A COMPARISON OF TREATMENT EFFECTS FOR NONSURGICAL THERAPIES AND THE MINIMUM CLINICALLY IMPORTANT DIFFERENCE IN KNEE OSTEOARTHRITIS

A Systematic Review

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Abstract

Background: The minimum clinically important difference (MCID) was developed to ascertain the smallest change in an outcome that patients perceive as beneficial. The objectives of the present review were (1) to compare the MCIDs for pain assessments used among guidelines and meta-analyses investigating different nonsurgical therapies for knee osteoarthritis and (2) to compare the effect estimates of different nonsurgical interventions against a single commonly-utilized MCID threshold.

Methods: Systematic and manual searches were conducted to identify guidelines and meta-analyses evaluating pain outcomes for nonsurgical knee osteoarthritis interventions. Individual treatment effects for pain were presented on a common scale (the standardized mean difference [SMD]). To evaluate the perception of the relative benefit of each nonsurgical treatment, the variation in MCIDs selected from the published MCID literature was assessed.

Results: Thirty-seven guidelines and meta-analyses were included. MCIDs were often presented as an SMD or a mean difference (MD) on a validated scale and varied in magnitude across sources. This analysis demonstrated that intra-articular hyaluronic acid, intra-articular corticosteroids, and acetaminophen all had relatively larger effect sizes than topical nonsteroidal anti-inflammatory drugs (NSAIDs). Higher-molecular-weight intra-articular hyaluronic acid had a greater relative effect compared with both non-selective and cyclooxygenase-2-selective oral NSAIDs. Evaluating the treatment effect estimates against a commonly utilized MCID revealed similarities in which observations attained clinical significance among treatments; however, this observation varied across the range of reported MCIDs.

Conclusions: The present review confirmed the variability in the MCIDs for pain assessments that are used across guidelines and meta-analyses evaluating nonsurgical interventions for knee osteoarthritis. This variability may yield conflicting treatment recommendations, ranging

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from rejecting treatments that are indeed efficacious to accepting treatments that may not be beneficial. Additional research is required to determine why some nonsurgical therapies are more consistently recommended in knee osteoarthritis guidelines than others as these findings suggest similarities in their effect estimates for pain. Relevant stakeholders need to reach a consensus on a standard approach to determining the MCIDs for these therapies to ensure that appropriate and effective treatment options are available to patients prior to invasive surgical intervention.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Knee osteoarthritis is a leading cause of pain and disability worldwide, having a considerable impact on both the health-care system and a patient's long-term quality of life¹⁻⁴. The prevalence of osteoarthritis is rising with the aging population and the increased presence of its associated risk factors, such as obesity and low levels of physical activity^{1,5,6}. In the

United States, knee osteoarthritis affects approximately 9 million adults and has an estimated incidence of 240 per 100,000 people per year, with greater risk among women and obese individuals^{3,7-9}. By the year 2020, osteoarthritis is expected to be 1 of the top 10 causes of disability (measured in terms of disability-adjusted life-years) in developed countries¹⁰.

Osteoarthritis typically worsens slowly over time; treatments provide

symptomatic relief and may at least theoretically slow the progression of articular damage^{1,11}. The most common complaint of patients with osteoarthritis is pain, which often affects an individual's daily activities^{1,2,4}. Pharmacological treatment is uniformly recommended for initial management; however, a number of options are available, and recommendations as to the efficacy of these treatments are inconsistent between knee osteoarthritis guidelines and medical providers^{1,4,6,12-17}.

For a treatment to be approved for use in clinical practice, its efficacy and safety must be demonstrated in clinical trials. Proof of the statistical significance of trial results is established by a p value, but a more directly applicable determination for clinicians is whether or not these results are also clinically important¹⁸. The concept of the minimum clinically important difference (MCID) was introduced in 1989 by Jaeschke et al.¹⁸. This concept was developed in

Fig. 1
Flow diagram of search results.

