Comparison of meloxicam and a glucosamine-chondroitin supplement in management of feline osteoarthritis

A double-blind randomised, placebo-controlled, prospective trial

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Keywords
Feline, osteoarthritis, glucosamine, chondroitin, meloxicam

Summary
Objective: To compare the efficacy of meloxicam and a glucosamine-chondroitin (Glu-Ch) supplement in the management of feline osteoarthritis (OA).

Methods: Prospective, blinded, randomized clinical trial. Cats over eight years of age with clinical signs of chronic OA were assigned to one of two groups and Glu-Ch or meloxicam was administered orally for 70 days, followed by a placebo until day 98. Cats were assessed by a veterinarian on five occasions and the owner completed an assessment form at the same time.

Results: Data were collected from thirty cats. Pre-treatment disease scores were significantly higher in the meloxicam group for owner mobility (p = 0.01) and veterinary lameness (p = 0.02). Owner mobility scores at day 14 (p = 0.01) and day 42 (p = 0.002) were significantly improved compared to pre-treatment scores for the meloxicam group. When meloxicam and Glu-Ch were discontinued and the placebo commenced, a significant proportion of the meloxicam group showed worsening of all the owner-assessed scores between day 70 and day 98, when compared to the Glu-Ch group (mobility p = 0.01; activity p = 0.02; temperament p = 0.04; lifestyle p = 0.01).

Conclusions: Treatment with meloxicam resulted in a significant improvement in mobility and activity levels of cats with OA until the placebo was introduced. A greater proportion of cats receiving meloxicam medication showed a significant worsening of owner assessment scores once the placebo was introduced, when compared to the Glu-Ch group.

Introduction
Osteoarthritis is a very important and common clinical disease in the older cat (1–4). It is now accepted that joint pain in the cat is seldom associated with overt lameness. Changes in the cat’s usual behaviour, lifestyle, or both should alert the clinician that the animal may be suffering arthritic pain (1, 5). However these changes are often construed as being the effects of old age rather than as indicators of chronic pain. These behavioural alterations include changes in mobility (e.g. reduced frequency of jumping, stiffness), changes in activity levels (e.g. sleeping and resting more), changes in grooming (e.g. unkempt coat, reduced grooming), and changes in temperament (e.g. reduced tolerance of owner and other animals, less keen to interact, changes in general attitude or demeanour) (1, 2, 5).

Most cases of osteoarthritis in the cat appear to be of the primary or idiopathic type because there is generally no obvious underlying cause of arthritis which can be readily identified (4). Secondary osteoarthritis in the cat is most often associated with previous joint trauma, although osteoarthritis secondary to hip dysplasia and acromegaly is also recognised in the cat (3, 4, 6).

The presence of osteophytes is the key radiographic feature of feline osteoarthritis although these signs can sometimes be difficult to identify (3, 4). Soft tissue mineralisation and intra-articular mineralised
bodies are common features, whilst soft tissue thickening and synovial effusion are less apparent in feline osteoarthritis (7). Increased bone radio-opacity is a feature of feline osteoarthritis and although the assessment of this feature in arthritic joints is very subjective, it is more easily appreciated in the cat than the dog (4).

A detailed history is essential for diagnosis of osteoarthritis and this has to be based on changes in mobility, activity, grooming patterns and temperament (1). Non-steroidal anti-inflammatory drugs, matrix supplements (glucosamine and chondroitin), essential fatty acids, environmental modifications and weight control are all part of osteoarthritis management (8).

