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N-of-1 Trials to Facilitate Evidence-Based Deprescribing: Rationale and Case Study

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Abstract

Deprescribing has emerged as an important aspect of patient-centered medication management but is vastly underutilized in clinical practice. The current narrative review will describe an innovative patient-centered approach to deprescribing—N-of-1 trials. N-of-1 trials involve multiple-period crossover design experiments conducted within individual patients. They enable patients to compare the effects of two or more treatments or, in the case of deprescribing N-of-1 trials, continuation with a current treatment versus no treatment or placebo. N-of-1 trials are distinct from traditional between-patient studies such as parallel-group or crossover designs which provide an average effect across a group of patients and obscure differences between individuals. By generating data on the effect of an intervention for the individual rather than the population, N-of-1 trials can promote therapeutic precision. N-of-1 trials are a particularly appealing strategy to inform deprescribing because they can generate individual-level evidence for deprescribing when evidence is uncertain, and can thus allay patient and physician concerns about discontinuing medications. To illustrate the use of deprescribing N-of-1 trials, we share a case example of an ongoing series of N-of-1 trials that compare maintenance versus deprescribing of beta-

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blockers in patients with heart failure with preserved ejection fraction. By providing quantifiable data on patient-reported outcomes, promoting personalized pharmacotherapy, and facilitating shared decision making, N-of-1 trials represent a potentially transformative strategy to address polypharmacy.

Keywords

deprescribing; N-of-1; personalized medicine; beta-blockers

INTRODUCTION

With advances in basic biological understanding of disease and their translation through rigorous clinical research, the number of pharmacologic agents to treat various medical conditions continues to proliferate. Conditions that were once incurable and/or untreatable have now become chronic conditions that people can live with for many years. Indeed, with average life expectancy now exceeding 75 years,[1] over a quarter of adults in the United States have multiple chronic conditions.[2]

Parallel to improvements in disease management and life expectancy, the prevalence of polypharmacy has steadily increased. Polypharmacy is broadly defined as a large number of medications.[3] The most common definition uses a threshold of 5 medications, and an extreme version known as hyperpolypharmacy has been defined as at least 10 medications.[4] According to data from the National Health and Nutrition Examination Survey, the prevalence of polypharmacy has nearly doubled from 8% to 15% between 1999 and 2012, and approaches 40% among adults aged at least 65 years.[5] While this reflects increased availability of therapeutic interventions to treat various diseases, polypharmacy is also associated with myriad adverse effects including but not limited to falls,[6–9] disability,[10–12] and hospitalizations.[13–16]

The fundamental principle of medication management is to start (and/or continue) medications whose chance of benefits outweigh risks of harms; and to deprescribe medications whose risk of harms outweigh their chance of benefits. The concept of deprescribing has begun to gain traction in clinical medicine in the context of the proliferation of polypharmacy and rising concerns about its negative effects.[17] However, deprescribing is vastly underutilized due to barriers that span multiple domains. The current narrative review will describe an innovative patient-centered approach to deprescribing—N-of-1 trials. In this review, we will provide a primer of N-of-1 trials including a review of its history, required components and considerations for N-of-1 trials, and the current evidence base supporting the use of deprescribing N-of-1 trials. We will then describe how N-of-1 trials can combat many of the barriers to deprescribing. To clarify key concepts, we will use an ongoing series of N-of-1 trials evaluating deprescribing of beta-blockers in patients with heart failure with preserved ejection fraction (HFpEF) as a case example.

What are N-of-1 trials?

N-of-1 trials are a unique form of clinical trial that is conducted within an individual patient in which multiple-period crossover design experiments are prospectively performed comparing different treatments or treatments with placebo.[18] Pharmacologic-based N-of-1 trials can facilitate a comparison of different drug classes, different agents within the same class, or different doses of the same agent. They can also facilitate a comparison of continuing with a medication versus stopping a medication. Figure 1 depicts the structure of N-of-1 trials compared to conventional randomized clinical trials (RCTs). As shown, in an N-of-1 trial, two or more treatments vary over time within the same individual and the exposure to the treatments is usually repeated several times. Given this study design, N-of-1 trials would not be appropriate for an acute or rapidly progressive disease where delays or lapses in treatment can cause harm. Typically, the sequence of treatments is randomized to mitigate against confounding from time-varying clinical and environmental factors that could affect patient outcomes. Data evaluating the effects of each different treatment are then compared to identify the optimal and preferred treatment for the patient who participated in the experiment. Indeed, many N-of-1 trials are designed to involve patients in the treatment decision-making process. In these cases, the data showing treatment effects are shared with patients to assist patients in utilizing their own data to understand differences between treatments. This allows patients to apply their own values and preferences when evaluating treatment benefits based on N-of-1 trial data.