TABLE 1 Summary of the Included Studies (n = 37)

Study Type and Treatment Evaluated	No. of Studies
Study type	
Pairwise meta-analysis	22 (59.5%)
Cochrane review	5 (13.5%)
Network meta-analysis	5 (13.5%)
Guideline	4 (10.8%)
Health technology assessment*	1 (2.7%)
Treatment evaluated†	
Multiple treatments	11 (29.7%)
Intra-articular hyaluronic acid	11 (29.7%)
Exercise interventions	3 (8.1%)
Acupuncture	2 (5.4%)
Dietary supplements	2 (5.4%)
Corticosteroids	1 (2.7%)
Duloxetine (SNRI)	1 (2.7%)
NSAIDs	1 (2.7%)
PEMF	1 (2.7%)
TENS	1 (2.7%)
Ultrasound	1 (2.7%)
Valgus bracing	1 (2.7%)
Weight loss	1 (2.7%)

*Included a meta-analysis. †SNRI = serotonin and norepinephrine reuptake inhibitor, NSAIDs = nonsteroidal anti-inflammatory drugs, PEMF = pulsed electromagnetic field, and TENS = transcutaneous electrical nerve stimulation.

an effort to determine and communicate whether there was clinical relevance associated with the observed differences between treatments in a clinical trial. Jaeschke et al. defined the MCID as “the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management.” The MCID is typically determined through an anchor-based approach. This requires patients to respond to a questionnaire that asks an “anchor” question that assesses the extent to which they feel that their pain has improved. At the same time points, patients answer a continuous-scale patient-reported pain outcome measure, such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or a visual analog scale (VAS) pain score. This allows for calculation of the amount of pain reduction on the continuous scale that is associated with a patient changing his or her

opinion about clinical improvement on the anchor question¹⁹. The MCID is recognized to vary between different patient populations and the various health outcome measures used in clinical trials, but variability also may be seen among studies examining the same patient population as a result of differences in study design, study location, and treatment product administered.

Numerous clinical practice guidelines and meta-analyses have been published to guide physicians in the treatment of knee osteoarthritis; therefore, we conducted a systematic review of the literature to determine how much variation exists in the MCIDs used in the knee osteoarthritis literature.

Materials and Methods

Objectives

The primary objective was to identify and describe the variability in the MCID for pain assessments used in guidelines and meta-analyses evaluating nonsurgical interventions for knee osteoarthritis.

The secondary objective was to evaluate the treatment effects of nonsurgical interventions found in these guidelines and meta-analyses against a common MCID threshold from the literature.

Search and Eligibility Criteria

A systematic search (Appendix A) was conducted on September 2, 2016, in MEDLINE and Embase (via Ovid) to identify published guidelines and meta-analyses on nonsurgical treatments for knee osteoarthritis. A manual search was also performed in the National Guideline Clearinghouse web site (www.guideline.gov). The specific study eligibility criteria are included in Appendix A.

Duplicate references, conference proceedings, book chapters, and historical reviews were removed after completion of the search. The remaining titles and abstracts were screened. Full-text publications of potentially eligible abstracts were then reviewed for inclusion. An updated search was conducted on November 23, 2018 to identify any articles published between that date and the date of the original search.

Data Extraction

For each eligible guideline and meta-analysis, the publication information, methodological details, treatment effect estimate, and reported MCID value were extracted.

GRADE Assessment

When sufficient information was provided in the publication, the quality of evidence of pain outcomes was also assessed with use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach²⁰⁻²². GRADE is a tool that is used to evaluate the quality of a body of evidence through assessing the risks of bias, imprecision, inconsistency, indirectness, and potential publication bias within a body of literature²³. The methodology proposed by Salanti et al., which is based on the GRADE approach, was applied to evaluate network meta-analyses²⁴. For this assessment, interventions were categorized

TABLE II MCIDs for Pain

Comparison	Measure	Scale	MCID Values	
			Single Values Used (No. of Meta-Analyses/ Guidelines)	Range of MCID Values Used (No. of Meta-Analyses/ Guidelines)
Between-group difference	MD	VAS (0-100)	10 (1)	8.4-19.9 (1)
			14 (1)	10-30 (1)
			15 (2)	15-20 (1)
			17.5 (2)	
			19.9 (2)	
		WOMAC (0-100)	8.3 (1)	9-12 (1)
			9.7 (3)	
		WOMAC, Likert (0-20)	5 (1)	None reported
		SF-36, bodily pain (0-100)	7.8 (1)	None reported
		NRS (0-10)	1.0 (1)	None reported
	SMD	Standard deviation units	0.20 (3)	None reported
			0.37 (2)	
			0.39 (3)*	
			0.40 (4)	
			0.47 (1)*	
		0.50 (4)†		
		1.23 (1)*		
	%	Percent improvement relative to control	15 (1)	None reported
Within-group (pre-treatment to post-treatment) difference	MD	VAS (0-10)	2.0 (2)	None reported
		WOMAC (0-100)	20 (2)	None reported
	SMD	Standard deviation units	0.37 (1)	None reported
	Absolute score	VAS (0-100)	<32.3 (1)	None reported
	%	Percent decrease from baseline	None reported	10-20 (1)

