Journal of Clinical Epidemiology 116 (2019) 167−170

Journal of Clinical Epidemiology

COMMENTARY

Why mind-body medicine is poised to set a new standard for clinical research

Nadia M. Penrod*, Jason H. Moore*

Institute for Biomedical Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, PA 19104, USA

Accepted 14 May 2019; Published online 18 May 2019

1. Introduction

Stress is a pervasive force, one that can nudge our thoughts, feelings, and behaviors in imperceptible ways. The experience of stress is subjective but it's also all-encompassing; the brain does not differentiate between real and perceived, physical and emotional stressors. If left unmanaged, the burdens of our work and personal lives manifest in the body as a physiological state of chronic stress marked by elevated cortisol levels and low-grade, nonspecific inflammation [1].

The link between external stressors and internal physiological responses, that is, the stress response, was first described in 1936, following a series of experiments in rats, and has since become an increasingly active area of transdisciplinary research [2]. We now understand that stress can be classified into three broad categories: eustress is positive stress that motivates productive actions, distress is negative but normal stress for which coping mechanisms have been developed, and toxic stress is prolonged and/or high-grade distress for which coping mechanisms have not been developed [3]. Short-lived eustress and distress are positive effectors that drive biological adaptations like neuroplasticity. Toxic stress kindles chronic diseases and fuels existing conditions.

Chronic diseases are the largest burden on the health care system: they consume 86% of health care spending and are the leading causes of death and disability in the United States (Centers for Medicare and Medicaid Service, 2015). An estimated 150 million Americans are living with at least one chronic condition, and incidence is on the rise. These numbers are striking; they become unjustifiable in the context of epidemiological data showing that many chronic diseases, specifically, up to 80% of premature heart disease, type II diabetes, and stroke, and 40% of cancers, are preventable by modifying known risk factors [4].

Familiar behavioral risk factors including, unhealthy diet, lack of exercise, and alcohol and tobacco use, have been known drivers of mortality via chronic diseases in population based cohorts for decades [5]. Genetic factors also contribute to chronic diseases, but their role in driving disease is minor relative to external factors [6]. Stress is an external risk factor that is intrinsically linked to behavioral risk factors in a perpetual, self-reinforcing feedback loop. Stress is also modifiable, so while stress itself may be inevitable, a life of stress-induced chronic disease is not.

Stress management techniques based on mind-body medicine, for example, mindfulness-based stress reduction or moving meditations like yoga, have tremendous potential to impact public health at a reasonable cost. Mind-body practices work as a type of biofeedback that teach the practitioner to govern processes normally regulated by the involuntary nervous system including, heart rate, respiration, and muscle tension, that in effect, counteract the stress response [7].

While mind-body practices are an established entity in the lives of many patients, mind-body medicine is still a burgeoning field in the scientific community. Small-scale studies and anecdotal evidence suggest mind-body practices may effectively prevent and/or treat chronic diseases. However, few studies to date are both appropriately sized and methodologically rigorous, so statistical significance and replication have been largely elusive [8−11].

2. The evidence hierarchy is obsolete

On one hand, the design and interpretation of mind-body medicine research comes with a set of seemingly insurmountable challenges [20]. Studies in this domain are not suitable for customary randomized controlled trials, the practices are conceptually and practically difficult to dose, and the effects are highly subjective. On the other hand, these challenges are only barriers in the prevailing yet outmoded approach we take to clinical research, an approach that struggles with reproducibility and relevance in the world of complex chronic diseases and precision medicine [12-14,16,17,21].

Conflict of interest: None.

* Corresponding author. Tel.: 215-573-4411; fax: 215-573-3111.
E-mail addresses: npenrod@upenn.edu (N.M. Penrod), jhmoore@upenn.edu (J.H. Moore).

https://doi.org/10.1016/j.jclinepi.2019.05.001

What is new?

