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PERSON-CENTERED MEDICINE VERSUS PERSONALIZED MEDICINE: IS IT JUST A SOPHISM? A VIEW FROM CHRONIC PAIN MANAGEMENT

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SUMMARY

The main aim of this brief overview is to explore the concepts of person-centered medicine and personalized medicine in the areas of chronic pain research and management. Through several definitions and paradigms of pain, the authors introduce the complexity of pain phenomenology in order to establish the challenge of person-centered and personalized medicine in everyday practice. By providing deeper insight into fibromyalgia, its presentation, biology and treatment, several questions are addressed, ranging from person-centered diagnosis to personalizing the various processes of the fibromyalgia spectrum complex. By reviewing current treatment options and evaluating treatment pitfalls derived from methodological flaws in current research, the authors discuss various possibilities of personalizing treatment and, therefore, propose how the use of these two paradigms could enhance outcomes in chronic pain management.

If we wish to make comments about enhanced outcomes we need to talk about outcomes of pain treatments, we need to discuss what successful treatment is from the patient's point of view as well as in the reviewed models.

Key words: *patient-centered medicine - personalized medicine – fibromyalgia - chronic pain*

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ON PAIN

Before launching into a discussion about the main aims of this article and the differentiation between "person-centered medicine" and "personalized medicine" in pain research and management, the authors first present several paradigms of pain. Probably the most widely used definition of pain is derived from taxonomy and defined by the International Association for Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (1994). Furthermore, although often neglected in daily practice, the IASP Task Force notes, "This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause." In a critically review of this definition, these authors note several key terms, such as "sensory," "emotional," "psychological state," that lead to a feeling of vague terminology used to define pain in a circular fashion. Such vague terminology generates "Petitio Principii" or "begging the question" first desribed by Aristotles in "Prior Analytics," for one must ask oneself what do these terms actually mean in a phenomenological, subjective sense of human reasoning, regardless of whether of not this subjective reasoning comes from a pain patient, physician or researcher (Barnes 1995).

Another widely used paradigm is the concept of "total pain" introduced by Dame Cecily Saunders, which describes malignant pain consisting of the physical, mental, social and spiritual components to distress and suffering in terminally ill cancer patients. This term can be extrapolated to other chronic pain states (Saunders,1976). Such definition is much broader because it introduces other aspects of pain, which could translate into the modern term "quality of life," the ultimate outcome in pain management (Felce & Perry 1995). Yet again this definition suffers from the same pitfalls as the IASP definition: it avoids tying pain to the stimulus.

However, with the rise and development of neuroscience by advances in medical technology, various behavioral, cognitive and mental patterns in chronic pain are increasingly correlated to specific brain circuits. In these authors' opinion, this paradigm is best described by Melzack in his work on phantom limb pain (2001). A pioneer in pain research, Melzack introduced the "painful humunculus," a nociceptive image of the body stored primarily in the somatosensory cortex division of all pain circuits This model integrates the mind and the body, both subjective and objective, in

terms of modern pain science. This conceptual framework may be utilized as a starting point in our understanding of chronic pain syndromes, for it allows the application of objective scientific measurement of various behavioral and mental patterns in research and patient management.

Within these concepts lie the main issues we would like to address:

- the similarity and differences between personalized and person-centered medicine;
- the possible application of these concepts in settings that provide treatment for chronic pain;
- the outcomes in a personalized/person-centered approach to chronic pain management.

LESSONS LEARNT FROM FIBROMYALGIA

Fibromyalgia is a chronically painful condition affecting 2-5% of the population according to strict criteria. Furthermore, ten percent of the general population complains of chronic widespread musculoskeletal pain similar to fibromyalgia (Grant 2003). However, its phenomenology and biology remain unclear. The first step toward person-centered medicine is the establishment of a clear diagnosis as defined by valid diagnostic criteria. Predominating the last two decades are the simplistic criteria proposed by the American College of Rheumatology (ACR), which are characterized by pain lasting for more than 3 months in four quadrants of the body with a minimum of 11 out of 18 tender points throughout the body (1990). The main fault of these criteria is ignoring fibromyalgia as part of a spectrum by disregarding comorbid psychological states, other functional somatic disorders, and fatigue amongst certain individuals who suffer from fibromyalgia but are not diagnosed and treated properly.

