progress, may affect pain reporting in MS populations (9-11). As

an example from the general population, it has been realized that women often report more intensive pain, and may have lower pain tolerance than men (57). Ethnicity (58) and race (40) can alter pain perception as for example, different ethnic populations may have different pain tolerances. Psychological factors, such as psychiatric disorders, behavioral disturbances, fears, attitudes, and beliefs (59, 60), and type and dosage of medication and analgesic drug (61) have also been realized that may influence pain perception and thus the validity of results and should be considered by researchers while study on pain.

Limitations related to the study design

One of the other limitations of the study on pain is related to study design. As it is known randomized controlledtrial (RCT) is considered to be a gold standard design in research methodology (62) since it randomly allocate people into different groups, so protect most of the potential confounders and selection bias, thus, increase the accuracy of the study results (56). Unfortunately, the number of RCT in the area of MS population suffering pain is very limited and most of the studies in pain area are cross sectional which is often considered as a weaker design as it has considerable biases due to confounders (56) and failed to establish the timing between pain and other related variables (63).

Challenges of statistical analysis

The limitations and challenges of statistical analyses is another challenges that need to be taken into consideration when study on pain. As mentioned before, pain is a complex and multidimensional phenomenon. Thus, studies involved pain require complex models to simultaneously evaluate the complex interrelationships among pain related outcomes with different biological, psychological, and social factors under a specific health status. In addition, in pain research, there is a need for the development and evaluation of alternative

theoretically models delineating the relationship among all related factors. These complex relationships between multiple constructs cannot be analyzed and modeled with traditional statistical methods such as regression. Regression is the most well known statistical test for researchers and clinicians to analyze the simple relationship between different variables, while has several challenges that limit its application as the most appropriate statistical analysis in pain research. Regression does not have the ability to simultaneously compare the effects of different variables on more than one outcome in the same model and it only performs the evaluation in the sequential steps for each outcome of interest (64). One way of addressing this problem is to choose a smaller set of variables by using model selection methods, but since most model selection criteria are highly data dependent, this does not allow the model to reflect the subject-matter knowledge. This is also not encompassed by repeated measures analyses which deal with the same outcome at different time points. These limitations are intimately linked with one another, and as a whole, warrant very specific attention from a statistical point of view.

Solutions

General solution

Having a common framework: As mentioned before most methodological challenges of pain in MS are related to heterogeneity across studies. To solve this problem, it is necessary to have a universal interactional conceptual framework that could help researchers view pain as a multidimensional health outcome, measure pain in the same way, consider its mediating factors, and significantly help advance our understanding of some of the variability in individuals' adjustment to pain, especially chronic pain (41). Bringing interdisciplinary health professional teams together and facilitating communication and interaction are other benefits of having

a common framework (65). In this paper the International Classification of Functioning, Disability, and Health (ICF) (66) is proposed as a common framework to measure pain.

The ICF is a companion to the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD), which was developed "to simplify the process of describing, classifying, and measuring function and health" (66). ICF is considered to be a universal, interactive, comprehensive, and biopsychosocial framework that can be used over a broad range of any health condition and by all health care professionals to encourage multidisciplinary teamwork in the treatment of patients (66).

ICF core sets have been developed for a number of health conditions, such as MS (67) and rheumatoid arthritis (68). Most pain conditions in MS are probably symptom-based conditions rather than a specific, tissue-based pathology, so as a complex phenomenon the application of the ICF model to describe MS pain has challenges of the identification of the relationship between pain-related outcomes and the mediator factors that affect them, while addressing the most promising ways for their improvement. This structured approach to pain management helps to systematically review pain consequences, to define therapy goals, and to optimize pain treatment by matching interventions that may be most responsive to reducing pain and its related disability.

Comprehensive assessment: Considering that pain has a multidimensional nature, pain assessment should include a combination of some performance-based measures (e.g., sitting or standing tolerances) and external criterion variables (e.g., return to work) (25, 37). To provide a more comprehensive view of the patient's pain, pain information should also include severity, quality, location, and duration of pain experience (14). What causes, increases, and relieves the pain; and how the pain has affected the patient's

functional status and quality of life are also important factors that should be considered (7). In addition, to control and understand effects of psychological factors on pain perception, some of the variables, such as attitudes and beliefs, depression, anxiety, mood, pain coping strategy, and fear avoidance behavior, need to be evaluated as parts of a comprehensive pain assessment as well (54). As pain potentially affects many aspects of a person's life, in the assessment of pain, many domains, such as activities of daily living, social skills, social supports, employment status, life satisfaction, family relationships, and use of leisure time may also be relevant (37). However, it is important to notice that too many outcome measures for the sample size leads the large number of statistical calculations and reduces the ability to find a significant difference between the groups (69).

