Letter to the Editor

Response to Functional Medicine Case Study and Editorial

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Re: Plotnikoff G, Barber M. Refractory depression, fatigue, irritable bowel syndrome, and chronic pain: A functional medicine case report. Perm J 2016 Fall;20(4):15-242. DOI: https://doi.org/10.7812/TPP/15-242; and Hanaway P. Form follows function: A functional medicine overview. Perm J 2016 Fall;20(4):16-109. DOI: https://doi.org/10.7812/TPP/16-109.

Dear Editor,

In the Fall 2016 edition of *The Permanente Journal* (*TPJ*), one case report[1] and one editorial[2] were published on the topic of functional medicine. As Permanente physicians who aspire to practice medicine in an evidence-based manner, we were surprised to see these articles published in *TPJ*. Although we understand that *TPJ* tries to give voice to areas of medicine that are innovative and provide different perspectives, there are several unsubstantiated claims across these articles that we hope will not be broadly incorporated in practice by Permanente physicians.

In his editorial, Hanaway[2] provides the following definition of functional medicine:

"Functional Medicine is a systems-biology-based model that empowers patients and practitioners to work together to achieve the highest expression of health by addressing the underlying causes of disease. Functional Medicine uses a unique operating system and personalized therapeutic interventions to support individuals in achieving optimal wellness."

We certainly agree that approaching our patients in a holistic and caring manner is always best, but we are unaware of a scientific basis for the "unique operating system" and "personalized therapeutic interventions" suggested in these articles. Perhaps accidentally, Hanaway acknowledges that functional medicine does not have an adequate evidence base and relies on unproven suppositions when he writes, "As we move from Case Reports to randomized controlled trials and population-based trials, Functional Medicine research will offer insight into the best ways to improve the value of the care we offer."[2]

In the case report, Plotnikoff and Barber[1] discuss a 72-year-old man with long-standing depression, fatigue, irritable bowel syndrome, and chronic pain. As primary care physicians, we can envision this patient and many others like him. These are challenging clinical situations without easy answers. Though presenting an N of 1 case report, Plotnikoff and Barber suggest that many patients with multiple chronic conditions would benefit from the functional medicine approach. They propose "seven potential core imbalances" that may serve as the "root" causes of any disease:

1. Assimilation (digestion, absorption, microbiomics, respiration)
2. Defense and repair (immune function, inflammation, infection)
3. Energy (production, regulation)
4. Biotransformation and elimination (toxicity, detoxification)
5. Transport (cardiovascular and lymphatic systems)
6. Communication (hormones, neurotransmitters, cytokines), and
7. Structural integrity (membranes, fascia, bacterial translocation).

The patient in the case was assessed with a Comprehensive Digestive Stool Analysis 2.0 (CDSA 2.0) and a Nutritional Evaluation (NutrEval) by Genova Diagnostics.[a] Plotnikoff and Barber[1] claim that these tests offer insight into the patient's functional status with regard to several of the proposed core pathways comprising functional medicine. The patient was diagnosed with vitamin D deficiency, low normal dehydroepiandrosterone-sulfate (DHEAS), pancreatic insufficiency, and persistent *Candida glabrata* overgrowth in the stool. His treatment included pancreatic enzyme support, probiotics, a diet rich in prebiotiocs, and four weeks of daily fluconazole. Although the case report documents improvement in patient-reported outcomes scores across three scales (Brief Fatigue Inventory, Brief Pain Inventory, and Patient Health Questionnaire-9), attributing this improvement to the multitude of interventions presented in Table 3 of the article, "Stool and urine metabolic testing results and therapeutic interventions," is dubious. Association is not necessarily causation.

Sackett et al[3] provided the classic definition of evidence-based medicine as, "… the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients." We find it somewhat audacious for Plotnikoff and Barber to quote Sackett in their conclusions. Case reports and suppositions do not represent best evidence, and conclusions based on them are not broadly generalizable to larger groups of patients. In Hanaway's editorial,[2] we noted with interest that randomized controlled trials comparing functional medicine with current standard care are underway at the Cleveland Clinic. But unless and until such clinical trials demonstrate efficacy of the functional medicine approach, we believe *TPJ* should not encourage Permanente physicians to incorporate functional medicine into clinical practice as it has done implicitly by publishing this case study and editorial. ❖

Sincerely,
Craig W Robbins, MD, Medical Director, Evidence-Based Practice, Care Management Institute, Denver, CO;
Meighan Elder, MD, Internal Medicine, Boulder, CO;
Michelene A Kuhr, MD, Family Medicine, Boulder, CO; Mark S Hoskinson, MD, Internal Medicine, Boulder, CO

[a] Dr Hanaway was Chief Medical Officer at Genova Diagnostics from 2002-2012.