N-of-1 trials are distinct from traditional between-patient studies such as parallel-group or crossover designs which provide an average effect across a group of patients and obscure differences between individuals.[19] By generating data on the effect of an intervention for the individual rather than the population, N-of-1 trials can promote therapeutic precision.[20] For this reason, N-of-1 trials are classified as providing Level 1 evidence for making treatment decisions in individual patients by the Oxford Centre for Evidence-Based Medicine.[21]

In many ways, N-of-1 trials mimic real-world clinical practice in which individual patients and clinicians trial medications, and make refinements to medication regimens based on perceived treatment effects. N-of-1 trials add rigor to usual clinical practice by facilitating the prospective collection of quantifiable data on multiple treatments. In this manner, N-of-1 trials preclude recall bias that is prevalent when evaluating treatments in usual practice. N-of-1 trials can be further guided by advanced statistical techniques that determine whether there are clinically and statistically significant differences in treatment effects. Finally, data from N-of-1 trials can be shared with patients and subsequently used to make rational clinical decisions. Accordingly, N-of-1 trials can promote patient understanding and awareness of their disease,[22] and can facilitate patient-engagement and shared decision-making,[23–25] key pillars of patient-centered care.[26]

The History of N-of-1 Trials

The notion of self-controlled clinical trials was first introduced within medicine in 1953 by Hogben and Sim,[27] and later championed as N-of-1 trials by Guyatt through a seminal publication in the New England Journal of Medicine.[18] In this article, Guyatt and colleagues outlined an important paradox when trying to practice evidence-based medicine—they

asserted that clinicians cannot necessarily trust their own uncontrolled trials of therapeutic agents to make evidence-based clinical decisions due to biases inherent to patient and physician behavior as well as biases in the interpretation of “improvement.” They further asserted that clinicians cannot blindly rely on large-scale RCTs to make evidence-based clinical decisions since the findings may not apply to patients excluded from the trials. Finally, and perhaps most crucially, evidence from conventional RCTs may not apply to every individual patient in the trial due to differences in how treatments influence individual patient (i.e., heterogeneity of treatment effect). They thus outlined the potential for N-of-1 trials to fill this evidence gap for the individual patient.

Over the years, N-of-1 trials have been utilized to compare pharmacological and behavioral treatments across multiple settings.[28] Although most commonly used to compare treatments prescribed for neuropsychiatric disorders such as attention deficit-hyperactivity disorder, N-of-1 trials have also been used to examine medications treating pulmonary, musculoskeletal, gastrointestinal, and cardiovascular conditions.

With growing interest in strategies that can facilitate patient-centered care as well as advances in mobile health technologies that can ensure efficient and user-friendly collection of data pertaining to treatment effects and subsequently maximize power and rigor, there has been renewed interest in N-of-1 trials. Recently published work includes a study examining N-of-1 trials as a strategy to select medications for musculoskeletal pain;[25] a study examining efficacy of on-demand sildenafil use versus placebo for Raynaud phenomenon;[29] a study examining efficacy of mexiletine versus placebo in a rare disease, non-dystrophic myotonia;[30] and a study examining nocebo effects from statins.[31]

How to conduct N-of-1 Trials?

To guide decision-making about the appropriateness of N-of-1 trials and the appropriate study parameters, the Agency for Healthcare Research and Quality (AHRQ) published a user’s guide that enumerates key considerations for designing N-of-1 trials (Table 1).[32] The first consideration is whether N-of-1 trials are suitable for the clinical question of interest. N-of-1 trials are most appropriate for chronic symptomatic conditions where the treatment has a relatively rapid onset and offset. Acute conditions may not last a sufficient amount of time to complete an N-of-1 trial; and therapies with a slow onset/offset may require prolonged treatment period durations making N-of-1 trials less practical. This is a natural limitation of the N-of-1 trial study design; accordingly, some medications and some clinical scenarios do not lend themselves to N-of-1 trials. Addtionally, N-of-1 trials are most suitable when there is substantial clinical uncertainty as to which treatment is best for a given patient. Notably, N-of-1 trials have been used to examine treatment effects in rare diseases—a setting whereby large population-based studies are not feasible.[33]

After confirming that an N-of-1 trial is suitable, it is necessary to determine the trial design. This includes selecting the number of treatment period repetitions and the duration of each treatment period. The number of treatment periods are intertwined with statistical power—an increasing number of treatment periods permits an increased number of comparisons, which increases rigor and certitude of the effect. To a lesser extent, power is also derived from the number of treatment effect assessments during each treatment

period. The duration of each treatment period should incorporate pharmacokinetic and pharmacodynamic properties such as onset of action, duration of action, and half-life of both the medication and its target receptors which may be prone to upregulation or downregulation in response to changes in medication dose. This underscores the importance of invoking a suitable washout period to ensure that the data collected at the time of an intervention is not residual or "carried over" from the prior intervention. When there is uncertainty regarding pharmacokinetic and pharmacodynamic properties such as a broad range of reported half-life, it may be reasonable to determine period duration based on the upper limit to ensure adequate washout. Adaptations to the study design (in particular, number of treatment periods and/or period duration) have been used in prior N-of-1 trials, and may be reasonable to ensure that the objectives of the study are met while considering patient preference.[34]

Balancing the treatment assignments is also important to minimize the contributions of confounders. To maximize balance, there should be an equal number of periods for each intervention. The sequence of periods within each block may be randomized to mitigate risks of measured and unmeasured confounders. Alternatively, if time effects are of special concern, the sequence of periods can be counterbalanced, whereby the periods are organized into blocks so that each block contains each treatment assignment, and then the sequence within each block are predetermined and unique. For example, for a 2-intervention deprescribing N-of-1 trial with 4-periods, intervention A (on drug) and intervention B (off drug) could be sequenced as ABAB or BABA or ABBA or BAAB (Figure 2). Specific statistical methodology can also provide strategies to address confounding factors inherent to the study design, such as those related to an insufficient washout period and/or time-based effects.[35]

Determination of whether to invoke blinding is another important consideration. The use of blinding in N-of-1 trials is not required and depends on the purpose of the study.[25,32,36] Similar to its use in conventional RCTs, the major benefit of blinding is that it allows separation of the biological effects of an intervention from the indirect effects related to psychological processes and personal biases of patients and physicians.[25,32,36] Blinding can accordingly reduce personal biases from clinician, the patient, and the investigative team. This may be particularly important when study outcomes are subjective and preference based, as is often the case in N-of-1 trials. However, blinding must be considered in conjunction with the associated challenges. Many N-of-1 trial participants report reluctance toward blinding and dislike placebo comparisons.[37] Blinding and placebo also require additional personnel and cost which make blinding impractical in clinical settings without a clear funding source. Finally, if the goal is to help patients understand the real-life treatment effect, inclusive of the non-pharmacologic properties of a treatment such as the size or color of a pill, then placebo-controlled N-of-1 trials may be counter-productive.