Moreover, pain should be assessed at regular interval; however, the frequency may vary depends on the situation of patients and purpose of study (14). For example, a patient in relapse or with acute pain may require day-by-day measurements, while a patient in remitting or with chronic pain may require to be controlled for weeks or months. Efforts are also needed to improve health cares' awareness of patients' pain characteristics to provide appropriate assessment using reliable and valid approaches (65).

Specific solutions

Solution for recall bias

As it has been assumed, to minimize memory bias and obtain accurate data the ideal time to recall pain should be short, for example one week proceeded of the data collection, because the general literature on the recall of past events have indicated that "the longer the length of time between the event and the administration of a survey/interview, the more likely the event may be underreported" (71). One month and three months, are considered long time

and are prone to bias. In addition, this type of bias can be avoided by using recorded data to supplement information obtained from other sources (29). For example, verification of accuracy of data can be achieved by comparison between patient reports with their medical record, or their health-cares reviews, or in-person interviews (29).

Solution for response shift

Response shift assessment should be part of any self-reported pain measures as it will add to the understanding of how people adapt to their pain symptoms with chronic illness, such as MS (30). The following methodological approaches can be considered to reduce the effects of response shift: "(1) obtain a consensus on terminology and theoretical models used, to ensure that all researchers and clinicians are at the same starting point; (2) determine the clinical importance of response shift; (3) determine the best way to measure and adjust for response shift as a clinically important confounder; (4) ascertain how response shift can best be identified when response shift is the focus of clinical treatment; and (5) establish what methods can be used to translate response shift knowledge into real-world settings" (72, 77). In practice, various methods for response shift detection have been proposed (72, 31). Most methods involve design consideration (pre- test, post- test) and other additional administrations of the same measure (e.g., then-test, or ideal-test), or additional alternative assessments of the target construct (e.g., interviews, or preferences and pair wise comparisons) (36). Plus these methods, there are several analytic methods to evaluate response shift (72). They include the 'Transformation Method', the Coefficients of Congruence Method, and the Analyses of Covariance Structures (72), which are all special cases of structural equation modeling (SEM) (36). Because of the limited feasibility and challenges of other methods, analytical approach continues to be a promising

method for evaluating response shift in clinical studies (72).

Solving challenges related to measurement tools

The choice of pain scale requires careful consideration as any instrument can meet the many demands for pain data across various settings (43). The potential utility of any instrument needs to be evaluated based on the specific questions that are being asked within their target group. For example, this may happen in participants suffering MS with disability and physical illness, when a long pain inventory's reliance may be affected by some physical symptoms, so bias the scores due to symptoms of illness, rather than of real pain. The solution is to use a screening scale consisting of items to be independent of physical dysfunction may be considered (15). In addition, it has widely been accepted that pain has at least two dimensions, a sensory and an affective one (52, 53). Thus, there is a need to develop an assessment tool that not only assess both pain sensory and affective components, but assess pain in relation with all other related factors, such as activity, work, and other symptoms (54). Such an assessment tool deals with the complexities of pain and also allows clinicians to assess pain comprehensively within the biopsychosocial model (15). For example, the Pain Outcomes Profile (POP) which was developed by the American Academy of Pain Management is a questionnaire that assesses pain perception, perceived physical impairment due to pain, and several aspects of emotional functioning (73). In addition, it includes three scales in the domain of perceived functional impairment due to pain including mobility, activities of daily living, and vitality. Self-reported emotional functioning can also be assessed with two scales: negative effect sub scale, which measures feelings of depression and anxiety, and fear sub scale which measures fear of re-injury due to increasing activity (73).

The conceptual simplicity of the tool and the amount of effort demanded from the responders in completion are the other factors that affect the compliance rates, and should be considered (75). The choice of pain scale also requires considering issues such as age, language facility, and psychological capabilities of their target group (54).

