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Effect of different financial competing interest statements on readers' perceptions of clinical educational articles: a randomised controlled trial

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ABSTRACT

Objectives

To investigate how different competing interest (COI) statements affect clinical readers' perceptions of education articles.

Design

Parallel group randomised controlled trial.

Setting and participants

Random sample of UK doctors who are members of the British Medical Association.

Interventions

We created four permutations of each of two clinical reviews (on gout or dyspepsia) which varied only in terms of the COI statement. Volunteers were blinded and randomised to receive one review and asked to complete a short questionnaire after reading it. Blinded factorial analyses of variance and analyses of covariance were carried out to assess the influence of each review and type of COI on outcomes.

Primary and secondary outcomes

Confidence in the article's conclusions (primary outcome), its importance, their level of interest in the article, and their likelihood to change practice after reading it.

Results

Of 10,889 doctors invited to participate, 1,065 (10%) volunteered. Of these volunteers, 749 (70%) completed the survey. Analysis of covariance adjusting for age, sex, job type, and years since qualification showed no significant difference between the groups in participants' confidence in the article (gout: *P*=.32, dyspepsia: *P*=.78) or their rating of its importance (gout: *P*=.09, dyspepsia: *P*=.79). For the gout review, participants rated articles with advisory board and consultancies COI as significantly less interesting than those with no COI (*P*=.028 with Bonferroni correction). Among participants indicating that they treat the condition and that the article's recommendations differed from their own practice, there was no significant difference in likelihood to change practice between groups (gout: *P*=.59, n=59; dyspepsia: *P*=.56, n=80).

Conclusions Doctors' confidence in educational articles was not influenced by the COI statements. Further work is required to determine if doctors do not perceive these COIs as important in educational articles or if they do not pay attention to these statements.

Trial registration: ClinicalTrials.gov (NCT02548312)

Article Summary

Strengths and limitations of this study

- Competing interest (COI) statements have been shown to influence readers' perceptions of research but this is the first experimental study to look at the effect of COIs in clinical educational material.
- A key strength of this study is its randomised study design in a research area where there are few experimental studies.
- Financial competing interests are varied. We were only able to evaluate the effect of three financial COI statements compared with none due to the large sample size required.
- We focused only on financial competing interests. Non-financial interests are also of importance but more difficult to capture and measure.

INTRODUCTION

Researchers, clinicians and academic institutions often have competing interests (COIs), and collaborations with industry are often considered necessary to facilitate progress and innovation in medical research.[1] COIs are characterised by the possibility that the professional views held by an individual acting to achieve a primary interest, such as enhancing patient outcomes, may be influenced or compromised by a competing secondary interest, such as financial profit.[1][2] Widespread recognition of the potential influence of COIs in decision-making has rendered their open disclosure a common requirement for the publication of research articles in academic medical journals.[3] A systematic review reported that the presence of financial COIs and industry collaborations are concerning to academic and clinical researchers, particularly as such interests may potentially influence research project decisions, the conduct of research, and subsequent publication.[4] Financial ties with industry were considered more acceptable where these were not directly related to the research, disclosure of COIs was upfront, and the results of research was freely published.[4] However, there is a lack of research exploring the actual, rather than perceived, effect of competing interests on reader perceptions. In a randomised trial investigating the effect of the funding source of a clinical trial on clinicians' interpretation of trial results, it was observed that industry sponsorship negatively affected the perceived methodological rigor of a trial and the willingness to change practice based on its findings, independent of trial quality.[5] We have previously reported the results of two randomised controlled trials comparing the effect of COI statements related to financial interests against no competing interests and demonstrated a significant influence of COIs on readers' perceptions of the credibility of medical research.[6, 7] Surveys have previously reported a similarly low perceived credibility of industry-initiated or funded drug trials among clinicians.[8]

Clinical education articles are intended to provide guidance on clinical care for clinicians, yet our understanding of the role of COIs on readers' perceptions of the credibility of such articles, rather than primary research articles, is limited. Educational articles are prone to bias as they typically use non-systematic methods of literature acquisition, and broadly rely on the interpretation of one author, or a small number of authors, on their chosen included literature. Such potential biases may therefore be extensive, but potentially less visible to their targeted broader clinician readership. In 2015 *The BMJ* implemented a 'zero tolerance' policy on the presence of any relevant financial COI related to industry for authors of its clinical editorials and some education articles.[9] However, other journals have questioned the need for strict restrictions on the presence of COIs, discussing whether such policies may limit trust, effective industry collaborations, or the ability for some experts to contribute to clinical education.[10-13] Evidence is missing in characterising how COI statements influence reader perceptions of educational articles, or indeed if awareness exists of the potential for COIs to influence the conclusions of such articles. We describe a randomised controlled trial to test the effect

of a range of common COI statements in educational articles on a clinician readership's confidence in the conclusions of an article, their interest in the article, its perceived importance, and on the likelihood that they would change their clinical practice based on the article's findings.

METHODS

Design

Parallel group randomised controlled trial. The study protocol has previously been published.[14]

Study sample

We took two approaches to the sampling for this study as the first approach did not yield adequate numbers.

Inclusion criteria and exclusion criteria

We included practising doctors in the UK who were receiving *The BMJ* through their membership of the British Medical Association (BMA). We excluded members who had opted out of receiving a copy of *The BMJ*, public health doctors, consultant oral/dental surgeons, retired doctors and student members. We also excluded doctors listed as doing private practice as this was necessary due to the way the data about specialty and grade are stored to ensure compliance with our other exclusion criteria.

Sample 1

We generated a random sample of 2,040 BMA members (680 general practitioners (GPs), 680 hospital consultants and 680 junior doctors), randomised each to a group (see methods below), and sent them a personalised email invitation from *The BMJ's* editor-in-chief in September 2015 to take part in a research project along with the relevant study materials.

Sample 2

We broadened the sampling frame and took a very large random sample of 11,004 BMA members and asked for volunteers to take part in a research project before assigning them to a study group, as per our protocol. Recruitment for volunteers was open between 06/01/16 and 28/01/16.

Intervention

Participants were sent an email with a link to one of two clinical reviews depending on randomised group allocation, on the management of dyspepsia (Appendix 1) or gout (Appendix 2), and a link to a short questionnaire on SurveyMonkey on 02/02/16. Study participants were asked to read the article and then complete the questionnaire. Data collection closed on 03/05/16.

We selected two clinical reviews previously published by *The BMJ* describing two conditions commonly seen by doctors, requiring treatment by drugs, and familiar to all clinical specialties. We

shortened and modified these after obtaining permission from the original authors. We changed the authors on the authorship byline to fictional author names and listed fictional institutions. Each of the two clinical reviews had four permutations differing only in the COI statement (from no competing interests to a range of financial interests) for the last of the three authors (Table 1). All COI statements appeared at the end of the article's main text, just before the references, in line with usual practice. These statements all had the same fictional author names and where there was a financial COI we used the same fictional pharmaceutical company name but did not mention the company name in the main text of the clinical reviews.

Randomisation and blinding

A random sample of eligible BMA members was generated from the database of all members by staff at the BMA using computer generated random numbers. JM then randomised members to one of eight groups to receive one of the eight permutations of the clinical reviews using a computer-generated block randomisation procedure, stratified by type of doctor (GPs/hospital consultants/junior doctors) and gender. The eight permutations of the clinical reviews were then randomly assigned a number from 1 to 8 by SS. SS enrolled participants and managed the survey. JM conducted the statistical analysis blinded to the group allocation; participants were identified only by study group number, which was not revealed to JM until after all analysis was completed. Participants were blinded to their study group and were not told that we were testing the effect of various COIs on their perceptions of the articles.

Data collection

We piloted the draft survey with a convenience sample of doctors to ensure the instructions were clear and the questions were not ambiguous. Study participants were asked to read the article and indicate on a 10-point Likert scale (0=Not at all, 10=Extremely): how confident they were in the conclusions drawn in the article they received, how interesting and important they found the article and how likely they were to change their practice on the basis of the article (see protocol supplementary materials for the questionnaire).[14] To reduce question order bias, the presentation order of the questions was randomised for the first three items (confidence, interest and importance).

Contact details and demographic information about BMA members were obtained from the BMA membership database: name, title, email address, specialty, sex, age, and date qualified. Survey data was gathered using SurveyMonkey. Non-responding volunteers were sent up to five reminders to complete the survey.

Outcome measures

Primary outcome measure

The primary outcome was the readers' level of confidence in the conclusions drawn in the article, measured on a 10-point Likert scale from 1= 'not at all confident' to 10= 'extremely confident'.

Secondary outcome measures

The three secondary outcomes, all measured on similar 10-point Likert scales, were: readers' ratings of the importance of the article, interest in the article, and likelihood to change practice on the basis of the article.

Ethics and trial registration

We did not submit the study for ethical approval but the study proposal and study materials were reviewed by members of *The BMJ's* Ethics Committee and they did not have substantive ethical concerns. To avoid biasing participants' responses, details of the study objectives and design were not given to participants. The study protocol[14] was not published until data collection was complete so as not to potentially influence participants' responses. Consent to take part was assumed by completion of the study questionnaire. The trial was registered at ClinicalTrials.gov (NCT02548312) just before recruitment commenced.

Statistical analysis

Sample size justification

We calculated that to have 90% power to detect a one-unit difference on the 10-point 'confidence' scale between the groups, 121 readers were needed in each of the four COI statement groups, based on a simple Student's t test with an estimated standard deviation of 2, with a two-sided 1% significance level to provide some adjustment for multiple testing between the four COI statements. However, as differences between the results for the two clinical reviews were considered important to quantify, a total of 968 readers were required to account for the eight permutations. Assuming a response rate of around 50% based on previous *BMJ* trials of similar design,[6, 7] we calculated we needed to invite at least 1,936 readers to take part. Accordingly, in Sample 1, for each of the eight groups, 255 readers (85 GPs, 85 consultants and 85 junior doctors) were invited to take part. We assumed that a one-unit difference on the 10-point scale was important on the basis that a 0.5-unit difference was important in our previous studies using a 5-point scale.[6, 7] Similarly, the observed SD for the 5-point scale was ~1, and hence we assumed that, for a 10-point scale, the SD would be twice as large. As Sample 1 only yielded a 9% response rate and we anticipated a similar yield when asking for volunteers, we broadened the sample to 11,004 in Sample 2.

Statistical analysis

A factorial analysis of covariance (with COI statement and clinical review type as the two factors) was carried out to assess their impact on the primary outcome (level of confidence) and secondary outcomes (importance, interest and likelihood to change practice) adjusting for the effect of doctor type (GP, consultant or junior doctor), gender, age and the number of years since qualification. Separate analyses of covariance (ANCOVA) were performed for each of the two clinical reviews, and, in addition, for the subgroups who were currently treating the conditions. The impact on the likelihood to change practice was assessed using chi-square tests. Analyses of variance and chi-tests were used to compare non-responders with responders in terms of age, gender, doctor type (GP, consultant or junior doctor) and number of years since qualification.

Patient and Public Involvement

We did not include patients as study participants. Patients were not involved in setting the research question, designing the study, the conduct of the study, or the interpretation of the results.

RESULTS

Samples

Sample 1

Overall, 182/2040 (9%) responded, but the response rate was lower for the article on dyspepsia (81/1,020, 8%) than gout (101/1020, 10%). On reading responses to the survey for those who received the dyspepsia review, we identified a problem with the content of the manuscript. A few respondents queried the appropriateness of including a section on prokinetic drugs given the recent withdrawal of drugs and safety concerns but no mention of this in the article. As such, we removed this section from the manuscript before using it in Sample 2 and started the study again.

