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Randomized Controlled Trials Studying Nonoperative Treatments of Osteoarthritis Often Use Misleading and Uninformative Control Groups: A Systematic Review

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Abstract

Background Because there are no known treatments that alter the natural course of the pathophysiology of osteoarthritis, nonoperative treatment needs to be compared with known effective treatments that seek to mitigate symptoms or with similarly invasive inert (placebo) treatments to determine effectiveness. Comparing a treatment to an uninformative control group may inappropriately legitimize and support the use of potentially ineffective treatments. We therefore investigated the prevalence of inappropriate control groups in musculoskeletal research and asked whether these are associated with reporting a positive treatment effect.

Questions/purposes We systematically reviewed randomized trials of nonoperative treatments of osteoarthritis and asked: (1) What proportion of randomized trials use uninformative control groups (defined as a treatment less invasive than the tested treatment, or a treatment that might possibly not outperform placebo but is not acknowledged as such)? (2) Is the use of uninformative control groups independently associated with reporting a positive treatment effect (defined as $p < 0.05$ in favor of the intervention, or as making a recommendation favoring the intervention over the control treatment)?

Methods In a systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we searched PubMed, Cochrane, and Embase up to September 2023 for randomized controlled trials published between 2020 to 2022 that compared one or more nonoperative treatments for the symptoms of osteoarthritis. We excluded studies that contained a surgical treatment group. We identified 103 trials that met eligibility criteria, with a total of 15,491 patients. The risk of bias was high in 60% (n = 62) of trials using the Cochrane Risk of Bias Tool, version 2. Although the high risk of bias in the included studies is concerning, it does not invalidate our design; instead, it highlights that some studies may use flawed methods to recommend treatments with unproven effectiveness beyond nonspecific effects because the kinds of bias observed would tend to increase the apparent benefit of the treatment(s) being evaluated. We used logistic regression to test the association of uninformative control groups with a positive treatment effect, accounting for potential confounders such as conflict of interest and study bias using the Cochrane Risk of Bias score.

Results The use of uninformative control groups (treatments less invasive than the tested treatment, or treatments that might not outperform placebo but are not acknowledged as such) was found in 46% (47 of 103) of included studies. After accounting for potential confounding, there was no

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association between reporting positive treatment effects and the use of an uninformative control group. Studies with a low risk of bias had a lower likelihood of reporting a positive treatment effect (OR 0.2 [95% confidence interval 0.05 to 0.9]; p = 0.04, model pseudo R^2 = 0.21).

Conclusion The finding that recent studies that mimic high-level evidence often use uninformative control groups that do not adequately account for nonspecific effects (perceived treatment benefits unrelated to a treatment's direct physiological effects) points to a high risk of legitimizing ineffective treatments. This raises the ethical imperative for patients, clinicians, journal peer reviewers, and journal editors to hold researchers to the standard of an adequate, informative control group. Awareness and risk of bias checklists might help patients and clinicians forgo new treatments based on seemingly high-level evidence that may carry only iatrogenic, financial, and psychological harm (false hope, in particular).

Level of Evidence Level I, therapeutic study.

Introduction

There are no treatments experimentally confirmed to alter the natural history of pathophysiologies of musculoskeletal senescence including osteoarthritis and mucoid degeneration [78]. In other words, these conditions have no disease-modifying treatments. Symptom alleviation through symptomatic (or palliative) treatments can occur through two mechanisms: (1) specific effects: temporary changes in pathophysiology, such as NSAIDs inhibiting prostaglandins and reducing pain intensity, and (2) nonspecific effects: psychological changes (placebo/nocebo effects, accommodation), regression to the mean, and the self-limiting course of many illnesses, among other factors [45]. To account for these nonspecific effects, randomized controlled trials (RCTs) should compare a treatment to a treatment with known specific effects, or to a convincing simulation (placebo), with adequate blinding of patient, clinician, and evaluator.

In fact, when tested, a large part of the effect of surgical treatment for non-life-threatening, non-limb-threatening conditions arises from nonspecific effects. For instance, a meta-analysis of 100 RCTs of operative treatments that included a simulated (placebo) surgery found that a mean of 67% of observed improvements could be attributed to nonspecific effects. Notably, 100% of improvements from arthroscopic lavage and debridement for osteoarthritis were found to be attributed to nonspecific effects [45].

