TBM

REVIEW

Chronic pain assessment from bench to bedside: lessons along the translation continuum

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Cite this as: *TBM* 2016;6:596–604
doi: 10.1007/s13142-015-0370-8

Abstract

The first step to providing effective healthcare is accurate assessment and diagnosis. The importance of accurate assessment is particularly important for chronic pain, given its subjective and multidimensional nature. The purpose of the current review is to discuss the dilemma of chronic pain assessment within a translational framework. First, assessment issues specific to chronic pain will be introduced along the entire continuum of translational activities. Important barriers along the continuum include inconsistent measurement of pain, possibly inaccurate preclinical models, and other practical limitations such as time, cost, and training. Second, the review will highlight promising areas worth further consideration in research and practice to bridge some of the gaps that currently impede effective chronic pain assessment and care. Specifically, consideration will be given to observational, biological, and technology-driven measures of chronic pain.

Keywords

Pain, Chronic pain, Assessment, Translation, Implementation, PROMIS, Pain biomarker

Chronic pain is a pervasive condition affecting millions of individuals and families. Epidemiological estimates indicate 43 % of Americans suffer from some form of chronic pain [1], with lifetime estimates as high as 85 % [2], accounting for up to $635 billion annually in medical costs and lost productivity [3]. This burden is complicated by the comorbid emotional struggles individuals experience with chronic pain [4]. Given these statistics, it is no surprise that chronic pain conditions are difficult to treat–with most patients only experiencing modest improvement [5]. The World Health Organization (WHO) estimated across 14 countries in more than 3000 primary care patients with persistent pain that only 49 % of patients experienced resolution over a 12-month period [6]. Since primary care settings will often refer the most complicated patients to specialty clinics, actual resolution for all patients with chronic pain is likely even lower. Despite these discouraging numbers, if care for patients with chronic pain is going to improve, we need to begin with evaluating how we assess chronic pain.

Accurate and comprehensive assessment is the foundation for diagnosis and treatment in our current medical system. Currently, researchers and clinicians have a vast armamentarium of validated measures and techniques to assess chronic pain. Self-report measures of pain are the most commonly used tools to assess chronic pain [7, 8] and are considered a "gold standard" by many since pain is a subjective experience [9, 10]. This reporting is generally considered to be valid and reliable [8]. However, patients' self-reporting of pain do not always correlate with objective functional measures [11, 12], are subject to patient bias and misinterpretation [13], and yield large variations in response approaches between patients [14]. On the other hand, there is consistent evidence for the use of self-report measures when examining within-patient change [8, 12]. Overall, without the existence of an "objective thermometer reading" of pain, self-report measurement remains an essential component of chronic pain assessment [8, 11].

A number of reports have put forth suggested guidelines for chronic pain assessment [5, 11, 15–17] all informed by a biopsychosocial approach to pain management [4]. They outline the importance of measuring the whole person through initial physical examinations and gathering a detailed clinical history, diagnostic testing, psychosocial reports, and assessing the degree of impairment the person faces due to their pain. There are even algorithms to aid clinicians in accurate and comprehensive assessment practices [16]. While these guidelines have been helpful and practical tools for clinicians in treating patients, there is continued interest in finding more accurate and nuanced ways to measure chronic pain.

Over decades of research and practice, considerable interest has been shown in measuring a broader range of the biopsychosocial nature of chronic pain. Since chronic pain can exist in the absence of nociceptive input, there has been increasing attention given to biological systems that support the development and maintenance of chronic pain. These range from traditional medical diagnostic tests to measures of stress, HPA axis functioning, and inflammation [18]. Even recent research has shown the possibility of finding a pain neurosignature [19]. These findings have sparked a renewed interest in an ongoing debate in the field regarding the possibilities of chronic pain assessment.