Non-steroidal anti-inflammatory drugs are commonly used to treat both the initial (acute) and the later (chronic) manifestations of feline osteoarthritis (9, 10). Non-steroidal anti-inflammatory drugs have anti-inflammatory, antipyretic and analgesic activity and inhibit platelet aggregation and their efficacy has been documented in the cat (1, 5, 9–13). Bennett and co-workers reported a significant improvement in behaviour and lifestyle changes after administration of meloxicam to cats with chronic musculoskeletal pain (1). Lascelles and colleagues reported a significant improvement in demeanour, feed intake, weight bearing, and a significant reduction in lameness, signs of pain on palpation and inflammation in cats with locomotor disorders (10). However, prolonged use of these drugs can be associated with complications including gastric ulceration, renal toxicity and prolonged bleeding times (14–16). As a result there is considerable interest in finding new alternative analgesic and anti-inflammatory compounds with a high safety index in the cat; this goal has extra significance because meloxicam a is the only non-steroidal anti-inflammatory drug presently licensed for long-term use in cats in Europe and the United Kingdom.

Both glucosamine and chondroitin sulphate are involved in the metabolism of cartilage matrix proteins and are widely used to treat osteoarthritis in humans despite conflicting clinical trial results (17–29). While several trials have suggested that glucosamine has no effect compared with placebo, others report robust efficacy (20, 21, 23, 25, 29–32). Many reasons have been offered to explain the different conclusions. They include superiority of different preparations of the ingredient, industry bias, insensitive assessment metrics and poor methodology (28, 33). There is one study showing glucosamine-chondroitin to be effective in canine osteoarthritis (34). To our knowledge no studies have been done to assess the effect of glucosamine-chondroitin in treating feline osteoarthritis.

The purpose of this double-blind randomized, placebo-controlled, prospective trial was to compare the efficacy of meloxicam a and a glucosamine-chondroitin supplement b, in the management of feline osteoarthritis. The study was designed to test the hypothesis that a supplement of glucosamine and chondroitin is as good as meloxicam in improving mobility and activity levels in osteoarthritic cats.

Materials and methods

This study was approved by the Glasgow University Ethics Committee (in compliance with the EU-Convention on the protection of animals revised directive 86/609/EEC).

All clients signed a consent form (►Appendix 1– available online at www.vcot-online.com) after being fully informed about the study and the associated risks with participation. Client-owned cats were recruited from 16 veterinary practices across the UK. The animals were later randomised by tossing a coin and allocating them to one of the groups by one of the authors (DC) who was not involved in the assessment of the cats or the analysis of the data.

Before enrolment, haematology and serum biochemistry analyses including estimation of serum, total protein, albumin, urea, creatinine, alkaline phosphatase (ALP), alanine transaminase (ALT), bilirubin, sodium, potassium, chloride, calcium, phosphate, and total T4 were performed in all cats.

Inclusion criteria

All of the following criteria had to be met to be considered for inclusion in the study:

- Cats over eight years of age, of any sex or breed, and with a history and clinical signs of osteoarthritis.
- Evidence of joint pain or swelling, reduced joint range of movement or lameness on clinical evaluation.
- Completion of an owner questionnaire.
- Behavioural or lifestyle changes compatible with chronic pain, for at least one month.
- Only one cat per household was allowed.

Exclusion criteria

If any of the following were present, then the animals were excluded:

- Animals with lameness caused by diseases other than osteoarthritis such as infectious, immune-mediated, neurological or neoplastic disease.
- Animals which were pregnant or lactating.
- Animals with hepatic, renal or cardiovascular disease.
- Animals where the treatment would be contraindicated as indicated in the medication datasheet.
- Animals that had been treated with any drug, nutraceutical or dietary supplement for osteoarthritis in the two weeks prior to entering the trial.
- Animals with systemic illness.

Protocol

Cats were assigned randomly to one of two groups – glucosamine-chondroitin or meloxicam. Glucosamine-chondroitin or meloxicam was administered accordingly for the first 70 days. Treatments were administered according to the manufacturer’s instructions. One capsule of the glucosamine-chondroitin supplement – glucosamine 225 mg; chondroitin sulphate 175 mg; N acetyl glucosamine 25 mg; ascorbic

