EDITORIAL AND COMMENT

N-of-1 Trials in Hypertension Are Feasible, but Are They Worthwhile?

Richard L. Kravitz, MD, MSPH

UC Davis Division of General Medicine, Sacramento, CA, USA.

J Gen Intern Med 34(6):781–2
DOI: 10.1007/s11606-019-04938-3

The use of collective experience to generate expectations for an individual is an example of reference class forecasting.[1, 2] Most of what has come to be known as evidence-based medicine is in fact an application of this approach, in which average treatment effects, often derived from parallel group randomized controlled trials, are used to make predictions for individual patients. Unfortunately, while the use of average effects has generally proven superior to anecdote, averages do not always apply. The best reference class for an individual is, of course, him or herself. Therefore, the most direct way to estimate the effects of treatment on an individual is to evaluate an individual's own experience with two or more forms of treatment (where "treatment" may include active treatment, placebo, or routine care). This approach incorporates what have been referred to as single subject experiments, personalized experiments, or N-of-1 trials.

In the health care context, N-of-1 trials are repeated crossover experiments in a single patient.[3] The key operational features are repeated, randomized, or counterbalanced exposure to alternative therapeutic regimens (e.g., ABBABAAB); systematic outcomes measurement; and, depending on the nature of the intervention, blinding to treatment. N-of-1 trials have the potential to provide many benefits to participants, including (1) identifying more effective or better tolerated treatments; (2) determining if an adverse effect is actually caused by the alleged culprit treatment; (3) demonstrating no discernible difference in effectiveness between treatments that may separate along other patient-centered dimensions (e.g., cost, convenience, side effect profile); (4) finding an optimal dose of medication; (5) discovering useful information through self-tracking that is unrelated to comparative effectiveness or tolerability (e.g., disease trajectories, disease triggers, or treatment effect modifiers); and (6) providing practice in active engagement with care and—more broadly—in collecting, interpreting, and acting upon data (the role of the citizen-scientist).

In addition to addressing clinically meaningful questions at the individual level, N-of-1 trials examining the same treatments and conditions can be aggregated through meta-analysis.[4] This not only allows a direct estimate of heterogeneity of treatment effects but through the use of Bayesian shrinkage may produce more precise estimates of the effects of treatment for a given patient.[3]

Since Guyatt et al. introduced N-of-1 trials to the medical community in the early 1980s,[5] hundreds of N-of-1 trials and N-of-1 trial series have been published.[6] However, the approach has yet to go mainstream. There are several possible reasons. First, evidence that N-of-1 trial participation is beneficial in practice has been difficult to muster.[7] Second, neither patients nor clinicians are fully convinced that the putative benefits of enhanced therapeutic precision are worth the trouble of co-designing a trial, collecting data, and engaging in joint decision-making.[8] Finally, N-of-1 trials upend a number of remarkably sticky psychologically assumptions: that there is a "best treatment" for every patient, that the doctor knows what that treatment is, and that it is easy to tell if a treatment works just by trying it.

In this issue of JGIM, Kronish et al. report on a small series of N-of-1 trials in patients with high blood pressure.[9] The authors' choice of hypertension as a target condition makes sense for several reasons. Hypertension is a powerful, highly prevalent, and distinctly modifiable risk factor for coronary artery disease and stroke. Many effective pharmacotherapies exist, but most patients are treated empirically with no assurance that the regimen they land on is optimal for them. This may partially explain why at least 50% of Americans with hypertension do not achieve adequate control.[10] Blood pressure is easy to measure and record repeatedly. Finally, most antihypertensive medications have relatively rapid onset and short half-lives, and are therefore good candidates for a repeated crossover design.

Kronish et al. cast a wide net in an effort to enroll patients in their study. Nevertheless, only 13 patients were screened for eligibility; seven completed a personalized ("N-of-1") trial comparing at least three different antihypertensive medications. The prototypical trial ran for 12 weeks. The most common comparison involved a diuretic, amlodipine, and an angiotensin-converting enzyme inhibitor (ACE) or angiotensin receptor blocker (ARB). Patients measured their blood pressure using automated devices twice daily, and they were prompted to record side effects on a daily basis during the second week on each successive treatment (to allow for washout of the prior treatment). Results were supplied to patients in

Published online March 18, 2019

the form of colorful bar graphs; although statistical testing was performed (and showed "statistically significant differences in blood pressure between at least one pair of medications" in four of seven cases), the statistical tests per se were not shared with patients.

Of the seven patients starting a trial, six found participation "helpful," and even the sole dissenter would recommend the process to others. This high degree of patient satisfaction is consistent with other N-of-1 studies.[7] While changes in treatment based on the findings were uncommon (28.6%), it is plausible that patients electing to stick with current treatment based on their N-of-1 study results did so with newfound confidence. Such therapeutic confidence should not be discounted, as it might translate into improved adherence, enhanced placebo effects, or both.

This well-designed and carefully conducted study represents an important proof-of-concept for N-of-1 trials in hypertension. However, several questions remain on the table.

First, would the results have been different with blinding? Some of the observed differences in average blood pressure between treatments may have owed to prior patient (or physician) expectations. However, it could plausibly be argued that if one treatment lowers blood pressure more than another, the extent to which the difference owes to pharmacological versus psychological mechanisms is moot.

Second, are short term side effects as reported by patients an adequate measure of treatment harms? N-of-1 trials can readily assess short term tolerability, but they are unable to assess the relative prevalence of unusual or insidious adverse effects. In designing N-of-1 trials, clinicians and patients must actively consider external evidence on harms derived from large randomized controlled trials and cohort studies.

Third, is the magnitude of heterogeneity of treatment effects (HTE) in hypertension sufficient to warrant more widespread use of N-of-1 trials in this condition? Patients do respond differently to antihypertensives according to race and various genetic factors.[11] In addition, a secondary analysis of the ALLHAT study suggests that early responsiveness to antihypertensives (i.e., over the first 1 to 6 months) predicts long-term outcomes.[12] It is therefore reasonable to think that N-of-1 trial guided antihypertensive therapy might deliver improved long-term outcomes, perhaps at lower cost. However, undertaking an adequately powered randomized controlled trial of N-of-1 guided-therapy purporting to improve efficiency of care and reduce cardiovascular adverse events would require a large sample size, prolonged follow-up, and massive resources.

Bringing N-of-1 trials into the mainstream of research and practice will require more evidence of benefit and fewer barriers to entry. The evidence will come from randomized trials comparing N-of-1 based treatment strategies to usual care, and examining a full range of patient-centered outcomes. The barriers will fall as new patient monitoring devices, mobile apps, and statistical software make N-of-1 trials easier to design and implement.

The study by Kronish et al. demonstrates the feasibility of implementing N-of-1 trials in a self-selected group of patients with hypertension. This is an important first step in examining the utility of N-of-1 trials in chronic medical conditions using a validated biomarker (in this case, blood pressure). Looking to the future, one can imagine similar applications in diabetes, glaucoma, hyperlipidemia, and asthma. The reaction of many patients and physicians to N-of-1 trials is that they are simply "not worth the trouble."[13] For N-of-1 enthusiasts, the hope is that a combination of additional research evidence and technological advancements will begin to change hearts and minds.

Corresponding Author: *Richard L. Kravitz, MD, MSPH; UC Davis Division of General Medicine, 4150 V. Street, Suite 2400 PSSB, Sacramento, CA 95608, USA (e-mail: rlkravitz@ucdavis.edu).*

Compliance with Ethical Standards:

Conflict of Interest: *The author reports no relevant conflicts of interest.*

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