Sample 2

We obtained a random sample of 11,004 BMA members meeting the study eligibility criteria. After removing overlap with Sample 1, we invited 10,889 doctors to volunteer to take part in a research project for *The BMJ* (Figure 1). On sending the email invitation, 96 email addresses bounced and 97 had already opted out of SurveyMonkey so had to be excluded. Of the 10,696 eligible email addresses, we recruited 1,065 volunteers (10%) and 749 (70% of those who volunteered) completed the survey; n=376 dyspepsia and n=373 gout. A third of respondents were consultants, a third GPs, and a third junior doctors; 46% were male and the mean age was 44 years (Table 2). All analyses are based on data collected in Sample 2.

Primary outcome

There was no significant difference between the groups in the readers' level of confidence in the conclusions drawn in the article for the gout (p=0.32) or dyspepsia (p=0.78) reviews (Table 3). The mean confidence rating scores for all of the groups receiving the gout review was at least 7 out of 10, and for the dyspepsia review it was at least 6.

Combining results over both reviews showed no differences in confidence between the COI groups (p=0.54), and no evidence of a difference between reviews in the variability between the COI groups (p=0.53) but respondents had a higher level of confidence in the gout review than the dyspepsia review (p<0.001).

Secondary outcomes

Importance of the article

There was no significant difference between the groups in readers' ratings of the level of importance of the article for the gout (p=0.09) or dyspepsia (p=0.79) reviews (Table 3).

Combining results over both reviews showed no overall differences in level of importance between the COI groups (p=0.79) and no evidence of a difference between reviews in the variability between the COI groups (p=0.14), but respondents gave higher ratings of importance for the gout review (p=0.002).

Interest in the article

For the gout review, participants rated reviews with advisory board and consultancies COI as significantly less interesting than those with no COI (*P*=.018 with Bonferroni correction), but there was no significant difference between the groups for the dyspepsia review (p=0.83) (Table 3).

Combining results over both reviews showed no overall differences in level of interest between the COI groups (p=0.46) and no evidence of a difference between reviews in the variability between the COI groups (p=0.12), but respondents gave higher ratings of interest for the gout review (p<0.001).

Likelihood to change practice

Almost half of respondents (178/373, 48%) who received the gout review reported that they were currently treating patients with gout, 28% (103/373) were not currently treating them and 24% (90/373) reported they do not treat patients with this condition. Of those who were currently treating gout, 33% (59/103) indicated that the article recommended practice differing from their current practice.

Over half of respondents (207/376, 55%) who received the dyspepsia review reported that they were currently treating patients with dyspepsia, 23% (85/376) were not currently treating them and 22% (83/376) reported they do not treat patients with this condition. Of those who were currently treating dyspepsia, 39% (80/207) indicated that the article recommended practice differing from their current practice.

Among participants indicating that they treat the condition and that the article's recommendations differed from their own practice, there was no significant difference in likelihood to change practice between groups (gout: *P*=.59, n=59; dyspepsia: *P*=.56, n=80), (Table 4).

Subgroup analysis

Analysis of the subgroups who were currently treating the conditions showed no significant differences between the groups for the level of confidence (primary outcome) in the article (gout: *P*=.18; dyspepsia: *P*=.64), (Table 5).

Analysis of non-responders

Respondents who completed the survey were significantly older, had been qualified for longer and were more likely to be female than those who did not complete or volunteer, p<0.05 (Table 6).

DISCUSSION

Doctors' confidence in the conclusions drawn in two educational reviews was not significantly influenced by a range of financial COI statements that are commonly reported to journals and frequently occur in medical practice. When the results for the two reviews were combined, we found no significant difference between the COI statement groups in the importance or interest doctors attached to the article or their likelihood to change practice based on the article. However, we did find a significant difference between the groups in level of interest for the gout review; doctors rated the gout review with advisory board and consultancies COI as significantly less interesting than when there was no COI.

Three previous randomised controlled trials[5-7] on the effect of financial COIs on readers' perceptions of research found strikingly different results. In the first trial[6] readers randomised to receive a drug study written by authors with financial COIs (employees of a fictitious company who potentially held stock options in the company) indicated these as significantly less interesting, important, relevant, valid and believable than those randomised to receive the same article written by authors with no COIs declared. In the second trial,[7] we tested the effect on a non-drug study and also varied the type of COI statement (author potentially held stock options in the company versus author was a recipient of funding for studentships and research grants versus no competing interest declared). Once again, we found that overall, importance, relevance, validity, and believability ratings were significantly lower in the group with the financial COI statement than in the no competing interest group. Validity ratings for the financial COI statement group were also significantly lower than for the group receiving the research grants statement. The current study sampled doctors from the same large membership database and applied a similar methodology, but found no significant difference in the confidence in the conclusions drawn (primary outcome) between the groups. In a third randomised trial the authors explored the influence of clinical trial funding on clinician perceptions of trials with a high, medium, or low methodological rigor, and reported that industry funding negatively impacted on perceived methodological quality and willingness to implement trial findings regardless of the trial quality.[5] In contrast to previous trials, our study used a clinical review article (where possible biases may be less visible) and subtler financial COIs (although these were still typical of those seen in medical practice).

A key strength of this study is its randomised study design in a research area where there are few experimental studies. This study had several limitations. Firstly, our initial sampling approach yielded a very low response rate of 9% (not unusual for surveys of doctors and researchers)[15-17] and the study was underpowered to show an effect. As such we broadened the sampling frame by seeking volunteers at the outset and this yielded a response from 70% of those recruited. The initial low response rate was surprising as in both our earlier trials, with postal administration, we achieved response rates of 59%[6, 7] and sampled readers from the same membership database. However,

mode of administration can influence response rates[18] and response rates across all methods of survey administration have declined over time.[19] Secondly, we excluded doctors in private practice, so we are unable to generalise the results beyond practising National Health Service doctors. However, to get a representative sample, we sampled doctors from a wide range of clinical specialties. We also used two clinical reviews to help make the findings generalisable beyond a single clinical topic. Thirdly, participants were told they were taking part in a research project and this may have influenced the way they read the article and responded to the questions. Fourthly, participants were asked to read an article that they might not usually read; approximately half of participants in each group reported that they were not currently treating patients with gout/dyspepsia. Whilst this may have influenced responses, we deliberately selected two general clinical topics commonly presented and the task did not require respondents to have in-depth knowledge of the assigned topic. Fifthly, respondents were significantly older than non-respondents, but this was in keeping with both our previous trials.[6, 7] Finally, we were unable to pool the results from our two sampling approaches as we used different recruitment processes and modified one of the reviews.

In a recent cross-sectional study the authors reported a higher prevalence of disclosed COIs in commentaries, editorials and narrative reviews.[20] This finding, combined with the fact that author bias in educational articles may be less obvious to readers, and our own finding that COI statements do not seem to affect reader perception of such articles, is particularly concerning. Such articles are widely read by clinicians for their summaries of available evidence and clinical care recommendations.[21] Further, our trial used articles on common conditions with relatively uncontroversial treatments, but the role of COIs may be particularly pertinent in articles on the clinical use of novel, potentially expensive, therapeutic agents.

Our findings may be explained by a lower awareness among clinicians that competing interests may influence the conclusions of educational articles, just as they may research articles. Alternatively, readers may have considered the included COI statements too mild and not sufficiently alarming to warrant greater scepticism of the review's conclusions. For example, a prior randomised trial has demonstrated that COIs incorporating stocks and shares influenced perceptions of research articles more than COIs involving research grants.[7] Many readers in this study may also have been familiar with the medical conditions under discussion, and their own clinical practice already in alignment with the review conclusions. We further speculate that levels of trust in the educational reviews used in this study may also have been high due to their dissemination by *The BMJ*, a widely read and recognised UK-based general medical journal. Accordingly, our findings may not be generalisable to articles in smaller/specialty journals. However, the disseminated articles were not portrayed to participants as accepted or published BMJ articles, but rather formatted to mimic manuscript submissions without indication of whether the submission would be published in the journal.

Future research should aim to explore why COI statements in educational articles may not affect reader perceptions. For instance, as publishing COI statements has become standard practice, do readers now no longer pay attention to such statements? Or do they perceive these as unimportant and unlikely to bias an article's conclusions? Further, our research has focused only on financial COIs but it would also be important to evaluate the effect of non-financial COIs on readers' perceptions, such as unpaid consultancies which may include reimbursements for travel expenses, meals and drinks.[21] Against the backdrop of risk of industry-guided bias in clinical practice, journal editors need to tackle possible reader inattention toward COIs in educational articles. Possible mitigating solutions include policies that exclude authors with relevant COIs from authoring clinical educational articles (as has been adopted by *The BMJ),*[9, 22], or a requirement for such articles to be based on systematic, rather than narrative, reviews. Tackling readers' understanding of COIs in educational articles is also crucial. This may involve emphasising the role of COIs in critical appraisal, as part of the medical curriculum.

Author contributions

FG initiated the study. All authors contributed to the study design, including the wording of the competing interest statements, outcome measures, and sampling strategy. JM estimated the required sample size and carried out the statistical analysis. SS was responsible for running the trial and wrote the first draft of the manuscript with help from JP. All authors contributed to the interpretation of the results and the writing of the manuscript.

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Competing interests

SS and FG are employed full time by *The BMJ*; MC was formerly employed by *The BMJ*; JP was a Clegg Scholar at *The BMJ;* and JM is a statistics editor for *The BMJ*. None of the authors work directly for BMJ Open or are involved in the decision-making process for articles submitted to BMJ Open.

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Data sharing statement

The anonymised individual participant data will be shared on reasonable request.

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Table 1: Group allocations and competing interest (COI) statements

Group	Review	COI type	COI statement
1	Dyspepsia	Honoraria & travel	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received honoraria and travel expenses from Jenka Pharmaceuticals for lecturing at a conference.
2	Gout	Advisory board & consultancies	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received fees from Jenka Pharmaceuticals for consultancies and being an advisory board member.
3	Dyspepsia	Research funding	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received research funding from Jenka Pharmaceuticals
4	Dyspepsia	None	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has no competing interests.
5	Gout	Honoraria & travel	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received honoraria and travel expenses from Jenka Pharmaceuticals for lecturing at a conference.
6	Dyspepsia	Advisory board & consultancies	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received fees from Jenka Pharmaceuticals for consultancies and being an advisory board member.
7	Gout	Research funding	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received research funding from Jenka Pharmaceuticals.
8	Gout	None	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has no competing interests.

Table 2: Baseline characteristics by group of allocation

	Honoraria & travel	Research funding	Advisory board & consultancies	None
Gout review				
N	90	99	91	93
Type				
Consultant	37% (33)	37% (37)	33% (30)	37% (34)
General practice	38% (34)	33% (33)	32% (29)	36% (33)
Junior doctor	26% (23)	29% (29)	35% (32)	28% (26)
Male	49% (44)	46% (46)	44% (40)	45% (42)
Mean age (range)	45.5 (24,72)	44.9 (25,75)	42.9 (24,76)	42.8 (24,67)
Mean years' qualified (range)	20.5 (0,47)	19.7 (0,47)	17.7 (0,45)	18.3 (0,43)
Dyspepsia review				
N	100	96	93	87
Type				
Consultant	31% (31)	36% (35)	33% (31)	38% (33)
General practice	36% (36)	36% (35)	37% (34)	33% (29)
Junior doctor	33% (33)	27% (26)	30% (28)	29% (25)
Male	48% (48)	43% (41)	45% (42)	48% (42)
Mean age (range)	43.5 (23,79)	44.7 (25,75)	42.9 (24,76)	42.8 (24,67)
Mean years' qualified (range)	18.3 (0,54)	19.5 (0,47)	19.4 (0,44)	18.6 (0,39)

Table 3: ANCOVA analysis of the level of confidence, importance and interest in the reviews by intervention group adjusting for age, sex, job type, and years since qualification

	COI Allocation Group, Mean (95% CI)				
	Honoraria and travel	**Research funding**	**Advisory board & consultancies**	**None**	***P* Value**
Gout review					
N	99	93	90	90 [b]	
Primary outcome					
Level of confidence in conclusions drawn[a]	7.1 (6.8-7.5)	7.4 (7.1-7.8)	7.0 (6.7-7.4) [c]	7.4 (7.0-7.8)	.32
Secondary outcomes					
Importance of article[a]	6.9 (6.6-7.3)	6.7 (6.4-7.1)	6.4 (6.1-6.8)	7.0 (6.6-7.4)	.09
Level of interest in article[a]	6.7 (6.5-7.0)	6.5 (6.2-6.9)	6.2 (5.9-6.6)	7.0 (6.7-7.4)	.028 [f]
Dyspepsia review					
N	100	95 [d]	93	87	
Primary outcome					
Level of confidence in conclusions drawn[a]	6.2 (5.8-6.6)	6.1 (5.7-6.5)	6.2 (5.8-6.6) [e]	6.4 (6.0-6.8)	.78
Secondary outcomes					
Importance of article[a]	6.3 (6.0-6.7)	6.3 (5.9-6.7)	6.5 (6.2-6.9)	6.3 (5.9-6.7)	.79
Level of interest in article[a]	5.9 (5.5-6.3)	5.8 (5.4-6.2)	6.0 (5.6-6.4)	5.8 (5.4-6.2)	.83

Abbreviations: ANCOVA, analysis of covariance; COI, conflict of interest.