Selection of suitable outcome domains and measures is the next step. The outcome must be relevant to the patient's wellbeing,[18] measurable, modifiable, and occur frequently enough to permit detection of changes over the course of an N-of-1 trial. Accordingly, mortality and rare clinical events are not suitable outcomes for N-of-1 trials; whereas patient-reported outcomes using valid and reliable measures sensitive to change are well-suited. There

should be a plan for analyzing the data and subsequently sharing the data with patients. Deduction from the experience itself may be sufficient for patients and physicians to make long-term therapeutic decisions. This may be complemented by specific statistical methodologies that can account for the unique N-of-1 trial study design—for example, such methodologies should account for correlation structure since treatment arms of N-of-1 trials are not independent. While N-of-1 trials should be conducted during a phase of clinical stability, acute conditions can occur and confound interpretation of data. New-onset chronic conditions can also occur in the middle of the study. This underscores the importance of inquiring about these potential events, and then subsequently exercising caution when interpreting data if/when concurrent acute or new chronic conditions occur during a specific treatment arm.

While data may be most easily analyzed and interpreted by a biostatistician, approaches to ensure interpretability by physicians as well as patients is an important priority. Although bar and line graphs have been used in recent contemporary N-of-1 trials,[25] analogy-based pictorials like gas gauges for energy levels can maximize interpretability across a broad range of patient health literacy and numeracy.[38] Data can also be pooled to provide insights on a broader population, but this is beyond the scope of this review.[39]

Why N-of-1 trials for deprescribing?

Deprescribing has emerged as an important aspect of patient-centered medication management, and is defined as the systematic process of discontinuing drugs when existing/potential harms outweigh existing/potential benefits in the context of an individual's care goals, level of functioning, life expectancy, values, and preferences.[17] Yet, despite its role as an integral part of patient-centric and goal-concordant prescribing practice and existing protocols for deprescribing,[40] deprescribing is seldom incorporated into usual clinical practice. While existing protocols outline steps for deprescribing,[17,41,42] they do not provide strategies to address the implementation challenges. To improve patient-centered medication management, there is a need to develop processes that can overcome barriers to deprescribing. N-of-1 trials as a strategy (not just a study design that generates generalizable data like other traditional clinical trial formats) can achieve the following objectives, thereby addressing key barriers to deprescribing: 1. Generate evidence for deprescribing in an individual, 2. Allay patient concerns about deprescribing, 3. Allay physician concerns about deprescribing, and 4. Circumvent the time constraints of clinical encounters (Table 2).

N-of-1 trials can generate evidence for deprescribing in an individual—One important barrier to broader use of deprescribing relates to the current state of the scientific evidence underlying deprescribing decisions. While there is some compelling data supporting the potential benefits of deprescribing in the nursing home setting,[43] there are a limited number of well-designed multicenter parallel group RCTs examining the efficacy and safety of deprescribing among ambulatory patients. Several studies have demonstrated successful reductions in the number of medications following the intervention, but few have demonstrated improvements in clinical outcomes.[44] While there is value in establishing that a deprescribing strategy is feasible and can safely decrease medication burden, demonstrating improvements in outcomes that patients and physicians care about

is paramount to advancing the field. An additional challenge is that conventional RCTs (including those studying medication prescribing or deprescribing) can only provide information on the intervention's average effect within a given study population, and cannot provide data on how an intervention will impact any single patient.[19]

N-of-1 trials are particularly well-suited to address these evidence-gap barriers since N-of-1 trials can facilitate evidence ascertainment across multiple outcomes for an individual patient. Indeed, deprescribing N-of-1 trials can permit a comparison of the short-term effects of continuing versus discontinuing a medication, and can thus generate individual-level evidence for the effects of deprescribing.[45] Accordingly, N-of-1 trials can facilitate therapeutic precision[20] in the face of the inherent complexity of patients as it relates to personal characteristics, clinical setting, and patient priorities. This is especially relevant for older adults who are mostly likely to experience adverse effects from medications[46] but are highly heterogeneous,[47,48] often have varying health priorities,[49] and are frequently excluded from clinical trials.[50,51] Indeed, N-of-1 trials may be an appealing innovative approach that the field needs.[52]

N-of-1 trials can allay patient concerns about deprescribing—Patient uncertainty and conflicting attitudes toward deprescribing are important patient-based barriers. Patients report feeling *uncertain* about the individual-level risks and benefits of deprescribing,[53–55] an observation that relates closely to the aforementioned evidence gaps. This issue may be exacerbated by suboptimal physician-patient communication regarding the chance of benefit and risk of harms for medications.[56] In addition to their limited understanding about the potential harms of their medications, patients often overestimate the potential benefits of their medications.[56] Moreover, patients can understandably be confused when a clinician tells them that they no longer need a medication after years of emphasizing the importance of taking all of their prescribed medication. Consequently, many patients may feel fear or anxiety about deprescribing.[57] On the other hand, studies have shown that many patients do not like taking a high number of medications, are negatively impacted by high pull burden, and would be willing to stop their medications if their physician recommended it.[58,59] Simultaneously holding these seemingly conflicting attitudes toward deprescribing[60–64] can make it difficult for patients to determine whether they wish to proceed with deprescribing.