One side heralds the necessity of finding pain biomarkers to objectively quantify an individual's pain, indicating the subjective reports currently relied upon are limiting the field's progress [20]. Others suggest that finding a pain biomarker is fundamentally not possible since pain is a subjective experience, not amendable to thermometer-like readings [8]. What appears to have happened is this, schism has led researchers to undervalue avenues towards developing integrative and pragmatic chronic pain tools and procedures. While there are still no definitive answers to this debate, what can be done now to move the field toward a more comprehensive biopsychosocial assessment of chronic pain? The current review will suggest that there are lessons from translational research that highlight important areas for growth and possible change that could yield advances in chronic pain assessment.

DATA SOURCES, SCREENING, AND SELECTION

A broad search of the literature was performed to find all relevant articles on the topic of chronic pain assessment. Electronic searches were performed to identify studies using MEDLINE, PsychInfo, and Google Scholar between 1980 and 2013. Search terms utilized combinations of the following phrases: chronic pain, assessment, translation, animal models, IMMPACT, biomarkers, PROMIS, and UAB. Using these search criteria, articles were identified, and initial screening of the title and abstract were performed based on its relevance to the topic of translational chronic pain assessment. Once an article was found to be appropriate, MEDLINE searches were used to find similar articles. Lastly, articles themselves were manually searched using their citation sections to find any other possible studies pertaining to translational chronic pain assessment. Studies were included for further review based on their utility to inform the issue of translational chronic pain assessment.

TRANSLATIONAL CHRONIC PAIN ASSESSMENT

Nearly 40 years ago, the discussion of translation began about how to narrow the gaps between "bench and bedside" [21]. Subsequently, the Institute of Medicine, the National Institutes of Health, and the American Medical Association have called for a renewed focus on translational research [22–24]. Since then, chronic pain researchers have increased their focus on translation issues, however, have primarily examined the link between basic science and clinical trials, leaving other important aspects of translation unanswered [25]. This has left us with an impressive understanding of chronic pain pathophysiology that has been vetted through rigorous efficacy and safety testing; however, less is known about their clinical effectiveness to warrant practical use [12, 25, 26]. This has highlighted a need to consider a broader range of translational issues as we look to move chronic pain assessment forward. Seeing translation as a broad spectrum of activities can lead us to see that there are issues all along the path from bench to bedside that stop scientific discoveries from reaching routine clinical application [27] and leave potentially promising work "lost in translation" [26, 28, 29].

Chronic pain assessment along the translation continuum

Drolet and Lorenzi proposed the Biomedical Translation Continuum model to provide clear guidance for engaging the full range of translational activities to improve healthcare [26]. The translation continuum grew out of the National Institutes of Health (NIH) Roadmap [23] and other translational research models [29] specifically anchored by four key "landmarks" where scientists develop knowledge about a specific tool or intervention of interest. The process starts with the discovery of basic science innovations. Once established, these innovations are tested for proposed human applications and then examined for proven clinical usefulness. The last phases of the continuum involve clinical practices that are impactful to public health. Each landmark yields different scientific information necessary for successful translation.

Importantly, between each landmark are gaps, or "translation chasms," that represent key areas where translation activities can "bridge" knowledge from the neighboring landmarks [26, 30] and make the process of bringing bench to bedside possible. Drolet and Lorenzi point out that there are well-established translational procedures (i.e., clinical trial research) to bridge the T2 chasm (Safety and Efficacy Research); however, the processes for bridging the T1 (Laboratory to Clinical) and T3 (Implementation and Adoption) chasms are far less understood. As the model suggests, it provides a clear and concise framework to guide researchers and clinicians to key areas for improving translation. The following sections will point to critical issues within each of the translation gaps.

T1: Laboratory to Clinical–The first translation chasm encompasses activities related to translating basic science into methods and procedures that could have useful applications for human health. In considering chronic pain assessment, this entails the basic foundations of how we define, conceptualize, and measure chronic pain. Two fundamental and closely related issues hindering the translation of the T1 chasm that need to be addressed are as follows: 1. reconsidering traditional animal models and 2. our basic definitions and measurement of pain.