In an editorial curiously named "Stop using the American College of Rheumatology criteria in the clinic," Wolfe stated a crucial point: "…by placing diagnosis at the end of the severity spectrum we lost the appreciation of the spectrum itself, of the range of human distress that exists across all illness and persons, not just in those with 11 tender points" (2003). This publication was perhaps the pivotal moment leading to a shift away from the fibromyalgia paradigm that used only sensory aspects of the IASP definition of pain. The result has been the emergence of more person-centered criteria recently published by the ACR (Wolfe et al. 2010).

These new ACR criteria somewhat reduce the importance of tender points while concentrating more on other features. The primary aspects newly introduced are fatigue, cognitive problems and waking without feeling rested. Secondary aspects include symptoms varying from irritable bowel disease to dizziness and nervousness. These two aspects are united on a symptom severity scale and accompanied by tender points, together leading to a diagnosis of along the fibromyalgia spectrum. This approach attempts to collapse symptoms into a globally perceived measure of dysfunction. Such an approach may be helpful in some respects, however, being able to identify key symptom clusters may reflect significant individual variability. Measurement of this variability may allow for more individualized therapeutic strategies.

These preliminary criteria are a step toward person-centered medicine and a person-centered diagnosis (PID) defined across three domains of health: ill health and its burden, a personalized narrative of one's ill health (suffering, beliefs), and contributors to ill health such as risk factors (Salloum & Mezzih 2010). When analyzing ACR preliminary criteria, one may conclude that they take into account the first two levels of PID. But the question remains: could these criteria could be translated into personalized medicine using objective tools to achieve diagnosis and treatment prognosis, while at the same time, optimize treatment outcomes?

The answer to objective measurement may be found in utilizing widely available physiological tools with established normative databases. Unbiased algometry used in parallel with paradigms of unexpected, spontaneous, noxious stimuli typically utilized in imaging studies (Williams & Gracely 2006) could potentially replace the current measure of palpation of tender points. Similarly, problems of cognition such as "fibro fog" could be assessed with simple, culturally- and motivationally-unbiased measurements (preferably qEEG) of prefrontal cortex activities during cognitive task paradigms (Bangert et al. 2003). In addition, a patient's beliefs system is related to the outcome of therapeutic efficacy. A greater internal locus of control, for example, is associated with the greater neuronal activity in the contralateral SII, which allows a patient to discriminate pain and improve daily function (Farrell et al. 2001). Catastrophizing is a phenomenon characterized by emotional processing of pain as unbearable and is a belief pattern common among fibromyalgia patients. This catastrophizing process is associated with perfusion abnormalities in the brain areas involved in anticipation of pain, attention to pain, affective response and motor control (Gracely et al. 2004).

Another important variable includes patient risk factors, both genetic and environmental, which are potentially translated in into epigenetic modulation of the human genome. Several candidate genes and their polymorphisms, mainly COMT, DRD4 and 5HTT, have been implicated in fibromyalgia, but the results remain inconclusive with limited utility due to low statistical power (Bazzichi et al. 2010). Progress is slow and data are inconsistent, as recently stated by Jakovljević et al: "The history of psychiatric genetics is mainly a story of unreplicated discoveries and disappointed expectations…" (2010). However, we must not forsake genetics without genome-wide associated studies in large sam-

ples that are clearly defined. Clear definition of the sample popultaions may enhance study outcomes if more attetnion is paid to objectively defined variables such as neurophysiological responses to pain.

With these examples of diagnostic procedures, we have demonstrated the striking similarities of person-centered medicine and personalized medicine in diagnostic issues. Person-centered medicine is holistic in approach, but lacks the evidence-based structure of modern medical science. The main critique of personalized medicine against the medical model lies in turning patients into medical objects while offending the moral and existential approach to patients as human beings. By fusing of these two very similar, but yet different paradigms, a third approach may be defined as the medicine "of the person, for the person, by the person and with the person"(Mezzich et al. 2011, Jakovljević 2008).

And yet the ultimate question stands, can this approach to the pain management enhance the outcome?

OUTCOME: THE DOWNFALL OF TREATING CHRONIC PAIN DISORDERS

In the last decade, three major scientific societies have published guidelines on treatment of fibromyalgia: American Pain Society (APS), European League Against Rheumatism Level of Evidence (EULAR) and Association of Scientific Medical Societies in Germany (AWFM) (Burckhardt et al. 2005, Carville et al. 2008, Klement et al. 2008). The striking difference among these guidelines lies in EULAR, which, in contrast to APS and AWFM, does not recommend the use of aerobic exercise and cognitive-behavioral therapy in the treatment of fibromyalgia. Furthermore, it does not address several other therapies available such as balneotherapy, biofeedback, and hypnotherapy, and it ignores multicomponent therapy. The reason for the omission of multiple treatment modalities may be in their strict meta-analysis or various methodological difficulties that arise from conducting randomized controlled trials of complementary therapeutic approaches (Hauser et al. 2010). The reason may also lie in ignoring person-centered and/or personalized medicine while only focusing on pharmacotherapy with SSRIs (fluoxetine), SNRIs (duloxetine, milnacipran), alpha 2 delta ligands (pregabalin), tramadol and TCAs (amytriptiline).