N-of-1 trials have the potential to be patient-centered and can thus combat these patient-based barriers through its inherent nature of generating individual data that accounts for the biologic heterogeneity of adults[47,48] and variation in health priorities.[49] In some N-of-1 trials, patients can even participate in the selection of treatment outcomes that they care about. By quantifying individual-level experience and the effects of a medication across multiple domains, N-of-1 trials can be used to help patients make decisions,[65] and can accordingly address patient uncertainty and conflicting attitudes toward deprescribing.

Some may worry that N-of-1 trials put too much burden of the decision on the patient. They may also recognize that some patients prefer their doctors to make decisions for them.[66] However, N-of-1 trials do not necessitate that the patient alone make decisions, and, moreover, lend themselves to varying approaches to clinical decision-making. N-of-1 trials can provide quantifiable data that can be used by the patient, family member, or physician—

accordingly, they can facilitate decision-making based on objective data regardless of the decision-making process and/or decision-making agent.

N-of-1 trials can allay physician concerns about deprescribing—Yet another important barrier to deprescribing relates to physicians. Prior work has shown that physician-based barriers to deprescribing include preconceived physician biases based on training and/or experience,[67] and concern about interfering with another physician's prescribing practice.[68] From aspects of formal training and the experience of caring for patients, physicians are conditioned to the notion that prescribing medications can relieve suffering and prolong life.[69] Prescribing thus becomes closely intertwined with providing high quality care, whereby the benefits of medications are frequently overestimated and its harms are frequently underestimated.[70] Consequently, physicians may view the inverse of prescribing—deprescribing—negatively and equate deprescribing with treatment withholding and/or abandonment. In cases of multimorbid patients comanaged by two or more physicians, physicians across multiple disciplines also worry that deprescribing a medication might interfere with another other physician's treatment plan.[68] Moreover, there is concern that the act of deprescribing may be interpreted as a critique of another physician's treatment plan, which can result in devolving responsibility or 'passing the buck' between physicians.[71] With age and an accumulating number of chronic conditions, many patients will see multiple physicians for management of their health problems.[72] One of the problems with having multiple physicians is that it often leads to fragmented care with suboptimal communication among physicians.[73] Without an effective approach to communicating varying opinions on the risks and benefits of a medication,[74] clinical inertia[26] and diffusion of responsibility[68] may ultimately lead to inaction, even in situations where deprescribing a medication is the most logical and beneficial course of action.

N-of-1 trials can facilitate physician-patient communication about deprescribing based on rigorously measured experience rather than theory, mitigating physician (and patient) biases that frequently result in overestimating the benefits and underestimating the harms of medications.[75] Moreover, objective data from N-of-1 trials can supersede underlying biases about deprescribing that result from lack of knowledge and/or prior experiences; and also combat biases of standard practice that frequently favor un-necessary treatment.[76] For example, even if a physician was biased toward continuing a medication, it would be hard to overlook objective data collected from the N-of-1 trial showing that the patient felt better without the medication. Thus, N-of-1 trials have the capacity to shift decision-making toward patient-centered data and away from preconceived biases and the status quo. Although N-of-1 trials are not well-suited to determine the long-term effects of medications, ascertaining data related to short-term symptomatic effects can also facilitate discussions about the tradeoff of the short-term risks and potential long-term benefits of specific agents. In addition, N-of-1 trials can provide a platform to facilitate communication between physicians across different specialties regarding the potential utility of deprescribing. Making decisions based on objective data would likely lead to increased physician consensus regarding medication decisions, with less concern about interference or criticism.

N-of-1 trial services can circumvent the time constraints of clinical encounters—Prior work has shown that the time constraints of an office visit are also an important barrier to deprescribing. Indeed, medical encounters in the United States for example only last an average of 15 minutes[77–81]—for patients with multiple chronic conditions and polypharmacy, 15 minutes is unlikely to be sufficient to discuss the risks and benefits of each medication. Moreover, time constraints[82] undermine shared decision making and lead to medical decisions that incorporate less information and fewer tradeoffs, with increased dependence on preconceived notions and biases.[83–86] This is particularly problematic in older adults, who frequently report difficulties in interpreting quantitative and probabilistic information, experience cognitive overload in the setting of uncertainty, and often feel that they lack knowledge leading to low self-efficacy.[41,87]

N-of-1 trials can provide a scaffold for shared decision making and subsequently improve the quality of prescribing with increased use of deprescribing when appropriate;[41] this notion is supported by the observation that N-of-1 trial participants report increased understanding and awareness of their conditions and feel a greater sense of control in decision-making;[22,25] and can improve patient understanding of deprescribing harms/benefits. Importantly, the majority of N-of-1 trials can occur outside of the physician's office, with asynchronous data collection. Moreover, N-of-1 trials can be coordinated by stand-alone services which takes the onus of explaining and conducting the trial off of the busy physician. This could facilitate the use of N-of-1 trials in the context of routine clinical care without a substantial increase in time and/or effort of the physician. This would permit the physician to focus their time on identifying areas of therapeutic equipoise where deprescribing may be indicated, engaging and enrolling the patient in the N-of-1 trial, and weighing the risks of harm and potential benefits of the medication, informed by the findings of the N-of-1 trial. Accordingly, N-of-1 trials have the potential to promote shared decision making and deprescribing even in the setting of the usual time constraints of an office visit.