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a TN Metacam: Boehringer Ingelheim Vetmedica GmbH, Ingelheim/Rhein, Germany
b Glucosamine-chondroitin supplement, Synoquin Cat: VetPlus Ltd, Lytham, UK
acid 25 mg; zinc sulphate 15 mg) twice daily for six weeks, followed by one capsule once daily thereafter. Meloxicam was given at a dose of 0.1 mg per Kg of body weight on day one followed by 0.05 mg per Kg of bodyweight thereafter. The medication was stopped in both groups on day 70 and an oral placebo was administered until day 98. All compounds – meloxicam, glucosamine-chondroitin, and placebo – were removed from their original package. Meloxicam and glucosamine-chondroitin were re-labelled ‘Medication X’ and the placebo ‘Medication Y’ and then delivered by the postal system directly to the owners, asking them to administer ‘Medication X’ until day 70, followed by ‘Medication Y’ from day 70 to day 98. The placebo had the same frequency of administration and formulation as the treatment drug; liquid for meloxicam and capsule for glucosamine-chondroitin. Each owner was aware that their animal was enrolled in a study in which two different osteoarthritic management protocols would be used, one a prescription medicine and the other a joint supplement. Consent was obtained to enrol the animals in a study comparing the two types of management protocols. The owners were not informed of the existence of a placebo and were directly asked to conceal information from the veterinarian regarding the nature of the compounds and the frequency of administration, in an attempt to ensure the study was double blind. The veterinarian was aware that a placebo may be used in the trial but was unaware of when this would be initiated. Rescue therapy consisted of orally administered buprenorphine. Cats were assessed by the veterinarian at the beginning of the trial (day 0) and a veterinary assessment form was completed (Appendix 2 – available online at www.vcot-online.com). This assessment was repeated at each assessment point throughout the trial (day 14, day 42, day 70 and day 98). The owner also completed five owner assessment questionnaires (Appendices 3 and 4 – available online at www.vcot-online.com) at the same assessment points, but separately from the veterinarian. Owners were asked to assess and grade changes in four behavioural domains (mobility levels, activity levels, grooming habits, demeanour) and, in addition, to provide an overall assessment of these changes. If there was any major change in body weight during the trial the cat was to be removed from the study. A compliance check was performed at each visit by a veterinary nurse confirming the amount of medication left was correct. Poor compliance would again lead to withdrawal from the trial; this was addressed by the trial coordinators on a case per case basis. If there was any clinical deterioration during the trial requiring additional treatment, this would be implemented by the veterinarian and the cat removed from the study. If any adverse reaction was suspected or occurred, the treatment would be stopped and the animal removed from the trial. A summary of the study protocol is shown in Appendix (available online at www.vcot-online.com).

Sample size calculation

Assuming that almost all (>97%) cats improve to some extent on either treatment and that a 10% reduction in success would be clinically noticeable, a total of 50 cats would provide 80% power to reject the null hypothesis that the percentage of cats responding well on the standard treatment is more than 10% better than the percentage doing well on the alternative treatment.

Statistical analysis

All data distributions were tested for normality and equality of variances if appropriate. Student T-tests, Mann-Whitney tests or Chi-squared tests were used to identify differences in treatment group age, weight and gender at the start of the study. Student T-tests and Mann-Whitney tests were used to identify differences between treatment group owner and veterinarian scores before the start of the treatment protocols. Mann-Whitney tests were used to identify differences in scores, at different stages of the study, within and between the two treatment groups. A p-value of less than 0.05 was considered significant.

Results

Forty-seven cats from 16 veterinary practices across the United Kingdom were enrolled in the trial. One practice contributed seven cases, four practices five cases, two had three cases, five had two cases and four practices provided a single case each. Nine cats were rejected after the initial assessment when the haematology and biochemistry results became available; eight due to azotaemia and one due to hyperthyroidism. Eight cats were withdrawn during the trial, one due to vomiting (day 42, glucosamine-chondroitin group), five due to poor owner compliance (two from the glucosamine-chondroitin group at day 14, and three from the meloxicam group at days 14, 14 and 42), one due to worsening of musculoskeletal pain (glucosamine-chondroitin group, day 42) and one due to the diagnosis of neoplasia (glucosamine-chondroitin, day 98).