Animal models provide the basic foundation for doing physiological pain research and are important to consider in the context of chronic pain assessment because they define and constrain how researchers measure pain in the laboratory. Over the years, animal models have transformed our basic understanding of pain mechanisms [12, 31]. Animal models in pain research are prescribed procedures used to duplicate precise experimental conditions. These models first specify animals that are appropriate to use based on anatomical and physiological similarity to humans,

mostly being rodents [32]. The rest of the model outlines specific procedures and measurement techniques to examine a desired response. These procedures are generally thought of as behavioral tests that examine an "input-output" or "stimulus-response" system [33]. The experimental manipulation (e.g., lesion, stimulation) leads to an observable behavior–typically a withdraw response or vocalization [12, 34] as the key outcome variables. The underlying assumption of this process asserts the observed behavior in the animal is caused by an experienced noxious sensation. Even despite strong environmental controls to rule out other potential explanations of the animal's behavior [33], this assumption and other limitations of animal models are problematic when considering chronic pain assessment.

Traditional practices for measuring pain responses in animal models pose threats to translational chronic pain assessment for multiple reasons. First, there is a distinct divide between researchers in basic science and practitioners in the clinic measure pain [12]. While basic scientists use withdraw responses and verbalizations to measure pain [34], the most commonly applied pain measurement tool with humans are numeric rating scales and visual analog scales [12, 15, 35, 36]. This highlights the lack of translational communication and collaboration between bench and bedside when it comes to measuring pain. Another problem results from the brief period in which animal studies are typically performed. Given that chronic pain is typically defined as pain that persists for longer than three months, a problem arises when experimenters generally test animal models for a period of days or weeks [32]. This again points to the idea that basic science is not capturing the full complexity of human chronic pain. Additionally, it is still debated whether a withdraw response is simply a sensory response or a true nociceptive behavior [34]. At best, the reliance of measuring nociceptive responses results in conditions of tissue damage (i.e., nociception) that do not incorporate other important psychosocial (i.e., subjective) aspects of pain [12, 32]. Together, these concerns put into question the very validity of the measurement process, highlight divides in how we measure pain along the continuum, and suggest animal models might measure a distinct process not representative of human pain conditions. These problems with measuring chronic pain are significant, but not insurmountable.

Recognizing the need for animal models to include subjective aspects of pain (e.g., depression and anxiety [32]), there have been recent efforts to add affective components of pain into preclinical models. Depressive behaviors have been modeled in rats for decades [37]; however, only recently have they been included in preclinical animal models of chronic pain. One such model used Wistar-Kyoto (WKY) rats because of their behavioral and hormonal similarities to humans with depression. These WKY rats have shown to display psychomotor retardation and exhibit exaggerated responses to stress [38]. In studies of pain response, these depressive WKY rats under the condition of chronic constriction nerve injury have displayed exaggerated mechanical allodynia during von Frey stimulation [38] (procedure discussed later). A similar model using Wistar rats injected Freund's Complete Adjuvant into the hind paw to induce a form of arthritic pain [39]. Then, a depressive condition was introduced through a modified resident-intruder social stress interaction. This social stressor commonly produces anhedonic-like behaviors in the rat. This model showed that the pro-inflammatory interleukin 6 (IL-6) mediated mechanical allodynia, thermal hyperalgesia, and depressive behaviors [39]. Both these models provide evidence for the utility of including depressive behaviors in animal models of chronic pain and while also identifying potential mechanisms between chronic pain and depression.

While depression is common for patients with chronic pain, anxiety is also part of the pain experience for many people [4], and there have been recent efforts to add anxiety behaviors into animal models. One such model subjects rats to multiple behavioral tests (i.e., elevated plus maze, open field task) and codes for specific anxiety-like behaviors typical of rodents (i.e., decreased locomotion, rearing less, more time spent at the perimeter of the apparatus, and making fewer exists from the closed arms of the elevated plus maze) [40]. Once a baseline measure of anxiety-like behaviors was obtained, they induced a form of chronic neuropathic pain using a spared nerve injury (SNI) model by surgically blocking two of the three sciatic terminal branches [41]. A SNI model was chosen over other models of neuropathic pain because it is highly reproducible and the effects of SNI persist for months following the procedure [40]. After surgery, the rats performed the behavioral tasks at specified intervals over the next six months. Results revealed that anxiety-like behaviors were more likely to appear in the SNI rats compared to sham rats and they typically emerged around 4 weeks after surgery [40].