Prior evidence in support of N-of-1 trials for deprescribing

In 1990, Guyatt et al published on their early experience of conducting 70 N-of-1 trials, and reported that 11 of them led the physician to stop a medication, demonstrating its potential utility for the purposes of deprescribing.[88] A recent systematic review identified 6 studies that specifically examined deprescribing N-of-1 trials. Use cases included deprescribing or continuing digoxin in the setting of heart failure, quinine for muscle cramps, and various medications including theophylline in the setting of airway limitations such as those observed in asthma. The review concluded that deprescribing N-of-1 trials were feasible (>78% of patients completed the trials) and potentially useful for informing deprescribing. The two studies with long-term follow-up data after the N-of-1 trial found that approximately half of patients (17 of 32) discontinued their medication after completion of the trial.[45] Given the paucity of data on the feasibility of deprescribing N-of-1 trials, the authors called for additional work in this area to determine the potential role for N-of-1 trials to inform deprescribing.

Case Example: Deprescribing beta-blockers in patients with heart failure with preserved ejection fraction (HFpEF)

To illustrate the use of N-of-1 trials for the purpose of deprescribing, we share a specific case example of ongoing serial N-of-1 trials for deprescribing beta-blockers in patients with HFpEF.[89] HFpEF affects >3 million[90] people across the US and is a prototypical geriatric syndrome[91]—it disproportionately affects older adults;[92] age-related changes to the cardiovascular system and common age-related comorbid conditions are implicated in its pathogenesis;[93] and multiple chronic conditions and polypharmacy are nearly universal.[94] While beta-blockers are the most commonly-used medication for HFpEF (86% prevalence in a recent RCT),[95] there is substantial uncertainty regarding their benefits in HFpEF.[96,97] Although the benefits of beta-blockers in HF with reduced ejection fraction are well-documented,[98] RCTs of beta-blockers in HFpEF have been neutral to date, failing to consistently improve or worsen long-term outcomes including mortality and hospitalization rates.[99,100] Short-term effects of beta-blockers on patient-reported outcomes like physical function and quality of life are not well-described, with a signal of harm in some trials.[101] The resulting uncertainty stems from opposing pathophysiologic mechanisms—on the one hand, beta-blockers can slow down heart rate, improve left ventricular filling, and thus improve cardiac output and overall functioning.[102] On the other hand, beta-blockers can exacerbate chronotropic incompetence, worsen cardiac output, and reduce exercise tolerance.[103] Beta-blockers are also a common cause of adverse drug reactions and can worsen function in some older adults.[14,97,104] A recent randomized crossover study showed that deprescribing beta-blocker in patients with HFpEF led to an improvement in functional capacity. However, the study was small and did not characterize those who improved and those who did not.[101] Accordingly, there is no readily discernable way to determine which patients will feel better and which will feel worse from their beta-blocker. In contrast, patients with clear indications for beta-blockers, whereby the evidence indicates that the majority of patients are believed to have a substantial clinical benefit (reduction in mortality and/or major adverse cardiovascular events) would not be candidates for deprescribing, and therefore would not be appropriate for N-of-1 trials. For example, patients with heart failure with a reduced ejection fraction,[98,105] hypertrophic cardiomyopathy,[106] or a recent myocardial infarction[107] would not be appropriate candidates as there is strong evidence that beta-blockers reduce mortality and/or major adverse cardiovascular events; there is consequently significant concern that deprescribing could cause harm in these settings. In contrast, a prior study indicated that at least 40% of patients with HFpEF who take beta-blockers do not have a compelling evidence-based indication for their beta-blocker;[97] this indicates that many patients with HFpEF who take beta-blockers are good candidates for deprescribing N-of-1 trials.

Reasons that beta-blockers are not deprescribed in patients with HFpEF are multi-fold. First, from a scientific evidence standpoint, there is gap in knowledge regarding the potential benefits and risks of deprescribing beta-blockers in HFpEF. This is because of the paucity of well-designed studies and also the inherent limitations of relying on evidence from conventional RCTs which obscure clinically relevant differences between individuals.[19] Second, from a patient perspective, uncertainty about the individual-level risks and benefits of deprescribing,[53–55] and conflicting attitudes toward deprescribing[60–64] were important

barriers that emerged from interviews specifically of older adults with HFpEF when asked about deprescribing their beta-blocker.[108] In particular, patients reported concerns about developing worse arrhythmias and/or worse heart failure if their beta-blocker was stopped; and also reported skepticism about whether their beta-blocker was actually achieving anything, had concerns about their beta-blocker worsening other conditions, and were willing to try to stop their beta-blocker at least temporarily. Third, physicians managing cardiovascular medications, including primary care physicians as well as cardiologists, have expressed concern about interfering with another physician's prescribing practice.[68] Finally, time constraints of an office visit have been outlined as an important challenge to patient-centered medication management in older adults with HF,[109] which are paramount to discussions about deprescribing.

As previously outlined, N-of-1 trials can address each of these sets of barriers—they can generate evidence demonstrating the benefit of deprescribing, they can address patient uncertainty and conflicting attitudes, they can supersede preconceived biases of physicians and create a platform for physician-physician communication, and they can potentially circumvent time constraints of a patient-physician encounter that frequently undermine the shared decision-making processes.