Clinicians, and investigators should come to obtain a consensus to determine what is required from an adequate measure for pain and also to help to design and develop such a comprehensive and accurate measure (65). A combination of patients, clinicians, and investigators centered evaluation tool help to acknowledge the views, experience, and perspectives of all participants involved in the health care process (74). Ideally, such a tool should satisfy the clinical needs of both the patient and clinicians, should be simple to use, should be reliable, valid, and responsiveness (13). The use of standardized measures also facilitates the evaluation of treatment interventions, and enables comparisons between patients (65, 54).

Solutions to control confounding

Several methods are available to control confounding, either by preventing confounding or by adjusting for it in the analysis. First, restriction which means to reduce ranges of values for confounders in determining admissibility into the study, for example restriction to males only, or to a specific age range. The disadvantage of this approach is that the generalizability of the study is limited to the narrow group included in the study, so limits the external validity of study. Second, matching which means to match the comparison groups with respect to the confounders, for example for age or gender. So, this can be less restricted than selecting a narrow population of interest. Analysis of results from matched studies needs to the two groups that are not statistically independent, so often reduces the precision (56). In addition, matching for several variables simultaneously can cause

that any potential association drops off, and results are never statistically significant (76). Third, stratification, which means restriction of the analysis to narrower ranges of the confounders for example disease severity (62). Advanced statistical methods of analysis such as multiple regressions may explore the specific types of relationships as well (76). Finally, confounding could also be minimized by appropriate design of study for potential confounders (76) that the following section will discuss about this.

Solutions for study design

To better reflect the pain experiences of persons with MS, research methods which examine the pain experiences of patients within the social and environmental context, in which they occur, are preferred. As mentioned before, although in theory doing more RCTs in clinical studies is encouraged (62), it is often not possible in the area of pain to run a RCT. Running longitudinal studies perhaps can be suggested as one of the best study designs in pain research. A longitudinal study, which is one type of observational studies, means repeated measures of the same variables over long periods of time; thus, it has more power than cross-sectional studies (56). Additionally, in contrast to cross-sectional design, longitudinal studies follow up the same patients over long time; therefore, the differences observed in those patients are less likely to be the result of developmental differences, natural history, predictors, or confounders (56). Conducting case control studies, with cases (defined as individuals with MS who have pain) and controls (defined as individuals with MS who have no pain) compared on outcome of interests could be another adequate study design (77).

Solving challenges of statistical analyses

To be able to study pain in a modeler framework with complex interrelationships between multiple variables, a more

complicated or complex statistical method is needed to simultaneously test and analyze data in a hypothesized framework model that may not be directly testable with simple analysis methods, such as correlation and regression. Structural equation modeling (SEM) is often the only statistical analysis by which many of the issues that addressed before can be solved by testing and comparing the proposed theoretical models. Two main goals in SEM are: to understand the patterns of correlation among a set of variables, and to explain as much of their variance as possible with the model specified (80). The use of SEM in the medical sciences has increased considerably in recent years (79, 80). SEM is a powerful, flexible, and comprehensive statistical approach to compare the effects of different variables at one point in time, and provides a flexible framework for testing a range of possible relationships between the variables in the model, including mediating effects and possible confounding variables (81). SEM, a mix of correlation, regression, factor analysis, and path analysis, can model all regression equations simultaneously, thus providing a flexible framework for testing a range of possible relationships between the variables in the theoretical model, including mediating effects and possible latent confounding variables. SEM is a useful tool for health outcomes research, but it requires a sound conceptual understanding of the variables that are measured and the hypothetical relationships among the measured and latent variables that go beyond the technical issues summarized in this paper.

Conclusion

This study addressed several methodological challenges in the study of pain. A major challenge is lack of pain definition in a way that best reflects its perspective (3, 9). The multilevel nature of pain also establishes the complexity of pain and emphasizes that pain should be studied within a multidimensional approach

targeting all contributing factors. Other methodological challenges include use of different instruments, the self-reported nature of pain (17, 18), inappropriate study design (56, 63), confounders (9, 10), response shift (30), recall bias (18), and challenges related to statistical analysis (64). These limitations are intimately linked with one another, and as a whole, warrant very specific attention from a methodological point of view.

ICF was introduced as a general approach to solve the methodological challenges related to complexity and multidimensionality nature of pain (66). Additionally, it became clear that researchers need to come to obtain a consensus on an appropriate approach to assess pain comprehensively (65, 74). Moreover, to be able to study pain in a modeler framework with complex interrelationships between multiple variables, a more complicated statistical method such as SEM is needed to simultaneously analyze the data (79, 80). The issue of response bias and response shift also was adequately addressed using a mix of modern statistical and qualitative approaches. Confounding could also be minimized by appropriate design of

study, and proper statistical adjustment for potential confounding variables (76).

