

## COMMENT

## Scientific evaluation of Ayurvedic drugs — the use of N-of-1 clinical trials

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**Abstract**

Despite its ancient roots and prominence in India as an accepted alternative to modern medicine, Ayurveda's growth has been hampered by an inability to carry out clinical studies of its effectiveness and safety using modern scientific methods — while preserving the core of Ayurveda, which is personalised medicine. In this comment, we propose that the N-of-1 trial be used as a practical method to evaluate Ayurvedic treatments, which is simultaneously consistent with the canons of modern medicine and of Ayurveda. We emphasise the importance of doing this as a practical alternative that will benefit patients. We need not wait to resolve the epistemic inconsistency between Ayurveda and modern medicine to take steps in this direction.

**Keywords:** Ayurveda, N-of-1 trials, evidence based medicine, traditional medicine, clinical trials

The credibility of Ayurveda is based on empirical evidence of the safety and efficacy of Ayurvedic treatments from centuries of use. Today, Ayurveda faces the same issue that other traditional systems of medicine face — namely declining salience for the healthcare consumer who prefers modern medicines that are tested and proven based on scientific methods. Despite this, Ayurveda has survived the onslaught of modern medicine, which suggests that it has sufficient utility to warrant systematic investigation. If we can establish the usefulness of Ayurvedic treatments, it would benefit patients by giving them an additional treatment option, especially for diseases where modern medicines are unsatisfactory. In our opinion, such Ayurvedic medicines would be cost-effective

alternatives, since they are not subject to monopolistic pricing practices seen with patent-protected products.

The current discourse on Ayurveda is focused on epistemological issues: Is Ayurveda a science? Can it be re-interpreted through the prism of modern medicine? What counterparts can be found for Ayurvedic concepts of *dosha* in modern medicine? etc [1-3]. While these questions are relevant and worthy of exploration, such an exercise need not precede or preclude the evaluation of Ayurvedic treatments using modern methods given the potential utility of Ayurveda interventions [4-7].

The core of Ayurveda is the concept of *dosha*, wherein the whole individual, including her individual lifestyle factors and environment, needs to be considered to personalise treatment. Scientific studies have sought to address *dosha* or *prakriti* concepts using tools from modern biomedical science (eg, the use of Ayurgenomics to explore the molecular correlates of *prakriti* and *tridosha*) [8-10]. However, the prevailing gold standard for the objective evaluation of a treatment in mainstream medicine is the randomised controlled trial (RCT). The use of methods like randomisation, and homogenisation of the study population through inclusion and exclusion criteria, ignores the very foundation of Ayurveda that dictates personalisation of treatment, based on individual patient characteristics. This makes evaluation of Ayurvedic medicines using scientific methods like RCTs problematic [11]. The “N-of-1” trial design has been proposed as an alternative to the RCT to accommodate this objection [12].

**N-of-1 trial design as viable option**

An N-of-1 trial treats a single patient as the object of study, and compares the effects of different treatments in the same patient using a crossover design, with suitable intervening washout periods when no treatment is administered. This permits comparison of a “particular” patient’s response to different treatments, administered in sequence. Each treatment can be administered at least twice in order to compensate for time-dependent effects, eg A-B-A-B. An N-of-1 trial follows the basic tenets of clinical trials, and can incorporate blinding and randomisation of the sequence of a series of treatments. In order to compensate for the sparseness of data from ‘one’ patient, multiple measures of the relevant clinical parameter can be made over the treatment period to reduce intra-patient variability and increase the power of the statistical comparison. For example, serial measures of blood pressure (BP) using an

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ambulatory BP recorder can be a means to improve the precision of the measurement.