In RCTs of nonoperative symptomatic treatments, comparison with a control treatment that has not proven more effective than simulated (sham or placebo) treatment but is not acknowledged as such is misleading because it cannot discern specific from nonspecific treatment effects and risks legitimizing either treatment. For example, a study comparing hyaluronic acid and platelet-rich plasma for palliation of osteoarthritis symptoms may be comparing two treatments that are no better than placebo, meaning neither has specific effects. But without acknowledging that either treatment effectively functions as a placebo, one risks legitimizing both treatments regardless of effectiveness, which raises ethical concerns. Moreover, nonspecific effects generally increase with invasiveness, so an injection is expected to have greater nonspecific effects than a tablet. By using a less-invasive (inappropriate) control group, studies might be more likely to find a positive treatment effect (defined as $p < 0.05$ in favor of the intervention, or as making a recommendation favoring the intervention over the control treatment), further promoting ineffective treatments that at that point may risk iatrogenic harm. Inappropriate, uninformative control groups might go unnoticed because the trial can otherwise be methodologically sound, and specifics on informative control group selection are not part of RCT quality checklists such as the Consolidated Standards of Reporting Trials (CONSORT) statement [12]. It is currently unclear how often inappropriate control groups are used and if this is associated with reporting a positive treatment effect. Knowledge of the prevalence of the use of uninformative control groups and the potential association with positive treatment effect might improve the quality of future RCTs and could guide reviewers and editors to be more cautious in publishing these types of trials. In addition, it has the potential to help patients and clinicians not accept randomized trials as high-level evidence when the control group is inadequate, potentially shielding them from conceivably ineffective treatments that risk only iatrogenic harms (such as adverse events and financial and psychological harms).

Therefore we systematically reviewed recent RCTs of one or more nonoperative symptomatic treatment for osteoarthritis and asked: (1) What proportion of randomized trials use uninformative control groups (defined as a treatment less invasive than the tested treatment, or a treatment that might possibly not outperform placebo but is not acknowledged as such)? (2) Is the use of uninformative control groups independently associated with reporting a positive treatment effect (defined as $p < 0.05$ in favor of the intervention, or as making a recommendation favoring the intervention over the control treatment)?

Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility Criteria

The search was limited to studies with text in English and those with full-text availability. RCTs published between

2020 to 2022 that compared the efficacy of one or more symptomatic treatments with a control group or another symptomatic treatment for osteoarthritis were included. After a preliminary search, we expected that this time period would be long enough to provide an adequate sample size with enough variation to analyze the current state of appropriate control group utilization.

Articles found in preprint servers, those outside of the databases used, and RCTs including a surgical treatment group were excluded. We did not search conference proceedings.

Information Sources and Search Strategy

We searched PubMed, Cochrane, and Embase up to September 2023 using a list of search terms: "randomized controlled trial" or "clinical trial" AND "arthritis," "knee arthritis," "hip arthritis," "osteoarthritis." The reference list and related article list of each included article were also searched to identify additional articles for inclusion. Reference lists were cross-referenced, and articles not initially included were added.

Selection Process

Two reviewers (YA and an assistant) independently reviewed articles for inclusion. Discrepancies for inclusion were addressed through discussion until a consensus was reached. If there was continued disagreement, the senior authors (DR, TT) were available to assist in reaching a final decision. The selection process was facilitated using the Rayyan web-based application for systematic reviews (Qatar Computing Research Institute). Rayyan is a computer program that supports researchers in the systematic review process by assisting with screening of large volumes of articles and allowing reviewers to work independently by blinding them to each other's decisions.

Data Collection Process

Data collection was done independently by two reviewers (YA and an assistant). Discrepancies in data collection were addressed through discussion between the reviewers until a consensus was reached with help from the other authors if necessary (DR, TT).

Data Items: Primary and Secondary Study Outcomes

Our primary study outcome was the use of inadequate or misleading control groups. We used the following definitions: inappropriate or misleading control groups include treatments less invasive than the tested treatment (for example, comparing a cream to an injection) or a treatment that might not outperform placebo but is not acknowledged as such (for example, comparing hyaluronic acid and platelet-rich plasma without mentioning that neither outperforms placebo). Appropriate control groups include equally invasive treatments that are a placebo and presented as such or treatments that are better than a placebo (have specific effects) according to available evidence.

Our secondary study outcome was association of an inadequate control group with reporting a positive treatment effect. We defined a reported positive effect if in the Results section the intervention showed a benefit over the control group with $p < 0.05$, or if in the Discussion or Conclusion sections of the paper the authors specifically used language favoring the intervention over the control group. One reviewer independently rated the studies (YA), and a second reviewer (TT) randomly rated a subset of 30 studies, blinded to the initial ratings. We found an intraclass correlation of 0.85 (95% confidence interval [CI] 0.69 to 0.93), with only three diverging opinions. This suggests that we were able to reliably identify when a study was "positive" using our definition.