[a] Outcomes measured on 10-point Likert scales with high scores indicating high levels of confidence, importance, and interest.

[b] One respondent did not give ratings for confidence, importance or interest level, hence data here relates to n=90

[c] One respondent did not give a rating for confidence, hence for this outcome the data relates to n=89

[d] One respondent did not give ratings for confidence, importance or interest level, hence data here relates to n=95

[e] One respondent did not give a rating for confidence or interest, hence for these outcomes the data relates to n=92

[f] Allocation group "none" had a significantly higher level of interest compared with allocation group "advisory board and consultancies" (*P*=.018 with Bonferroni correction).

Table 4: Likelihood to change practice for those currently treating gout/dyspepsia and their own practice differed from the recommendations given in the review

	Allocation group; % (number)				*P* Value
	Honoraria & travel	Research funding	Advisory board & consultancies	None	
Gout review					
N	16	11	17	15	P=0.59 [b]
Likely to change practice [a]	6% (1)	18% (2)	24% (4)	20% (3)	
Dyspepsia review					
N	20	29	19	12	P=0.56 [b]
Likely to change practice [a]	0% (0)	7% (2)	10% (2)	8% (1)	

[a] Respondents who scored 10 ("Extremely likely") on the rating scale of 1 to 10 for likelihood to change practice.
[b] Chi-square test.

Table 5: ANCOVA analysis of the level of confidence in the reviews by intervention group adjusting for age, sex, job type, and years since qualification for subgroups who were currently treating patients with gout or dyspepsia

	Mean (95% CI)				
	Honoraria & travel	Research funding	Advisory board & consultancies	None	*P* Value
Gout review					
N	46	42	43	46	
Level of confidence in conclusions drawn	7.3 (6.8,7.5)	7.7 (7.1, 8.2)	7.0 (6.4,7.5)	7.6 (7.1, 8.1)	P=0.18
Dyspepsia review					
N	48	43	59	56	
Level of confidence in conclusions drawn	6.3 (5.7,6.8)	6.8 (6.2, 7.3)	6.4 (5.9, 6.9)	6.4 (5.9, 6.9)	P=0.64

Table 6: Characteristics of volunteers, completers and non-responders

	Volunteered and completed survey (n=749)	Volunteered but did not complete survey (n=316)	Did not volunteer (n=9824)	*P* Value
Type Consultant General practice Junior doctor	 35% (264) 35% (263) 30% (222)	 36% (114) 29% (92) 35% (110)	 33% (3251) 33% (3269) 34% (3304)	P=0.11[1]
Male	46% (345)	50% (157)	53% (5189)	P=0.001[1]
Mean age (range)	44.0 (23, 79)	41.9 (23, 71)	42.3 (22,84)	P=0.001[2]
Mean years' qualified (range)	19.0 (0, 54)	17.1 (0, 47)	17.5 (0,58)	P=0.003[2]

[1] Chi-square test
[2] ANOVA

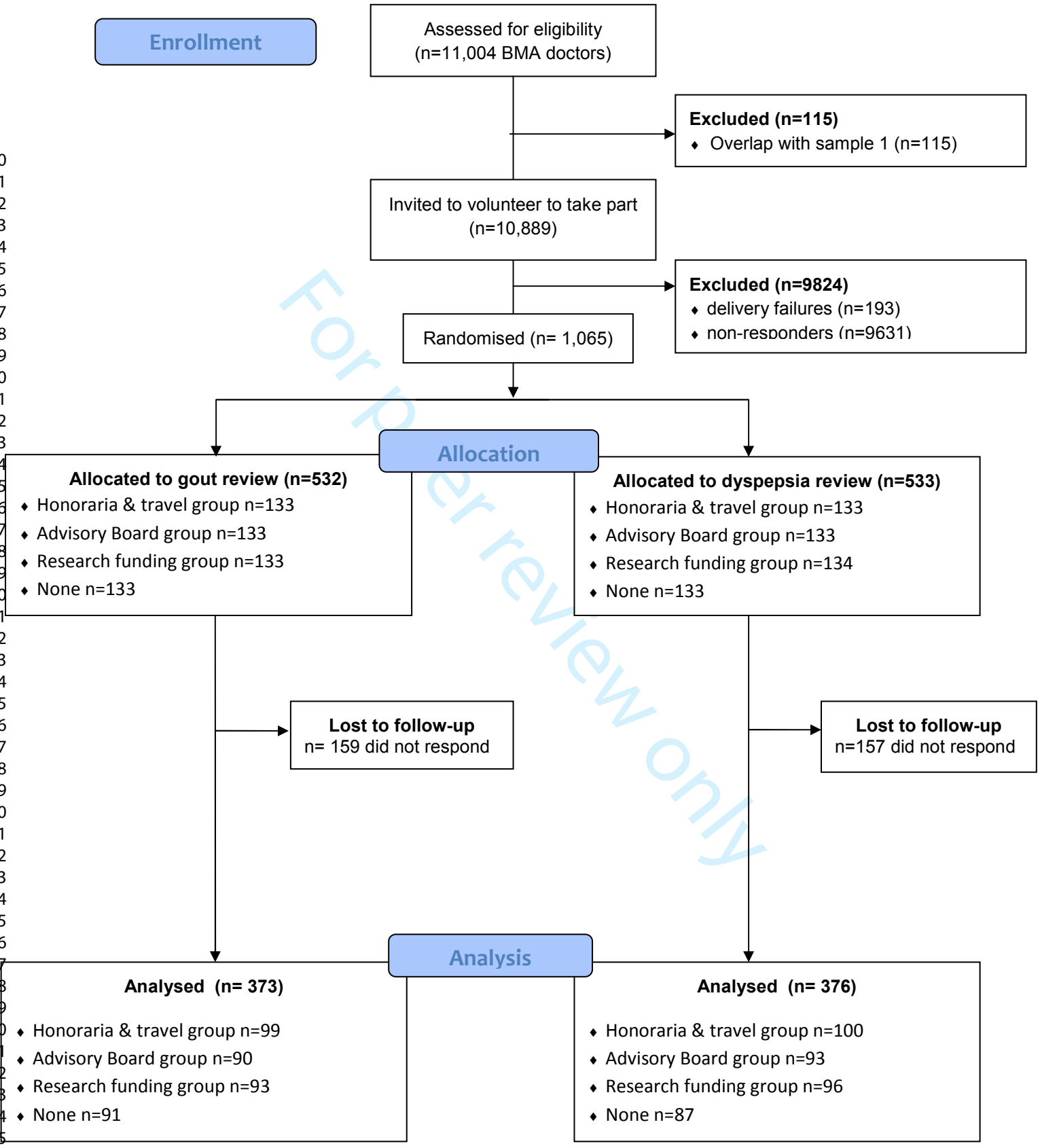
Figure legends

Figure 1: Participant flow chart

Appendix 1: Dyspepsia article showing the travel & honoraria COI

Appendix 2: Gout article showing the advisory board & consultancies COI

Figure 1: Flow Diagram



Clinical Review: Management of dyspepsia

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Definitions of the term dyspepsia vary but generally describe pain or discomfort in the epigastric region. People with dyspepsia have a normal life expectancy,[1] but symptoms impair quality of life,[2-3] and affect productivity.[4] In this review we summarise recent evidence, to provide the general reader with an update on how to treat this disorder effectively.

What are the treatment options?

Uninvestigated dyspepsia in primary care or the community

An individual patient data meta-analysis of randomised controlled trials found that—although prompt endoscopy was superior to testing patients with uninvestigated dyspepsia for *H pylori*, and treating with eradication therapy if positive, in terms of symptom control at 12 months—it was not cost effective.[5] However, it is unclear whether a test and treat approach is preferable to empirical acid suppression first line, because a second individual patient data meta-analysis found no significant difference in symptoms or costs between the two.[6] Current guidelines state that either option can be used.[7] If the prevalence of *H pylori* in the population is known, it makes sense to use an acid suppression strategy first if prevalence is low (<10%) and an *H pylori* test and treat strategy if the prevalence is higher.[8] If these strategies are unsuccessful, other options (discussed below) can be considered, or the patient can be referred to secondary care for advice and further investigation if appropriate.

A six month primary care based Dutch trial compared two management strategies for uninvestigated dyspepsia based around empirical acid suppression.[9] One strategy used a step-up approach, starting with antacids, with treatment escalated to H2 antihistamines and then proton pump inhibitors (PPIs) if symptoms remained uncontrolled. The second used a step-down approach, with the drugs given in the reverse order and de-escalated if symptoms improved. Treatment success (adequate relief of symptoms) was similar at six months (72% with step-up*v* 70% with step-down), but costs were significantly lower with the step-up approach. This, together with the small treatment effect in favour of step-up, meant that it came out top in a cost effectiveness analysis.

Another group of primary care patients who may benefit from *H pylori* test and treat are those who do not consult with dyspepsia very often but who require PPIs long term. A trial screened long term PPI users for *H pylori* and randomised those who were positive to eradication therapy or placebo.[10] Eradication therapy significantly reduced symptom scores, PPI prescriptions, consultations for dyspepsia, and dyspepsia related costs. The costs of detection and treatment were less than the money saved after two years of follow-up. Sensitivity analysis showed that the prevalence of *H pylori* would need to be less than 12% before this was no longer cost saving.

It has been estimated that 5% of dyspepsia in the community is attributable to *H pylori*,[11] so population screening and treatment for this organism could theoretically reduce dyspepsia related costs. Results from follow-up studies of people recruited to two large randomised controlled trials of population based screening (and eradication therapy or placebo if *H pylori* positive) in the UK suggest this might be the case, with significantly lower costs and fewer consultations after seven to 10 years.[12-13] However, these studies did not follow up all recruited people successfully, so currently there is insufficient evidence to institute population screening and treatment in the UK.

Peptic ulcer disease

The causal role of *H pylori* in peptic ulcer disease is well established, and patients with *H pylori* positive disease should receive eradication therapy. A Cochrane review found that the number needed to treat (NNT) with eradication therapy to prevent one duodenal ulcer relapse (26 placebo controlled trials) was 2 and for gastric ulcer (nine trials) the number was 3.[14] Although there was significant heterogeneity between studies in both analyses, all but one trial showed a significant benefit with eradication therapy. PPI triple therapy (a PPI plus two antibiotics (clarithromycin with amoxicillin or metronidazole)) should be used in areas like the UK where clarithromycin resistance is less than 10%, with bismuth quadruple therapy (bismuth plus a PPI and two antibiotics) being given where resistance is higher.[15] Most cases of *H pylori* negative peptic ulcer disease are caused by NSAIDs, and trials show that PPIs are superior to H2 antihistamines for ulcer healing in this

situation.[16-17] *H pylori* negative, NSAID negative peptic ulcer disease is rare and probably requires long term PPI treatment.