The N-of-1 trial design allows flexibility in the choice of treatment — a cornerstone of Ayurveda. This, however, means that the results cannot be generalised to the wider population. There are two possible solutions to this problem. First, to include for the purpose of analysis for generalisability only those patients given a particular Ayurvedic treatment whose properties we seek to generalise to the wider population. Since the comparisons are intra-patient, this will not affect statistical integrity. A second option is to simply compare the relative efficacies of the two systems by freely allowing any Ayurvedic treatment and at least in the first instance, treat the trial as a comparison of Ayurveda with modern medicine rather than as a comparison of a particular Ayurvedic treatment with a particular modern medicine treatment. Such an approach would treat the trial as a comparison of Ayurvedic treatment approaches collectively against modern medicine; rather than as a comparison of a particular Ayurvedic treatment with modern medicine treatment. Furthermore, data from N-of-1 trials on many patients can be subject to meta-analysis to get population estimates of safety and efficacy measures [13]. Such a strategy has been successfully employed in the evaluation of statins for placebo effects [14].

### Challenges in implementation

We believe that rigorously designed and conducted N-of-1 trials can be a gold standard for demonstrating the efficacy of Ayurvedic treatments in individual patients without violating the basic tenets of Ayurveda. However, the study of traditional treatments like Ayurveda introduces special issues. For example, given the multiple modalities incorporated in Ayurvedic treatments and the strong odour and taste associated with these formulations, it may not be easy or even possible to develop matching comparators or placebos. This could make it difficult or impossible to blind the study. Another problem with some Ayurvedic treatments will be the long duration of treatment over which their effects stabilise, which may also necessitate long washout periods between treatments. This may not be feasible in the setting of a trial. For these reasons, the disease condition being evaluated and the choice of treatments being evaluated have to be made in a manner that minimises these issues. Selecting Ayurvedic formulations where taste and odour can be masked for testing, and the measurement of objective clinical parameters (such as readouts from a wearable device) may help minimise these problems. Another approach could be to consider the two treatments as black boxes, and evaluate the treatment response in each treatment group as the sum of a treatment response driven by the constituents present in the medicine and the placebo effect. If the Ayurveda group performs meaningfully better than the standard modern medicine group in such a paradigm, the contribution of the Ayurvedic formulation versus the contribution of a potential placebo

effect due to the taste and odour of the formulation can be clarified at a later stage, perhaps by devising placebos that have their own unique odour and taste; so that any placebo effect due to these signals can be netted out.

The N-of-1 trial design also raises unique ethical concerns that must be addressed. Equipoise is a necessary precondition for a trial comparing two treatments. The canons of Ayurveda and modern medicine are not congruent. There is therefore the ethical question of whether the investigator comparing therapies from those two domains can claim clinical equipoise. It may be difficult to find individual investigators who do not have a preference for one treatment over another. We must also remember that Ayurvedic treatments, in comparison to modern medicine counterparts, will come with fewer or sometimes no published papers on their clinical use in a scientific setting. In such cases we must take recourse to the recommendation made by Freedman in his 1987 paper [15].

### *Equipoise*

Freedman justifies conducting a clinical trial on the basis of clinical equipoise in the wider community, even though an individual investigator may hold a preference for one treatment over the other. Such equipoise may be a “developed” position based on a careful study of the extant literature including a study of anecdotal evidence and patient experience. If based on this, a committee of 10–12 trained clinical investigators is unable to determine the superiority of one treatment over another then equipoise can be said to exist. The next question is whether the committee should consist of physicians trained in the modern canon or whether it should have representation from Ayurveda. Our position is that it may be best to give weightage to the experience of Ayurvedic practitioners provided they have an understanding of the scientific method of evaluating evidence.

### *Patient preferences*

A secondary question is how patient preferences can be accommodated. Some patients have faith in Ayurveda while others may be clear that they will only subject themselves to treatment with medicines developed as per the scientific canon. If a patient seeks a better alternative to the current standard of care, then such a patient may volunteer for a trial comparing Ayurvedic treatments with their current treatment regime. In any case, the informed consent process should explain to the participant the basis on which the trial has been designed and the two comparator treatments chosen. Fully informed consent under such conditions should address the question of whether it is ethically acceptable to subject a patient to treatments from vastly different systems of medicine. However, the “informed consent” (participant information sheet — language and contents in particular) needs to be validated before administration in such N-of-1 trials as investigators (of N-of-

1 trials) from Ayurveda/Ayush systems need to fulfil the promise of “informed” decision-making by the study participants.