- Stress-induced chronic diseases are an enormous burden on our health care system.
- Stress management is a skill that can be honed through mind-body practices such as yoga and meditation.
- Mind-body medicine, for the prevention and treatment of chronic diseases, has potential to impact public health at a reasonable cost, but currently lacks a strong evidence base.
- This is partly due to attempts to design studies that adhere to the principles of traditional randomized controlled trials, which ensures the research will not be useful.
- However, mind-body medicine research is an ideal candidate for n-of-1 trials, a patient-centered approach to clinical research, and provides a low-risk, low-cost, high-reward space to prototype novel n-of-1 trial designs for precision medicine in real-world relevant settings.

Randomized controlled trials (RCTs) are considered the gold standard for clinical research, but using RCTs by default, under the presumption that they are invariably the most rigorous method, can be counterproductive [12,13]. The utility of RCTs lies in the randomization process, which in theory, distributes confounding factors evenly among cases and controls, minimizing the internal bias of a study. However, it is well established that results of RCTs lack generalizability to patient populations outside of the study population and importantly, that summary statistics from RCTs rarely represent an accurate risk-benefit ratio for individual patients [14–17].

These limitations are a consequence of RCTs producing relative treatment effect sizes between the randomized groups, a statistic based on averages. In studies of diseases with a single cause and effect, for example, selecting an antibiotic to treat pneumonia, average treatment effects can be informative. But in studies of diseases with a diversity of causes and effects, such as the demographic, genetic, and treatment heterogeneities, and comorbidities underlying chronic diseases, average treatment effects are unavailing. The problem is not that RCTs do not work, the problem is that they are not designed to address contemporary research questions, specifically, the types of research questions we must answer to deliver on the promises of precision medicine.

Precision medicine is broadly defined as disease prevention and treatment that takes into account individual differences in people's biologies, environments, and lifestyles [18]. Mind-body medicine is a type of precision medicine that, for stress-induced chronic diseases, can act both as a lifestyle-based factor in disease prevention and as a nonpharmacological treatment. In a healthy state, the stress response and the reciprocal relaxation response both propagate through the mind-brain-body axis, always re-establishing a homeostatic balance. Mind-body practices fortify this balance by training the relaxation response to robustly counter a protracted response. However, just as the experience of stress is subjective, the experiences that invoke a relaxation response are subjective. Therefore, when designing research studies in mind-body medicine, we should expect the effects of mind-body practices to be idiosyncratic and personal.

Specifically, the personalized effects of a mind-body intervention will be largely dependent on the state of mind. In studies of the mind, psychologists use the terminology set and setting to refer to the mindset and the environment, respectively [19]. Here, mindset includes attributes like personality, and previous knowledge of, and expectations for, a given mind-body practice. Setting encompasses the character and atmosphere of the physical space and includes social interactions. A patient's response to mind-body medicine will be dependent on set and setting; not all practices, environments, or teachers will resonate with every patient, and not every patient will derive benefit from a mind-body practice. Set and setting are personalized confounding factors that cannot be evenly distributed among treatment groups a priori. For this reason, one of the greatest shortcomings in mind-body medicine research has been the attempt to design studies that adhere to the principles of traditional RCTs.

A recent critique of clinical research calls for rethinking common but flawed study designs that fail to focus on key features of useful research including information gain, patient-centeredness, and transparency [22]. To this end, we ought to be tailoring study designs to more precisely fit the objectives and circumstances of every clinical research question independently, instead of forcing clinical research designs to fit a predefined model. In studies of mind-body medicine, for the prevention and treatment of chronic diseases, the way to deliver useful research is through n-of-1 trials.

3. N-of-1 trials produce useful and actionable results

The n-of-1 trial is a type of single-case design that investigates the efficacy of therapeutic interventions, in individual patients, through standalone experiments [23]. In an n-of-1 trial, a patient serves as their own control, mitigating biological and environmental confounding and tackling the issue of treatment heterogeneity by directly estimating risk-benefit ratios for individual patients [24]. The framework of an n-of-1 trial is flexible and can, for example, include randomization and cross-over of therapeutic interventions

for comparative effectiveness research, or provide a cost-effective way to study longer term, behavior-based interventions. When study designs are coordinated, data from independent n-of-1 trials can be aggregated from the bottom-up to estimate treatment effects in comparable populations [25].

