N-of-1 trials: an opportunity to tailor treatment in individual patients

During a consultation, a situation may arise in which the benefits or harms associated with a particular treatment are uncertain. These uncertainties may occur for a number of reasons: well conducted randomised controlled trials (RCTs) may not have been performed; the patient may possess certain characteristics, for example multiple chronic diseases, that might attenuate the benefit of the therapy or increase the likelihood of harm; or there may be a disagreement between the patient and the healthcare professional about the potential benefits or harms of alternative therapies, particularly as RCTs only give 'average' estimates of benefit and harm, with some patients benefiting while others do not.[1] When these situations occur, subjective forms of decision making, such as 'trials of therapy', have often been relied upon. In these situations of trials of therapy, benefit or harm from treatment is decided on loose criteria and weak methodology, and the individual patient's response to treatment provides little rigorous support concerning the actual efficacy of treatment.[2]

N-of-1 studies are randomised, double blinded, multiple crossover comparisons of an active drug against a placebo or an alternative treatment in a single patient.[1,3,4] They limit biases of standard practice such as trials of therapy. More than 50 *n*-of-1 trials have been reported, each one designed to improve the care being delivered to an individual patient.[3] Patients in these studies have suffered from a wide variety of conditions, including chronic obstructive airways disease, asthma, osteoarthritis, allergic rhinitis, gastrooesophageal reflux disease, insomnia, hypertension and angina. In patients with chronic obstructive airways disease, a randomised trial demonstrated that the objectivity of *n*-of-1 trials in determining treatment in individual patients is superior to standard practice.[5] In those patients randomised to an *n*-of-1 trial of therapy compared with those randomised to standard clinical practice, unnecessary theophylline prescribing led to reduced adverse effects and improved exercise capacity and quality of life.[5] Despite this objective evidence concerning their benefit, *n*-of-1 trials are rarely used in routine clinical care regardless of their suitability for many clinical situations, particularly in the community.[3] *N*-of-1 trials are particularly useful for chronic medical conditions that run a prolonged course in which the proposed treatment has a rapid onset of action with readily observable effects, and ceases to act soon after it is discontinued.[6]

It is for these reasons that two reports in this month's Journal are particularly welcome. Woodfield and colleagues in Auckland performed a series of *n*-of-1 trials in 13 patients who were complaining of nocturnal leg cramps. The authors highlight the fact that symptomatic drug treatment with quinine is supported by some evidence from RCTs, but that quinine also has well recognised side effects. Of the 10 patients who completed three cycles of 4-week treatment periods (2 weeks on active and 2 weeks on placebo), three derived clear benefit, six non-significant benefit and one no benefit. All 13 patients elected to continue with their quinine treatment after the end of the study.[7] Woodfield and colleagues argue that once started on medication for a chronic condition, it is hard to change patient preference, despite evidence of marginal or no benefit. A second study by Nikles *et al* from Australia, reports on patients and carers perspectives and their experience of using *n*-of-1 trials for osteoarthritis (paracetamol versus ibuprofen) or for attention deficit hyperactivity disorder (dexamphetamine/methylphenidate versus placebo).[8] Their results show that patients and carers viewed participation in these *n*-of-trials positively. Patients reported increased knowledge, awareness and understanding of their condition. The positive response was attributed to patients collecting information about their condition and participating actively in therapeutic decision making at the end of the *n*-of-1 trial period. One of the reasons given by patients for participating was the trial's ability to give them individual information about their condition. The expectation of symptomatic pain improvement (in patients with osteoarthritis) and increased knowledge and awareness resulting in a greater sense of control and increased ability to help themselves or their child (for patients or parents with attention deficit hyperactivity disorder) were linked to their adherence to the trial. Taken together these two studies show that carefully planned *n*-of-1 trials are likely to be well received by patients and to enhance patient-centred care.[8]

