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Using *n*-of-1 trials as a clinical tool to improve prescribing

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ABSTRACT

Background

N-of-1 trials are within-patient, randomised, double-blind, placebo-controlled cross-over comparisons of two drugs for chronic illnesses. We have investigated the use of these, offered to doctors as individualised medication effectiveness tests (IMETs), as a tool to improve drug prescribing.

Aim

To examine patient perspectives and experiences of *n*-of-1 trials.

Design of study

We provided *n*-of-1 trials for osteoarthritis (OA), comparing paracetamol and ibuprofen; and attention deficit hyperactivity disorder (ADHD), comparing dexamphetamine or methylphenidate and placebo. Patients or their carers were surveyed before and after the trials by questionnaire, and after the trial by semi-structured interview with thematic analysis.

Setting

Australian community-based patients and practitioners.

Method

Forty-two patients with OA and 21 carers of patients with ADHD, for whom the effectiveness of proposed or existing medication was uncertain, completed the questionnaires, and 25 patients/carers (11 with OA and 14 with ADHD) participated in semi-structured interviews.

Results

Patients in this purposive sample were generally very satisfied with the *n*-of-1 trial process. Their participation led to increased knowledge, awareness and understanding of their condition, their bodies' response to it, and its management. Some of this arose specifically from use of daily symptom diaries. This led to a sense of empowerment and control as well as improved individually-focused care.

Conclusions

N-of-1 trials appeared to empower these patients as a result of both collecting information about their responses to different treatment options, and participating actively in subsequent therapeutic decisions. They are a patient-centred intervention that may improve medication management in suitable chronic diseases.

Keywords

attention deficit hyperactivity disorder; osteoarthritis; patient-centred care

INTRODUCTION

N-of-1 trials or individualised medication effectiveness tests (IMETs) are an innovative patient-centred approach to drug management. They are within-patient, randomised, double-blind, placebo-controlled crossover comparisons of a drug with another drug or a placebo, designed to remove any placebo effect in deciding the best of two therapeutic choices for an individual with a chronic disease. Patients are actively involved in: accepting a double-blind process, keeping a diary of symptoms, and afterwards discussing the results with their doctor, when a decision is made about future management.

The widespread use of *n*-of-1 trials as a clinical tool depends to a large extent on patients' positive attitudes towards the process. In the US, where *n*-of-1 trials have recently become available commercially, patient post-trial questionnaires showed a high level of acceptability.^{1,2} However, little has been documented about how patients experience *n*-of-1 trials, although they have been performed in medicine for over a decade.

Previous published work has been limited to small sections describing patient experiences within reports of *n*-of-1 trials research. For example, most patients in a previous osteoarthritis *n*-of-1 trial viewed the process favourably, obtaining a better understanding of their condition, and enjoying the discussion of their results and future treatment.³ Patients of a US *n*-of-1 trials service consistently

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Table 1. Summary of characteristics of questionnaire responders.

Patients	OA	ADHD carers	Children with ADHD	Total
Age range (years)	40–80	26–58	7–15	7–80
Female (%)	25 (59)	23 (92)	5 (24)	53 (60)
Male (%)	17 (40)	2 (8)	16 (76)	35 (40)
Non-English speaking background (%)	6 (14)	-	-	6 (7)
Highest educational level grade 10 ^a or less (%)	25 (59)	16 (38)	-	41 (47)
Employed (%)	11 (26)	12 (48)	-	23 (26)
Married (%)	28 (67)	14 (56)	-	42 (48)
Prior treatment for depressive disorder (%)	-	5 (20)	-	-
Total	42	25	21	88

ADHD = attention deficit hyperactivity disorder. OA = osteoarthritis. ^aCompulsory education.

rated their trials as 'extremely useful'.⁴ An Australian doctor reported that the result of a single attention deficit hyperactivity disorder (ADHD) *n*-of-1 trial was well accepted by the patients' parents⁵ and a Canadian study found that ADHD *n*-of-1 trials were endorsed by families, who used the results to make treatment decisions.⁶ This is the first qualitative report we are aware of that focuses entirely on patients' experiences of *n*-of-1 trials.

