

## EXTENDED REPORT

## Switching from NSAIDs to paracetamol: a series of n of 1 trials for individual patients with osteoarthritis

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**Objectives:** To investigate for individual patients who have been using NSAIDs regularly, whether paracetamol is as effective as non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of pain and disability related to osteoarthritis of the hip or knee.

**Methods:** A series of n of 1 trials were conducted in general practices in Amsterdam and the surrounding area. Each patient was his or her own control and received five pairs of treatments comprising two weeks of an NSAID and two weeks of paracetamol. For each pair, the order of treatments was randomised. Outcome measures were severity of individual main complaints, intensity of pain, satisfaction with drugs, function test, and side effects.

**Results:** Thirteen patients were selected. Six patients did not complete the study. For five patients completing the study little or no difference was found between NSAIDs and paracetamol, for one patient the results favoured the NSAID, and for one patient there was no association between outcome and type of drug. It was recommended that six patients changed to paracetamol; the others continued with NSAIDs. Three months after the end of the study, four of the six patients for whom paracetamol had been recommended were taking NSAIDs for practical reasons or perceived lack of efficacy.

**Conclusion:** The results of the n of 1 trials varied across patients. n of 1 trials can be used to investigate which treatment is best for any specific person, thus avoiding unnecessary prolonged treatment with NSAIDs. However, practical reasons may cause patients to switch from NSAIDs to paracetamol or not.

Osteoarthritis (OA) is a common musculoskeletal disorder. The prevalence of OA increases with age to over 50% in the knee and about 20% in the hip in women aged 80 years and older. In elderly men the prevalence of OA of the knee is about 25%, and the hip is affected in more than 10%.<sup>1</sup>

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for OA. Available evidence from three randomised trials on the relative effectiveness of NSAIDs compared with paracetamol (acetaminophen) for OA of the hip or knee shows consistent, yet modest, differences in their effect on pain in favour of NSAIDs.<sup>2–6</sup> However, it is generally known that NSAIDs are associated with gastrointestinal complications, whereas paracetamol is associated with very few side effects.<sup>7–9</sup> Therefore, the national practice guidelines for OA management, issued by the Dutch College of General Practitioners, recommend paracetamol as initial treatment in the treatment of pain and disability related to OA of the knee.<sup>10</sup> Similar recommendations are made in the EULAR guidelines and the British, Canadian, and American guidelines.<sup>11–14</sup>

The EULAR guideline explicitly emphasises the need to tailor treatment to the individual patient. Indeed, for OA there may be reasonable doubt whether the results of large randomised controlled trials (RCTs) can be generalised to individual patients in general practice. For instance, a patient who consults a general practitioner for chronic knee pain and stiffness may not meet all the selection criteria of the RCTs, reported outcome measures may not be relevant for this specific patient, or the type or dosage of drugs studied in the RCTs may not be similar to the drugs the patient is using. Normally, when a doctor has any doubts about the applicability of treatment recommendations to a specific patient, the trial and error method is used. This means that a particular drug will be prescribed, continued if considered effective, or changed if considered not beneficial. However,

the fact that both patient and doctor are aware of the change in treatment can influence the evaluation of its effectiveness. Individual preferences and expectations of both doctor and patient can play an important part in the assessment. If the doctor or the patient doubts the effectiveness of a treatment with a drug, and prefers an objective evaluation, the n of 1 trial is a useful tool.<sup>15</sup>

n of 1 trials are carried out with one patient. The patient is his or her own control and receives several periods of both the intervention treatment and the control treatment. The sequence of treatments is randomised. Because n of 1 trials are meant to evaluate the effects of treatments for each individual patient (and not to estimate the average effect for a larger population), the size of a series of n of 1 trials is of minor importance. Nevertheless, a series of n of 1 trials will be able to demonstrate the potential variation in outcome across patients.