To ensure that beta-blocker deprescribing in HFpEF was an appropriate clinical scenario for N-of-1 trials, we consulted the AHRQ checklist (Table 1). We considered this use case appropriate since HFpEF is a chronic symptomatic condition; beta-blockers have a reasonably short half-life and washout period allowing for multiple repetitions in a feasible time period; and there are measurable patient-important treatment effects. In designing the current ongoing study, we decided to compare continuing beta-blocker (Treatment A) with deprescribing beta-blocker (Treatment B), using a total of 4 periods with a randomized sequencing scheme (either ABAB or BABA as the sequencing schema) to allow us to examine the potential time effect in this specific use case. Given the potential need for additional information, rigor, and increased power, we used an adaptive approach whereby patients had the option of participating in additional treatment periods to gain increased confidence about their treatment decisions.

A challenge for beta-blocker deprescribing trials is that sudden withdrawal of high-dose beta-blockers can cause adverse drug withdrawal effects and/or sudden cardiac death.[110,111] To overcome this concern, we designed treatment periods to include a tapering strategy based on the pharmacologic properties of beta-blockers and their receptors, with consultation from a pharmacologist. In particular, the duration of treatment periods permit halving of the beta-blocker dose every week until off (during the deprescribing intervention phase), similar to a prior deprescribing study.[112] This schedule accounts for a sufficient number of half-lives to ensure drug clearance and accounts for changes in receptor density (half-life of 1.5 days)[113,114] which mitigates the risks of adrenergic hypersensitivity such as withdrawal symptoms and/or adverse drug withdrawal events observed after abrupt ß-blocker cessation.[110,111] This period duration also facilitates sufficient time for the washout period, and thus minimizes risk of contamination between treatments. For the periods following deprescribing whereby the medication is continued (Treatment A), the medication is reintroduced and doubled every week until the usual home dose is reached.

We extensively debating the pros and cons of invoking blinding and the use of placebo, and subsequently opted to conduct N-of-1 trials without the use of blinding or placebo. Prior work has shown that patients can feel psychological and/or emotional burden when they stop taking a medication that has potential future benefit.[108] These are real-world phenomena that can affect shared decision making,[115,116] and will impact the effectiveness of any deprescribing intervention. We therefore believed that deprescribing N-of-1 trials for the purposes of shared decision making should account for the biological effects *as well as* the psychological effects and personal biases of patients and physicians toward deprescribing, as has previously been done.[34]

With regard to outcomes, we are collecting physiological data daily (heart rate and blood pressure via remote monitoring devices), safety data weekly (concerning symptoms like palpitations and clinical events including hospitalization), and patient-reported outcomes weekly (which include heart failure-related quality of life outcomes from the Kansas City Cardiomyopathy Questionnaire every two weeks,[117] and general quality of life outcomes from Patient-Reported Outcome Measure Information System [PROMIS] questionnaires every week).[118] Upon completion of each period, we are sharing patient-reported outcomes data via gas gauges (Figure 3), since our prior work has shown that this display option is understood by a majority of patients.[38] Moreover, to understand feasibility and acceptability, we are conducting qualitative interviews of patients and physicians; and also collecting data on decision confidence measured by the Decisional Conflict Scale,[119] shared decision making measured by the Shared Decision Making Questionnaire-9,[120] patient activation measured by the Patient Activation Measure,[121] and patient attitudes toward deprescribing measured by the revised Patient Attitudes Toward Deprescribing questionnaire.[122] In the future, we plan to examine whether N-of-1 trials can ultimately improve quality of life through improved personalized data-driven decision-making.

Future Steps:

Integrating N-of-1 trials into real-world practice as a shared decision-making strategy to facilitate deprescribing has great potential to improve care. There are myriad use cases for such a tool. For example, N-of-1 trials could help quantify the potential effects of deprescribing tamsulosin for lower urinary tract symptoms.[123] N-of-1 trials could also serve as a potential strategy to address therapeutic competition—an increasingly common scenario whereby a medication that treats one condition could cause harm to another[124] However, evidence for the efficacy and safety of N-of-1 trials, as well as its effectiveness and implementability will be needed to advance this unique strategy. Historically, cost and time have been important barriers to N-of-1 trials.[125] Technologic advances such as remote monitoring and mobile health have mitigated some of these concerns, facilitating data collection at a reasonable cost and time burden.[37] However, stakeholder engagement and integration of implementation science concepts will be critical to advance deprescribing N-of-1 trials. Indeed, the need to conceptualize, synthesize, and evaluate successful deprescribing strategies and studies are especially relevant to translating deprescribing research into practice.[126] In our ongoing pilot N-of-1 trials of beta-blockers for HFpEF, we are collecting data on deprescribing, shared-decision making, and decision conflict to better understand the impact of N-of-1 trials on these patient-centered processes.

We are also conducting interviews with stakeholders including patients, physicians, and caregivers to understand key implementation outcomes including fidelity, acceptability, and appropriateness of the N-of-1 trial approach. If our pilot study confirms feasibility and acceptability, we plan to conduct a type 1 hybrid effectiveness-implementation RCT comparing the N-of-1 trial approach with usual care across a group of HFpEF patients prescribed beta-blockers. Hybrid effectiveness-implementation trials permit concurrent collection of data on intervention effectiveness and empirical observational data on aspects of implementation, and can accelerate the development and implementation of behavioral interventions into real-world practice.[127] Implementation science frameworks such as the Practical, Robust Implementation and Sustainability Model (PRISM)[128] and behavioral models like COM-B[129] may be particularly helpful. Regardless of framework, consideration of implementation along with efficacy is critical to advancing deprescribing N-of-1 trials.