Other Variables

We aimed to account for potential confounding of the potential factors associated with inadequate control groups and reporting a positive effect. Therefore, we collected the following data: Year published was recorded to identify the number of studies published per year. Discipline of the first author was categorized as orthopaedic surgery, physical medicine, rehabilitation, and "other authors" (physical therapy, rheumatology, and others). Different medical specialties have distinct perspectives, training, and priorities when it comes to managing osteoarthritis that could influence how a trial is set up. Promoted/cash treatment, which was defined as therapies not currently covered by Medicare as identified through the Centers for Medicare & Medicaid Services (CMS) website, was recoded because trials might use uninformative controls in an effort to reach a positive outcome and support market entry of products without Medicare coverage. Competing or conflicts of interest may have the potential to bias study design and were recorded for each study. Types of funding, which were separated into public funding, private funding, both public and private funding, no funding, or no mention of funding in the article, were also recorded because bias introduced by the source of funding can potentially influence study design. Data on defined primary outcomes

were collected because changing the study's primary outcome has been used to report more favorable results. Continent of origin was categorized as Europe, Asia, or other (North America, South America, Australia, and Africa) because the vast majority of included studies were from Europe and Asia. Research practices and standards, such as regulatory scrutiny and funding availability, can vary across different regions. Journal Impact Factor (Clarivate) at time of publication was recorded because this can potentially serve as a proxy for the quality of the studies. This information was obtained from Journal Citation Reports (Clarivate). In cases where the Impact Factor for the publication year was unavailable, the most recent Impact Factor was utilized for the analysis. Type of blinding was included because this has a known effect on outcome. Because of discrepancies in descriptions of blinding methods, we established the criteria for "double-blind" as studies in which two of three entities—patient, evaluator, or clinician—were blinded, whereas single-blind studies were identified by the blinding of only one of these groups. Sample size of the study was recorded because larger sample sizes might be a proxy for the robustness of findings. Last, risk of bias was determined using the revised Cochrane Risk of Bias Tool, which is another measure of overall study quality.

Risk of Bias and Study Quality

Risk of bias was assessed by two independent reviewers (YA and an assistant) using the revised Cochrane Risk of Bias Tool, version 2, for randomized trials. Studies were