The animal models described above are promising because they attempt to include affective components common in human chronic pain and more closely approximate the time duration of human chronic pain. The social stress test used by Kim and colleagues [39] is particularly interesting because it can implicate multiple affective as well as social components to chronic pain. The social stress task in many ways mimics social aspects (e.g., breakdown in communication, isolation) for many people with chronic pain. Additionally, feelings of hopelessness are common in chronic pain–something similar to the helplessness induced by the multiple attacks of the resident rat on the intruding rat. The next step is to consider other common aspects of chronic pain (i.e., anger and substance abuse) that could be incorporated into these models.

T2: Safety and Efficacy Research–The second translation chasm along the continuum involves activities that bridge knowledge gained from human studies to clinical settings, otherwise known as clinical trials. As previously indicated, T2 activities are the most

thoroughly investigated area along the translation continuum although chronic pain assessment is still an area with important T2 barriers. There have been significant concerns raised about study design and statistical analysis methods used for chronic pain trials [12, 42, 43]; however, these topics are beyond the scope of the current review. Additionally, since most techniques used to assess chronic pain come with minimal risks, safety issues will also not be reviewed. What the current review will examine are the T2 chronic pain measurement tools used in efficacy trials to yield clinically meaningful practices for use at the bedside.

Assessment is essential in clinical trials because determining efficacy hinges on the accurate measurement of outcome variables. However, despite the importance of assessment to the success of clinical trials, there is significant heterogeneity in how researchers define and measure chronic pain across studies. One review of 50 chronic musculoskeletal pain clinical trials identified 34 % used only a single item to assess pain intensity with a total of 28 different scales used overall [36]. This variability has hindered comparability between studies and limits their validity, calling into question the efficacy of the treatments currently available to manage chronic pain [44].

In response to this problem, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) was organized in 2002 to develop an international team of experts tasked to create uniform procedures for researchers to consider when performing clinical trials. Its goal is to facilitate the generation of tools and procedures that yield higher specificity, greater validity, and allow for comparability across studies [44]. At its outset, the IMMPACT team identified key methodological and measurement issues related to pain assessment in clinical trials and had select members review the literature to provide summaries to the team for analysis. The group convenes regularly to debate key points and develop expert consensus documents. The IMMPACT group's first consensus meeting resulted in the identification of six core domains to be assessed when measuring pain in clinical trials as: pain intensity, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition [9, 44]. These domains are not meant to be all-inclusive and are considered general domains of pain functioning [44]. Importantly, the IMMPACT group also provides pointed recommendations regarding specific assessment tools to use to capture data from each domain of interest.

While the IMMPACT recommendations represent some of the best knowledge we have about pain assessment in clinical trials, they are not without their limitations and require further research [9, 42, 44]. It should be noted that IMMPACT's publications are always clear to highlight that their findings should be considered when developing and performing pain clinical trials [42, 44] and thus do not limit researchers from including additional domains of functioning in their assessment. While there needs to be careful attention and adaption of these methods to the individual needs of specific pain populations and environmental constraints [9], following the IMMPACT guidelines will serve to help unify the heterogeneous methods used to assess chronic pain in clinical trials. These recommendations while targeted for use in clinical trials also offer insight for approaching chronic pain assessment in clinical practice.