The medication driven studies are compromised of important issues, for example, in the randomized control trials of fibromyalgia, pharmacotherapy defines the primary end-points. Yet most trials conducted use various psychometric self-reported scales such as the Fibromyalgia Impact Questionnaire, the Brief Pain Inventory or simple changes in visual-analogue pain scales as primary end-points (Burckhardt et al. 1990, Cleeland et al. 1994, Recla 2010). In the authors' opinion, through the use of these end-points without well-defined endophenotypes, we may be missing or mixing subpopulations of fibromyalgia patients with distinct neurobiological and behavioral characteristics. Patients may belong to separate subgroups defined by certain cognitive beliefs (pain catastrophizing and loss of internal locus of control), which are known negative predictors in fibromyalgia therapy. Furthermore, the simple use of SPECT can differentiate the responders from non-responders to certain drugs such as gabapentin (Usui et al. 2010). By ignoring the possibility of subpopulations in fibromyalgia syndrome, the use of person-centered/personalized medicine in research and clinical practice remains only a remote possibility.

Another issue arising in person-centered/personalized medicine research is a lack of data defining variability within patient populations. This lack of data may be due to rather small sample sizes used in studies that employ imaging or other biological marker methods as distinguishing features of the neuronal correlates along the fibromyalgia spectrum. Most studies, especially fMRI studies, use a small number of subjects (up to 50) and yield low statistical power that is potentially driven by interpersonal variability. Therefore, it is reasonable to propose a paradigm shift consisting of redefining dependent and independent variables, as well as employing more objective assessment tools with standardized commercially available normative databases. One such tool may be qEEG, which provides for relatively inexpensive, noninvasive and database driven assessment (Konopka & Poprawski 2009). Other physiological measurements, such as heart rate variability, algometry and skin conductance, may be employed to evaluate larger numbers of subjects or patients in order to avoid type I and type II error and, ultimately, to enhance our understanding and treatment of chronic pain syndromes.

A third issue in a person-centered/personalized medicine approach is the presence of outliers, in other words, the discrepancy between a model based on average data and the patient as a distinct individual. To avoid this possible pitfall, the biological model is needed to serve as the foundation of our understanding of chronic pan syndromes, and its measures must be applicable in every day clinical practice, i.e. tools such as peripheral physiology, qEEG, SPECT and behaviorally driven measures. These tools may be used to address clinical pharmacological interventions. Ultimately, the use of these tools will generate cost-effective outcomes due to reduced variability and more consistent results that will directly inform the clinical practice. Overall, this practice may potentially reduce the incremental cost-effectiveness ratio (ICER). Through these steps, with knowledge based on a large dataset and the establishment of databases, individual differences will be appreciated. Thus, based on these findings it may be possible to individualize treatment according to person-centered/personalized medicine.

CONCLUSION: SOME THOUGHTS ON THE FUTURE

Up to now, most authors viewed personalized medicine and person-centered medicine as different concepts. We have tried to show the similarities of these paradigms in the complex clinical setting of chronic pain research and management, suggesting the need for the fusion of these paradigms into a single new approach in order to avoid possible miscommunication, duplication of efforts, and ineffective treatment of patients.

By analyzing current research paradigms in the biology and pharmacology of fibromyalgia, we have identified various methodological shortcomings used by person-centered/personalized medicine paradigms. We hypothesized that a change of paradigm would result in enhancement of outcomes, which would be the largest benefit of using this approach. However, the implementation of this approach into daily clinical practice is currently limited due to lack of data.

In order to introduce person-centered/personalized medicine into chronic pain management, we suggest the following steps:

- further research using simple measures applicable in clinical practice that are characterized by intrinsic stability, universality, and common normative data sets;
- development of large, available data sets across various laboratories and countries in order to define distinct subpopulations;
- construction of a global biological model of chronic pain disorders in order to define therapies accordingly;
- shifting the focus on the treatment outcome from patient behavior to presenting neurobiological patterns in order to enhance the clarity of results and treatment efficacy,

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