*MCID reported in the American Academy of Orthopaedic Surgeons (AAOS) guideline. †MCID reported in the European League Against Rheumatism (EULAR) and National Institute for Health and Care Excellence (NICE) guidelines.

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as nonpharmacological interventions, intra-articular injections, or oral pharmacological interventions.

Comparison of MCIDs Used for Pain Assessments

During the extraction of the MCIDs for pain outcomes, the specific pain scale, whether the comparison was a between-group or within-group difference, and whether the MCID was a single value or range of values were also recorded. The results were then compared directly with the American Academy of Orthopaedic Surgeons (AAOS) guideline, which is considered the gold standard for orthopaedic surgeons in North America⁷, as well as other included knee osteoarthritis guidelines. The findings were tabulated and described qualitatively.

Comparison of Treatment Effects and Their Clinical Significance

Only interventions that had a treatment effect for pain outcomes reported in the AAOS guideline and that were evaluated in at least 1 other meta-analysis or guideline were included in this specific comparison. Also, only effect estimates provided on the WOMAC pain subscale, or that listed WOMAC pain at the top of the study's hierarchy of outcomes²⁵, were included to limit the potential heterogeneity between the various pain scales. The WOMAC was prioritized on the basis of its priority in a previously published hierarchy that is commonly used in knee osteoarthritis meta-analyses²⁵. All estimates for a given treatment were plotted with the range of MCIDs identified from the search to assess their clinical signifi-

cance relative to common thresholds. This was also done to compare the different pharmacological therapies relative to their respective placebos, but only estimates from most recent or comprehensive meta-analyses were summarized to ensure that the most accurate and up-to-date effect estimates were presented. The standardized mean difference (SMD)²⁶ was used to ensure that effect estimates were on a common scale. The values provided in the AAOS guideline were converted to SMD units as the estimates in that guideline were not presented on this scale (a weighted mean difference or MCID units may have been used instead). For example, if the effect estimate was presented as 0.5 MCID unit, the corresponding value on the SMD scale (x) was calculated as:

Fig. 2-A

Fig. 2-B

Fig. 2-A and 2-B Comparison of treatment effect estimates (in SD units) for oral NSAIDs^{7,30,32,34,51} (**Fig. 2-A**) and topical NSAIDs^{7,30} (**Fig. 2-B**) with corresponding 95% confidence intervals. The blue line indicates the AAOS MCID for WOMAC pain (0.39), and the dotted red lines indicate the range of other reported MCIDs (0.20 to 0.50). AAOS 5 American Academy of Orthopaedic Surgeons, NSAID 5 nonsteroidal anti-inflammatory drug, SMD 5 standardized mean difference.

$$\frac{0.5}{1}(\text{MCID units}) = \frac{x}{\text{MCID}}(\text{on the SMD scale})$$

$$x = (0.5)(\text{MCID on the SMD scale})$$

The same descriptions for clinical significance provided in the AAOS guideline were used (Appendix B). These definitions are dependent on the confidence interval (CI) surrounding the estimate; however, meta-analyses conducted via Bayesian methods calculate a credible interval (CrI)²⁷. For the purposes of the present study, it was assumed that these 2 measures of precision were equivalent.

Last, the ratios of the point estimates of effect size for nonsteroidal anti-inflammatory drug (NSAID) therapies, because of their consistently positive recommendations in the guideline literature²⁸, were calculated relative to the effect sizes of the other pharmacological interventions.