Knowing that patients with OA may continue to use analgesics for a prolonged period of time, it is worthwhile reconsidering drug treatment. This study aimed at investigating for individual patients who have been using NSAIDs regularly, whether paracetamol is as effective as NSAIDs in the treatment of pain and disability related to OA of the hip or knee.

## METHODS

## Patient selection

Twenty five general practitioners in Amsterdam and the surrounding area were asked to select patients from their medical records. Selection criteria were OA of the hip or knee (as diagnosed by the general practitioner); regular use of

**Abbreviations:** NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; RCT, randomised controlled trial

diclofenac, ibuprofen, or naproxen (at least for a period of one month, five days a week); no contraindications for NSAIDs; no contraindications for paracetamol; no corticosteroid injections in the three months preceding the study; no (planned) arthroplasty; and no concomitant physiotherapeutic treatment. Additionally, the patients had to be able to fill in a questionnaire in Dutch. If more than one hip or knee was affected by OA the patient was asked to indicate the joint that caused the most severe complaints.

### Design

The study comprised a series of *n* of 1 trials. Each patient received five pairs of treatments starting between November 1999 and May 2000. Each pair consisted of a two week period of NSAID treatment and a two week period of paracetamol treatment. For each pair of treatments the order of NSAIDs and paracetamol was randomised. The random sequence was prepared in advance by the hospital pharmacist for each patient separately. The patient, the general practitioner and the investigator were unaware of the sequence of treatment. Identical capsules with similar colour, smell, and taste were used to ensure blinding. If necessary, placebos were given, so that the patients received the same number of capsules in all treatment periods. For example, if 1000 mg paracetamol three times daily was compared with 50 mg diclofenac twice daily, the patient received additional placebos once daily in each diclofenac period. The study was approved by the ethics review board of the VU University Medical Centre, and all participating patients gave written informed consent at the start of the study.

### Drug treatment

During the NSAID treatment periods each patient received the same type of NSAID and, if possible, in the same dosage, as before the start of the study. The dosage of paracetamol was adjusted to the dosage of the NSAID. For example, if a patient took 400 mg ibuprofen three times daily, 1000 mg paracetamol was prescribed three times daily. Maximum dosages were 3000 mg paracetamol divided into three or four doses a day, 400 mg ibuprofen four times daily, 50 mg diclofenac twice daily or 25 mg diclofenac three times daily, and 750 mg naproxen divided into two doses a day. Pill counts were taken to measure compliance.

### Outcome assessment

Outcomes were assessed by daily diaries and during home visits made by the investigator every two weeks at the end of each treatment period. Because of the possibility of carry-over effects in the first week of each treatment period, only data for the second week of each treatment period were taken into account in the analysis. We considered a washout period of one week sufficient, given the short half life of the NSAIDs used in our study.<sup>9</sup> Previous *n* of 1 series and RCTs comparing NSAIDs with paracetamol have used a similar washout period.<sup>2 6 16-18</sup>

Primary outcome measures were (a) individual main complaints and (b) the intensity of pain. To compose a total diary score, each patient was instructed during the selection procedure to identify their individual main complaints of pain, stiffness, or limitations in daily functioning. These individual main complaints (four to eight symptoms for each patient) were scored daily on seven point ordinal scales ranging from 0 = no complaints at all to 6 = unbearable complaints.<sup>19 20</sup> A total diary score was computed by calculating for each day the median score of all these four to eight individual main complaints. The severity of the most important individual complaint, according to the patient, was analysed separately. The intensity of pain during the previous week was scored by the patient on an 11 point numerical

rating scale (0–10, 10 indicating very severe pain) after each treatment period during the home visits made by the investigator.

Secondary outcome measures were (a) satisfaction with drugs, scored on a seven point ordinal scale ranging from 0 = very satisfied to 6 = very dissatisfied and (b) one of three possible function tests partially derived from previously described function tests<sup>21</sup> (walking 2.5 metres to and fro, sitting down and standing up five times, or going up and down stairs (time in seconds)). Every two weeks the same function test was performed by the patient. The choice of the type of test depended on the main complaints of the patient, the ability of the patient to perform the function test, and the possibility that the test could be performed at the patient's home. Both secondary outcome measures were scored every two weeks. Furthermore, every two weeks, information was collected on the occurrence of side effects and co-interventions (including concomitant drugs and other conservative methods of treatments).