METHOD

The Discipline of General Practice at The University of Queensland has established and previously described a post-and-telephone *n*-of-1 trial service throughout Australia.^{7,8} Here we present some of the comments of the initial patients in the osteoarthritis (OA) *n*-of-1 trial comparing paracetamol and ibuprofen⁷ (11 interviewees and 42 questionnaire completers) and ADHD *n*-of-1 trial comparing dexamphetamine or methylphenidate with placebo (14 interviewees [four were children aged 12 years and under] and 25 adult questionnaire completers).⁸

Community patients/caregivers were referred by GPs or paediatricians and provided informed consent. Patient characteristics are given in Table 1. Many patients were already on medication, but either the doctor or patient (or their caregiver) was uncertain as to the effectiveness of the medication.

Data collection

Pre- and post-trial questionnaires used a series of open-ended questions to elucidate the reasons for participation in the *n*-of-1 trials, general subjective experiences of participation and patients' participation in the decision-making process after the trial. We also conducted qualitative semi-structured interviews with a subgroup of questionnaire responders to explore issues raised in the questionnaires, and other relevant

issues, in more detail. From June to September 2001 we interviewed patients either face to face (*n* = 11) or by telephone (*n* = 14) until no new data were obtained. Interviewees in the sample who did not complete the *n*-of-1 trial were asked about reasons for withdrawal (OA, *n* = 2; ADHD, *n* = 2). All interviews were recorded and transcribed verbatim.

Sample

In accordance with well accepted qualitative techniques the interview sample was purposively selected from different categories; for example: male/female; responder/non-responder/non-completer; metropolitan/provincial/rural; caregiver/child, to provide as broad a range of data as possible, highlighting the variety of perspectives and experiences. Most interviewees belonged to several of these categories simultaneously. The sample did not attempt to be representative as this was a qualitative study describing patients' experiences.

Data analysis

Data from both sources (interviews and questionnaires) were treated as text, combined and analysed. A thematic coding scheme was developed on the basis of the analysis of pilot interviews. All data were coded by two researchers and any differences resolved by consensus. All reasonable steps have been taken to maintain patient confidentiality.

RESULTS

There were three groups of patients: children with ADHD, the carers of these children, and older adults with OA. Only children over 12 years completed questionnaires.

Reasons for participation

Participants commenced *n*-of-1 trials after hearing about them either from their doctor (the majority), directly from the media, or from a chronic disease support group. The ability of the trials to give

How this fits in

Although *n*-of-1 trials have been performed in medicine for over a decade, little has been documented about how patients experience them. This is the first qualitative report we are aware of focusing entirely on patients' experiences of these trials. *N*-of-1 trials appeared to empower patients as a result of both collecting information about their responses to different treatment options, enabling them to participate actively in subsequent therapeutic decisions. They are a patient-centred intervention that may improve medication management.

individual information appealed to many patients.

For a number of patients, getting the correct medication was of considerable importance:

'[I would like to] get the right medication which is right for me!' (Female, OA, aged 59 years.)

'I will look back and see if I need the tablets.' (Male, ADHD, aged 12 years.)

Several also participated to learn more about the disease, and particularly pain control:

'I hope to be able to gain valuable knowledge and experience to help our family and child through the torment of ADHD.' (Female carer, ADHD, aged 26 years.)

For the majority of patients with OA, the predominant expectation was that symptoms, particularly pain, would improve. They wanted to:

'... learn more about the effects of arthritis and relief of pain. To learn about what medication would help me.' (Female, OA, aged 73 years.)

'... be able to live a little more pain free, also to understand my body and pain. To have better control.' (Male, OA, aged 75 years.)

Functional outcomes were important to some OA patients — clearly, the OA had great impact on their lives, and the ability to work and lead a normal life was important.