In short, the practical difficulties of research in patients with pain are considerable but, with adequate planning, they can be overcome. This would be valuable for clinical practice because a more successful pain measurement leads to optimize pain symptom management. By taking a systematic approach to the literature on pain, a methodological agenda for research could be proposed.

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Conflict of Interest

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References

1. Moulin DE, Clark AJ, Speechley M, Morley PK. Chronic pain in Canada--prevalence, treatment, impact and the role of opioid analgesia. *Pain Res Manag.* 2002; 7(4):179-84. doi:10.1155/2002/323085.
2. American Pain Society Quality of Care Committee. Quality improvement guidelines for the treatment of acute pain and cancer pain. *JAMA.* 1995; 274(23):1874-80. doi:10.1001/jama.1995.03530230060032.
3. Fine PG, Hare BD. The pathways and mechanisms of pain and analgesia: A review and clinical perspective. *Hasp Formal.* 1985; 20: 972-85.
4. IASP Subcommittee on Taxonomy, Pain terms: A list with definitions and notes on usage. *Pain.* 1979; 6 (3): 249-52.
5. Von Korff M, Crane P, Lane M. Chronic spinal pain and physical-mental comorbidity in the United States: Results from the national comorbidity survey replication. *Pain.* 2005; 113(3):331-9. doi:10.1016/j.pain.2004.11.010.
6. DeGrazia D, Rowan A. Pain, suffering, and anxiety in animals and humans. *Theor Med Bioeth.* 1991; 12 (3): 193-211. doi:10.1007/BF00489606.
7. Hester NO, Miller KL, Foster RL, Vojir CP. Symptom Management Outcomes: Do They Reflect Variations in Care

- Delivery Systems. *Med Care*. 1997; 35 (11): 69-83. doi: 10.1097/00005650-199711001-00008.
8. Turk DC, Dworkin RH, Allen RR. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2003; 106(3):337-345. doi:10.1016/j.pain.2003.08.001.
 9. Ehde DM, Osborne TL, Jensen MP. Chronic Pain in Persons with Multiple Sclerosis. *Phys Med Rehabil Clin N Am*. 2005; 16(2): 503-12. doi:10.1016/j.pmr.2005.01.001.
 10. EhdeDM, Gibbons LE, Chwastiak L. Chronic pain in a large community sample of persons with multiple sclerosis. *Mult Scler*. 2003; 9 (6): 605-11. doi:10.1191/1352458503ms939oa.
 11. Archibald CJ, McGrath PJ, Ritvo PG. Pain prevalence, severity and impact in a clinic sample of multiple sclerosis patients. *Pain*. 1994; 58 (1): 89-93. doi:10.1016/0304-3959(94)90188-0.
 12. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med*. 2000; 160(2):221-7. doi:10.1001/archinte.160.2.221.
 13. Steiner WA, Ryser L, Huber E, Uebelhart D, Aeschlimann A, Stucki G. Use of the ICF Model as a Clinical Problem-Solving Tool in Physical Therapy and Rehabilitation Medicine. *Phys Ther*. 2002; 82 (11): 1098-107. doi:10.1093/ptj/82.11.1098.
 14. Erstad LB. An Introduction to Acute Pain Assessment and Management. *Am J Pharm Educ*. 1995; 59: 180-4.
 15. Weissman DE, Matson S. Pain Assessment and management in long term care setting. *Theo Med*. 1999; 20: 31-43. doi: 10.1023/a:1009923907285.
 16. McCaffery M. Pain Control: Barriers to the use of available information. *Cancer*. 1992; 70(5): 1438-49. doi:10.1002/1097-0142(19920901)70:3+<1438::aid-cnrcr2820701536>3.0.co;2-w.
 17. Schwarz N, Strack F. Reports of subjective well-being: Judgmental processes and their methodological implications. The foundations of hedonic psychology. In book: *Well-being: The foundations of hedonic psychology*, Edition 1; Publisher: Russell-Sage, Editors: D. Kahneman, E. Diener, N. Schwarz, 1999; P: 61-84.
 18. Smith DM, Brown SL, Ubel PA. Mispredictions and mis-recollections: Challenges for subjective outcome measurement. *Disabil Rehabil*. 2007; 30(6): 418-24. doi:10.1080/09638280701625237.
 19. Dickerson FB, Boronow JJ, Ringel N. Lack of insight among outpatients with schizophrenia. *Psychiatr Serv*. 1997; 48(2):195-9. doi: 10.1176/ps.48.2.195.
 20. McGlynn EA. Setting the context for measuring patient outcomes. *New Dir Ment Health Serv*. 1996; 71:19-32. doi: 10.1002/ym.23319960304.
 21. Larsen RJ, Fredrickson BL. Measurement issues in emotion research. In: Kahneman D, Diener E, Schwarz N, editors. *Well-being: The foundations of hedonic psychology*. New York: Russell Sage Foundation, 1999. p. 116.
 22. Diener E, Suh EM, Lucas RE, Smith HL. Subjective well-being: Three decades of progress. *Psychol Bull*. 1999; 125(2): 276-302. doi: 10.1037/0033-2909.125.2.276.
 23. Bradley BP, Mogg K, Millar N. Implicit memory bias in clinical and non-clinical depression. *Behav Res Ther*. 1996; 34(11-12):865-79. doi:10.1016/s0005-7967(96)00074-5.
 24. Robinson MD, Clore GL. Episodic and semantic knowledge in emotional self-report: Evidence for two judgment processes. *J Personality Social Psychol*. 2002; 83(1):198-215. doi: 10.1037/0022-3514.83.1.198.
 25. Campbell J. Toward collaborative mental health outcomes systems. *New*