Conclusions:

N-of-1 trials represent a potentially transformative strategy to address polypharmacy and improve the wellbeing of older adults with multiple chronic conditions and polypharmacy. By providing quantifiable data on patient-reported outcomes, N-of-1 trials can help patients make confident decisions about deprescribing across a broader set of circumstances than has been done before, thereby promoting personalized pharmacotherapy[130] and therapeutic precision[20] in the face of heterogenous clinical phenotypes,[94] drug metabolism,[47] responsiveness to therapy,[48] and health priorities;[49] as well as embracing the core of shared decision making[131,132] While the focus of the current ongoing trial is beta-blocker use in HFpEF, this protoype has the potential for future application to many other clinical contexts.

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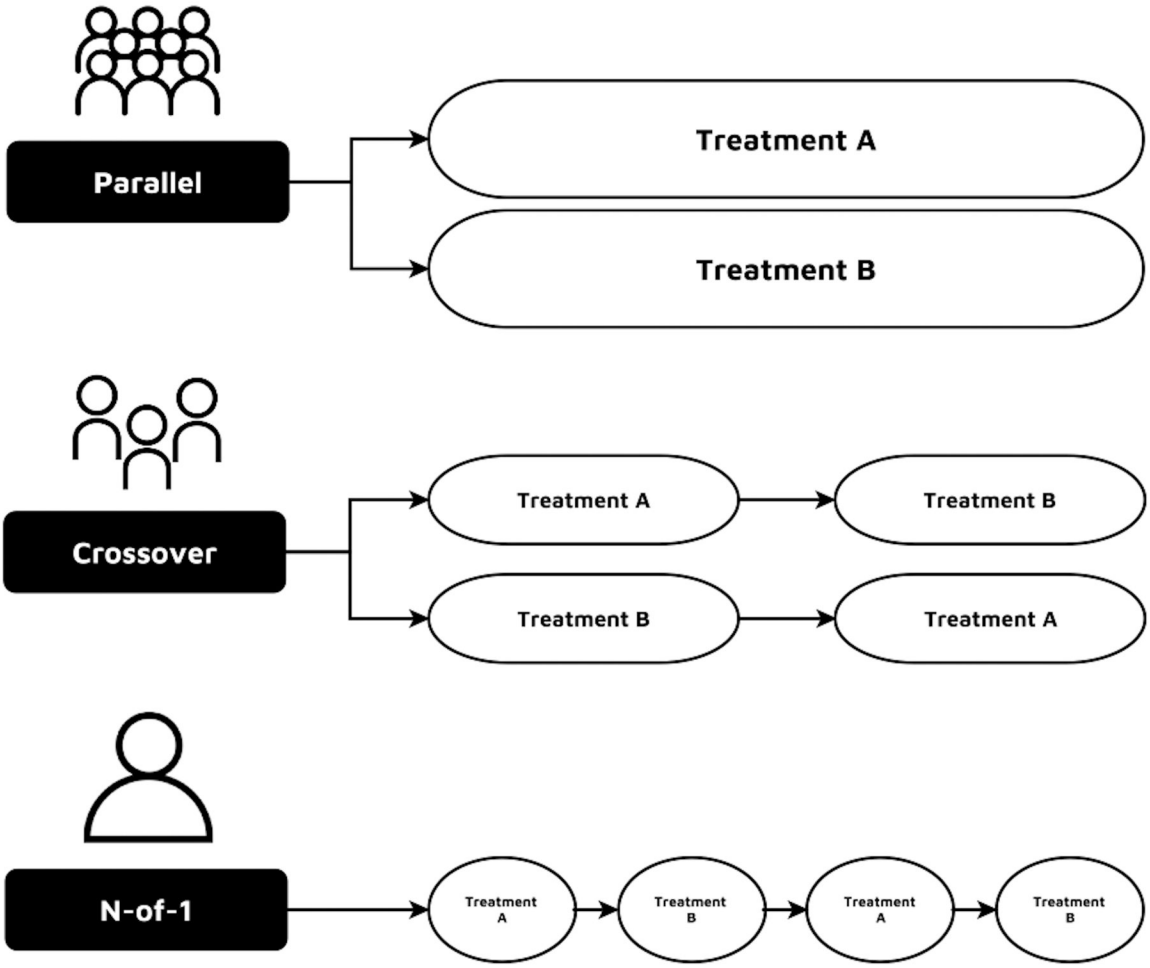

Figure 1:
Comparison of N-of-1 trial design to conventional randomized clinical trials

Sequence Options	Period 1	Period 2	Period 3	Period 4
1 ABAB On, Off, On ,Off	On (A)	Off (B)	On (A)	Off (B)
2 BABA Off, On, Off, On	Off (B)	On (A)	Off (B)	On (A)
3 ABBA On, Off, Off, On	On (A)	Off (B)	Off (B)	On (A)
4 BAAB Off, On, On, Off	Off (B)	On (A)	On (A)	Off (B)