The influence of the results of the *n* of 1 trials on the treatment policy of the general practitioners was also investigated. Both before the start of the study and at the end of the study each general practitioner was asked which drug (NSAID, paracetamol, or other) they thought to be best for each specific patient. Subsequently, the general practitioners scored how sure they were about this answer on a five point ordinal scale ranging from 1 = very certain to 5 = very uncertain.

### Breaking the randomisation code

Before analysis of the data the randomisation code was partially broken. This means that the type of treatment was indicated as either A or B, without the investigator (AW) knowing whether A or B represented treatment with an NSAID or treatment with paracetamol. Subsequently, recommendations were formulated for further treatment. After analysing and formulating the recommendations, the supervisor (DW) decoded the randomisation completely and conferred with the general practitioner about the results of the trial. Finally, the recommendation was discussed with the patient.

### Analysis

Because the single case design was used, all outcome measures were analysed for each patient separately. For the second week of each treatment period, median scores were calculated for the total diary score and the individual main complaint. Differences in scores between the NSAID and paracetamol were calculated for each outcome measure. Finally, the proportion of pairs of treatment periods for which treatment A was better than treatment B, and vice versa, was calculated for the primary outcome measures.

### Decisions for future treatment (recommendations)

The following rules were used to decide on treatment recommendations: firstly, the median difference between treatments for the total diary score had to be at least one point in favour of the NSAID to recommend NSAID treatment, otherwise paracetamol was recommended; secondly, the results for at least 75% of the treatment pairs had to be in favour of the NSAID for at least one of the primary outcome measures (for example, 4/5 pairs) to recommend NSAID treatment, otherwise paracetamol was recommended; and finally, improvements in severe complaints were considered to be more important than improvements in only mild or moderate complaints. Three months after completion of the *n* of 1 trials, the patients were contacted by telephone and asked to indicate which drugs they were currently using for their OA.

## RESULTS

### Subjects

A search in the medical records identified 22 patients who were eligible for participation according to their general practitioners. Nine patients were excluded for the following reasons: (a) no actual use of diclofenac, ibuprofen, or naproxen (three patients used paracetamol and one patient piroxicam); (b) no frequent use of NSAIDs (one patient); (c) contraindications for NSAIDs (three patients); and (d) no informed consent (one patient used suppositories and refused oral drugs). Thirteen patients were selected for participation: 11 women and two men (table 1). Their ages ranged between 50 and 91 years (median 77 years). In 12 patients the main problems concerned the knee, and in one patient the hip. Before the start of the study nine patients were taking diclofenac, three ibuprofen, and one naproxen.

Six patients did not complete the study: four because of perceived lack of efficacy, one because of perceived side effects, and one because of concomitant disease and loss of motivation (table 1). After withdrawal, these patients continued to use NSAIDs. Seven patients did complete their 20 week trial period. All seven patients who completed the study took more than 94% of their trial capsules. From the third week, patient No 7 was prescribed additional paracetamol by the general practitioner for concomitant disease. As a consequence, for this patient the first two weeks could not be compared with the other 18 weeks, and only four pairs of treatments could be analysed.

### Effectiveness of paracetamol compared with NSAID

In five patients who completed the study there was little or no difference in outcome between NSAIDs and paracetamol, and paracetamol was recommended (patients Nos 1, 3, 4, 5,

and 9). In two patients (patients Nos 6 and 7) the median difference between treatments for the total diary score was one point in favour of NSAIDs (table 2). The percentage of pairs in which NSAIDs were favoured above paracetamol was  $\geq 75\%$  for at least one of the primary outcome measures in both these patients. However, the improvements in complaints for patient No 7 mainly concerned changes from mild to very mild, whereas in patient No 6 improvements in complaints in favour of the NSAID were from severe to moderate. For these reasons, only patient No 6 was recommended to continue with NSAID treatment. For the other patients who completed the study (including patient No 7) paracetamol treatment was recommended.