Functional dyspepsia

Diet and lifestyle

Food diaries from a small study of 29 patients suggest that people with functional dyspepsia eat fewer meals and consume less energy and fat than healthy controls,[18] but whether this is a cause or a consequence of symptoms is unclear. Although the prevalence of undiagnosed coeliac disease is higher in people with symptoms of irritable bowel syndrome,[19] this is not the case in dyspepsia.[20] It is also unclear whether non-coeliac gluten sensitivity is involved in symptom generation in some patients with functional dyspepsia. Doctors often advise people with dyspepsia to lose weight, avoid fatty food and alcohol, or stop smoking, but there is little evidence that these measures improve symptoms.[21] As a result, drugs are the mainstay of treatment.

Acid suppression therapy

Antacids neutralise gastric acid, the production of which is controlled by gastrin, histamine, and acetylcholine receptors. Once stimulated, these receptors activate proton pumps in the parietal cell. H2 antihistamines and PPIs reduce acid production by blocking H2 receptors or the proton pump, respectively. Because PPIs act on the proton pump itself, these drugs lead to more profound acid suppression than H2 antihistamines or antacids. A Cochrane review has studied the efficacy of acid suppressants in functional dyspepsia.[22] One placebo controlled trial of antacids showed no benefit. Twelve randomised controlled trials of H2 antihistamines versus placebo found that these drugs were effective for the treatment of functional dyspepsia (NNT=7). However, there was significant heterogeneity between studies, which was not explained by sensitivity analysis, and evidence of funnel plot asymmetry, suggesting publication bias or other small study effects. Their efficacy may therefore have been overestimated. Ten trials studied PPIs. Again, there was a significant benefit over placebo, although this was modest (NNT=10). There was significant heterogeneity between studies, with no obvious explanation, but no funnel plot asymmetry. A subgroup analysis conducted according to predominant symptom showed that PPIs were most beneficial in patients with reflux-type symptoms and more effective than placebo in patients with epigastric pain. However, they were no more effective than placebo in those with dysmotility-like functional dyspepsia.[23] Most trials used PPIs for four to eight weeks. This seems a reasonable duration, especially as concerns have been raised recently about the safety of long term PPI use. Observational studies suggest that hip fracture, community acquired pneumonia, and *Clostridium difficile* infection are more common in PPI users,[24-25] although all these associations were extremely modest, and direct causation cannot be assumed from studies such as these.

H pylori eradication therapy

The benefit of eradication therapy is less pronounced in functional dyspepsia than in peptic ulcer disease, but treatment is still more effective than placebo. In a Cochrane review of 21 placebo controlled trials the NNT for improvement in symptoms after eradicating *H pylori* was 14, with no heterogeneity between studies and no evidence of funnel plot asymmetry.[26]

Footnotes

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Clinical Review: Management of gout

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Gout is the most common inflammatory arthritis, affecting 1-2% of the population. The major risk factor is a raised serum urate concentration (hyperuricaemia), which results in the deposition of monosodium urate crystals in and around joints. Untreated, continuing crystal deposition can result in irreversible joint damage. Although effective treatments are available for acute and chronic gout, uptake is poor, and many patients experience repeated acute attacks and reduced quality of life. This clinical review summarises current evidence for the management of acute and chronic gout.

How are acute attacks of gout treated?

Treatment of acute gout aims to provide rapid relief of joint pain and swelling. First line oral drugs are usually non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine.[1] There is no evidence that any one NSAID is more effective than another. A systematic review commented on the poor quality of existing NSAID trials in acute gout, with the exception of two moderately sized RCTs, which found an equivalent effect of indometacin 50 mg three times daily and etoricoxib 120 mg daily on pain.[2-4] More recently, two well conducted trials have found indometacin (50 mg three times daily for two days, then 25 mg three times daily for three days) and naproxen 500 mg twice daily to be as effective as oral prednisolone.[5-6] Indometacin was associated with more gastrointestinal adverse events, however, and is best avoided.[5]

British Society for Rheumatology and American College of Rheumatology guidelines suggest using a fast acting NSAID, such as naproxen, at full dose. Caution is needed, however, in people with heart failure, ischaemic heart disease, renal insufficiency, or a history of gastrointestinal ulcers, bleeds, or perforations.[7-8] Continue treatment until the attack has resolved (typically a few days to two weeks).

Colchicine is a naturally occurring alkaloid that inhibits leucocytic phagocytosis of monosodium urate crystals, the inflammasome, and cell mediated immune responses. It has traditionally been used in high doses (1 mg initially, followed by 500 µg every two to three hours until pain relief is obtained). Although a small trial showed the effectiveness of high dose regimens over placebo, all participants randomised to receive colchicine developed diarrhoea or vomiting (or both).[9] Lower doses of colchicine are as effective and better tolerated than high dose regimens.

A recent well conducted moderately sized RCT found at least a 50% reduction in pain within 24 hours in 33% of participants treated with high dose colchicine (1.2 mg initially and then 600 µg hourly for six hours). There was also a 38% reduction in those treated with low dose colchicine (1.2 mg initially, followed by 600 µg after one hour) and a 16% reduction in those receiving placebo.[10] Diarrhoea affected 77% of the high dose group, 23% of the low dose group, and 14% receiving placebo. The *British National Formulary* recommends 500 µg two to four times daily.[11] Although no head to head comparison between colchicine and a NSAID exists, oral NSAIDs are generally considered to be the first line treatment for acute gout, with colchicine reserved for those with contraindications to, or intolerance of, NSAIDs.[7] Several drugs can increase the risk of colchicine toxicity.

Corticosteroids provide a further treatment option. Although there are no RCTs,[12] expert consensus agrees that joint aspiration and intra-articular injection of corticosteroids is a rapid and highly effective treatment for acute gout.[1,7] The diagnosis can be confirmed by microscopy of aspirated fluid, and such treatment is probably best practice in a hospital setting. However, the necessary skills to perform aspiration and injection might not be present in all settings, particularly primary care. Intramuscular or oral corticosteroids provide a useful option, particularly when there are contraindications to NSAIDs and colchicine and more than one joint is affected or joint injection is not possible.[1,8] Two high quality RCTs found that oral prednisolone at doses of 30-35 mg daily for five days are as effective as NSAIDs[5-6]

Rest and cooling of the joint are also effective for acute gout. A small RCT found that the application of topical ice in combination with oral prednisolone and colchicine reduces pain more effectively than combined prednisolone and colchicine alone.[13]

What does non-drug based management of gout consist of?
Non-drug based management consists of risk factor modification, including lifestyle factors. Dietary modification comprises restriction of, but not total abstinence from, purine-rich foods (including red meat and seafood) and alcohol (particularly beer).[1,7] Weight loss is recommended if appropriate. Uncontrolled intervention studies have confirmed modest effects of weight loss and low purine diet on urate lowering and frequency of attacks.[14-15]

How and when should urate lowering drugs be used?
There is debate about the indications for urate lowering therapy. Expert consensus advocates offering such drugs to patients with recurrent acute gout, tophi, radiographic damage, renal insufficiency, or uric acid urolithiasis.[1,7] The precise threshold at which recurrence of acute attacks warrants treatment is controversial. Opinions vary from starting these drugs after the first attack, when the crystal load is small and substantial joint damage has not yet occurred, to waiting until two or more attacks have occurred over 12 months. Urate lowering therapy is usually started two to four weeks after resolution of an acute attack to reduce the risk of the drug exacerbating the attack. However, one RCT of 51 patients found no difference in pain between those started on allopurinol during an attack and those given placebo.[16] Delaying initiation of allopurinol also allows a rational discussion about treatment when the patient is no longer in pain. When fully informed about urate lowering therapy, most people wish to receive it, and subsequent adherence can be excellent.[17]
The most commonly used drug is allopurinol—a purine, non-specific xanthine oxidase inhibitor. Allopurinol should be started at low dose (usually 100 mg daily) and increased in 100 mg increments monthly until serum uric acid is below 360 µmol/L. Two small observational studies reported that the effect on cessation of acute attacks, resolution of tophi, and reduction of crystal load is greatest if uric acid is reduced below this value.[18-19] Some expert consensus groups recommend reducing uric acid further, to below 300 µmol/L,[7] at least for the first one to two years of treatment, because this speeds up the rate of crystal elimination and tophus reduction.[20]

The maximum permitted dose of allopurinol in the UK is 900 mg per day. Although such doses are rarely needed, many patients need doses of 400-500 mg daily to reduce uric acid.[17] During the dose escalation phase, measure full blood count, renal function, liver function, and serum uric acid monthly. The active metabolite of allopurinol (oxypurinol) is excreted through the kidney, so lower doses and more cautious upward titration are recommended in people with renal failure because of the risk of the rare but potentially life threatening allopurinol hypersensitivity syndrome, which involves severe skin reactions and hepatic and renal dysfunction.[21-22] Clinical risk factors for allopurinol hypersensitivity syndrome include renal failure, diuretic use, and higher allopurinol dose at initiation.[21-22]

Ninety per cent of people tolerate allopurinol without problems. As with all urate lowering drugs, patients may experience an acute attack of gout when they start allopurinol because it encourages crystal shedding through partial crystal dissolution. Although the likelihood of this is reduced by gradual dose escalation, prophylactic low dose colchicine or an NSAID can be coprescribed for up to six months until a stable dose is reached. One small placebo controlled RCT showed fewer gout flares when allopurinol was coprescribed with colchicine 600 µg twice daily.[23] Allopurinol should not be discontinued if an acute attack occurs. The main alternative to allopurinol is the specific non-purine xanthine oxidase inhibitor, febuxostat.
Urate lowering therapy in patients who cannot tolerate or have contraindications to allopurinol (or alternatives) is challenging. Options include uricosuric drugs such as sulfinpyrazone, probenecid, and benzbromarone, but these have limited availability. Such patients are best referred to a rheumatologist for specialist care.

Treatment is life long. Once a stable target serum urate concentration has been achieved, measurements must be repeated about every six months to ensure the therapeutic target is being maintained.

Footnotes

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Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received fees from Jenka Pharmaceuticals for consultancies and being an advisory board member.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 3,4,5,6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-11 &Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12 & Table 5
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13-14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Effect of different financial competing interest statements on readers' perceptions of clinical educational articles: a randomised controlled trial

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ABSTRACT

Objectives

To investigate how different competing interest (COI) statements affect clinical readers' perceptions of education articles.

Design

Randomised controlled trial.

Setting and participants

Random sample of UK doctors..

Interventions

We created four permutations of each of two clinical reviews (on gout or dyspepsia) which varied only in terms of the COI statement. Volunteers were blinded and randomised to receive one review and asked to complete a questionnaire after reading it. Blinded factorial analyses of variance and analyses of covariance were carried out to assess the influence of each review and type of COI on outcomes.

Primary and secondary outcomes

Confidence in the article's conclusions (primary outcome), its importance, their level of interest in the article, and their likelihood to change practice after reading it.

Results

Of 10,889 doctors invited to participate, 1,065 (10%) volunteered. Of these, 749 (70%) completed the survey. Analysis of covariance (adjusting for age, sex, job type, years since qualification) showed no significant difference between the groups in participants' confidence in the article (gout: *P*=.32, dyspepsia: *P*=.78) or their rating of its importance (gout: *P*=.09, dyspepsia: *P*=.79). For the gout review, participants rated articles with advisory board and consultancies COI as significantly less interesting than those with no COI (*P*=.028 with Bonferroni correction). Among participants indicating that they treat the condition and that the article's recommendations differed from their own practice, there was no significant difference in likelihood to change practice between groups (gout: *P*=.59, n=59; dyspepsia: *P*=.56, n=80).

Conclusions Doctors' confidence in educational articles was not influenced by the COI statements. Further work is required to determine if doctors do not perceive these COIs as important in educational articles or if they do not pay attention to these statements. More meaningful COI

disclosure practices may be needed, which highlight context-specific potential sources of bias to readers.