Figure 2:
Potential treatment schemes for deprescribing N-of-1 trials

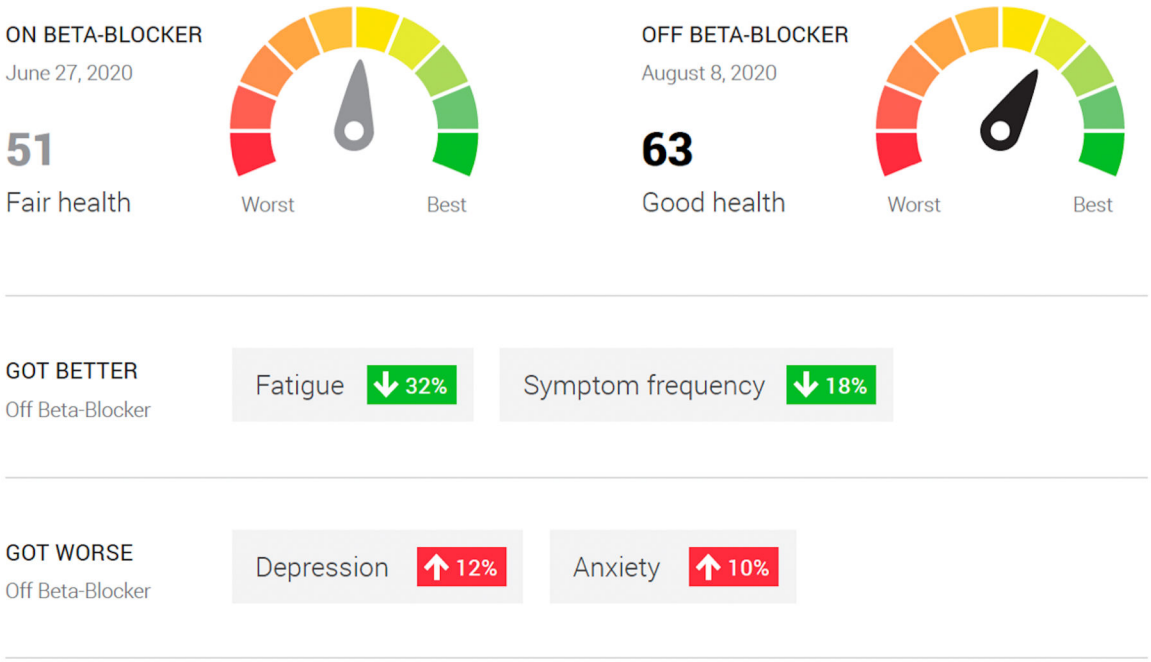

Figure 3:
Data visualization scheme using gas gauges
*Adapted from a prototype developed by Lisa Grossman Liu.

Table 1:

AHRQ Checklist for N-of-1 Trials

N-of-1 Trial Consideration:	**Application to Case Example:**
Determine whether N-of-1 trial methodology is suitable to the clinical question of interest.	All *3 requisite conditions* are present: **1** There is clinical uncertainty about the benefit/risks of beta-blockers for treatment of HFpEF **2** HFpEF is a chronic symptomatic condition **3** Beta-blockers have a reasonably rapid onset/offset
Select trial duration, treatment period length, and sequencing scheme.	*Trial duration*: 4 periods with patient option for additional periods (adaptive design) • *Treatment period length:* Based on therapeutic half-life of beta-blockers and the beta-receptor • *Sequencing scheme*: Randomized to either ABAB or BABA
Invoke a suitable washout period, if indicated.	We chose to *invoke a washout period* by selecting a treatment period length that is long enough to account for the therapeutic half-life of beta-blockers and the beta-receptor.
Decide whether or not to invoke blinding.	We *did not invoke blinding (or placebo)* because we did not want to separate the biological effects of beta-blockers from the indirect effects related to psychological processes and personal biases of patients and physicians
Select suitable outcome domains and measures.	*Patient-reported outcomes* including KCCQ and PROMIS measures; as well as physiologic measures and safety data
Analyze and present data to support clinical decision making by patients and clinicians.	We will apply the necessary statistical methods to account for correlation structure, and share data via gas gauges (Figure 2)

Table 2:

Barriers to deprescribing and the potential impact of N-of-1 trials

Domain	Barrier	Impact of N-of-1 trials
Scientific evidence	Lack of clarity on the individual-level risks and benefits of medications	• Permits *comparison* of the short-term effects of continuing and discontinuing a medication, generating *individual-level evidence* for the effects of deprescribing (and prescribing) • Facilitates *therapeutic precision* in the face of the inherent complexity of older adults
Patient	Uncertainty and conflicting attitudes	• Accounts for the *biologic heterogeneity* of older adults and variation in health priorities • Provides the *individual-level experience* and *quantifiable effects* across multiple domains that are necessary for older adults to effectively make decisions in accordance with their preferences • Can thus *reduce patient feelings of uncertainty and conflicting attitudes* toward deprescribing. • Can *facilitate decision-making* based on objective data regardless of the decision-making agent
Physician	Preconceived biases; Concern for interfering with other physicians' prescribing	• Can *facilitate decision-making* about deprescribing *based on experience* rather than theory, mitigating pre-conceived biases that frequently result in overestimating the benefits and underestimating the harms of medications. • Provides a *platform for discussion* between physicians across different specialties (geriatricians, general internists, and cardiologists), and can thus *facilitate physician-physician communication* regarding the potential utility of deprescribing
Health system	Time constraints preventing shared decision making	• Provides a *scaffold for SDM*, a key aspect of both prescribing and deprescribing; this notion is supported by the observation that N-of-1 trial participants report increased understanding and awareness of their conditions and feel a greater sense of control in decision-making. • Can improve *patient understanding* of deprescribing risks/benefits *despite time constraints* of an office visit through a process that primarily occurs outside of the physician office.