### Side effects and co-interventions

There were no differences in the occurrence of side effects between the NSAID and the paracetamol treatment periods. The patient who did not complete the study because of perceived side effects reported increasing stomach complaints during treatment with both diclofenac and paracetamol (patient No 11). There were no differences in co-interventions between the NSAID and the paracetamol treatment periods. Patient No 10 had back pain and used more additional paracetamol as the study progressed. She finally withdrew from the study after eight weeks.

### Treatment policy

Table 2 presents the treatment which the general practitioners thought to be best for each patient before the start and at the end of the study for the seven patients who completed the study. In general, after completion of the n of 1 trials, the general practitioners were at least as certain about their treatment preferences as before the n of 1 trials.

**Table 1** Patient characteristics and reasons for withdrawal of 13 participants with OA of the hip or knee in a series of n of 1 trials

Patient No	Sex (M/F), age, joint	Drug treatment before the start of the trial	Trial drug	Number of weeks completed, reasons for withdrawal
1	F, 71, hip	3×day 400 mg ibuprofen	3×day 400 mg ibuprofen v 3×day 1000 mg paracetamol	20
2	M, 82, knee	3×day 50 mg diclofenac	2×day 50 mg diclofenac v 3×day 1000 mg paracetamol	0, (only 3 days): Perceived lack of efficacy (stiffness)
3	F, 80, knee	3 (sometimes 4) ×day 400 mg ibuprofen	3×day 400 mg ibuprofen v 3×day 1000 mg paracetamol	20
4	F, 91, knee	Mostly 1×day 50 mg diclofenac (sometimes more)	1×day 50 mg diclofenac v 1×day 1000 mg paracetamol and 1×day 500 mg paracetamol	20
5	M, 50, knee	1×day 50 mg diclofenac	1×day 50 mg diclofenac v 1×day 1000 mg paracetamol and 1×day 500 mg paracetamol	20
6	F, 54, knee	1 or 2×day 500 mg naproxen	1×day 250 mg naproxen and 1×day 500 mg naproxen v 3×day 1000 mg paracetamol	20
7	F, 73, knee	1×day 50 mg diclofenac	1×day 50 mg diclofenac v 1×day 1000 mg paracetamol and 1×day 500 mg paracetamol. After 2 weeks she was prescribed 1000 mg additional paracetamol because of concomitant disease (gout)	20
8	F, 62, knee	1 or 2×day 100 mg diclofenac	2×day 50 mg diclofenac v 2×day 1000 mg paracetamol*	4: Perceived lack of efficacy (pain)
9	F, 82, knee	1×day 75 mg diclofenac and 500 mg paracetamol	1×day 25 mg diclofenac and 1×day 50 mg diclofenac v 3×day 1000 mg paracetamol (after 4 weeks 2×day 1000 mg paracetamol)	20
10	F, 72, knee	1×day 50 mg diclofenac, sometimes 2×day 50 mg diclofenac	1×day 50 mg diclofenac v 1×day 1000 mg paracetamol and 1×day 500 mg paracetamol	8: Concomitant disease (back pain) and loss of motivation
11	F, 77, knee	3×day 50 mg diclofenac	2×day 50 mg diclofenac v 3×day 1000 mg paracetamol	4: Perceived side effects stomach complaints and nausea)
12	F, 79, knee	3×day 50 mg diclofenac	2×day 50 mg diclofenac v 3×day 1000 mg paracetamol	4: Perceived lack of efficacy (pain)
13	F, 90, knee	3×day 400 mg ibuprofen (and almost every day 500 mg paracetamol/codeine, sometimes also 1×day 500 g paracetamol)	3×day 400 mg ibuprofen v 3×day 1000 mg paracetamol	2: Perceived lack of efficacy (pain)

\*The patient received 2000 mg instead of 3000 mg paracetamol daily because of alcohol use (about six units a day).