- Dir Ment Health Serv. 1996; 1996(71):69-78. doi: 10.1002/yd.23319960308.
26. Parmelee PA, Smith B, Katz IR. Pain complaints and cognitive status among elderly institution residents. *J Am Geriatr Soc.* 1993; 41(5): 517-22. doi:10.1111/j.1532-5415.1993.tb01888.x.
 27. Atkinson M, Zibin S, Chuang H. Characterizing quality of life among patients with chronic mental illness: a critical examination of the self-report method. *Am J Psychiatr.* 1997; 154(1):99-105. doi:10.1176/ajp.154.1.99.
 28. Marrie RA, Miller DM, Chelune GJ, Cohen JA. Validity and reliability of the MSQ LI in cognitively impaired patients with multiple sclerosis. *Mult Scler.* 2003; 9(6): 621-6. doi:10.1191/1352458503ms971oa.
 29. Neugebauer R, Ng S. Differential recall as a source of bias in epidemiologic research. *J Clin Epidemiol.* 1990; 43(12):1337-41. doi: 10.1016/0895-4356(90)90100-4.
 30. Hoff A. Neuropsychological function in schizophrenia, in *Contemporary Issues in the Treatment of Schizophrenia*. Washington, DC, American Psychiatric Press, 1995.P.65.
 31. Schwartz CE, Sprangers MAG. Methodological approaches for assessing response shift in longitudinal healthrelated quality-of-life research. *Soc Sci Med.* 1999; 48(11): 1531- 48. doi:10.1016/s0277-9536(99)00047-7.
 32. Schwarz N. Accessible content and accessibility experiences: The interplay of declarative and experimental information in judgment. *Personality Social Psychol Rev.* 1998; 2(2):87-99. doi: 10.1207/s15327957pspr0202_2.
 33. Sprangers MAG, Schwartz CE. Integrating response shift into health related quality-of-life research: A theoretical model. *Soc Sci Med.* 1999; 48(11): 1507-15. doi:10.1016/s0277-9536(99)00045-3.
 34. Ahmed S, Mayo NE, Wood-Dauphinee S, Hanley J. Response shift in the assessment of health-related quality of life post-stroke. *Qual Life Res.* 2001; 10, 204. doi: 10.1007/s11136-005-8118-4.
 35. Oort FJ, Visser MRM, Sprangers MAG. Incorporating the then-test into the structural equation modeling approach to response-shift detection. *Qual Life Res.* 2003; 7:784.
 36. Oort FJ. Using Structural Equation Modeling to Detect Response Shifts and True Change. *Qual Life Res.* 2005; 14 (3): 587-98. doi: 10.1007/s11136-004-0830-y.
 37. Schatman ME. *Chronic Pain Management: Guidelines for Multidisciplinary Program Development*. First Edition, Published: 2007.P.198.
 38. Campbell A, Cole BE. *Interdisciplinary Pain Management Programs: The AAPM Model*. In *Weiner's Pain Management: A practical guide for clinicians*. 7th Edition. . Taylor & Francis, NY; 2006.
 39. McGrath PA. Psychological aspects of pain perception. *Arch Oral Biol.*1994; 39: 55-62. doi:10.1016/0003-9969(94)90189-9.
 40. Keefe FJ, Lumley M, Anderson T. Pain and emotion: new research directions. *J Clin Psychol.* 2001; 57(4):587-607. doi:10.1002/jclp.1030.
 41. Fernandez E, Milburn TW. Sensory and affective predictors of overall pain and emotions associated with affective pain. *Clin J Pain.* 1994; 10:3-9. doi:10.1097/00002508-199403000-00002.
 42. Hooper D, Coughlan J, Mullen MR. *Structural Equation Modelling: Guidelines for Determining Model Fit*. *EJBRM.* 2008; 6 (1): 53-60. doi: 10.21427/D7CF7R.
 43. Ruehlman LS, Karoly P, Newton C, Aiken LS. The development and preliminary validation of a brief measure of chronic pain impact for use in the general population. *Pain.* 2005; 113: 82-90. doi:10.1016/j.pain.2004.09.037.