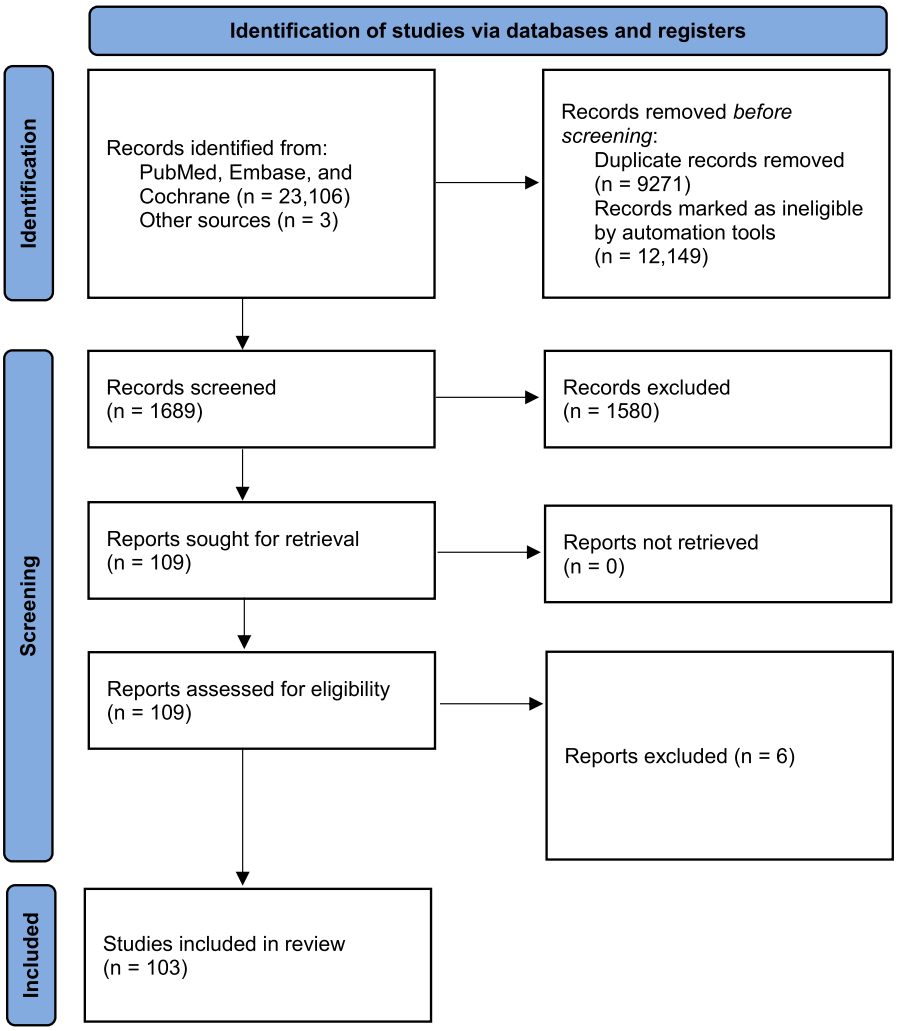

Fig. 1 The PRISMA flowchart showing the selection of studies for inclusion in the systematic review is shown here.

evaluated as either "low risk," "some concerns," "unclear," or "high risk" [36, 88]. Discrepancies in quality ratings were addressed through discussion until a consensus was reached. In cases of persistent disagreement, one of the authors (DR) was available to facilitate resolution and assist in reaching a final decision. Overall, the risk of bias of included studies was "high" in 60% (62) of studies, "some concerns" in 10% (11), and "low" in 29% (30), with most studies neglecting proper blinding of the patient, interventionist, or evaluator or lacking information on how long the allocation sequence was concealed (Supplemental Table 1; http://links.lww.com/CORR/B346). While the presence of high risk of bias in the included studies may be concerning, it does not invalidate our study design; rather, this finding supports it. In general, studies with a high risk of bias will tend to overestimate the apparent benefits of the treatments being studied and will result in recommendations favoring the use of those treatments when they may be no better than placebo.

Study Selection

Among 23,106 studies screened, 9271 duplicates and 12,149 animal studies, systematic reviews, meta-analysis, studies including a surgical intervention group, and studies not comparing at least one symptomatic, nonoperative treatment were removed. Reviewer screening of 1686 articles by title and abstract excluded 1580 studies that were not randomized trials or included a surgical intervention. The remaining 106 studies with an additional 3 found in related articles listing were analyzed and assessed for eligibility. Six studies were excluded because they did not fit inclusion criteria, resulting in a total of 103 included studies (Fig. 1) [1-11, 13-23, 25-35, 37-44, 46-60, 62-77, 79-87, 89-110].

Study Characteristics

The studies addressed a total of 15,491 patients with an average age of 59 years; 64% were women. Knee osteoarthritis was addressed in 92 studies, hand osteoarthritis in 3 studies, and glenohumeral osteoarthritis, subtalar osteoarthritis, trapeziometacarpal osteoarthritis, patellar osteoarthritis, ankle osteoarthritis, hip osteoarthritis alone, both hip and knee osteoarthritis, and hip, knee, shoulder, or elbow osteoarthritis each in a single study (Supplemental Table 2; http://links.lww.com/CORR/B346). In 2020, 2021, and 2022, 35%, 35%, and 30% of articles were published each year, respectively. Among these, 28% of the articles had first authors with a discipline in orthopaedic surgery, and 95% of the studies included promoted/cash treatments (Table 1).

Statistical Analysis

Descriptive statistics were utilized to present study demographic characteristics as percentages and frequencies. We set statistical significance at a p value of < 0.05. All variables with an association with $p < 0.10$ on bivariate analysis (Supplemental Table 3; http://links.lww.com/CORR/B346) were included in a multivariable logistic regression model except for Impact Factor because it resulted in collinearity with risk of bias. Logistic regressions were performed using Stata, version 18 (StataCorp). We reported pseudo R^2 as a measure of effect size of any found association.

Results

Proportion of Studies That Used Uninformative Control Groups

Nearly one-half (46% [47 of 103]) of the randomized studies we analyzed used uninformative control groups, defined as treatments less invasive than the tested treatment or treatments that might not outperform placebo but are not acknowledged as such (Table 1).