Like the OA patients, the majority of caregivers of children with ADHD wanted to know whether the test drug was effective and whether their child really needed it. Gaining knowledge about ADHD was another important reason to do the *n*-of-1 trial. For rural and remote parents, the ADHD *n*-of-1 trial delivered by post and telephone provided an opportunity for them to actively participate in their child's management.

'We live 250 km from [regional Australian city]. The test gave us the chance to be doing something. It's not just doctor oriented, it's something we can do, we can see and observe.' (Female carer, ADHD, aged 31 years.)

Older children understood clearly why they were doing the *n*-of-1 trials — to find out whether they could cease the medication.

'[After doing IMET] I'll get of my dex[amphetamine].' (Male, ADHD, aged 15 years.)

Benefits of participation in the *n*-of-1 trials

For both OA and ADHD there were common themes relating to benefits of the trials.

Many OA patients in particular had a long history of searching for effective medications, and the *n*-of-1 trial helped to clarify which medication worked for them:

'[What] I've found is one that works and one that doesn't.' (Female, OA, aged 58 years.)

'It proves that taking paracetamol regular[ly] is better than anti-inflammatory drugs.' (Female, OA, aged 75 years.)

There was an enhanced awareness and understanding of their condition, which was not obtained from usual patient–doctor interaction:

'When I feel the start of the pain I take a pill. Nip it in the bud. The only way to do that is to think about it in the morning. Once I get control it goes out of my mind.' (Male, OA, aged 60 years.)

'Yes! I am more knowledgeable about ADHD. Just my reading all the relevant info! ... We received a more thorough evaluation of A. One which we would not have received if she was not placed on the trial.' (Female carer, ADHD, aged 35 years.)

N-of-1 trials increased knowledge about proper use of the medication:

'I tried [ibuprofen] once years and years ago and I got a sore stomach. I was taking them for pain but I was taking them without a feed, that's why this time I make sure I take a sandwich.' (Male, OA, aged 60 years, responder to NSAIDs for stiffness.)

Several patients commented on the extra information the results gave their doctor, including how they responded to their medication:

'Once the program is complete you will, and your doctor will, know much more about you and your condition.' (Male, OA, aged 43 years.)

As a result of increased knowledge and awareness, patients and parents felt a greater sense of control and were more able to help themselves or their child:

'I feel more in control of treatment.' (Male carer, ADHD, aged 40 years.)

They felt that they were treated more individually and more thoroughly during the trial than they were used to:

'That's what I liked about it; it doesn't matter if you're in a class of people, the teacher isn't talking to you directly. I like this one-on-one. You do better.' (Male, OA, aged 60 years.)

It is not uncommon for parents and children to be equivocal about taking ADHD medication. Issues for parents include public opinion against stimulant medication, a desire for the best treatment for their child, uncertainty about whether they had made the right decision to medicate their child, and concerns about the long-term effects of having their child on stimulants. The key issue for children on stimulant medication is their desire to cease it. *N-of-1* trials showed whether or not the ADHD medication was really necessary and provided what was seen as 'proof' and reassurance.

'R could see the difference between the two medications ... he has accepted the medication and his test results ... he accepted his condition because of the test. It proved a point — that we were heading down the right track ... It proved I was morally right ... and proved how much the dex worked ... At this stage he cannot control himself without them.' (Female carer, ADHD, aged 42 years.)

When the *n-of-1* trial demonstrated the need for medication, children with ADHD (responders)

Table 2. Timing of and reasons for withdrawal from OA and ADHD *n-of-1* trials.

	Number of patients
OA <i>n-of-1</i> trial	
Timing of withdrawal	
In first treatment period	10
In second treatment period	4
In third treatment period	0
Reason for withdrawal	
Side effects	6 (1 on placebo)
Tablets not helping	4
Could not cope	1
Ill health	1
Too many tablets	1
Serious adverse event	1
ADHD <i>n-of-1</i> trial	
Timing of withdrawal	
In first treatment period	1
In second treatment period	2
In third treatment period	1
Reason for withdrawal	
Deterioration on placebo	2
Side effects	1
No teacher input	1

ADHD = attention deficit hyperactivity disorder. OA = osteoarthritis.

volunteered that they could accept their condition better, and some parents also felt reassured about their parenting skills:

'The trial showed that it's not my fault the way he is. It has made me feel better about my parenting skills.' (Female carer, ADHD, aged 42 years.)