The n-of-1 approach is most applicable for studying chronic, stable conditions that have measurable biomarkers; mind-body medicine research, as it relates to stress management for the prevention and treatment of chronic diseases, fits this bill. With advanced molecular biology and commercially available wearable devices, the adaptive stress-response can be measured in response to a mind-body practice by monitoring salivary cortisol levels, a well-established biomarker of stress, and complementary physiological signals such as electrodermal activity and heart rate variability, proxies for arousal of the sympathetic nervous system. These technologies produce quantifiable data that can be synced with a patient's electronic health records, and they enable the collection of data outside of clinical research sites, eliminating time and location barriers to participation, which in turn fosters more inclusive, community-based research with real-world relevance.

Although the literature on n-of-1 trials for mind-body medicine is meager, some progress has been made in related fields. For example, an n-of-1 design with continuous activity monitoring was used in a study that showed significant interindividual variability in the relationship between stress and exercise [26]. Another study showed that cognitive-behavioral therapy for mood and anxiety can efficiently be tailored to individual patients with an n-of-1 approach, and that the data can be aggregated to estimate the average effect per unit time across patients, which in turn provides a timeframe to determine whether or not a treatment is working for an individual [27]. These studies demonstrate that n-of-1 trials provide an objective way to assess efficacy of behavioral determinants of health, in individuals and across broad populations, by aggregating data, patient by patient.

4. Mind-body medicine and reciprocal progress

An estimated 46 million Americans practice yoga, the most commonly used mind-body intervention, and 86% of yoga practitioners, surveyed by the Centers for Disease Control and Prevention, report stress reduction as the greatest perceived wellness-related outcome [28,29]. When 1 in 7 Americans are investing time and money in an ad hoc health and wellness plan, we ought to be able to provide credible scientific evidence to support or counter the assumption that mind-body practices reduce stress and improve health outcomes.

But there are much broader implications for studying mind-body medicine through n-of-1 trials. In the era of precision medicine, n-of-1 trials are a promising way to compensate for the limitations in the status quo of clinical research. Statistical guidelines and methodological recommendations, including software to optimize n-of-1 study designs, have been published [23,30]. The next step is large-scale implementation. Because mind-body practices are generally safe, accessible, and inexpensive relative to the cost of pharmaceutical and surgical interventions, they provide an unprecedented opportunity to prototype novel n-of-1 study designs in a low-risk, low-cost, high-reward space.

Using mind-body medicine as a proving ground to advance clinical research, in effect, fosters the development of a unified evidence base for precision medicine that covers treating diseases and promoting health. This has significant implications for delivering value-based health care to confront the rising incidence of lifestyle-based chronic diseases, especially those that are linked to pervasive, modifiable risk factors such as chronic stress.

5. Conclusion

As a burgeoning field, unconstrained by an established dogma, mind-body medicine research, as it relates to stress management for the prevention and treatment of chronic diseases, is particularly well-suited to set a new standard for useful clinical research.

CRediT authorship contribution statement

Nadia M. Penrod: Conceptualization, Writing - original draft. **Jason H. Moore:** Conceptualization, Writing - review & editing.

Acknowledgments

The study is funded by the Perelman School of Medicine at the University of Pennsylvania, United States.

References

[1] Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol 2005;5:243−51.
[2] Fink G. In retrospect: eighty years of stress. Nature 2016;539:175−6.
[3] McEwen BS. In pursuit of resilience: stress, epigenetics, and brain plasticity. Ann N Y Acad Sci 2016;1373(1):56−64.
[4] World Health Organization. Global health observatory. 2017. Available at http://www.who.int/gho/ncd/en/. Accessed October 9, 2018.
[5] McGinnis JM, Foege WH. Actual causes of death in the United States. JAMA 1993;270:2207−12.
[6] Rappaport SM. Genetic factors are not the major causes of chronic diseases. PLoS One 2016;11:e0154387.
[7] Benson H, Greenwood MM, Klemchuk H. The relaxation response: psychophysiologic aspects and clinical applications. Int J Psychiatry Med 1975;6(1−2):87−98.
[8] Desveaux L, Lee A, Goldstein R, Brooks D. Yoga in the management of chronic disease. Med Care 2015;53:653−61.
[9] Cramer H, Haller H, Lauche R, Steckhan N, Michalsen A, Dobos G. A systematic review and meta-analysis of yoga for hypertension. Am J Hypertens 2014;27:1146−51.