Association Between the Use of Uninformative Control Groups and Reporting a Positive Effect

Accounting for potential confounding, there was no association between using an uninformative control group and reporting a positive treatment effect (defined as $p < 0.05$ in favor of the intervention or as making a recommendation favoring the intervention over the control treatment [OR 0.2 (95% CI 0.05 to 0.9); $p = 0.04$, model pseudo $R^2 = 0.21$, indicating that this association accounted for some of the variation in positive effects reported]) (Table 2).

Discussion

Because currently there are no disease-modifying treatments of osteoarthritis (no treatments that alter the natural course of untreated pathophysiology), to determine effectiveness in alleviation of symptoms, new therapies must be compared with placebo or treatments experimentally proven to specifically and effectively alleviate symptoms. When studies compare new treatments to inappropriate controls, such as less-invasive treatments or treatments that are no better than placebo, this risks legitimizing the treatments studied and potentially even promoting them if a spurious positive treatment effect is reported. In this systematic review of recently published RCTs addressing

Table 1. Demographic characteristics of included studies (n = 103)

Characteristic	Value
Year	
2020	35 (36)
2021	35 (36)
2022	30 (31)
Discipline of first author	
Orthopaedic surgery	28 (29)
Physical medicine and rehabilitation	23 (24)
Other authors	49 (50)
Promoted/cash treatments for osteoarthritis[a]	
Yes	95 (98)
No	4.9 (5)
Conflict of interest/disclosure/ competing interest[b]	
Yes	23 (24)
No	72 (74)
Not mentioned	4.9 (5)
Funding[c]	
Public	41 (42)
Private	17 (18)
Both	8.7 (9)
None	23 (24)
Not mentioned	9.7 (10)
Continent	
Not Europe or Asia	22 (23)
Europe	19 (20)
Asia	58 (60)
Control group(s)	
Uninformative control group	46 (47)
Informative control group	54 (56)
Types of blinding	
Single	18 (19)
Double	20 (21)
Triple	45 (46)
None	17 (17)
Positive effect reported[d]	
Yes	76 (78)
No	24 (25)
Primary outcome defined	
Yes	71 (73)
No	29 (30)
Statistical difference reported in primary outcome	
Yes	41 (42)
No	48 (49)
Unclear	12 (12)
Impact Factor of the journal the year the study was published[e]	3 (2.3-4.9)
Risk of bias	
High	60 (62)
Low	29 (30)
Some concerns	11 (11)
Location	
Knee	89 (92)
Other	11 (11)

Data presented as % (n) or median (IQR).
[a]Promoted/cash treatments are those that are marketed but not currently covered by the Centers for Medicare & Medicaid Services.
[b]Conflicts of interest were counted as present if any author benefited financially from the result of the study based on their declared associations.
[c]Public funding is a university or government agency such as the National Institutes for Health or the equivalent in another country. Private funding is from a corporation or private organization, such as the food and beverage company JLK Nutrition.
[d]A positive effect reported means that the study favored the test intervention over the control intervention.
[e]For studies in journals with Impact Factors not available on Journal Citation Reports for the year they were published, the most recent Impact Factor was used.

symptomatic treatments for osteoarthritis, we found that uninformative control groups are common (46% [47 of 103]) but not associated with reporting a positive treatment effect. These findings point to a high risk of legitimizing ineffective treatments. This highlights the need for patients, clinicians, journal peer reviewers, and journal editors to hold researchers to the standard of an adequate control group. Awareness and risk of bias checklists might help patients and clinicians forgo new treatments based on seemingly high-level evidence in misleading control groups, and that may carry only iatrogenic, financial, and psychological harm (false hope, in particular).

Limitations

This study has some limitations. First, our method for classifying reporting on positive effect depended on both p values and the language used by authors in the Discussion and Conclusion sections of their papers. This approach introduces a degree of subjectivity. Despite the potential for variability, the high intraclass correlation between the two raters that we observed indicated adequate reliability of

Table 2. Multivariable analysis of variables associated with reporting a positive effect

Variable	OR (95% CI)	p value
Conflict of interest	0.4 (0.1-1.3)	0.13
Continent of origin		
Europe	Ref.	
Asia	0.8 (0.2-3.5)	0.76
Other	0.3 (0.06-1.4)	0.13
Risk of bias		
High	Ref.	
Low	0.2 (0.05-0.9)	0.04
Some concerns	0.2 (0.03-1.4)	0.11
Inadequate control group	1.3 (0.4-4.5)	0.68
Types of blinding		
Single	Ref.	
Double	0.5 (0.04-5.6)	0.55
Triple	0.5 (0.04-5.6)	0.53
None	0.2 (0.02-2.5)	0.21