Trial registration: ClinicalTrials.gov (NCT02548312)

Article Summary

Strengths and limitations of this study

- Competing interest (COI) statements have been shown to influence readers' perceptions of research but this is the first experimental study to look at the effect of COIs in clinical educational material.
- A key strength of this study is its randomised study design in a research area where there are few experimental studies.
- Financial competing interests are varied; we were only able to evaluate the effect of three financial COI statements compared with none due to the large sample size required.
- Our outcome measures were all self-reported and we did not assess objective changes to practice.

INTRODUCTION

Researchers, clinicians and academic institutions often have competing interests, also known as conflicts of interest (COIs), and collaborations with industry are often considered necessary to facilitate progress and innovation in medical research.[1] COIs are defined as 'circumstances that create a risk that professional judgements or actions regarding a primary interest will be unduly influenced by a secondary interest'.[1][2] The possibility that COIs may bias the medical literature and potentially affect patient care has been highlighted in many studies. For example, a 2017 Cochrane review found that drug and device studies sponsored by the manufacturer demonstrated more favorable efficacy and conclusions than studies sponsored by other sources.[3] Whether bias is conscious or unconscious, COIs may therefore compromise the medical evidence which drives development of recommendations for clinical care.[3]

Widespread recognition that COIs may potentially influence decision-making has rendered their open disclosure a common requirement for the publication of research articles in academic medical journals.[3] A systematic review reported that the presence of financial COIs and industry collaborations are concerning to academic and clinical researchers, particularly as such interests may potentially influence research project decisions, the conduct of research, and subsequent publication.[4] Financial ties with industry were considered more acceptable where these were not directly related to the research, disclosure of COIs was upfront, and the results of research was freely published.[4]

However, there has been little research exploring the effect of competing interests on reader perceptions. In a randomised trial investigating the effect of the funding source of a clinical trial on clinicians' interpretation of trial results, it was observed that industry sponsorship negatively affected the perceived methodological rigor of a trial and the willingness to change practice based on its findings, independent of trial quality.[5] We have previously reported the results of two randomised controlled trials comparing the effect of COI statements related to financial interests against no competing interests and demonstrated a significantly negative influence of COIs on readers' perceptions of the credibility of medical research.[6, 7] Surveys have previously reported a similarly low perceived credibility of industry-initiated or funded drug trials among clinicians.[8] However, in a trial of US physicians who were provided with a clinical trial abstract presenting positive findings of a new drug, randomised to differ in their COI statement, it was found that doctors did not significantly discount for COIs when reporting their likelihood to prescribe the fictitious drug.[9] Nonetheless, when directly asked about the COI, the majority reported that they feel that they should to some degree discount information on the basis of COIs, highlighting that simply publishing COI disclosures may not be sufficient.[9] Similarly, a randomised trial of French GPs found no evidence of a significant impact of reporting of COIs on GP's confidence in the conclusions of trial abstracts.[10]

Clinical education articles are intended to provide guidance on clinical care for clinicians, yet our understanding of the role of COIs on readers' perceptions of the credibility of such articles, rather than primary research articles, is limited. Educational articles are prone to bias as they typically use non-systematic methods of literature acquisition, and broadly rely on the interpretation of one author, or a small number of authors, on their chosen included literature. Of concern too is evidence from the social sciences suggesting that disclosure of COIs may even enhance bias: conflicted authors may feel a 'moral release' from having simply declared they are conflicted, or may even exaggerate to counteract any expected discounting of their opinion.[11-12] Such potential biases may therefore be extensive, but potentially less visible to their targeted broader clinician readership.

Many years ago the *American Family Physician* became the first journal to introduce a 'zero tolerance' policy for COIs in clinical educational articles.[13] In the 1990s *The New England Journal of Medicine* implemented a stringent policy whereby editorialists had to be free from financial ties to drugs or devices discussed in the editorial,[14, 15] but this policy was relaxed in 2002 to exclude only those with significant ($10,000) financial interest due to difficulties in recruiting authors.[16] In 2015 *The BMJ* implemented a 'zero tolerance' policy on the presence of any relevant financial COI related to industry for authors of its clinical editorials and some education articles.[17] However, some have questioned the need for strict restrictions on the presence of COIs, discussing whether such policies may limit trust, effective industry collaborations, or the ability for some experts to contribute to clinical education.[18-21] Evidence is missing in characterising how COI statements influence reader perceptions of educational articles, or indeed if awareness exists of the potential for COIs to influence the conclusions of such articles. We describe a randomised controlled trial to test the effect of a range of common COI statements in educational articles on a clinician readership's confidence in the conclusions of an article, their interest in the article, its perceived importance, and on the likelihood that they would change their clinical practice based on the article's findings.

METHODS

Design

Parallel group randomised controlled trial. The study protocol has previously been published.[22]

Study sample

We took two approaches to the sampling for this study as the first approach did not yield adequate numbers.

Inclusion criteria and exclusion criteria

We included practising doctors in the UK who were receiving *The BMJ* through their membership of the British Medical Association (BMA). We excluded members who had opted out of receiving a copy of *The BMJ*, public health doctors, consultant oral/dental surgeons, retired doctors and student members. We also excluded doctors listed as doing private practice as this was necessary due to the way the data about specialty and grade are stored to ensure compliance with our other exclusion criteria.

Sample 1

We generated a random sample of 2,040 BMA members (680 general practitioners (GPs), 680 hospital consultants and 680 junior doctors), randomised each to a group (see methods below), and sent them a personalised email invitation from *The BMJ's* editor-in-chief in September 2015 to take part in a research project along with the relevant study materials. A range of clinical specialties and stages of training were included to facilitate generalisability of study findings to the clinical workforce, and the clinical conditions of the educational articles were accordingly selected to reflect conditions which the vast majority of clinicians would be expected to have had experience in managing. Participants were not told the purpose of the study to avoid biasing responses.

Sample 2

We broadened the sampling frame and took a very large random sample of 11,004 BMA members and asked for volunteers to take part in a research project before assigning them to a study group, as per our protocol. Recruitment for volunteers was open between 06/01/16 and 28/01/16.

Intervention

Participants were sent an email with a link to one of two clinical reviews depending on randomised group allocation, on the management of dyspepsia (Appendix 1) or gout (Appendix 2), and a link to a short questionnaire on SurveyMonkey on 02/02/16. Study participants were asked to read the article and then complete the questionnaire. Data collection closed on 03/05/16.

We selected two clinical reviews previously published by *The BMJ* in 2013 describing two conditions commonly seen by doctors, requiring treatment by drugs, and familiar to all clinical specialties. We shortened and modified these after obtaining permission from the original authors. We changed the authors on the authorship byline to fictional author names and listed fictional institutions. Each of the two clinical reviews had four permutations differing only in the COI statement (from no competing interests to a range of financial interests) for the last of the three authors (Table 1). All COI statements appeared at the end of the article's main text, just before the references, in line with usual practice. These statements all had the same fictional author names and where there was a financial COI we used the same fictional pharmaceutical company name but did not mention the company name in the main text of the clinical reviews.

Randomisation and blinding

A random sample of eligible BMA members was generated from the database of all members by staff at the BMA using computer generated random numbers. JM then randomised members to one of eight groups to receive one of the eight permutations of the clinical reviews using a computer-generated block randomisation procedure, stratified by type of doctor (GPs/hospital consultants/junior doctors) and gender. The eight permutations of the clinical reviews were then randomly assigned a number from 1 to 8 by SS. SS enrolled participants and managed the survey. JM conducted the statistical analysis blinded to the group allocation; participants were identified only by study group number, which was not revealed to JM until after all analysis was completed. Participants were blinded to their study group and were not told that we were testing the effect of various COIs on their perceptions of the articles.

Data collection

We piloted the draft survey with a convenience sample of doctors to ensure the instructions were clear and the questions were not ambiguous. Study participants were asked to read the article and indicate on a 10-point Likert scale (0=Not at all, 10=Extremely): how confident they were in the conclusions drawn in the article they received, how interesting and important they found the article and how likely they were to change their practice on the basis of the article (see the supplementary materials of the published protocol for the questionnaire).[22] To reduce question order bias, the presentation order of the questions was randomised for the first three items (confidence, interest and importance).

Contact details and demographic information about BMA members were obtained from the BMA membership database: name, title, email address, specialty, sex, age, and date qualified. Survey data was gathered using SurveyMonkey. Non-responding volunteers were sent up to five reminders to complete the survey.

Outcome measures

Primary outcome measure

The primary outcome was the readers' level of confidence in the conclusions drawn in the article, measured on a 10-point Likert scale from 1= 'not at all confident' to 10= 'extremely confident'.

Secondary outcome measures

The three secondary outcomes, all measured on similar 10-point Likert scales, were: readers' ratings of the importance of the article, interest in the article, and likelihood to change practice on the basis of the article.

Ethics and trial registration

We did not submit the study for ethical approval as this is not required for this type of survey with doctors in the UK. However, the study proposal and study materials were reviewed by *The BMJ's* Ethics Committee and they did not have substantive ethical concerns. To avoid biasing participants' responses, details of the study objectives and design were not given to participants. The study protocol[22] was not published until data collection was complete so as not to potentially influence participants' responses. Consent to take part was assumed by completion of the study questionnaire. The trial was registered at ClinicalTrials.gov (NCT02548312) just before recruitment commenced.

Statistical analysis

Sample size justification

We calculated that to have 90% power to detect a one-unit difference on the 10-point 'confidence' scale between the groups, 121 readers were needed in each of the four COI statement groups, based on a simple Student's t test with an estimated standard deviation of 2, with a two-sided 1% significance level to provide some adjustment for multiple testing between the four COI statements. However, as differences between the results for the two clinical reviews were considered important to quantify, a total of 968 readers were required to account for the eight permutations. Assuming a response rate of around 50% based on previous *BMJ* trials of similar design,[6, 7] we calculated we needed to invite at least 1,936 readers to take part. Accordingly, in Sample 1, for each of the eight groups, 255 readers (85 GPs, 85 consultants and 85 junior doctors) were invited to take part. We assumed that a one-unit difference on the 10-point scale was important on the basis that a 0.5-unit difference was important in our previous studies using a 5-point scale.[6, 7] Similarly, the observed SD for the 5-point scale was ~1, and hence we assumed that, for a 10-point scale, the SD would be twice as large. As Sample 1 only yielded a 9% response rate and we anticipated a similar yield when asking for volunteers, we broadened the sample to 11,004 in Sample 2.

Statistical analysis

A factorial analysis of covariance (with COI statement and clinical review type as the two factors) was carried out to assess their impact on the primary outcome (level of confidence) and secondary outcomes (importance, interest and likelihood to change practice) adjusting for the effect of doctor type (GP, consultant or junior doctor), gender, age and the number of years since qualification. Separate analyses of covariance (ANCOVA) were performed for each of the two clinical reviews, and, in addition, for the subgroups who were currently treating the conditions. The impact on the likelihood to change practice was assessed using chi-square tests. Analyses of variance and chi-tests were used to compare non-responders with responders in terms of age, gender, doctor type (GP, consultant or junior doctor) and number of years since qualification.

Patient and Public Involvement

We did not include patients as study participants. Patients were not involved in setting the research question, designing the study, the conduct of the study, or the interpretation of the results. Our patient editor, recently invited patients and members of the public attending a workshop at the Cochrane Colloquium 2018

on "*Meeting the challenge of research empowerment through co-production and expert patient review*" how patients and the public could have been involved in this research and they reported that they did not see relevant opportunities to do so. However, a patient and public reviewer for The BMJ did make an interesting suggestion for a further study with the general public as the participants as it is important to know how people value and consider COIs when reading articles.