**Table 2** Results of the seven patients who completed the n of 1 trials: outcome measures, recommendations, drugs after three months, and confidence

Patient No	Joint	Most important complaint	Median difference N - P* (median N, median P)†					Proportion of pairs N > P for the primary outcome measures					Drug treatment after 3 months	δ Confidence GP (choice before, choice after)‡
			Function test	Total diary score	Individual main complaint	Pain	Satisfaction	Function test (seconds)	Total diary score	Individual main complaint	Pain	Recommendation		
1	H	Pain during standing up from a chair or couch	W	0 (3, 3)	0 (3, 3)	-1 (6, 7)	0 (2, 2)	0.5 (10.5, 10.6)	1/5	3/5	P	N	0 (N, P)	
3	K	Pain during walking	W	-0.5 (3, 3.5)	0 (4, 4)	0 (6, 6)	0 (3, 3)	0 (12.0, 11.7)	3/5	0/5	P	N and P	1 (N, P)	
4	K	pain during walking	W	0 (2.5, 2.5)	0 (3, 3)	0 (7, 7)	0 (3, 2)	-0.7 (16.0, 16.9)	2/5	2/5	P	N	0 (N, P)	
5	K	Pain during sleeping	W	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.2 (6.8, 6.6)	0/5	2/5	P	P	2 (N, P)	
6	K	Pain during standing up from the toilet	ST	-1 (3, 4)	-1 (3, 4)	0 (7, 8)	0 (3, 5)	-0.8; -2.0 (12.2, 13.2); 17.7, 19.4)§	4/5	2/5	N	N	2 (N, N)	
7¶	K	Pain during standing up from a chair	S	-1 (1, 2)	-0.5 (1, 2)	-3 (3, 5.5)	0.5 (1.5, 1)	0.8 (18.6, 18.9)	3/4	3/4	P	N	1 (P, P)	
9	K	Pain during standing	W	0 (3, 3)	0 (3, 3)	-1 (6, 7)	0 (2, 2)	-3.6 (20.2, 22.7)	1/5	3/5	P	N (and P)	0 (P, P)	

H, hip; K, knee; W, walking; ST, walking stairs; S, sitting and standing up; N, NSAID; P, paracetamol.

\*Negative scores favour NSAIDs; †scores range between 0 = no complaints and 6 = unbearable complaints for the total diary score and the individual main complaint; ‡between 0 = no pain and 10 = very severe pain for the intensity of pain, and between 0 = very satisfied and 6 = very dissatisfied for the satisfaction with drugs; †confidence of general practitioner in the preferred drug at the start of the study minus at the end of the study. Positive scores indicate that the general practitioner is more certain after the study; §walking up stairs; ¶data of only four pairs could be compared.

**Follow up**

Three months after the end of the study, four of the six patients who had been recommended paracetamol treatment were taking NSAIDs for OA; one because of a misunderstanding about the recommended dosage of paracetamol (patient No 1), one because she preferred taking one small tablet of diclofenac rather than two large tablets of paracetamol (patient No 4), and two because of perceived lack of efficacy (patients No 7 and 9). Patient No 9 had been taking paracetamol for almost three months, when the complaints relating to OA deteriorated. This patient was therefore prescribed a high dose of NSAIDs at the time of the three month evaluation, shortly after which the patient was prescribed both NSAIDs and paracetamol. Furthermore, one patient was taking both paracetamol and NSAIDs (patient No 3), because she thought it was a waste to throw away the NSAIDs she still had in her possession.