Results

Search Results

The initial search resulted in a total of 5,936 citations. After removing duplicates, conference proceedings, book chapters, and historical reviews, 4,204 titles and abstracts were screened. Four hundred and seventy full-text articles were reviewed. After full-text screening,

33 guidelines and meta-analyses met the eligibility criteria. One additional guideline was identified from the manual search. Three eligible guidelines or meta-analyses were found from the updated search; therefore, 37 references were included in the current analysis (Fig. 1)^{1-3,5-7,11-14,16,17,29-53}.

Twenty-two pairwise (or traditional) meta-analyses, 5 Cochrane reviews, 5 network meta-analyses, 4 guidelines (1 of which only focused on exercise interventions), and 1 health technology assessment that included a meta-analysis on intra-articular hyaluronic acid were included (Table I). Eleven of the guidelines and meta-analyses examined >1 knee osteoarthritis

Fig. 3-A

Fig. 3-B

Figs. 3-A and 3-B Comparison of treatment effect estimates (in SD units) for intra-articular corticosteroids^{7,30,32,51} (**Fig. 3-A**) and intra-articular hyaluronic acid^{7,30-32,45,49,51} (**Fig. 3-B**) with corresponding 95% confidence intervals. The blue line indicates the AAOS MCID for WOMAC pain (0.39), and the dotted red lines indicate the range of other reported MCIDs (0.20 to 0.50). AAOS = American Academy of Orthopaedic Surgeons, MW = molecular weight, IA = intra-articular, SMD = standardized mean difference.

treatment, whereas the other 26 investigated just 1 therapy. Variations in items related to the search strategy and identification of eligible studies, inclusion and exclusion criteria, and statistical methodology were noted across these investigations. Additional publication characteristics and methodological details for each of the included guidelines and meta-analyses are summarized in Appendix B.

GRADE Assessment

The quality of evidence was evaluated for 87 effect estimates for pain across 33 publications (Appendix C); the information provided in the other 4 publications was not sufficient to perform a GRADE assessment. The quality of evidence was rated as very low for 16 effect estimates (18.4%), low for 42

(48.3%), moderate for 21 (24.1%), and high for 8 (9.2%). The effect estimates were categorized as high for 16.7% of oral pharmacological therapies, compared with 3.4% of intra-articular interventions and 10.9% of nonpharmacological interventions. The categorization of the quality of evidence by intervention type for all effect estimates is summarized in Appendix D.

Comparison of MCIDs Used for Pain Assessments

MCIDs for pain values were often presented as an SMD or mean difference (MD) on a pain-specific outcome measure (Table II). The most common scales were the WOMAC pain subscale and visual analog scale (VAS) for pain.

When the MCID was expressed as an SMD, values ranged from 0.20 to 1.23

standard deviation (SD) units. When the MCID for pain was presented on the VAS (0 to 100), values ranged from 10 to 19.9 points. MCID ranges of 8.4 to 19.9, 10 to 30, and 15 to 20 points were also reported for the VAS (0 to 100). When the MCID was on the WOMAC pain subscale (0 to 100), either 8.3 or 9.7 points were used; however, a range of 9 to 12 points was also reported for this scale. The authors of 1 meta-analysis used an MCID of 5 points for the WOMAC pain (0 to 20-point) Likert scale¹⁶. MCIDs for the Short Form-36 (SF-36) bodily pain subscale (100-point scale) and numerical rating scale (NRS, 10-point scale) were 7.8 points and 1 point, respectively. Last, the authors of a guideline used a percentage value as their MCID, stating that a $\geq 15\%$ improvement relative to a control on

Fig. 4-A

Fig. 4-B

Figs. 4-A and 4-B Comparison of treatment effect estimates (in SD units) for acetaminophen^{7,30,32} (Fig. 4-A) and acupuncture.^{1,7,38,42,43} (Fig. 4-B) with corresponding 95% confidence intervals. The blue line indicates the AAOS MCID for WOMAC pain (0.39), and the dotted red lines indicate the range of other reported MCIDs (0.20 to 0.50). AAOS 5 American Academy of Orthopaedic Surgeons, NICE 5 National Institute for Health and Care Excellence, SMD 5 standardized mean difference.

a continuous outcome measure was clinically relevant⁵.