Data from 30 cats (meloxicam n = 17; glucosamine-chondroitin n = 13) were analysed (Table 1). These cats comprised fourteen neutered males, fourteen neutered females, and two entire females. Twenty-two cats were Domestic Shorthaired cats, the remaining eight included six pure breeds (Table 1).

The variables of age, weight, breed and gender were not found to be significantly different between the groups.

The pre-treatment scores (veterinary and owner assessments) of the 30 cats com-

<table>
<thead>
<tr>
<th>Gender</th>
<th>Weight (median)</th>
<th>Age (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>5.1 Kg</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>4.5 Kg</td>
</tr>
</tbody>
</table>

Glu/Ch = glucosamine-chondroitin

Table 1
Details of sex, age and body weight in the two groups.

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pleting the trial are presented in ▶ Table 2. Owner mobility scores (p = 0.01) and veterinarian lameness scores (p = 0.02) were significantly higher (indicating more severe clinical disease) in the meloxicam group compared to the glucosamine-chondroitin group (▶ Table 2), even though the groups had been randomized (▶ Table 2).

Cats in the meloxicam treatment group showed improvement in most of the owner assessment scores until day 70, when the drug was stopped and the placebo initiated. Owner mobility scores at day 14 (p = 0.01) and day 42 (p = 0.002) were significantly improved compared to pre-treatment scores for the meloxicam group although improvements in the other parameters were not significant. There were not any significant improvements in any of the parameters for the glucosamine-chondroitin group (▶ Figure 1, ▶ Figure 2, ▶ Table 3).

There were not any significant differences in the veterinary assessment scores for any parameter, at any time point in any of the two groups (▶ Figure 3).

After day 70, when the administration of meloxicam or glucosamine-chondroitin were discontinued and the placebo initiated, a high proportion of the meloxicam group showed worsening of all the owner-assessed parameters (▶ Table 4). The change in mobility (p = 0.01), activity (p = 0.02), temperament (p = 0.04), and lifestyle (p = 0.01) scores between 70 day and 98 day assessments were all significantly worse for the meloxicam group.

Discussion

The present study was designed to compare the efficacy of meloxicam and glucosamine-chondroitin in the treatment of feline osteoarthritis. Improvement in owner-assessed mobility scores between pre-treatment and assessments one (p = 0.01) and two (p = 0.02) were significant for the meloxicam group. These findings are not surprising because of the proven anti-inflammatory and analgesic effects of non-steroidal anti-inflammatory drugs. Meloxicam is a common drug used in the management of osteoarthritis in cats and its efficacy has been previously documented (9, 10, 35, 36).

Individual cats receiving the glucosamine-chondroitin supplement also appeared to improve during the first 70 days although to a lesser extent and this improvement was not significant. This may be explained by insufficient case numbers, although it may purely be the result of a placebo effect or even by the natural fluctuation in clinical signs typical of osteoarthritis. Unfortunately a specific control/placebo population could not be used in this study because of ethical concerns. Our study involved client-owned cases in a general practice environment, where a veterinary diagnosis of musculoskeletal pain had been made. It was therefore considered unethical to use a placebo from the start and hence the reason for adopting the study design described here.

The clinical deterioration detected in the meloxicam group after day 70 could be explained by the sudden cessation of analgesia or the anti-inflammatory effect. In contrast the glucosamine-chondroitin group maintained an improvement and in some cases improved further according to the owners’ assessment scores after the supplement was stopped and the placebo initiated (▶ Table 4).