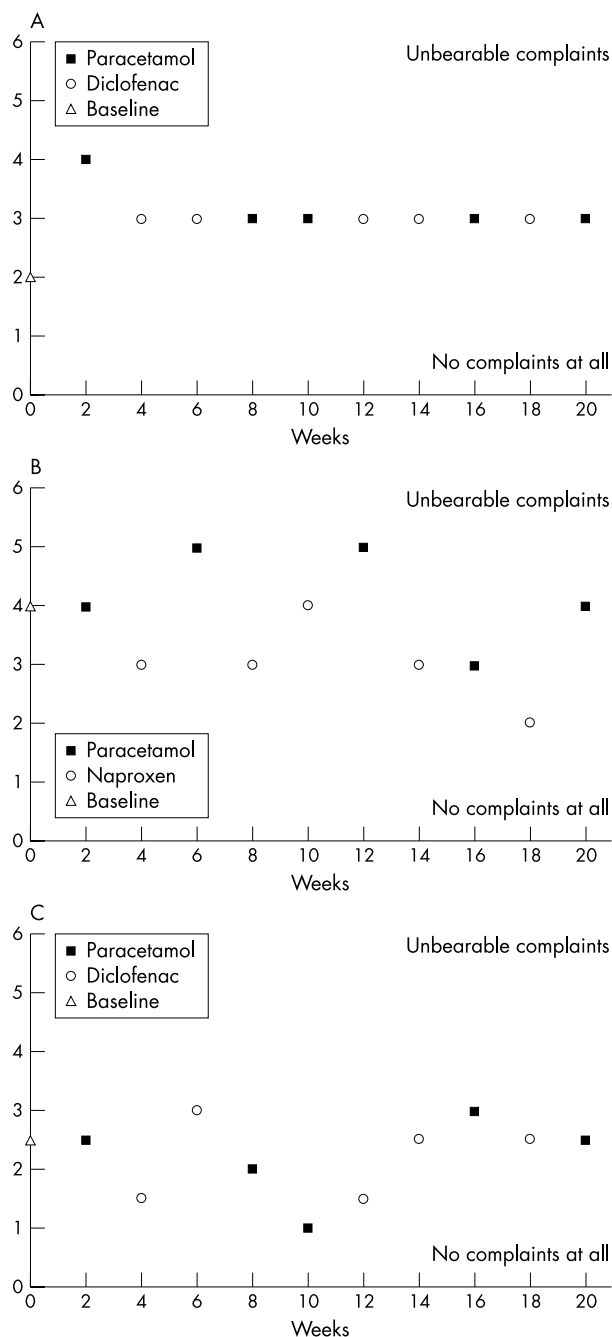
**DISCUSSION**

In this study for each individual patient of the 13 selected, it was investigated whether paracetamol was as effective as NSAIDs in the treatment of pain and disability related to OA of the hip or knee. Six patients did not complete the study because of a perceived lack of efficacy, perceived side effects, concomitant disease, or loss of motivation. Seven patients did complete the study. The results of the n of 1 trials varied across these patients. Six patients were recommended to change to paracetamol treatment. All other patients (including the six who did not complete their trial) continued with NSAID treatment.

At the end of the follow up period one of the six patients who were recommended to change to paracetamol treatment was using paracetamol and all others were using NSAIDs or both NSAIDs and paracetamol. Apparently, the use of NSAIDs was preferred by these patients, despite the equal effects of paracetamol. In a large survey<sup>22</sup> and in a few randomised trials<sup>6, 16</sup> preferences of patients for either NSAIDs or paracetamol have been studied. About 60% of the patients in these studies preferred NSAIDs rather than paracetamol. However, this also implies that a considerable proportion (about 40%) indicated that paracetamol was better or as effective as NSAIDs. Preferring one drug to another is the result of several factors, including subjective benefit, side effects (actual or potential), doctor or patient beliefs and interactions, severity of disease, and ease of administration (for example, in our study one patient preferred taking one small tablet of diclofenac rather than two large ones of paracetamol).<sup>22, 23</sup> To avoid wasting time and effort, these issues should be discussed and patients should be well informed about the objectives and consequences of the trials before starting an n of 1 trial.