T3: Implementation and Adoption–The final chasm along the translation continuum involves bridging clinical trial efficacy and clinical practice effectiveness. Closing the T3 gap has been the work of implementation research and is particularly important for improving chronic pain assessment practices. Most successful clinical trials do not reach widespread use in clinical practice [27], and one explanation for this T3 gap is differing assumptions, values, and goals between efficacy and effectiveness research [45]. Our current research culture and environment has fostered the development of clinical trials requiring high levels of control and accuracy to yield strong internal validity. On the other hand, effectiveness trials place more emphasis on real-world context, flexibility, and feasibility [45]. While both internal validity and broad application are important, these seemingly dissimilar goals between clinical trials and effectiveness research have left some lingering questions about the generalizability of trial results to practical settings [46]. In order to bridge the gap, we have to consider some key causes of the rift: time, cost, provider training, and acceptability.

Time is a large barrier when trying to bring clinical assessment tools into practice. Despite physicians' priority to provide the highest quality of care, there are many secondary competing interests (e.g., making a living, managing workload, simplifying paperwork) that make running busy medical clinics within the confines of industry and reimbursement restrictions complicated and time-consuming [47]. Consistent with this idea is evidence that the majority of clinicians feel they do not have time for an adequate assessment for patients with chronic pain [48]. The first T3 hurdle is helping providers recognize that chronic pain assessment does not need to unduly burden their practice and should save them time in the long run. Many techniques and tools do not even require being in the physician's office–either being completed at home or in a waiting room. An accurate diagnostic assessment, and regular follow-up measurement, should increase patient satisfaction and reduce unnecessary physician visits. However, in order to "sell" physicians and health care agencies on the utility of a comprehensive chronic pain assessment requires empirical evidence, specifically evidence suggesting cost effectiveness.

Cost is a significant barrier to the implementation of chronic pain assessment tools in clinical settings. With burgeoning costs for chronic pain care [3], providers and policy makers are scrutinizing the utility of

medical procedures [49]. These costs are significant limiting factors in what procedures clinicians have available for chronic pain assessment. While MRI and other imaging techniques are effective for diagnostic purposes and can potentially be used to evaluate outcomes, the cost associated with these procedures make them questionable to be used for routine clinical use. Other procedures like observational techniques and self-report are relatively low-cost [50] and yield important assessment data. If we can implement low-cost, effective assessment tools early in the diagnostic process, they should reduce the need for providers to use more costly imaging techniques later in treatment. While different assessment procedures incur different financial burden, it is also important for T3 activities to objectively evaluate and report these costs. A lack of reporting cost-benefit analyses is thought to contribute to clinicians' hesitance to implement proven techniques [51]. Traditionally, there have been two approaches for researchers to examine cost: retroactively or prospectively. Retroactive analyses are used more frequently because it is easy and researchers often do not plan these analyses a priori. However, this method is more likely to provide less detail about specific costs and is subject to recall bias [51]. Prospective research avoids the problem of recall bias and allows researchers to specifically plan what types of cost analyses they want to perform. This is particularly helpful when performing sensitivity analyses to estimate the differential costs of your procedure within different settings and under different criteria (e.g., the differential cost of implementing *X* assessment in your clinic versus a wider population or the cost of using *Y* assessment). While cost-benefit analysis is common in evaluating chronic pain interventions, to date, the current author is not aware of any investigations examining direct cost-benefit of specific chronic pain assessment procedures. This highlights the importance for researchers to perform cost-benefit and sensitivity analyses early in the development and implementation process [52, 53].