RESULTS

Samples

Sample 1

Overall, 182/2040 (9%) responded, but the response rate was lower for the article on dyspepsia (81/1,020, 8%) than gout (101/1020, 10%). On reading responses to the survey for those who received the dyspepsia review, we identified a problem with the content of the manuscript. A few respondents queried the appropriateness of including a section on prokinetic drugs given the recent withdrawal of drugs and safety concerns but no mention of this in the article. As such, we removed this section from the manuscript before using it in Sample 2 and started the study again.

Sample 2

We obtained a random sample of 11,004 BMA members meeting the study eligibility criteria. After removing overlap with Sample 1, we invited 10,889 doctors to volunteer to take part in a research project for *The BMJ* (Figure 1). On sending the email invitation, 96 email addresses bounced and 97 had already opted out of SurveyMonkey so had to be excluded. Of the 10,696 eligible email addresses, we recruited 1,065 volunteers (10%) and 749 (70% of those who volunteered) completed the survey; n=376 dyspepsia and n=373 gout. A third of respondents were consultants, a third GPs, and a third junior doctors; 46% were male and the mean age was 44 years (Table 2). All analyses are based on data collected in Sample 2.

Primary outcome

There was no significant difference between the groups in the readers' level of confidence in the conclusions drawn in the article for the gout (p=0.32) or dyspepsia (p=0.78) reviews (Table 3). The mean confidence rating scores for all of the groups receiving the gout review was at least 7 out of 10, and for the dyspepsia review it was at least 6.

Combining results over both reviews showed no differences in confidence between the COI groups (p=0.54), and no evidence of a difference between reviews in the variability between the COI groups (p=0.53) but respondents had a higher level of confidence in the gout review than the dyspepsia review (p<0.001).

Secondary outcomes

Importance of the article

There was no significant difference between the groups in readers' ratings of the level of importance of the article for the gout (p=0.09) or dyspepsia (p=0.79) reviews (Table 3).

Combining results over both reviews showed no overall differences in level of importance between the COI groups (p=0.79) and no evidence of a difference between reviews in the variability between the COI groups (p=0.14), but respondents gave higher ratings of importance for the gout review (p=0.002).

Interest in the article

For the gout review, participants rated reviews with advisory board and consultancies COI as significantly less interesting than those with no COI (*P*=.018 with Bonferroni correction), but there was no significant difference between the groups for the dyspepsia review (p=0.83) (Table 3).

Combining results over both reviews showed no overall differences in level of interest between the COI groups (p=0.46) and no evidence of a difference between reviews in the variability between the COI groups (p=0.12), but respondents gave higher ratings of interest for the gout review (p<0.001).

Likelihood to change practice

Almost half of respondents (178/373, 48%) who received the gout review reported that they were currently treating patients with gout, 28% (103/373) were not currently treating them and 24% (90/373) reported they do not treat patients with this condition. Of those who were currently treating gout, 33% (59/103) indicated that the article recommended practice differing from their current practice.

Over half of respondents (207/376, 55%) who received the dyspepsia review reported that they were currently treating patients with dyspepsia, 23% (85/376) were not currently treating them and 22% (83/376) reported they do not treat patients with this condition. Of those who were currently treating dyspepsia, 39% (80/207) indicated that the article recommended practice differing from their current practice.

Among participants indicating that they treat the condition and that the article's recommendations differed from their own practice, there was no significant difference in likelihood to change practice between groups (gout: *P*=.59, n=59; dyspepsia: *P*=.56, n=80), (Table 4).

Subgroup analysis

Analysis of the subgroups who were currently treating the conditions showed no significant differences between the groups for the level of confidence (primary outcome) in the article (gout: *P*=.18; dyspepsia: *P*=.64), (Table 5).

Analysis of non-responders

Respondents who completed the survey were significantly older, had been qualified for longer and were more likely to be female than those who did not complete or volunteer, p<0.05 (Table 6).

DISCUSSION

Doctors' confidence in the conclusions drawn in two educational reviews was not significantly influenced by a range of financial COI statements that are commonly reported to journals and frequently occur in medical practice. When the results for the two reviews were combined, we found no significant difference between the COI statement groups in the importance or interest doctors attached to the article or their self-reported likelihood to change practice based on the article. However, we did find a significant difference between the groups in level of interest for the gout review; doctors rated the gout review with advisory board and consultancies COI as significantly less interesting than when there was no COI. Subgroup analysis of those who were currently treating the conditions found no significant difference in the level of confidence in the article.

Three previous randomised controlled trials[5-7] on the effect of financial COIs on readers' perceptions of research found strikingly different results. In our first trial[6] readers randomised to receive a drug study written by three authors with financial COIs (employees of a fictitious company who potentially held stock options in the company) indicated these as significantly less interesting, important, relevant, valid and believable than those randomised to receive the same article written by authors with no COIs declared. In our second trial,[7] we tested the effect on a non-drug study and also varied the type of COI statement (author potentially held stock options in the company versus author was a recipient of funding for studentships and research grants versus no competing interest declared). Once again, we found that overall, importance, relevance, validity, and believability ratings were significantly lower in the group with the financial COI statement than in the no competing interest group. Validity ratings for the financial COI statement group were also significantly lower than for the group receiving the research grants statement. The current study sampled doctors from the same large membership database and applied a similar methodology, but found no significant difference in the confidence in the conclusions drawn (primary outcome) between the groups. A third randomised trial exploring the influence of clinical trial funding on clinician perceptions of trials with a high, medium, or low methodological rigor, found that industry funding negatively impacted on perceived methodological quality and willingness to implement trial findings regardless of trial quality.[5] However, two further trials of the effects of COIs in trial abstracts, one with US physicians and another with French physicians, found no significant evidence, respectively, that COIs influenced the likelihood to prescribe a fictitious drug or the confidence of physicians in the abstract conclusions.[9, 10] In contrast to previous trials evaluating the influence of COIs on readers' perceptions, our study used a clinical review article (where possible biases may be less visible) and subtler financial COIs (although these were still typical of those seen in medical practice).[6-7]

A key strength of this study is its randomised study design in a research area where there are few experimental studies. This study had several limitations. Firstly, our initial sampling approach yielded a very

low response rate of 9% (not unusual for surveys of doctors and researchers)[23-25] and the study was underpowered to show an effect. As such we broadened the sampling frame by seeking volunteers at the outset and this yielded a response from 70% of those recruited. The initial low response rate was surprising as in both our earlier trials, with postal administration, we achieved response rates of 59%[6, 7] and sampled readers from the same membership database. However, mode of administration can influence response rates[26] and response rates across all methods of survey administration have declined over time.[27] The extent to which we can generalise the findings from the small sample of volunteers who had the time, interest and motivation to take part to all readers is unknown; those who volunteered may differ from their peers in ways we did not capture. Secondly, we excluded doctors in private practice, so we are unable to generalise the results beyond practising National Health Service doctors. However, to get a representative sample, we sampled doctors from a wide range of clinical specialties. We also used two clinical reviews to help make the findings generalisable beyond a single clinical topic. Thirdly, participants were told they were taking part in a research project and this may have influenced the way they read the article and responded to the questions. Fourthly, participants were asked to read an article that they might not usually read; approximately half of participants in each group reported that they were not currently treating patients with gout/dyspepsia. Whilst this may have influenced responses, we deliberately selected two general clinical topics commonly presented and the task did not require respondents to have in-depth knowledge of the assigned topic. Further research could study the effects of COI statements in the context of articles that are highly relevant to readers' own clinical practice. Fifthly, respondents were significantly older than non-respondents, but this was in keeping with both our previous trials.[6, 7] Sixthly, we only looked at the effect on self-reported outcome measures not on actual changes to practice. Finally, we were unable to pool the results from our two sampling approaches as we used different recruitment processes and modified one of the reviews.

In a recent cross-sectional study the authors reported a higher prevalence of disclosed COIs in commentaries, editorials and narrative reviews.[28] This finding, combined with the fact that author bias in educational articles may be less obvious to readers, and our own finding that COI statements do not seem to affect reader perception of such articles, is particularly concerning. Such articles are widely read by clinicians for their summaries of available evidence and clinical care recommendations.[29] Further, our trial used articles on common conditions with relatively uncontroversial treatments, but the role of COIs may be particularly pertinent in articles on the clinical use of novel, potentially expensive, therapeutic agents.

Our findings may be explained by a lower awareness among clinicians that competing interests may influence the conclusions of educational articles, just as they may research articles. Further, educational articles are typically written by highly regarded clinicians who are well known or 'trusted' experts in their field, which may

mean that COIs are considered by readers to be less influential or less important in this context. It is also possible that readers did not consider the COIs to be directly relevant to the topics of the educational articles, and the perceived role of COIs may be context-dependent. COI statements may therefore be more meaningful if they were to specify the relevance of a COI to the subject topic, rather than, as an example, simply stating the existence of a tie with a pharmaceutical company. Alternatively, readers may have considered the included COI statements too mild and not sufficiently alarming to warrant greater scepticism of the review's conclusions. For example, a prior randomised trial has demonstrated that COIs incorporating stocks and shares influenced perceptions of research articles more than COIs involving research grants.[7] We only included a COI for the last of the three listed authors and this may have influenced the magnitude of any effect, but our earlier trial only reported a COI for one of three authors and did find a significant effect.[7] Many readers in this study may also have been familiar with the medical conditions under discussion, and their own clinical practice already in alignment with the review conclusions. We further speculate that levels of trust in the educational reviews used in this study may also have been high due to their dissemination by *The BMJ*, a widely read and recognised UK-based general medical journal. Accordingly, our findings may not be generalisable to articles in smaller/specialty journals. However, the disseminated articles were not portrayed to participants as accepted or published BMJ articles, but rather formatted to mimic manuscript submissions without indication of whether the submission would be published in the journal.

Future research should aim to explore why COI statements in educational articles may not affect reader perceptions. For instance, as publishing COI statements has become standard practice, do readers now no longer pay attention to such statements? Or do they perceive these as unimportant and unlikely to bias an article's conclusions? Further, our research has focused only on financial COIs but it would also be important to evaluate the effect of non-financial or indirect COIs on readers' perceptions, such as unpaid consultancies which may include reimbursements for travel expenses, meals and drinks.[29] Against the backdrop of risk of industry-guided bias in clinical practice, journal editors need to tackle possible reader inattention toward COIs in educational articles. Possible mitigating solutions include policies that exclude authors with relevant COIs from authoring clinical educational articles (as has been adopted by *The BMJ),*[13, 17, 30], or a requirement for such articles to be based on systematic, rather than narrative, reviews. Tackling readers' understanding of COIs in educational articles is also crucial. This may involve emphasising the role of COIs in critical appraisal, as part of the medical curriculum. In addition, given that some form of COI among leadership figures in clinical research is now very common, it is possible that the simple presence of a COI is not sufficient to attract attention. Rather, in addition to reporting COIs, authors or journal editors should consider positioning the COI in relation to the topic of the article so that any context-specific risk of bias is clearer to the reader.

Author contributions

FG initiated the study. SS, JP, JM, MC, FG contributed to the study design, including the wording of the competing interest statements, outcome measures, and sampling strategy. JM estimated the required sample size and carried out the statistical analysis. SS was responsible for running the trial and wrote the first draft of the manuscript with help from JP. SS, JP, JM, MC, FG contributed to the interpretation of the results and the writing of the manuscript.

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Competing interests

SS and FG are employed full time by *The BMJ*; MC was formerly employed by *The BMJ*; JP was a Clegg Scholar at *The BMJ;* and JM is a statistics editor for *The BMJ*. None of the authors work directly for BMJ Open or are involved in the decision-making process for articles submitted to BMJ Open.

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Data sharing statement

The anonymised individual participant data will be shared on reasonable request.