Considering the risk of side effects, the dosages were kept within the recommendations for chronic use of NSAIDs for OA published by the Dutch National Formulary.<sup>9</sup> Before the start of the study, however, higher dosages had sometimes been prescribed by the general practitioners. Three of the four patients who did not complete the study because of perceived lack of efficacy had been taking, before the start of the study, dosages of NSAIDs that were higher than the maximum dosages allowed in the study; this was not the case with any of the patients who completed the study. One other patient (No 13) who withdrew because of perceived lack of efficacy had used additional paracetamol/codeine before the study. These findings suggest that the withdrawal of these patients was due to subtherapeutic dosages of drugs during the study.

A series of n of 1 trials will be able to demonstrate the potential variation in outcome across individual patients, but only if a large proportion of the participants complete their trial. However, drop out from an n of 1 trial is an important



**Figure 1** Three typical plots for the total diary score. (A) no difference between NSAID and paracetamol; (B) NSAID better than paracetamol; (C) wide range in scores—no association between outcome and type of drug.

outcome itself. As stated above, four of the six patients who did not complete their trial almost certainly withdrew because of subtherapeutic dosages of drugs during the study. Therefore, we suggest that future research should consider comparing paracetamol with NSAIDs in the actual dosage taken by the patient just before the start of the study. In this way, we believe that drop out can be prevented in many cases.

March *et al* and Nikles *et al* conducted n of 1 trials in patients with OA, using three pairs of treatment periods consisting of paracetamol and diclofenac<sup>17</sup> or paracetamol and ibuprofen.<sup>18</sup> The proportion of patients who did not complete their trial in our series (46%) is comparable with the results for these two other series (40%<sup>17</sup> and 43%<sup>18</sup>).

Although a direct comparison is difficult (because of differences in selection criteria, drugs, and outcome measures), all three studies show that for some patients paracetamol is as effective as NSAIDs, but that there is a large variation in outcome among individual patients. The series by March *et al* received some criticism of the statistical analysis and the interpretation of the results.<sup>24, 25</sup> March *et al* considered paracetamol as the preferred drug if diclofenac was not significantly better than paracetamol. However, each patient received only three pairs of treatments, which limited the statistical power to detect treatment differences. Additionally, failure to find a significant difference in favour of diclofenac may not be regarded as proof of equivalence.

In our study each patient received five pairs of treatments. In contrast with March *et al*, we used the individualised questionnaire developed by Guyatt *et al* for n of 1 trials.<sup>19</sup> This questionnaire examines the severity of symptoms as identified by the individual patient and scored by the patient on seven point ordinal scales. Our data were not suitable for quantitative analysis, partly owing to the non-normal distribution of the data. More importantly, we did not investigate whether one treatment was better than the other, but whether one treatment was as effective as the other. In other words, the n of 1 trials were equivalence trials, rather than superiority trials. This implies that conventional significance testing could not be used for analysis and for formulating recommendations.<sup>26</sup> Therefore, we applied decision rules, which were formulated in advance. Although these rules can be considered to be arbitrary, for five of the seven patients who completed the study the differences between NSAIDs and paracetamol were very small and the recommendations were straightforward (table 2). In two patients (Nos 6 and 7) the decision rules were very helpful in deciding on recommendations.

In conclusion, the results of the n of 1 trials varied across patients (fig 1). These findings support the assumption that the best treatment for OA differs in individual patients. However, there is, as yet, insufficient evidence about which factors predict which patient can or cannot successfully switch from NSAIDs to paracetamol. Therefore, an n of 1 trial can be used to investigate which treatment is best for any specific individual patient. Practical reasons, such as the size or the number of tablets that needs to be taken, may play an important part in a patient's decision to switch from NSAIDs to paracetamol or not. Therefore, before the start of the n of 1 trial, patients should be well informed about the objectives and consequences of the trial. When the results of the trial become available patients should be well instructed to follow the recommendations. In this way, unnecessary prolonged treatment with NSAIDs may be avoided in patients with complaints due to OA of the hip or knee.

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