Removal of some of the stigma and scepticism regarding drug treatment was important:

'I am now not as sceptic[a] about taking drugs.' (Female carer, ADHD, aged 35 years.)

However, the *n-of-1* trials were not suitable for all patients. Most OA withdrawals ($n = 10$) occurred in the first treatment period, the majority because of side effects and ineffectiveness of tablets (Table 2). Relatively few ADHD withdrawals ($n = 4$) occurred. These were mostly in the second treatment pair and they withdrew due to deterioration of symptoms on placebo (Table 3). The protocol now allows those experiencing deterioration to switch to the next treatment period after a couple of days, rather than waiting a week.

The results and post-trial management decision-making

Different perspectives towards their reports are demonstrated by responders and non-responders. Responders commented on the differences between the medications:

'It gave me a proper indication of what the pills were actually doing and how I felt when I was taking them. It gave Dr L an indication of which pill was really working. [The graphs] really pointed it out.' (Male, OA, aged 43 years.)

'[With the] charts — the teacher's and mine — [there was a] difference between placebo and active ... [we] could see differences in behaviour.' (Female ADHD carer, aged 34 years.)

Some non-responders felt that because they did not have a response, the *n-of-1* trial had not helped. However, most of them came to the conclusion that the test medication simply did not work for them and another approach needed to be sought:

'I obtained what I thought I would achieve, [that is, finding out whether] arthritis medications [for example, ibuprofen] [could] help me or not, but quite obviously I am just as well on painkiller[s] when necessary.' (Female, OA, aged 70 years.)

In many cases, ADHD non-responders and their parents were pleased that stimulant medication could be ceased:

'W thought she was special because she was doing the [n-of-1 trial. The trial] proved that Mum was right ... and W is happy not to be on tablets.'
(Female ADHD carer, aged 42 years, mother of non-responder.)

For both OA and ADHD, a continuum of responsibility for the post-test management decision was observed, ranging from those who believed that the final decision about medication was up to them, to those who wanted the doctor to make the decision:

'I had a lot of say in the final decision, and the doctor and I had a talk together and we decided together what would be the best way to go.'
(Female, OA, aged 58 years.)

For ADHD, there was a complex interplay of input from caregivers, teachers, children and doctors:

'We were a bit nervous about taking control and making the decision. I feel relieved now — we're confident she is on the right medication.'
(Female, ADHD carer, aged 31 years.)

DISCUSSION

Summary of main findings

In this varied group of patients, *n*-of-1 trials were well accepted and highly beneficial. Patients in this sample were generally very satisfied with the *n*-of-1 trial process. Their participation led to increased knowledge, awareness and understanding of their condition; their bodies' response to it, and its management. This led to a sense of empowerment and control as well as increased individually-focused care.

Strengths and the limitations of this study

This study provides more depth than the existing literature on patients' experiences of the *n*-of-1 trial process. As *n*-of-1 trials are becoming more commonly used, patients' experiences and feedback can be used to improve the way in which they are delivered, and could make a valuable contribution towards both the frequency of use and the usefulness of *n*-of-1 trials in clinical practice.

There may be some positive bias in the interview data (participants may have been less likely to mention negative experiences) because of the presence of one of the researchers; however, the interviewer did not have any patient contact during the actual trials. As all participants had ongoing

contact with the research team, it is unlikely that the type of interview (face-to-face or by telephone) would have greatly biased the data obtained. Additionally, more patients who completed the *n*-of-1 trials than withdrew were willing to complete both pre- and post-trial questionnaires, and the interview sample was drawn from this group. No patients were unwilling to be interviewed.