Several issues are converging that may make the establishment of *n*-of-1 trials more commonplace. Currently, there is a great deal of interest about and funding into identifying patients by genomic profile so that drugs can be tailored to individuals, minimising possible adverse drug reactions and maximising potential benefits.[9] There is increasing recognition that uncritical application of treatment estimates from RCTs may not benefit all patients and that sub-groups of patients are likely to differ in their response to treatment, both in terms of benefit and harm.[10] Shared decision making is now firmly recognised as a key ingredient to patient-centred care, particularly in the context of making treatment decisions concerning chronic disease and life-long preventive treatment.[11] *N*-of-1 trials appear to be the solution to these related issues: offering objective evidence of individual benefit and harm from therapy while increasing patients' involvement and encouraging them to become involved in the management of their own chronic illness. Lastly, *n*-of-1 trials are being used with increasing success in the US, in terms of establishing the most cost-effective option in situations of drug equivalence but where costs differ. Prior to the recent travails with cyclo-oxygenase-2 (COX-2) inhibitors, several health maintenance organisations (HMOs) insist that patients with osteoarthritis who wish to take long-term COX-2 inhibitor therapy undergo a series of *n*-of-1 trials to establish their superiority to conventional non-steroidal anti-inflammatory or paracetamol therapy. Independent, for-profit

companies are now established offering an *n*-of-1 trial service to HMOs so that cost-effectiveness studies can be established in individual patients seeking long-term medical treatment.

Barriers to the wider dissemination and implementation of *n*-of-1 trials include a lack of intellectual and administrative experience. The effort of setting up an *n*-of-1 trial service in primary care is substantial: this includes the time and cost of paperwork and consent forms, arranging identical placebos from a pharmacy, and printing and distribution of patient diaries. Collaboration with pharmacy colleagues and funding and interest from primary care organisations (PCOs) will be essential. Despite these barriers, we should remember that *n*-of-1 trials are at the top of the hierarchy of strength of evidence for treatment decisions. If we are truly interested in patient-centred care and shared decision making, we should invest in *n*-of-1 trials placing them firmly in the arena of usual patient care.

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Hormone replacement therapy after the menopause — where are we now?

The Million Women Study[1] generated a renewed concern about the use of hormone therapy, and it is now timely to review the current role of hormone replacement therapy (HRT) for women around and after the menopause. While therapy may result in improved quality of life, recent studies have provided some clarification of potential risks. Some have even questioned whether such therapy should be prescribed at all, but, assuming that it is still suitable, the recent concerns have implications on what we should prescribe, to whom, and for how long.

The Million Women Study was a large, observational study that recruited women involved in the UK breast screening programme. The study showed that HRT is associated with a duration-dependent increase in the risk of breast cancer. The increase associated with combined oestrogen–progestogen HRT is significantly higher (relative risk = 2.0 compared with no use) than for oestrogen-only therapy (relative risk = 1.30) and for tibolone (relative risk = 1.45). HRT also increases breast density, delaying the diagnosis of breast cancer. There was no difference in the risk of breast cancer with the type of oestrogen or progestogen used or sequential or continuous combined regimens. When therapy is stopped, the risk decreases — and after 5 years cessation reaches the same level as in women who have never taken the treatment. Interestingly, the authors contrast the estimated cumulative incidence of breast and endometrial cancer in women in developed countries, comparing oestrogen-only and combined hormone therapy. They imply that unopposed oestrogen should be preferred, even in women with a uterus, even though there is a consequent small increased risk of endometrial cancer.

The Million Women Study confirmed what was already known about the overall risk of breast cancer with HRT. In addition, the study emphasised the significantly higher risk of breast cancer associated with combined preparations compared to oestrogen-only preparations. It went on to document the surprising and not previously reported fact that tibolone is also associated with an increased risk of breast cancer, and that the longer a patient takes HRT, the higher the risk. The Women's Health Initiative (WHI), a large randomised controlled trial, reported similar risks for breast cancer with combined hormone therapy,[2] but no increased risk with unopposed oestrogen when taken for 7 years.[3]

The WHI study involved healthy postmenopausal women who were randomly assigned to combined oestrogen–progestogen, oestrogen-only or placebo, with the study endpoints being the number of women who died of coronary causes or who had a nonfatal myocardial infarction. The final results