Another barrier to T3 translation is practitioner training. Training is problematic for two main reasons. Firstly, the majority of practicing clinicians do not feel adequately trained to manage and assess chronic pain [48, 54]. The ongoing need for staff to be appropriately trained about current procedures is burdensome for busy clinics and overloaded staff [45]. In surveys of medical provider's chronic pain education, the majority indicate they had "insufficient" training [54] with one report showing 30 % had received no formal training [48]. This highlights a significant need for medical schools, residencies, and other medical training programs to devote more attention to chronic pain [3]. Some clinicians have pointed to the lack of empirical evidence and strong evidence-based guidelines for the lack of training [48], which further suggests the importance of reconsidering our assessment practices. The second reason training issues impede translation is because they require time and personnel for consistent and accurate implementation [45]. Clinical trials often employ trained research staff whose sole responsibility in that setting is to administer intervention protocols, while medical practices utilize busy healthcare staff (e.g., nurses, medical assistance) to provide these interventions on top of their many other duties [45]. If clinicians are going to take chronic pain assessment seriously, it requires either hiring a trained provider or training nurses and medical assistants on staff. Individual providers will need to consider the needs of their patient population and the constraints of their clinic when making these decisions, but training cannot be ignored. One solution is implementing pragmatic staff meetings focused on training, as they directly influence healthcare team involvement and increase the likelihood of successful implementation [55].

The last implementation barrier discussed in this review is the acceptability of chronic pain assessment procedures. Activities in the T3 gap tend to emphasize flexibility and adaptation [56] to facilitate procedures being acceptable to both clinicians and patients. While there is concern that deviating from prescribed empirical protocols will taint the efficacy of the interventions provided [57], others suggest alterations are necessary [45]. In practice, deviations from treatment fidelity occur frequently while often maintaining the key "active ingredients" of the intervention [55]. For example, one investigation found frequent adaptations when implementing their behavioral health intervention across a collaborative care network of clinics. One procedure called for patients to fill out behavior assessment questionnaires at a kiosk. Some of the clinics recognized the kiosk required nurses and doctors to wait on patients filling out forms, and that a PC tablet was an alternative way to increase acceptability without altering the core of the intervention [55]. Given the evidence that comparable and valid results from self-report measures can be obtained via multiple platforms [58, 59], this modification of the assessment procedure increased patient and physician acceptability and is a good example of creative ways to translate clinical research into practice.

Overall, effective bridging of the T3 chasm will require flexibility on the part of both researchers and clinicians. There has been a call to fundamentally change how we conceptualize the research and translation process to give greater emphasis on implementation issues [60]. Some have even suggested suspending traditional clinical trial research to redirect time and resources to find optimal avenues for implementation efforts [53]. However, a more moderate approach to bring both clinical science and clinical practice together has been the promotion of practical trials where researchers work at the bedside with clinicians to determine the real-world effectiveness of efficacious interventions [52]. These approaches are promising to bridge the T3 gap and help make validated assessment techniques more available for clinical use.

As discussed, Drolet and Lorenzi's translation continuum provides a useful framework in determining appropriate chronic pain assessment strategies across the full range of research and clinical activities from

bench to bedside. While each chasm along the continuum has unique barriers and challenges, there are also opportunities for growth that can transform our current chronic pain assessment practices.

FUTURE DIRECTIONS

It is an understatement to say that chronic pain is complex and difficult to accurately measure. Despite decades of research and many advances in our understanding of pain pathophysiology, researchers and clinicians continue to struggle to meaningfully assess a patient's pain. Even though chronic pain is a subjective, complex, and multidimensional phenomenon, the insights from translational research provide guidance on areas of growth. While all areas of potential growth cannot be discussed, the current review will consider three assessment approaches that if implemented more broadly could move the field forward and bridge translation chasms, namely observational measurement, biochemical measurement tools, and technology-administered self-report instruments. Among the many exciting advances in chronic pain assessment, these methods have been identified for further consideration given their support in the literature, clinical utility, and ability to help bridge translation gaps, as discussed below.

Measures of pain behavior are a tool frequently used in research and to a lesser degree, in clinical practice. A patient's observable pain-related behaviors are an important part of the biopsychosocial nature of chronic pain and help provide a more complete picture of the patient's experience [10]. This data provides clinicians information about potential physical damage, the patient's coping strategies, and avenues to guide treatment [50, 61]. Methods for measuring pain through observation largely developed to help assess patients who could not self-report pain (e.g., infants, patients with severe cognitive impairment) and to capture the complex multidimensional nature of chronic pain [61]. As a result, a number of systems to systematically rate and approximate an individual's level of pain through observation have been developed [62, 63]; however, these approaches employ labor-intensive videotaping and coding to score the behaviors [61]. Aside from these videotaped coding systems, there have been a limited number of observational behavior scales developed.