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Table 1: Group allocations and competing interest (COI) statements

Group	Review	COI type	COI statement
1	Dyspepsia	Honoraria & travel	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received honoraria and travel expenses from Jenka Pharmaceuticals for lecturing at a conference.
2	Gout	Advisory board & consultancies	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received fees from Jenka Pharmaceuticals for consultancies and being an advisory board member.
3	Dyspepsia	Research funding	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received research funding from Jenka Pharmaceuticals
4	Dyspepsia	None	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has no competing interests.
5	Gout	Honoraria & travel	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received honoraria and travel expenses from Jenka Pharmaceuticals for lecturing at a conference.
6	Dyspepsia	Advisory board & consultancies	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received fees from Jenka Pharmaceuticals for consultancies and being an advisory board member.
7	Gout	Research funding	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received research funding from Jenka Pharmaceuticals.
8	Gout	None	We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has no competing interests.

Table 2: Baseline characteristics by group of allocation

	Honoraria & travel	Research funding	Advisory board & consultancies	None
Gout review				
N	90	99	91	93
Type				
Consultant	37% (33)	37% (37)	33% (30)	37% (34)
General practice	38% (34)	33% (33)	32% (29)	36% (33)
Junior doctor	26% (23)	29% (29)	35% (32)	28% (26)
Male	49% (44)	46% (46)	44% (40)	45% (42)
Mean age (range)	45.5 (24,72)	44.9 (25,75)	42.9 (24,76)	42.8 (24,67)
Mean years' qualified (range)	20.5 (0,47)	19.7 (0,47)	17.7 (0,45)	18.3 (0,43)
Dyspepsia review				
N	100	96	93	87
Type				
Consultant	31% (31)	36% (35)	33% (31)	38% (33)
General practice	36% (36)	36% (35)	37% (34)	33% (29)
Junior doctor	33% (33)	27% (26)	30% (28)	29% (25)
Male	48% (48)	43% (41)	45% (42)	48% (42)
Mean age (range)	43.5 (23,79)	44.7 (25,75)	42.9 (24,76)	42.8 (24,67)
Mean years' qualified (range)	18.3 (0,54)	19.5 (0,47)	19.4 (0,44)	18.6 (0,39)

Table 3: ANCOVA analysis of the level of confidence, importance and interest in the reviews by intervention group adjusting for age, sex, job type, and years since qualification

	COI Allocation Group, Mean (95% CI)				
	Honoraria and travel	**Research funding**	**Advisory board & consultancies**	**None**	***P* Value**
Gout review					
N	99	93	90	90 [b]	
Primary outcome					
Level of confidence in conclusions drawn[a]	7.1 (6.8-7.5)	7.4 (7.1-7.8)	7.0 (6.7-7.4) [c]	7.4 (7.0-7.8)	.32
Secondary outcomes					
Importance of article[a]	6.9 (6.6-7.3)	6.7 (6.4-7.1)	6.4 (6.1-6.8)	7.0 (6.6-7.4)	.09
Level of interest in article[a]	6.7 (6.5-7.0)	6.5 (6.2-6.9)	6.2 (5.9-6.6)	7.0 (6.7-7.4)	.028 [f]
Dyspepsia review					
N	100	95 [d]	93	87	
Primary outcome					
Level of confidence in conclusions drawn[a]	6.2 (5.8-6.6)	6.1 (5.7-6.5)	6.2 (5.8-6.6) [e]	6.4 (6.0-6.8)	.78
Secondary outcomes					
Importance of article[a]	6.3 (6.0-6.7)	6.3 (5.9-6.7)	6.5 (6.2-6.9)	6.3 (5.9-6.7)	.79
Level of interest in article[a]	5.9 (5.5-6.3)	5.8 (5.4-6.2)	6.0 (5.6-6.4)	5.8 (5.4-6.2)	.83

Abbreviations: ANCOVA, analysis of covariance; COI, conflict of interest.

[a] Outcomes measured on 10-point Likert scales with high scores indicating high levels of confidence, importance, and interest.

[b] One respondent did not give ratings for confidence, importance or interest level, hence data here relates to n=90

[c] One respondent did not give a rating for confidence, hence for this outcome the data relates to n=89

[d] One respondent did not give ratings for confidence, importance or interest level, hence data here relates to n=95

[e] One respondent did not give a rating for confidence or interest, hence for these outcomes the data relates to n=92

[f] Allocation group "none" had a significantly higher level of interest compared with allocation group "advisory board and consultancies" (*P*=.018 with Bonferroni correction).

Table 4: Likelihood to change practice for those currently treating gout/dyspepsia and their own practice differed from the recommendations given in the review

	Allocation group; % (number)				*P* Value
	Honoraria & travel	Research funding	Advisory board & consultancies	None	
Gout review					
N	16	11	17	15	P=0.59 [b]
Likely to change practice [a]	6% (1)	18% (2)	24% (4)	20% (3)	
Dyspepsia review					
N	20	29	19	12	P=0.56 [b]
Likely to change practice [a]	0% (0)	7% (2)	10% (2)	8% (1)	

[a] Respondents who scored 10 ("Extremely likely") on the rating scale of 1 to 10 for likelihood to change practice.
[b] Chi-square test.

Table 5: ANCOVA analysis of the level of confidence in the reviews by intervention group adjusting for age, sex, job type, and years since qualification for subgroups who were currently treating patients with gout or dyspepsia

	Mean (95% CI)				
	Honoraria & travel	Research funding	Advisory board & consultancies	None	*P* Value
Gout review					
N	46	42	43	46	
Level of confidence in conclusions drawn	7.3 (6.8,7.5)	7.7 (7.1, 8.2)	7.0 (6.4,7.5)	7.6 (7.1, 8.1)	P=0.18
Dyspepsia review					
N	48	43	59	56	
Level of confidence in conclusions drawn	6.3 (5.7,6.8)	6.8 (6.2, 7.3)	6.4 (5.9, 6.9)	6.4 (5.9, 6.9)	P=0.64

Table 6: Characteristics of volunteers, completers and non-responders

	Volunteered and completed survey (n=749)	Volunteered but did not complete survey (n=316)	Did not volunteer (n=9824)	*P* Value
Type				
Consultant	35% (264)	36% (114)	33% (3251)	P=0.11[1]
General practice	35% (263)	29% (92)	33% (3269)	
Junior doctor	30% (222)	35% (110)	34% (3304)	
Male	46% (345)	50% (157)	53% (5189)	P=0.001[1]
Mean age (range)	44.0 (23, 79)	41.9 (23, 71)	42.3 (22,84)	P=0.001[2]
Mean years' qualified (range)	19.0 (0, 54)	17.1 (0, 47)	17.5 (0,58)	P=0.003[2]

[1] Chi-square test
[2] ANOVA

Figure legends

Figure 1: Participant flow chart

Appendix 1: Dyspepsia article showing the travel & honoraria COI

Appendix 2: Gout article showing the advisory board & consultancies COI

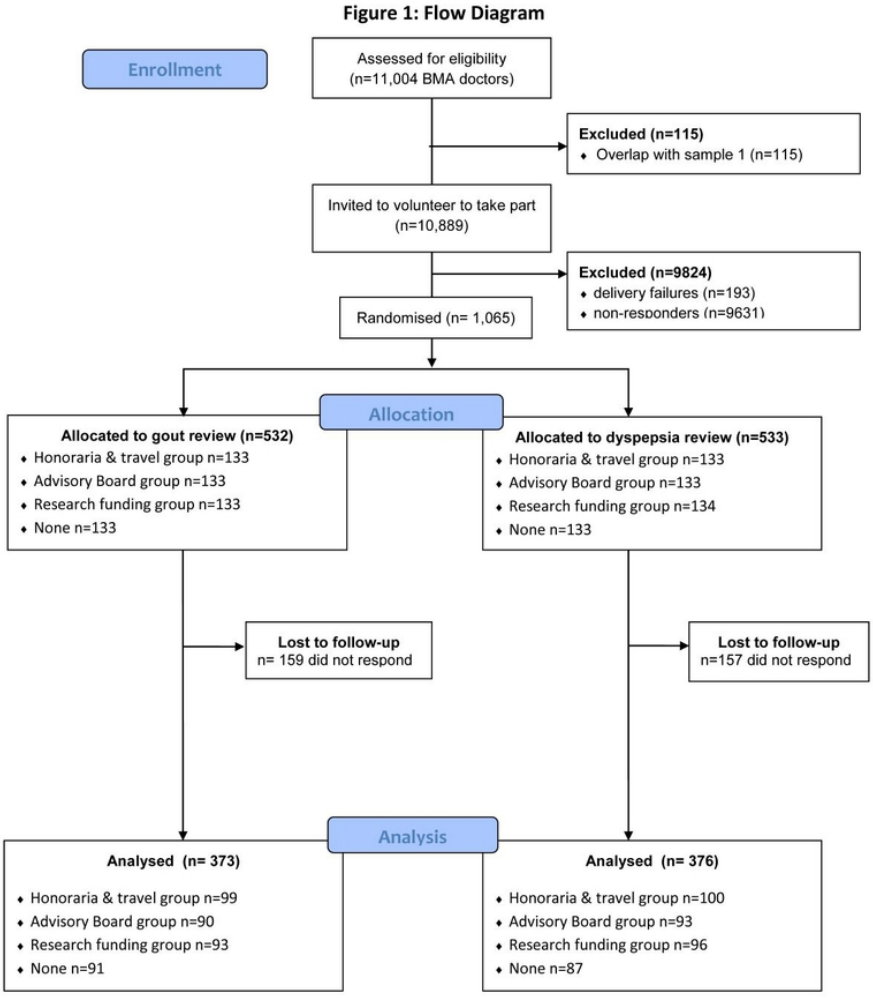

Figure 1 (jpeg)

34x44mm (600 x 600 DPI)

Clinical Review: Management of dyspepsia

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Definitions of the term dyspepsia vary but generally describe pain or discomfort in the epigastric region. People with dyspepsia have a normal life expectancy,[1] but symptoms impair quality of life,[2-3] and affect productivity.[4] In this review we summarise recent evidence, to provide the general reader with an update on how to treat this disorder effectively.

What are the treatment options?

Uninvestigated dyspepsia in primary care or the community

An individual patient data meta-analysis of randomised controlled trials found that—although prompt endoscopy was superior to testing patients with uninvestigated dyspepsia for *H pylori*, and treating with eradication therapy if positive, in terms of symptom control at 12 months—it was not cost effective.[5] However, it is unclear whether a test and treat approach is preferable to empirical acid suppression first line, because a second individual patient data meta-analysis found no significant difference in symptoms or costs between the two.[6] Current guidelines state that either option can be used.[7] If the prevalence of *H pylori* in the population is known, it makes sense to use an acid suppression strategy first if prevalence is low (<10%) and an *H pylori* test and treat strategy if the prevalence is higher.[8] If these strategies are unsuccessful, other options (discussed below) can be considered, or the patient can be referred to secondary care for advice and further investigation if appropriate.

A six month primary care based Dutch trial compared two management strategies for uninvestigated dyspepsia based around empirical acid suppression.[9] One strategy used a step-up approach, starting with antacids, with treatment escalated to H2 antihistamines and then proton pump inhibitors (PPIs) if symptoms remained uncontrolled. The second used a step-down approach, with the drugs given in the reverse order and de-escalated if symptoms improved. Treatment success (adequate relief of symptoms) was similar at six months (72% with step-up*v* 70% with step-down), but costs were significantly lower with the step-up approach. This, together with the small treatment effect in favour of step-up, meant that it came out top in a cost effectiveness analysis.

Another group of primary care patients who may benefit from *H pylori* test and treat are those who do not consult with dyspepsia very often but who require PPIs long term. A trial screened long term PPI users for *H pylori* and randomised those who were positive to eradication therapy or placebo.[10] Eradication therapy significantly reduced symptom scores, PPI prescriptions, consultations for dyspepsia, and dyspepsia related costs. The costs of detection and treatment were less than the money saved after two years of follow-up. Sensitivity analysis showed that the prevalence of *H pylori* would need to be less than 12% before this was no longer cost saving.