This is a qualitative study and these types of studies are not commonly conducted in general practice research. The actual numbers (63 patients in the group; 25 interviews) are not as important as in a quantitative study, which usually aims to be representative of a particular population. Patients were invited to participate in the interviews because they were considered to be 'information rich'; they had particular experiences or perspectives that were of interest to this study.

Interviews continued with additional responders until the data reached saturation (no new information was obtained). This was achieved with 25 patients, so there was no need to interview all 63. In other words, as we were interested in studying the breadth of issues, qualitative studies were best suited: had representativeness been our main interest, then quantitative methods would have been better. We are not attempting to apply the results from this sample to the whole population.

Our withdrawal rates (14/42 [33%] for OA and 4/21 [19%] for ADHD) are comparable with or better than withdrawal rates of other Australian *n*-of-1 studies (40% and 37%).^{3,9} Withdrawals were mostly due to factors other than the *n*-of-1 trial process itself. Withdrawals from the OA *n*-of-1 trial were mainly related to factors such as drug side effects or ineffectiveness (*n* = 11), and two of the ADHD withdrawals were due to side effects or lack of teacher input. However, the remaining two ADHD withdrawals occurred due to worsening behaviour on placebo, a design issue we subsequently addressed, with a noticeable reduction in withdrawal rates (CJ Nikles, unpublished data, 2005).

The withdrawal rates can be thought of as a general measure of the compliance ('adherence') of the patients, and adherence is not as good as many clinicians believe.¹⁰ Non-adherence rates of around 50% have been reported for several common chronic diseases.^{11,12-14} This is a normal phenomenon of clinical treatment.

Comparison with existing literature

The themes identified in this study are consistent with the existing literature. For example, previous work³⁻⁶ has reported favourable patient feedback and has documented the benefits of participating in *n*-of-1 trials. Feedback includes patients and carers

obtaining a better understanding of the condition, and benefiting from discussion of their results and future treatment. Patients found *n*-of-1 trials extremely valuable and used the results to make treatment decisions.

Patients appear to benefit from participation in such trials because the process provides an insight into their illness and provides a basis for discussion with their medical practitioner that is not commonly available in routine clinical practice.

The implications for clinical practice

When patients assume more responsibility for their own health care, health outcomes improve;^{15–18} this is particularly true for prescription drugs.¹⁹ When healthcare providers communicate with their patients about their condition, provide them with information and encourage them to participate in decision-making, patients can become more active in their medication management. *N*-of-1 trials provide a structured way of increasing this participation. Being patient-focused, *n*-of-1 trials can also be a useful and convenient tool that allows providers to tailor treatment to the individual.

Genetic variation (or polymorphism) may be an important factor underlying inter-individual variation in response to certain drugs. For example, genetic defects in the dopamine transporter gene might contribute to some forms of ADHD, explaining why some individuals may respond to psychostimulants, which interact with the dopamine, serotonin and noradrenaline transporters.

Pharmacogenetics may play a future role in predicting response to certain medications, in which case *n*-of-1 trials would not be necessary. Until then, the increasing burden of chronic illness, the rising costs of health care (including drugs), and the growing emphasis on patient-centred care provide a context in which *n*-of-1 trials could have an important place in the management of certain chronic conditions. *N*-of-1 trials have the potential to lessen the impact and burden of chronic disease by improving health outcomes via targeted prescribing and wiser self-medication.

We are not advocating the use of *n*-of-1 trials for all patients in symptomatic areas of clinical medicine — only for those where there is doubt about the benefit:harm ratio of a particular drug, and a suitable *n*-of-1 trial exists for that drug, condition and set of patient characteristics. Currently, empirical informal testing ('trial of treatment') is common in clinical practice, but this tends to over estimate benefits of particular therapies due to the placebo effect, the patient's desire to please the doctor, the expectations or beliefs of both patient and doctor, and the natural history of the condition. *N*-of-1 trials

delivered by a dedicated service may one day make a large contribution to changing the way we practice clinically.

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Ethics committee

The study was approved by The University of Queensland Behavioural and Social Sciences Ethics Research Committee

Competing interests

None

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