The University of Alabama at Birmingham (UAB) pain behavior scale [64] is a standardized observational behavior scale developed in response to the burdensome protocols available at the time. Its aim is to allow measurement of pain behaviors in medical settings without requiring videotaping and intensive training [64]. It is a 10-item scale where practitioners score patients' observable pain behaviors (e.g., facial grimacing, mobility, use of supportive equipment) as 0 (absent), 0.5 (occasional), or 1 (frequently). The UAB has demonstrated high inter-rater reliability and temporal stability [64] with good evidence for its concurrent validity with pain intensity measures [65–67]. Also, meta-analytic results found the UAB exhibited the highest correlations with pain intensity scores among existing methods to observe pain behaviors, even superior to the labor-intensive-videotaped protocols [68]. The high correlation between pain intensity and UAB scores is likely due to the timing of measurement [66, 68], differences between the populations studied, and the UAB's simple scoring procedure compared to the other systems. The empirical support and practical utility of the UAB make it a compelling observational measure of pain behaviors.

Behavioral measurement of pain is important to implement more often from a translational perspective because it increases consistency in measurement with laboratory research. The author recognizes that there are important differences between research and clinical settings and that complete uniformity is not possibly or even preferable. However, if we are measuring pain in completely different ways, then, there are fundamental questions about whether what we are assessing in research settings is comparable to human clinical experiences. Broader consideration of behavioral measurement can help narrow this T1 gap and provide clinicians useful information to guide treatment.

The second aspect of chronic pain assessment to consider as we bridge translation gaps is innovative biological measurements of chronic pain. Given the subjective nature of pain, a growing number of researchers and clinicians desire to have more objective data at their disposal to guide assessment and treatment. Since chronic pain can be experienced in the absence of objective nociceptive input, that requires us to look beyond only measuring nociceptor functioning and to also investigate the use of techniques that examine other systems implicated in chronic pain pathology. While there has been intriguing neuroimaging research suggesting the existence of neurological signatures of physical pain [19], the current author does not see widespread use of fMRI measurement as a viable option when compared to other biochemical sampling methods. Recognizing that chronic pain involves multiple interconnected systems [32], the allostatic load [69] and stress [70] models of chronic pain suggest that stress, HPA axis functioning, and inflammation are key mechanisms in the development and maintenance of many types of chronic pain [71]. These models suggest the use of other biomarkers (e.g., pro-inflammatory cytokines, cortisol, among others) as non-nociceptive measures of the chronic pain process.

For example, one group of cytokines, the chemokines, is thought to be likely mediator in the chronic pain experience due to their role in coordinating the immune response [72], directly acting on nociceptors in the periphery [73], and their prevalent production in areas of high pain sensitization (e.g., sunburn [74]). Evidence also shows IL-6 is directly involved in exacerbating inflammation through microglia activation in the spinal cord that has analgesic properties at the site of an injury [75]. Recent work has also shown the

utility of using chemokine and cytokine biochemicals as indicators of progress in treatment [76].

Evidence also suggests individuals with many chronic pain conditions have altered levels of circulating cortisol [70] and display reliable decreases in cortisol levels during treatment [77, 78]. However, there is still uncertainty whether chronic pain is associated with hypoactive or hyperactive cortisol secretion. Most findings indicate patients with chronic pain display higher 24-h levels of cortisol compared with controls [78–80] and show similar diurnal patterns as healthy persons [79]. However, other findings suggest chronic pain populations experience hypoactive cortisol levels with blunted diurnal patterns [81–83].

It is important to note that there is considerable need for further research in the area of pain biomarkers before their widespread use in clinical settings. Given the dynamic nature of these biological systems, it is still unclear what ranges of these chemicals would be clinically meaningful guidelines in patient care. It is also important to recognize that the search for pain biomarkers will not yield a "magic bullet" for chronic pain assessment; rather, these tools will provide valuable information to improve diagnostic accuracy and facilitate targeted treatment and outcome measurement [20].