It has been estimated that 5% of dyspepsia in the community is attributable to *H pylori*,[11] so population screening and treatment for this organism could theoretically reduce dyspepsia related costs. Results from follow-up studies of people recruited to two large randomised controlled trials of population based screening (and eradication therapy or placebo if *H pylori* positive) in the UK suggest this might be the case, with significantly lower costs and fewer consultations after seven to 10 years.[12-13] However, these studies did not follow up all recruited people successfully, so currently there is insufficient evidence to institute population screening and treatment in the UK.

Peptic ulcer disease

The causal role of *H pylori* in peptic ulcer disease is well established, and patients with *H pylori* positive disease should receive eradication therapy. A Cochrane review found that the number needed to treat (NNT) with eradication therapy to prevent one duodenal ulcer relapse (26 placebo controlled trials) was 2 and for gastric ulcer (nine trials) the number was 3.[14] Although there was significant heterogeneity between studies in both analyses, all but one trial showed a significant benefit with eradication therapy. PPI triple therapy (a PPI plus two antibiotics (clarithromycin with amoxicillin or metronidazole)) should be used in areas like the UK where clarithromycin resistance is less than 10%, with bismuth quadruple therapy (bismuth plus a PPI and two antibiotics) being given where resistance is higher.[15] Most cases of *H pylori* negative peptic ulcer disease are caused by NSAIDs, and trials show that PPIs are superior to H2 antihistamines for ulcer healing in this

situation.[16-17] *H pylori* negative, NSAID negative peptic ulcer disease is rare and probably requires long term PPI treatment.

Functional dyspepsia

Diet and lifestyle

Food diaries from a small study of 29 patients suggest that people with functional dyspepsia eat fewer meals and consume less energy and fat than healthy controls,[18] but whether this is a cause or a consequence of symptoms is unclear. Although the prevalence of undiagnosed coeliac disease is higher in people with symptoms of irritable bowel syndrome,[19] this is not the case in dyspepsia.[20] It is also unclear whether non-coeliac gluten sensitivity is involved in symptom generation in some patients with functional dyspepsia. Doctors often advise people with dyspepsia to lose weight, avoid fatty food and alcohol, or stop smoking, but there is little evidence that these measures improve symptoms.[21] As a result, drugs are the mainstay of treatment.

Acid suppression therapy

Antacids neutralise gastric acid, the production of which is controlled by gastrin, histamine, and acetylcholine receptors. Once stimulated, these receptors activate proton pumps in the parietal cell. H2 antihistamines and PPIs reduce acid production by blocking H2 receptors or the proton pump, respectively. Because PPIs act on the proton pump itself, these drugs lead to more profound acid suppression than H2 antihistamines or antacids. A Cochrane review has studied the efficacy of acid suppressants in functional dyspepsia.[22] One placebo controlled trial of antacids showed no benefit. Twelve randomised controlled trials of H2 antihistamines versus placebo found that these drugs were effective for the treatment of functional dyspepsia (NNT=7). However, there was significant heterogeneity between studies, which was not explained by sensitivity analysis, and evidence of funnel plot asymmetry, suggesting publication bias or other small study effects. Their efficacy may therefore have been overestimated. Ten trials studied PPIs. Again, there was a significant benefit over placebo, although this was modest (NNT=10). There was significant heterogeneity between studies, with no obvious explanation, but no funnel plot asymmetry. A subgroup analysis conducted according to predominant symptom showed that PPIs were most beneficial in patients with reflux-type symptoms and more effective than placebo in patients with epigastric pain. However, they were no more effective than placebo in those with dysmotility-like functional dyspepsia.[23] Most trials used PPIs for four to eight weeks. This seems a reasonable duration, especially as concerns have been raised recently about the safety of long term PPI use. Observational studies suggest that hip fracture, community acquired pneumonia, and *Clostridium difficile* infection are more common in PPI users,[24-25] although all these associations were extremely modest, and direct causation cannot be assumed from studies such as these.

H pylori eradication therapy

The benefit of eradication therapy is less pronounced in functional dyspepsia than in peptic ulcer disease, but treatment is still more effective than placebo. In a Cochrane review of 21 placebo controlled trials the NNT for improvement in symptoms after eradicating *H pylori* was 14, with no heterogeneity between studies and no evidence of funnel plot asymmetry.[26]

Footnotes

Contributors: All authors conceived and designed the article, drafted the manuscript, and approved the final version. JB is guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received honoraria and travel expenses from Jenka Pharmaceuticals for lecturing at a conference.

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Clinical Review: Management of gout

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Gout is the most common inflammatory arthritis, affecting 1-2% of the population. The major risk factor is a raised serum urate concentration (hyperuricaemia), which results in the deposition of monosodium urate crystals in and around joints. Untreated, continuing crystal deposition can result in irreversible joint damage. Although effective treatments are available for acute and chronic gout, uptake is poor, and many patients experience repeated acute attacks and reduced quality of life. This clinical review summarises current evidence for the management of acute and chronic gout.

How are acute attacks of gout treated?

Treatment of acute gout aims to provide rapid relief of joint pain and swelling. First line oral drugs are usually non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine.[1] There is no evidence that any one NSAID is more effective than another. A systematic review commented on the poor quality of existing NSAID trials in acute gout, with the exception of two moderately sized RCTs, which found an equivalent effect of indometacin 50 mg three times daily and etoricoxib 120 mg daily on pain.[2-4] More recently, two well conducted trials have found indometacin (50 mg three times daily for two days, then 25 mg three times daily for three days) and naproxen 500 mg twice daily to be as effective as oral prednisolone.[5-6] Indometacin was associated with more gastrointestinal adverse events, however, and is best avoided.[5]

British Society for Rheumatology and American College of Rheumatology guidelines suggest using a fast acting NSAID, such as naproxen, at full dose. Caution is needed, however, in people with heart failure, ischaemic heart disease, renal insufficiency, or a history of gastrointestinal ulcers, bleeds, or perforations.[7-8] Continue treatment until the attack has resolved (typically a few days to two weeks).

Colchicine is a naturally occurring alkaloid that inhibits leucocytic phagocytosis of monosodium urate crystals, the inflammasome, and cell mediated immune responses. It has traditionally been used in high doses (1 mg initially, followed by 500 µg every two to three hours until pain relief is obtained). Although a small trial showed the effectiveness of high dose regimens over placebo, all participants randomised to receive colchicine developed diarrhoea or vomiting (or both).[9] Lower doses of colchicine are as effective and better tolerated than high dose regimens.

A recent well conducted moderately sized RCT found at least a 50% reduction in pain within 24 hours in 33% of participants treated with high dose colchicine (1.2 mg initially and then 600 µg hourly for six hours). There was also a 38% reduction in those treated with low dose colchicine (1.2 mg initially, followed by 600 µg after one hour) and a 16% reduction in those receiving placebo.[10] Diarrhoea affected 77% of the high dose group, 23% of the low dose group, and 14% receiving placebo. The *British National Formulary* recommends 500 µg two to four times daily.[11] Although no head to head comparison between colchicine and a NSAID exists, oral NSAIDs are generally considered to be the first line treatment for acute gout, with colchicine reserved for those with contraindications to, or intolerance of, NSAIDs.[7] Several drugs can increase the risk of colchicine toxicity.

Corticosteroids provide a further treatment option. Although there are no RCTs,[12] expert consensus agrees that joint aspiration and intra-articular injection of corticosteroids is a rapid and highly effective treatment for acute gout.[1,7] The diagnosis can be confirmed by microscopy of aspirated fluid, and such treatment is probably best practice in a hospital setting. However, the necessary skills to perform aspiration and injection might not be present in all settings, particularly primary care. Intramuscular or oral corticosteroids provide a useful option, particularly when there are contraindications to NSAIDs and colchicine and more than one joint is affected or joint injection is not possible.[1,8] Two high quality RCTs found that oral prednisolone at doses of 30-35 mg daily for five days are as effective as NSAIDs.[5-6]

Rest and cooling of the joint are also effective for acute gout. A small RCT found that the application of topical ice in combination with oral prednisolone and colchicine reduces pain more effectively than combined prednisolone and colchicine alone.[13]

What does non-drug based management of gout consist of?

Non-drug based management consists of risk factor modification, including lifestyle factors. Dietary modification comprises restriction of, but not total abstinence from, purine-rich foods (including red meat and seafood) and alcohol (particularly beer).[1,7] Weight loss is recommended if appropriate. Uncontrolled intervention studies have confirmed modest effects of weight loss and low purine diet on urate lowering and frequency of attacks.[14-15]

How and when should urate lowering drugs be used?

There is debate about the indications for urate lowering therapy. Expert consensus advocates offering such drugs to patients with recurrent acute gout, tophi, radiographic damage, renal insufficiency, or uric acid urolithiasis.[1,7] The precise threshold at which recurrence of acute attacks warrants treatment is controversial. Opinions vary from starting these drugs after the first attack, when the crystal load is small and substantial joint damage has not yet occurred, to waiting until two or more attacks have occurred over 12 months. Urate lowering therapy is usually started two to four weeks after resolution of an acute attack to reduce the risk of the drug exacerbating the attack. However, one RCT of 51 patients found no difference in pain between those started on allopurinol during an attack and those given placebo.[16] Delaying initiation of allopurinol also allows a rational discussion about treatment when the patient is no longer in pain. When fully informed about urate lowering therapy, most people wish to receive it, and subsequent adherence can be excellent.[17]

The most commonly used drug is allopurinol—a purine, non-specific xanthine oxidase inhibitor. Allopurinol should be started at low dose (usually 100 mg daily) and increased in 100 mg increments monthly until serum uric acid is below 360 µmol/L. Two small observational studies reported that the effect on cessation of acute attacks, resolution of tophi, and reduction of crystal load is greatest if uric acid is reduced below this value.[18-19] Some expert consensus groups recommend reducing uric acid further, to below 300 µmol/L,[7] at least for the first one to two years of treatment, because this speeds up the rate of crystal elimination and tophus reduction.[20]

The maximum permitted dose of allopurinol in the UK is 900 mg per day. Although such doses are rarely needed, many patients need doses of 400-500 mg daily to reduce uric acid.[17] During the dose escalation phase, measure full blood count, renal function, liver function, and serum uric acid monthly. The active metabolite of allopurinol (oxypurinol) is excreted through the kidney, so lower doses and more cautious upward titration are recommended in people with renal failure because of the risk of the rare but potentially life threatening allopurinol hypersensitivity syndrome, which involves severe skin reactions and hepatic and renal dysfunction.[21-22] Clinical risk factors for allopurinol hypersensitivity syndrome include renal failure, diuretic use, and higher allopurinol dose at initiation.[21-22]

Ninety per cent of people tolerate allopurinol without problems. As with all urate lowering drugs, patients may experience an acute attack of gout when they start allopurinol because it encourages crystal shedding through partial crystal dissolution. Although the likelihood of this is reduced by gradual dose escalation, prophylactic low dose colchicine or an NSAID can be coprescribed for up to six months until a stable dose is reached. One small placebo controlled RCT showed fewer gout flares when allopurinol was coprescribed with colchicine 600 µg twice daily.[23] Allopurinol should not be discontinued if an acute attack occurs. The main alternative to allopurinol is the specific non-purine xanthine oxidase inhibitor, febuxostat.

Urate lowering therapy in patients who cannot tolerate or have contraindications to allopurinol (or alternatives) is challenging. Options include uricosuric drugs such as sulfinpyrazone, probenecid, and benzbromarone, but these have limited availability. Such patients are best referred to a rheumatologist for specialist care.

Treatment is life long. Once a stable target serum urate concentration has been achieved, measurements must be repeated about every six months to ensure the therapeutic target is being maintained.

Footnotes

Contributors: All authors conceived and designed the article, drafted the manuscript, and approved the final version. JB is guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following: DF is funded by a NIH clinician scientist award; SN receives no specific funding; JB has received fees from Jenka Pharmaceuticals for consultancies and being an advisory board member.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 3,4,5,6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-11 &Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12 & Table 5
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13-14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.