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# One Isn't the Loneliest of Numbers: N-of-1 Trials

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EDITORIAL

# One Isn't the Loneliest of Numbers: N-of-1 Trials

In this issue of *Advances in Chronic Kidney Disease* by Guest Editors, Donald Molony and Joshua Samuels, evidence-based medicine (EBM) once again comes to the fore. This issue represents an encore of sorts, reinvigorating many of the concepts which they promoted with their authors in Volume 19, Issue 1 of this journal, "Evidence-Based Nephrology."

EBM emphasizes the utilization of evidence in a hierarchically oriented fashion. The best evidence originates from expertly designed studies that become well-defined and carefully conducted research trials, which are ideally randomized, parallel grouped, and blinded. Such evidence facilitates the recommendations of guideline groups who bear the burden of informing best practice for large-scale populations. When such studies are not readily available or infeasible within a given time, EBM next gauges the epistemological strength of meta-analyses and systematic reviews, eg, Cochrane Database of Systematic Reviews (http://www.cochranelibrary.com/). When such evidence is unavailable, weaker evidence from weaker sources can only yield weak recommendations such as case-control studies.


EBM represents an approach to teaching how medicine is to be practiced.[1] EBM promotes excellent care of individual patients by their physicians. EBM is the clinician's guide to providing excellent care, ie, evidence-based decision making and practice. By its very nature, EBM cannot be flawless. High probability, on which many of EBM precepts are founded, permits one to do the best for a patient in most cases when that particular patient represents most patients. However, outlier patients are nearly always in the heterogeneous mix of a well-planned, multisite study. Representative of this group is the individual who defies the conclusions of a hallmark clinical trial. For example, the multicenter, open-label, randomized, controlled study Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) compared medical therapy alone with medical therapy plus renal artery stenting in patients with atherosclerotic renal artery stenosis and elevated blood pressure, chronic kidney disease, or both. The rare, elderly patient with resistant, three-drug high blood pressure who dramatically responds to renal artery stenting is the reason that the investigators of CORAL still had to state, "From this result, it is clear that medical therapy without stenting is the preferred management strategy for the majority of people with atherosclerotic renal-artery stenosis."[2] The small but finite amount of uncertainty intrinsic to the study alters the language of the conclusion from "for all people" to "for the majority of people."

To administer the best medicine to an individual when there is an absence of evidence (not evidence of absence), the clinician usually relies on a lifetime of experience or the experiences of colleagues. This approach is tried but not necessarily true because opposite or alternative approaches are rarely attempted, unless failure of treatment occurs. To determine the optimal approach to the "no evidence" circumstance, one may adopt an "N-of-1" strategy because the N-of-1 randomized trial ranks at the top of the Hierarchy of Strength of Evidence for Treatment Decisions list by Guyatt and colleagues,[3] which includes in descending order after the N-of-1 randomized trial, systematic reviews of randomized trials, single randomized trial, systematic review of observational studies addressing patient-important outcomes, single observational study addressing patient-important outcomes, physiological studies, and unsystematic clinical observations. The patient-centeredness of the N-of-1 randomized trial


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approach was acknowledged as important by the American Medical Association and consequently assigned CPT code 01030T as a personalized medicine test. Although nephrologists have been steeped in physiology, treatment assignment based on animal studies has been at best imperfect: man has been a poor model for the rat.

N-of-1 trials have been used in psychology and education historically. Medically based N-of-1 trials have been used previously to evaluate many common conditions: histamine receptor blockers for non-ulcer dyspepsia; tricyclic antidepressants for fibromyalgia; inhaled bronchodilators, inhaled steroids, and theophylline for chronic airflow limitation; nonsteroidal anti-inflammatory drugs and paracetamol for osteoarthritis; antihistamines for atopic dermatitis; and enalapril for hypertension.[4] The ingredients of the N-of-1 trial are not new, but its recipe must be followed for successful implementation.

Study design is the first and foremost and involves randomized, simple crossover, and replication. Namely, the application of a treatment A would be randomized against a treatment B, but this does not mean alternation. For example, the design of the two-drug study might be tested for the individual as ABBA or BAAB rather than ABAB. An eight-period crossover design with two interventions could proceed as ABBABAAB, but the smallest trial is represented as AB or BA—tantamount to what is done in clinical practice daily when one agent as treatment for a specific condition is changed to a different class of agent, with the exception that outcomes are not recorded in a scientifically rigorous manner. The number and length of treatments are dependent on the time required to obtain data on the outcomes of interest as well as the nature of the interventions—a drug with a rapid onset of action and rapid decay intrinsically requires a less lengthy trial interval than an agent with slow onset of action. More intervention periods reduce confounding from lifestyle interventions but do not completely eliminate confounding factors while entailing greater expense and obliging a longer time commitment for trial completion. The number of interventions would also be contingent to varying degrees on the statistical power associated with the defined number of interventions. An additional problem is that of treatment carryover effects, especially with biologically altering agents. This potential predicament begs the question of whether a "washout" period should be instituted. Answering this question reasonably depends in part on whether these periods of drug elimination render the patient susceptible to harm. Blinding is important and involves the patient, treating physician(s), and the clinical monitoring team.

The overarching premise of the N-of-1 trial is improvement in health care, but the overarching reality is feasibility. Mahon and associates[5] compared outcomes between groups of patients with irreversible chronic airflow limitation by N-of-1 trials or standard practice. The study explored whether value could be ascribed to the administration of theophylline following an uncertain conclusion rendered by an open trial of these patients. In the end, the N-of-1 trials informed practitioners that treatment without theophylline was reasonable in patients with limited airway flow. Furthermore, physicians who participated in N-of-1 trials also gained confidence regarding decision making after completion of the study. The cost to conduct the N-of-1 trial was considered reasonable and essentially equal to standard clinical practice.

Although relatively few have hopped onto the N-of-1 bandwagon, the ride is now easier because one may customize N-of-1 trials. The pharmacy benefit manager, Opt-e-scrip, Inc. (Bedminster, NJ), offers personalized medicine formularies by essentially establishing valid, single-patient clinical trials. In brief, they build an N-of-1 drug kit with instructions, having developed patented, personalized medicine tests that determine drug efficacy in individual patients to optimize drug prescribing. Certainly, N-of-1 is not for everyone, but the N-of-1 trial is a viable alternative for those patients for whom no drug appears effective or for those who seek the best drug for them. If successfully used in tandem with pharmacogenomics, N-of-1 has the potential to truly personalize medicine and achieve our aspirational goal.

One is the loneliest number that you'll ever do.
—Harry Nilsson

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