Despite these lingering questions, biochemical sampling would help to bridge important issues related to consistency in measurement as well as being a "low burden" tool for clinicians and patients. These types of measurements could easily be adapted to be comparable between research settings and clinical domains, bridging T1 gaps, but also importantly are minimally invasive to help overcome T3 barriers as well. Both patients and providers are familiar with blood draws, and it would not take any additional time away from clinicians. Thus, the possible value added by having these biochemical assessment tools to facilitate patient-centered pain treatment would be considerable.

The last area of pain assessment that will be considered to bridge translation gaps is that of technology-driven self-report instruments. Given the advances in technology and statistics, many have turned to item response theory (IRT) and computer adaptive testing (CAT) to develop novel chronic pain measurement tools [84, 85]. The largest of these initiatives is the NIH's Patient Reported Outcomes Measurement Information System (PROMIS) project. The PROMIS tool is a group of item pools developed through IRT that assess a broad range of patient functioning and utilize CAT to administer the smallest number of items needed. As part of the larger PROMIS assessment, there are two pain domains: pain interference and pain behaviors with an additional pain intensity numeric rating scale. Items that make up the two pain domains were created by developing comprehensive item pools from existing measures, literature reviews, talking with patients, and from experts in the field [50, 86]. These items then underwent IRT methods to refine the pool to the most psychometrically sound items representing the construct of interest. This project has surveyed close to 30,000 individuals and has developed robust item banks and IRT models [50, 86]. The PROMIS items can be administered in short-form, domain-specific, and full-length item banks. The length of administration depends on what form of PROMIS is administered and how many items a patient endorses (the current author was able to complete a demonstration of the full assessment in less than 5 min). There still remains significant research to be done to evaluate PROMIS's validity with existing pain measures and within specific pain populations [86]; however, this is an exciting step forward in the measurement of chronic pain. Given its high yield of information, low cost to providers, and minimal time for patients, it meets all the needs to help bridge the T3 translation gap.

Together, the use of observational measurement, biochemical sampling, and PROMIS within the context of medical evaluations should help bring the "measurement language" of researchers and clinicians closer together to increase the consistency of chronic pain assessment. Additionally, these assessment approaches narrow the T3 gap since they pose a minimal burden to patients and providers and present a clear path to move tools that look promising in clinical research to the bedside. While T2 translation barriers were not discussed within this section, they are still significant and warrant further attention; however, the influence of the IMMPACT recommendations should greatly narrow this chasm.

CONCLUSION

As Melzack and Torgerson explained over 40 years ago, "to describe pain solely in terms of intensity…is like specifying the visual world in terms of light flux only, without regard to pattern, color, texture, and the many other dimensions of the visual experience" [87]. Following this wisdom, there needs to be increased attention given to assessing the whole complexity of the pain experience. The areas discussed above are only some of the exciting developments in chronic pain assessment without the mention of advances in pharmacology, neuroscience, and innovative care models. To continue to move forward, researchers and clinicians must reach beyond their own perspectives on pain measurement and consider the complex patterns and dimensions of assessment along the entire translation continuum. The chasms along the continuum have developed over decades, and it will take time, resources, and continued effort to overcome these barriers, though the current author is optimistic that they can be bridged.

Acknowledgments: I would like to thank Sandra Gramling, Micheal Southam-Gerow, and Victoria Schivy in their assistance in reviewing the contents of the manuscript and providing invaluable feedback. I must also acknowledge the unending support from my wife, Crystal Jensen.

Compliance with ethical standards

Conflict of interest: The author declares that he has no competing interests.

Adherence to ethical principles: The current review involved no direct involvement from human subjects. All procedures followed were conducted in accordance with ethical standards and guidelines set out by Virginia Commonwealth Universities Institutional Review Board.

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