Ref. = reference value. Pseudo R^2 of model = 0.21.

this measure. Second, because some studies self-describe as double-blind when there was patient and clinician blinding without evaluator blinding, whereas others with these same parameters self-described as single-blind, we defined double-blind as studies in which two of the three entities—patient, evaluator, or clinician—were blinded and single-blind when only one group was blinded. This approach cannot fully represent the level of control of bias, but we feel that it created categories that are more easily interpreted. Third, although we adhered closely to PRISMA guidelines, there remains a possibility that relevant articles were inadvertently excluded during the filtering process. However, we are confident that any such omissions were unlikely to have impacted our results, as we thoroughly reviewed a substantial number of articles. Fourth, one article was retracted from its respective journal after our initial search was completed. Typically, in a systematic review, one would consider retracted evidence faulty and exclude it from consideration. Given the point of our systematic review, which underlines the importance of a skeptical eye toward claims of treatment validity and effectiveness, along with careful critique of published experiments—even those with a veneer of high-level evidence such as randomized trials—we felt that the retraction of one of the studies was part of the evidence regarding the hypothesis we tested. The fact that even seemingly well-performed experiments are sometimes retracted due to mistakes or misconduct contributes to an awareness of the importance of identifying factors, such as the use of an inadequate control group, that may signal evidence that is not trustworthy. Fifth, our definition of cash/promoted treatment as not approved by the CMS might not have accurately represented treatments paid for by insurance in countries other than the United States. Nevertheless, our approach was representative of the concept. It is notable that nearly all of the studies addressed treatments that are not reimbursed by health insurance in the United States (where treatments such as corticosteroid injections are reimbursed). Sixth, for our author discipline category, we relied on the associated department listed in author affiliations to determine discipline. This approach left the possibility open that some authors may have been researchers, students, or others affiliated with the department rather than practicing physicians. To mitigate this, we conducted additional verification through Google searches and checking academic profiles to confirm the professional positions of authors. However, a few author positions could not be confirmed.

Proportion of Studies That Used Uninformative Control Groups

Nearly one-half of the randomized studies on the symptomatic treatment of osteoarthritis that we analyzed used uninformative control groups, defined as treatments less invasive than the treatment of interest or treatments that likely would not outperform placebo but are not acknowledged as such. This indicates a high risk of legitimizing treatments that only carry risk of iatrogenic harm (such as adverse events and financial and psychological harms) and exposing patients to such harms. This raises an ethical imperative for patients, clinicians, journal peer reviewers, and journal editors to hold researchers to the standard of an adequate control group. Future studies could assess to what extent favorable RCTs (with or without adequate controls) influence doctor and patient decision-making to try symptomatic treatments for osteoarthritis. A previous analysis of nonrandomized studies in plastic surgery found that only one-half of the studies that should have included a control group did so, and the control group was often susceptible to selection bias [61]. We found that even in studies of a high level of evidence, such as RCTs, inappropriate control group selection was relatively common.

Association Between the Use of Uninformative Control Groups and Reporting a Positive Effect

Using uninformative control groups was not associated with reporting a positive treatment effect (defined as $p < 0.05$ in favor of the intervention or as making a recommendation favoring the intervention over the control treatment), but high risk of bias was. Although not

specifically tested, spuriously reporting a positive treatment effect not only legitimizes but also risks promoting a specific treatment that potentially carries only iatrogenic risk. The greater reporting of positive effects in lower quality studies might be related to the tendency to favor publishing statistically significant results [24]. The Cochrane Risk of Bias checklist used might help patients and doctors identify seemingly high-level evidence of questionable quality and shield them from using treatments without specific effects, but this remains to be tested.

Conclusion

RCTs on symptomatic treatments for osteoarthritis often use uninformative control groups that do not adequately account for nonspecific effects. This may legitimize treatments that expose patients to only iatrogenic risks, including financial and psychological harm. This creates an ethical imperative for patients, clinicians, journal peer reviewers, and journal editors to hold researchers to the standard of an adequate control group. All studies evaluating an unproven symptomatic, nonoperative treatment option must compare that treatment to a known inert substance (placebo) with randomization and adequate blinding of patient, clinician, and evaluator. Otherwise, there is a notable risk of erroneous attribution of nonspecific treatment effects to an ineffective intervention. Future studies could assess how high-profile randomized studies influence patients' and physicians' decisions to try treatments that have not been shown to provide more than nonspecific effects.

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