Owner mobility assessment on day 98 was worse in 64.3% of the meloxicam treated group when compared with the scores for day 70. In comparison, only 27.3% cats of the glucosamine-chondroitin

<table>
<thead>
<tr>
<th>Parameters</th>
<th>p-value</th>
<th>Meloxicam (median)</th>
<th>Glu/Ch (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Owner (1–10)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td>0.01</td>
<td>5.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Activity*</td>
<td>0.25</td>
<td>5.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Temperament</td>
<td>0.50</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Grooming</td>
<td>0.50</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Lifestyle*</td>
<td>0.15</td>
<td>5.3</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Veterinarian (1–5)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lameness</td>
<td>0.02</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Joint Mobility (ROM)</td>
<td>1.00</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>0.23</td>
<td>3.5</td>
<td>3.0</td>
</tr>
</tbody>
</table>

* = T-test, otherwise Mann-Whitney Test; ROM = range-of-motion; Glu/Ch = glucosamine-chondroitin; Owner: 1 = minimally affected, 10 = severely affected; Veterinarian: 1 = minimally affected, 5 = severely affected.

Figure 1
Box and whisker plots showing range, median, and the upper and lower quartiles for owner assessment of mobility for both groups. Glu/Ch = glucosamine-chondroitin. Asterisks represent outliers.
group had deteriorated during this period. For owner activity assessment, more than half the cats (57.1%) in the meloxicam group deteriorated compared to 18.2% in the glucosamine-chondroitin group and for temperament, 38% deteriorated in the meloxicam group and only 9.1% in the glucosamine-chondroitin group. When the owners were asked to assess the overall lifestyle of the cat, 61% of the cats had deteriorated in the meloxicam group but only 10% in the glucosamine-chondroitin group. The differences in owner assessment scores between the two groups were significant for the mobility, activity, temperament and lifestyle domains. No significant differences were recorded in any of the veterinary assessments (lameness, joint range of movement and joint pain) during this period. The apparent continued improvement in the glucosamine-chondroitin group after day 70 is difficult to explain. It could be the result of a continued placebo effect, where the glucosamine-chondroitin was never having any real positive effect. However it might be explained by the glucosamine-chondroitin having a prolonged anti-inflammatory effect, as suggested previously in dogs where improvement in disease scores was maintained for up to one month after cessation of treatment (34). Panchaphanpong et al. showed that glycosaminoglycan plasma concentrations were significantly increased by day 21 following the oral administration of glucosamine to normal cats and cats with idiopathic cystitis when compared to a placebo group (37). Twenty-eight days after cessation of therapy, glycosaminoglycans plasma concentrations were reduced but still above baseline levels and higher than values on day seven which could explain why a prolonged beneficial effect may be seen. Admittedly, these were plasma concentrations which may not reflect joint concentrations.

Table 3  Number of cats that improved during the trial in comparison to the day zero assessment.

<table>
<thead>
<tr>
<th>Assessment days compared:</th>
<th>Meloxicam</th>
<th></th>
<th>Glucosamine-Chondroitin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 and 14</td>
<td>0 and 42</td>
<td>0 and 70</td>
</tr>
<tr>
<td>Owner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td>13/16</td>
<td>15/17</td>
<td>11/15</td>
</tr>
<tr>
<td>Activity</td>
<td>13/16</td>
<td>12/17</td>
<td>11/15</td>
</tr>
<tr>
<td>Veterinarian</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lameness</td>
<td>6/16</td>
<td>13/17</td>
<td>10/16</td>
</tr>
<tr>
<td>Joint Mobility (ROM)</td>
<td>4/16</td>
<td>8/17</td>
<td>9/16</td>
</tr>
<tr>
<td>Pain</td>
<td>12/16</td>
<td>14/17</td>
<td>12/16</td>
</tr>
</tbody>
</table>

ROM = range-of-motion.
the entire trial when comparing the groups, suggesting veterinary assessment alone may not be sensitive enough in monitoring osteoarthritis in cats. A one-point assessment by the veterinarian in an unfamiliar environment for the cat may be insufficient to detect changes. Owner assessment of parameters such as animal mobility, activity, temperament and grooming habits in the cat’s natural environment (client specific outcome measures) is likely to be more accurate in diagnosing and managing response to treatment in feline osteoarthritis than physical examination on its own (1–5). It is apparent that when directed by their veterinarian, owners are able to detect changes in their cat’s behaviour and lifestyle (1, 5, 38). Bennett and Morton concluded that the greatest changes were observed in the activity domain, followed by mobility, but in our study mobility was the only domain where a significant difference was observed in the first 70 days (and only for the meloxicam group) (1). It is true that there are no fully validated objective or subjective assessment protocols for evaluating pain associated with osteoarthritis in cats and therefore we cannot completely assume the reliability of owner assessments, as used in our study (1, 5, 39).