44. O'Connor RJ, Cano SJ, Ramiói Torrentà L, Thompson AJ, Playford ED. Factors influencing work retention for people with multiple sclerosis Cross-sectional studies using qualitative and quantitative methods. *J Neurol*. 2005; 252: 892-6. doi:10.1007/s00415-005-0765-4.
45. Kerns RD, Kassirer M, Otis J. Pain in multiple sclerosis: a biopsychosocial perspective. *J Rehabil Res Dev*. 2002; 39(2):225-32.
46. Lenz ER, Pugh LC, Milligan RA, Gift A, Suppe F. The middle-range theory of unpleasant symptoms: an update. *Adv Nurs Sci*. 1997; 19(3):14-27. doi:10.1097/00012272-199703000-00003.
47. Motl RW, McAuley E. Symptom Cluster as a Predictor of Physical Activity in Multiple Sclerosis: Preliminary Evidence. *J Pain Symptom Manage*. 2009; 38(2):270-80. doi:10.1016/j.jpainsymman.2008.08.004.
48. Motl RW, Arnett PA, Smith MM. Worsening of symptoms is associated with lower physical activity levels in individuals with multiple sclerosis. *Mult Scler*. 2008; 14(1):140-2. doi:10.1177/1352458507079126.
49. McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. *Pain*. 2003; 106(1-2):127-33. doi:10.1016/s0304-3959(03)00301-4.
50. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: A literature review. *Arch Intern Med*. 2003; 163(20):2433-45. doi:10.1001/archinte.163.20.2433.
51. Melzack R, Casey KL. Sensory, motivational and central control determinants of pain: A new conceptual model. In: Kenshalo, D. (Ed.) *The skin senses*. Illinois: Thomas. 1968; p. 423.
52. DeGagne JA, Mikail SF, D'Eon JL. Confirmatory factor analysis of a 4-factor model of chronic pain evaluation. *Pain*. 1995; 60:195-202. doi:10.1016/0304-3959(94)00114-t.
53. Lowe NK, Walker SN, MacCallum RC. Confirming the theoretical structure of the McGill Pain Questionnaire in acute clinical pain. *Pain*. 1991; 46:53-60. doi:10.1016/0304-3959(91)90033-t.
54. Strong J. Assessment of pain perception in clinical practice. *Man Ther*. 1999; 4(4): 216-20. doi:10.1054/math.1999.0205.
55. Essex-Sorlie D. *Medical biostatistics & epidemiology: examination & board review*. 1st edition. Appleton & Lange. 1995.P. 359.
56. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical epidemiology: a basic science for clinical medicine*. Boston, Little, Brown and Company. 1991.
57. Wiesenfeld-Hallin Z. Sex differences in pain perception. *Gend Med*. 2005; 2(3):137-45. doi:10.1016/s1550-8579(05)80042-7.
58. Edwards CL, Fillingim RB, Keefe F. Race, ethnicity and pain. *Pain*. 2001; 94(2):133-7. doi:10.1016/s0304-3959(01)00408-0.
59. Cohen B, Clark ME, Gironde RW. Assessing fear of (re)injury among chronic pain patients: Revision of the Tampa Scale of Kinesiophobia. *Pain*. 2007; 127(1-2):42-51 doi: 10.1016/j.pain.2006.07.016.
60. Zusman M. Instigators of activity intolerance. *Man Ther*. 1997; 2(88): 75-86. doi:10.1054/math.1997.0288.
61. Rizzo MA. Treatment of pain, paresthesias, and paroxysmal disorders in multiple sclerosis. In: Cohen JA, Rudick RA, editors. *Multiple sclerosis therapeutics*. 2nd ed. London and New York: Martin Dunitz; 2003.
62. Schulz KF, Chalmers I, Hayes RJ. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995; 273(5):408-12. doi:10.1001/jama.273.5.408.
63. Levin KA. Study design III: Cross-sectional studies. *Evid Based Dent*.