References

1. Plotnikoff G, Barber M. Refractory depression, fatigue, irritable bowel syndrome, and chronic pain: A functional medicine case report. Perm J 2016 Fall;20(4):15-242. DOI: https://doi.org/10.7812/TPP/15-242.
2. Hanaway P. Form follows function: A functional medicine overview. Perm J 2016 Fall;20(4):16-109. DOI: https://doi.org/10.7812/TPP/16-109.
3. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: What it is and what it isn't. BMJ 1996 Jan 13;312(7023):71-2. DOI: https://doi.org/10.1136/bml.312.7023.71.

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Letter to the Editor Responses

To the editors:

I thank the authors of the letter to the editor for sharing their concerns. And I thank the editors of *The Permanente Journal* for this chance to respond.

The letter's authors affirmed their commitment to compassionate patient care and their aspiration to practice in an evidence-based manner. They also acknowledged the challenge of chronic, complex illness that evades easy answers.

I respond as a fellow clinician who also believes in clinical trials. I will continue to conduct and publish them. However, I recognize that clinical trials can only result in our capacity to state that, on average, for most people, intervention X can be helpful for condition Y. What if your patient is neither average nor the subject of a single intervention for a single condition? Additionally, since the Number Needed to Treat (NNT) for benefit for a single disease is rarely 1, there are still many patients with complex, multidimensional, intractable illness for whom the best existing evidence may not result in significant clinical improvement.

The bottom line is that the results from a randomized controlled trial are, at best, useful surrogate markers for clinical effectiveness.

And such was the case with the 72-year-old gentleman in this case. Despite years of intensive and expensive evaluations, he literally arrived in my office with multiple intractable symptoms that had worsened over time. A review of the medical literature did not generate any randomized controlled trials for his constellation of symptoms. However, a functional medicine perspective enabled me to ask different questions. Thus, I could generate different hypotheses that were grounded in the basic sciences, subject to laboratory measurements, and amenable to low-cost, low-toxicity interventions that could be monitored and modified.

When I called the patient to inform him that our case was published, I asked him how he was doing. "Great!" he responded. "My sons just took me skydiving for my 75th birthday!" Needless to say, enjoying this birthday treat[1] was inconceivable 3 years ago.

Publication of this case study is not an implicit encouragement to change practice. My intent is both to ignite curiosity and to generate a dialogue among fellow clinicians. Why? Should there be patients with complex, chronic, intractable, and expensive symptoms that have not responded well to the best efforts of multiple physicians practicing the best evidence-based interventions, there may be value in asking different questions. ❖

Sincerely,
Gregory A Plotnikoff, MD, MTS, FACP
Minneapolis, MN

Reference

1. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: Systematic review of randomised controlled trials. BMJ 2003 Dec 20;327(7429):1459-61. DOI: https://doi.org/10.1136/bmj.327.7429.1459.

To the editors:

I read with interest the letter from Drs Robbins, Elder, Kuhr, and Hoskinson. I appreciate their passion to respond to Plotnikoff's case report,[1] but I am perplexed by statements about "unsubtantiated claims," which are not specifically delineated.

Indeed, the concerns about evidence raise larger questions. Perhaps it is useful to re-examine Sackett's seminal article, in which he stated, "The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. By individual clinical experience we mean the proficiency and judgment that individual clinicians acquire through clinical experience and clinical practice. Increased expertise is reflected in many ways, but especially in more effective and efficient diagnosis and thoughtful identification and compassionate use of individual patients' predicaments, rights, and preferences in making clinical decisions about their care ... . Good doctors use both individual clinical expertise and the best available external evidence and neither alone is enough."[2]

Many recent expressions of evidence-based medicine move away from the inclusion of clinical expertise and patient preference. Yet these elements remain an essential part of current clinical practice. Must they be excluded from our evaluation/investigation of clinical practice?

The use of case studies following CARE Guidelines[3] allows us, as clinicians, to share important observations, including those from systems-based approaches that generate hypotheses for RCTs. A challenge for our next step in clinical research is that patients with multiple comorbidities are inherently difficult, if not impossible, to randomize. Needed now are next-generation studies to evaluate clinical effectiveness. One value-based example is the measurement of both outcomes and cost. At the Cleveland Clinic Center for Functional Medicine we measure outcomes through function, symptoms, and patient activation. Outcomes divided by cost (ie, claims-based data) equals "value." This approach is part of the framework for comparative effectiveness that is the basis for clinical trials to be published from our clinical operations, ranging from case series to randomized controlled trials.

I applaud *The Permanente Journal* for creating the opportunity to respond to this heartfelt inquiry and to offer the opportunity for its readers to engage in dialogue about new and innovative approaches to helping our patients. ❖

Sincerely,
Patrick Hanaway, MD
Medical Director, Center for Functional Medicine, Cleveland Clinic, OH

References

1. Plotnikoff G, Barber M. Refractory depression, fatigue, irritable bowel syndrome, and chronic pain: A functional medicine case report. Perm J 2016 Fall;20(4):15-242. DOI: https://doi.org/10.7812/TPP/15-242.
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