Radiography would have been helpful in this study to consolidate the diagnosis of osteoarthritis and exclude other sources of chronic pain but it would have slowed down the recruitment of cases. Many veterinarians are reluctant to anaesthetise or even sedate older cats for radiography. The prevalence of radiographic disease is very high in older cats but the radiographic presence of osteoarthritis does not necessarily equate with clinical disease (3, 4, 40). Radiographically normal joints can be pathologically and clinically affected, and radiographically affected joints can be pain free (2, 41–43). Nevertheless it is possible some of the cats in this study were suffering musculoskeletal pain other than from osteoarthritis (such as spondylosis) or other painful conditions (such as dental disease) (44).

The lack of objective assessments such as ground reaction forces and accelerometers, low patient numbers and no early placebo control population are obvious limitations of this study (45, 46). The lack of an early placebo control was addressed by the introduction of a ‘placebo period’ between days 70 and 98. The differences in pre-treatment scores, where the meloxicam group had a higher disease score, could have led to reduced sensitivity in recognising improvements in the glucosamine-chondroitin group where the disease severity appeared less. It has been suggested that inclusion of patients with low baseline pain may contribute to unsatisfactory treatment outcome (33). However it may also indicate that more meloxicam-treated cats were close to end-stage osteoarthritic disease and potentially less responsive to therapy. The drop-out rate in this study was high (21%) and because of this and the fact that nine cats were excluded after the initial blood tests, we did not achieve our desired number of fifty cats. This means the study is underpowered, thereby reducing our ability to reject the null hypothesis and this could have influenced our results and conclusions.

The glucosamine-chondroitin supplement used in our study contained other ingredients besides glucosamine and chondroitin and thus it cannot be concluded that any possible improvement attributable to the supplement was due to either of these; vitamin C for example is an anti-oxidant which could reduce articular inflammation and pain.

### Table 4
Number of cats showing deterioration and improvement during the placebo period (Assessment 45).

<table>
<thead>
<tr>
<th></th>
<th>Deteriorated</th>
<th>Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Meloxicam</td>
<td>Glu/Ch</td>
</tr>
<tr>
<td><strong>Owner</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td>9/14</td>
<td>3/11</td>
</tr>
<tr>
<td>Activity</td>
<td>8/14</td>
<td>2/11</td>
</tr>
<tr>
<td>Temperament</td>
<td>5/13</td>
<td>1/11</td>
</tr>
<tr>
<td>Grooming</td>
<td>4/12</td>
<td>0/10</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>8/13</td>
<td>1/10</td>
</tr>
<tr>
<td><strong>Veterinarian</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lameness</td>
<td>5/15</td>
<td>1/12</td>
</tr>
<tr>
<td>Joint mobility (ROM)</td>
<td>3/15</td>
<td>2/12</td>
</tr>
<tr>
<td>Joint pain</td>
<td>9/15</td>
<td>4/12</td>
</tr>
</tbody>
</table>

Glu/Ch = glucosamine-chondroitin; ROM = range-of-motion.

### Conclusion

Our hypothesis was not proven and improvements in owner-assessed parameters (particularly mobility and activity) were significantly greater for the meloxicam group until day 70. The owner questionnaire, based on behavioural and lifestyle changes, is a useful way of monitoring osteoarthritis in feline patients. The significance of the trend where some cats showed maintenance of improvement in owner assessment scores for the glucosamine-chondroitin group once treatment had been stopped is uncertain but is a finding worthy of further investigation.

### Acknowledgements

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### Conflict of interest

None of the authors has any conflict of interest to report.
References