- 2006; 7(1), 24-5.
doi:10.1038/sj.ebd.6400375.
64. Wall MM, Li R. Comparison of multiple regressions to two latent variable techniques for estimation and prediction. *Stat Med.* 2003; 22(23):3671-85. doi:10.1002/sim.1588.
 65. Haines R, Blair A, Osborn M. The challenges of assessing outcome in chronic pain. *Int J Health Care Qual Assur Inc Leadersh Health Serv.* 1997; 10(4-5):149-52. doi:10.1108/09526869710189315.
 66. World Health Organization. International Classification of Functioning, Disability and Health (ICF). Geneva, Switzerland: WHO. 2008.
 67. Kesselring J, Coenen M, Cieza A, Thompson A, Kostanjsek N, Stucki G. Developing the ICF Core Sets for multiple sclerosis to specify functioning. *Mult Scler.* 2008; 14: 252-254. doi:10.1177/1352458507082615.
 68. Stucki G, Cieza A. The International Classification of Functioning, Disability and Health (ICF) Core Sets for rheumatoid arthritis: a way to specify functioning. *Ann Rheum Dis.* 2004; 63(Suppl 2):ii40-ii45.
 69. Law M, Stewart D, Pollicj N, Letts L, Bosch J, Westmorland M. Critical review form – qualitative studies. McMaster University. 1998.
 70. Grant MD, Samson D. Special Report: Measuring and Reporting Pain Outcomes in Randomized Controlled Trials. Assess Program. Technol Eval Cent Assess Program Exec Summ. 2006; 21(11):1-2.
 71. Anderson JC, &Gerbing DW. Structural equation modeling in practice: A review and recommended two-step approach. *Psychol Bull.* 1988; 103(3):411-23. doi:10.1037/0033-2909.103.3.411.
 72. Ahmed S, Mayo N. Using structural equation modeling to evaluate response shift. *J Clin Epidemiol.* 2007; 60 (4): 427-8. doi:10.1007/s11136-004-0830-y.
 73. Clark ME, Gironda RJ, Young RW. Development and validation of the Pain Outcomes Questionnaire-VA. *J Rehabil Res Dev.* 2003; 40(5): 381. doi:10.1682/jrrd.2003.09.0381.
 74. Williams RC. Toward a set of reliable and valid measures for chronic pain assessment and outcome research. *Pain.* 1988; 35(3): 239-51. doi:10.1016/0304-3959(88)90133-9.
 75. Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Handbook of Pain Assessment, 2nd. Turk DC, Melzack R. eds. Guilford Press, New York. 2001
 76. Murray DM. Statistical models appropriate for designs often used in group-randomized trials. *Stat Med.* 2001; 20(9-10):1373-85. doi:10.1002/sim.675.
 77. Mayo NE, Goldberg MS. When is a case-control study not a case-control study? *J Rehabil Med.* 2009; 41(4):209-16. doi:10.2340/16501977-0343.
 78. Kline RB. Principles and Practice of Structural Equation Modeling. New York: The Guilford Press. 1998.
 79. Hays R, Revicki D, Coyne K. Application of Structure Equation Modeling to Health Outcome Research. *Eval Health Prof.* 2005; 28 (3): 295-309. doi:10.1177/0163278705278277.
 80. Fishbein M, Hennessy M, Kamb M, Bolan GA, Hoxworth T, Iatesta, M. Using intervention theory to model factors influencing behavior change. *Eval Health Prof.* 2001; 24(4): 363-84. doi:10.1177/01632780122034966.
 81. Kupek E. Beyond logistic regression: structural equations modeling for binary variables and its application to investigating unobserved confounders. *BMC Med Res Methodol.* 2006; 6:13. doi: 10.1186/1471-2288-6-13.