N-of-1 Trials: A New Future?

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J Gen Intern Med 25(9):891–2
DOI: 10.1007/s11606-010-1440-8

The idea of N-of-1 randomized trials first came to my attention at a clinical epidemiology meeting during a presentation by Gordon Guyatt in which he described a dramatic case report of a 65-year-old patient with steroid dependent asthma.[1] This case, subsequently published in the New England Journal of Medicine, demonstrated that aminophyllinee, then commonly prescribed for asthma and chronic lung disease was causing great harm to the patient as a result of exacerbation of gastroesophageal reflux. The prospect of improving therapeutic precision and avoiding harm inspired me to form an N-of-1 trial service at University of Washington Medical Center. Although this service was generally successful in achieving its goal of improving therapeutic precision it did not endure much beyond its two year pilot project phase.[2] I have since wondered at the contrast between how much effort and expense we devote to diagnostic precision compared with the degree to which medicine accepts imprecision in judging therapeutic effectiveness, especially for chronic disease. Since the initial Guyatt report of N-of 1 trials,[1]health care costs have skyrocketed[3] both collectively and for individual patients. Meanwhile our ability to accurately know which patients benefit from accepted therapy or which therapy is best for an individual patient has improved little.

As shown in the JGIM paper published in this issue[4] and our earlier report[2], costs of the N-of-1 service and individual trials are considerably less than the prices for high tech images in many countries. Single patient trials are time consuming, however, and results are not as immediate as a diagnostic image. Perhaps most importantly there has been no business case for their use until recently. In the more than 20 years since Guyatt's case report it seems that the time has not been right for more widespread use of N-of-1 trials[5].

With the expansion of drug therapies shown to be effective or somewhat effective in cohort trials, and especially with more and more very expensive drugs often used long term for chronic conditions, there may be a resurging interest in N-of-1 trials as shown in the Scuffham paper.[4] Given the growing expense of costly therapeutics and our inability to precisely assess therapeutic effectiveness, will N-of-1 trials make a comeback and finally achieve a place in medical care? Alternatively could consumers, increasingly interested in benefit and avoidance of harm, spark greater patient interest in therapeutic precision?[5]

One traditional stepped care strategy is to begin symptomatic or even disease modifying treatment with less expensive standard agents before moving on to more expensive newer drugs. Alternatively, many clinicians and patients, at times spurred on by direct to consumer (DTC) advertising will be drawn to the newest agent, especially for common conditions dominated by subjective complaints. In either strategy, assessment of benefit or harm often seems rather casual. Scuffham et al.[4], and others demonstrate that the N-of-1 trial can replace more subjective assessments or lack of value assessment by identifying responders and non-responders. This generally leads to concordance with trial results in subsequent treatment. Interestingly though, Scuffham et al., note the concordance was greatest for attention deficit disorder—a condition where many developmental practitioners have used the single patient trial for decades and where parents likely controlled treatment concordance.

For N-of-1 trials to be used more routinely and effectively, we will need to develop standardized, easily administered protocols that use self administered scales reflecting patient valued outcomes. Ideally patients and clinicians will not experience much added burden. For example, a clinician could order an N-of-1 trial involving a treatment of uncertain benefit for chronic pain[6] or for a commonly prescribed and heavily promoted anti-dementia drug (e.g., gabapentin or placebo and donepezil or placebo respectively). Prepackaged supplies of these medications arranged for randomly allocated treatment periods would then be made available. Outcome scales would be completed online three times per week by a patient with neuropathic or other chronic pain or by a patient with mild dementia or mild cognitive impairment and also by an observer. The clinician, patient, and possibly a caregiver, would arrange to meet 2 months later to review results and determine if treatment is beneficial enough to continue. This level of therapeutic precision starkly contrasts with current practice where medications of questionable value are often prescribed long term. All too often what I hear from patients taking such medications is a denouement characterized by a plaintive statement: "I'm not sure the treatment really helped or made any difference."

Gordon Guyatt told me many years after presenting the N-of-1 case study that they never had another case with such dramatic outcomes: worsened asthma related to aminophylline and reflux. Ironically, is it possible that an N-of-1 randomized trial with unusual results might have contributed to our distorted expectations of the value of N-of-1 trials?[7] We should not expect trials to have dramatic results, or at least not often.

I suspect that for N-of-1 trials to have broader acceptance they will need to be much more easily administered—like ordering a diagnostic test—with user friendly interfaces for clinician and patient. Most importantly doctors and patients will need to demand them, because they see their value in reducing risk of harm and possibly cost through avoidance of wasteful treatments.

Given the real, and perhaps exaggerated, promises of personalized medicine it is worth considering how N-of-1 trials might be related to results from advances in today's person-

Published online July 15, 2010

alized medicine movement based on recent advances in genomics. At some level, motivation for personalized medicine is similar to goals for N-of-1 trials. Ultimately, we and our patients want therapeutics tailored to individual patient characteristics and responses, not based on metrics like "numbers needed to treat" or results from research based in cohorts. Therein lies a tension between evidence based medicine, which thrives on randomized trials in populations and the use of that evidence for decisions in individual patients. It is astonishing how such a seemingly simple task has proved to be so difficult to accomplish with accuracy and precision.

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