[10] Cramer H, Langhorst J, Dobos G, Lauche R. Yoga for metabolic syndrome: a systematic review and meta-analysis. Eur J Prev Cardiol 2016;23(18):1982−93.
[11] Duncan M, Moschopoulou E, Herrington E, Deane J, Roylance R, Jones L, et al. Review of systematic reviews of non-pharmacological interventions to improve quality of life in cancer survivors. BMJ Open 2017;7(11):e015860.
[12] Deaton A, Cartwright N. Understanding and misunderstanding randomized controlled trials. Soc Sci Med 2018;210:2−21.
[13] Frieden TR. Evidence for health decision making − beyond randomized, controlled trials. N Engl J Med 2017;377(5):465−75.
[14] Rothwell PM. External validity of randomised controlled trials: to whom do the results of this trial apply? Lancet 2005;365:82−93.
[15] El Dib RP, Atallah A′N, Andriolo RB. Mapping the Cochrane evidence for decision making in health care. J Eval Clin Pract 2007;13:689−92.
[16] Kent DM, Hayward RA. Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. JAMA 2007;298:1209−12.
[17] Fisher AJ, Medaglia JD, Jeronimus BF. Lack of group-to-individual generalizability is a threat to human subjects research. Proc Natl Acad Sci U S A 2018;115(27):E6106−15.
[18] Department of Health and Human Services, National Institutes of Health. All of us research program. 2017. Available at https://allofus.nih.gov/. Accessed March 26, 2018.
[19] Hartogsohn I. Constructing drug effects: a history of set and setting. Drug Sci Policy Law 2017;3(0):1−17.
[20] Davidson RJ, Kaszniak AW. Conceptual and methodological issues in research on mindfulness and meditation. Am Psychol 2015;70(7):581−92.
[21] Smith GD, Egger M. Incommunicable knowledge? Interpreting and applying the results of clinical trials and meta-analyses. J Clin Epidemiol 1998;51:289−95.
[22] Ioannidis JP. Why most clinical research is not useful. PLoS Med 2016;13(6):e1002049.
[23] Kravitz R, Duan N, Duan N, Eslick I, Gabler N, Kaplan H, et al. Design and Implementation of N-of-1 Trials: a user's guide. Agency for Healthcare Research and Quality, US Department of Health and Human Services; 2014: AHQR Publication No. 13(14)-EHC122-EF.
[24] Duan N, Kravitz RL, Schmid CH. Single-patient (n-of-1) trials: a pragmatic clinical decision methodology for patient-centered comparative effectiveness research. J Clin Epidemiol 2013;66:S21−8.
[25] Zucker D, Schmid C, McIntosh M, D'agostino R, Selker H, Lau J. Combining single patient (N-of-1) trials to estimate population treatment effects and to evaluate individual patient responses to treatment. J Clin Epidemiol 1997;50:401−10.
[26] Burg MM, Schwartz JE, Kronish IM, Diaz KM, Alcantara C, Duer-Hefele J, et al. Does stress result in you exercising less? Or does exercising result in you being less stressed? Or is it both? Testing the bi-directional stress-exercise association at the group and person (N of 1) level. Ann Behav Med 2017;51(6):799−809.
[27] Fisher AJ, Bosley HG, Fernandez KC, Reeves JW, Soyster PD, Diamond AE, et al. Open trial of a personalized modular treatment for mood and anxiety. Behav Res Ther 2019;116:69−79.
[28] Clarke TC, Barnes P, Black L, Stussman B, Nahin R. Use of yoga, meditation, and chiropractors among US adults aged 18 and over. NCHS Data Brief 2018;325:1−8.
[29] Stussman B, Black L, Barnes P, Clarke TC, Nahin RL. Wellness-related use of common complementary health approaches among adults: United States, 2012. Natl Health Stat Report 2015;4(85):1−12.
[30] Percha B, Baskerville EB, Johnson M, Dudley J, Zimmerman N. Designing robust N-of-1 studies for precision medicine. J Med Internet Res 2019;21(4):e12641.