### *Unforeseen challenges*

The complex issues arising from the use of N-of-1 trials to evaluate Ayurvedic formulations cannot all be anticipated and addressed using a rules-based decision-making approach. They may require ongoing discussions on the pros and cons of various approaches and nuanced interpretation of available data. This may call for expertise and governance mechanisms that may be unavailable in smaller institutions. Some form of centralised governance that goes beyond a mere registry may be required, wherein a pool of experts must be made accessible to smaller institutions that wish to conduct N-of-1 trials in compliance with centrally developed frameworks.

### *Alternative trial designs and problems*

The N-of-1 trial is only one among many approaches that can be used to evaluate Ayurveda as per modern scientific methods. Alternative designs such as observational studies could play a role in generating preliminary clinical evidence for traditional systems like Ayurveda. However, observational studies possess little control over trial environments, as a result of which the quality of data obtained can be suspect.

An alternative design is the “Whole System Trial.” Generally, in whole system trials, patients are randomly assigned to treatment alternatives, which may include essentials of *ahara* (diet), *vihara*, (lifestyle), *panchakarma* (five cleansing actions), and *aushadhi* (medication), as prescribed by Ayurveda. Such trials may also evaluate whole system interventions implemented under defined manuals and protocols, to specify individualised treatments based on specific patient characteristics. However, in such cases, double blinding of physicians and patients to treatment allocation may not be feasible.

The N-of-1 trial is especially fit for purpose since it accommodates Ayurvedic principles that treat each patient as a unique entity for whom the treatment needs to be tailored. Arguments about the epistemology of Ayurveda can rage in the background even as effective Ayurvedic treatments are quickly identified by triaging these treatments for efficacy using the N-of-1 trial. If an Ayurvedic treatment is found effective through this mechanism, what next? First, it can be offered by physicians as a tried and tested alternative, either when the patient indicates a preference for Ayurvedic treatment; or if modern medicine options are unsatisfactory due to poor efficacy, safety profile or cost. Should such treatments also be prescribed by physicians who practise modern medicine? Not until they have been comprehensively evaluated and found suitable in the prevailing methodology of modern medical practice. Until then it may be best to have modern medicine practitioners refer such patients to their Ayurvedic colleagues for treatment.

A secondary benefit of adopting such a pragmatic approach is the possibility that molecular characterisation of proven Ayurvedic formulations can yield new chemotypes or even potentially new molecular targets that can be the basis for new drug discovery. Such an approach has been successful in the case of artemisinin, an antimalarial developed from Traditional Chinese Medicine [16]. As pointed out there have also been Indian attempts, based on Ayurgenomics which have led to the identification of biomarkers for potential targets. We need an “integrated” and “transdisciplinary” approach for such initiatives. The grafting of knowledge from an ancient traditional source onto modern scientific methods may not find universal acceptance. However, if effective novel molecules are discovered using this route, this will be welcomed by society and patients at large.

### **Possibilities and limitations**

The obvious limitation of N-of-1 trials is that complex procedures such as *panchakarma* will be difficult to evaluate using this design. Similarly, synthesising such trial results would be challenging, given the individualisation of Ayurveda treatments. Notwithstanding these limitations, work on this project can commence with the lowest hanging fruits — where empirical evidence on an Ayurvedic treatment is compelling and the alternatives in modern medicine are not perfect, eg psoriasis. This approach may be utilised to determine individual patient response to treatment with a single agent (topical corticosteroids, vitamin D analogues, retinoids or even coal tar) and/or the biologic response modifiers with comparison to an Ayurvedic single agent or even combination therapy. For these patients, the efficacy of therapy is determined by a combination of the efficacy intrinsic to the medications, their individual response to therapy, and even more important the patients’ own preference for and subsequent adherence to regular treatment. If found effective, such therapies could be put into practice as soon as favourable evidence is available. The danger of not doing this expeditiously is that the rich tradition of Ayurveda may be diminished over time and effective Ayurvedic treatments will remain unrecognised and unavailable to patients who may not subscribe to the beliefs that underlie Ayurvedic medicine. From a societal point of view such an outcome would be unfortunate.

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