A pre-treatment to post-treatment evaluation (i.e., the improvement from baseline within an individual group) for differences in pain was conducted in 6 meta-analyses^{14,17,30,32,48,49}. The MCIDs for these assessments also varied; a 20-point improvement on the WOMAC pain subscale (0 to 100), a 2-point difference on the VAS (0 to 10), an SMD of 0.37 SD unit, and a 10% to 20% decrease in pain from baseline were all used across these investigations. The authors of 1 meta-analysis also stated that patients who achieved a score of <32.3 on the VAS (0 to 100) after their baseline visit reached a clinically significant result⁴⁸.

In the methods section of the AAOS guideline, the authors reported an MCID in SD units for 3 different pain measures (the WOMAC pain subscale, VAS for pain, and SF-36 bodily pain scale). The MCID for WOMAC pain (SMD = 0.39) was also used in 2 other publications, but the MCIDs for the VAS (SMD = 1.23) and SF-36 (SMD = 0.47) were not reported in any other publication besides the AAOS guideline (Table II). Two other knee osteoarthritis guidelines, from the European League Against Rheumatism (EULAR) and National Institute for Health and Care Excellence (NICE), were included in the present review; both used an SMD of 0.50 SD unit as the MCID.

Comparison of Treatment Effects and Their Clinical Significance

According to the criteria established for this comparison, only treatment effects for intra-articular hyaluronic acid (also presented as low-molecular-weight [$<1,500$ kDa] and higher-molecular-weight [$\geq 1,500$ kDa] variations), intra-articular corticosteroids, oral (non-selective and cyclooxygenase [COX]-2-selective) and topical NSAIDs, acetaminophen, and acupuncture were included (i.e., effect estimates for the remaining nonsurgical therapies listed in the methods were not eligible for this analysis); however, the AAOS guideline did not synthesize trials examining intra-articular corticosteroids, so the estimates

Fig. 5

Comparison of treatment effect estimates for topical and oral NSAIDs, acetaminophen, and intra-articular corticosteroids and hyaluronic acid from recent meta-analyses^{30,32,45}. The blue line indicates the AAOS MCID for WOMAC pain (0.39), and the red line indicates the range of other reported MCIDs (0.20 to 0.50). IA = intra-articular, MW = molecular weight, NSAID = nonsteroidal anti-inflammatory drug, SMD = standardized mean difference.

reported for each individual trial were presented.

There were similarities in the effect estimates for oral NSAIDs^{7,30,32,34,51} (Fig. 2-A), topical NSAIDs^{7,30} (Fig. 2-B), and intra-articular corticosteroids^{7,30,32,51} (Fig. 3-A) reported across the included guidelines and meta-analyses; however, there were inconsistencies across the studies and guidelines in the estimates for intra-articular hyaluronic acid^{7,30-32,45,49,51} (Fig. 3-B), acetaminophen^{7,30,32} (Fig. 4-A), and acupuncture^{1,7,38,42,43} (Fig. 4-B). Figures 2, 3, and 4 also demonstrated how differences in the effect estimates and the selection of the MCID (the range of 0.20 to 0.50 SD units pre-

sented in the figures) can alter the clinical significance of these therapies.

The effect estimates used to compare therapies with a placebo control were 0.14 for topical NSAIDs, 0.43 for non-selective NSAIDs, 0.34 for COX-2-selective NSAIDs, 0.18 for acetaminophen, 0.32 for intra-articular corticosteroids, 0.34 for intra-articular hyaluronic acid, 0.57 for higher-molecular-weight intra-articular hyaluronic acid, and 0.23 for low-molecular-weight intra-articular hyaluronic acid (Fig. 5)^{30,32,45}. On the basis of these estimates and the descriptions for clinical significance outlined in Appendix B only non-selective NSAIDs, COX-2-selective NSAIDs,

intra-articular hyaluronic acid, and higher-molecular-weight intra-articular hyaluronic acid had precision intervals that exceeded the lowest MCID threshold (0.20 SD unit) and were, therefore, deemed “clinically significant,” whereas topical NSAIDs, acetaminophen, intra-articular corticosteroids, and low-molecular-weight intra-articular hyaluronic acid were considered “possibly clinically significant.” Compared with the AAOS MCID for WOMAC pain (0.39 SD unit), only higher-molecular-weight intra-articular hyaluronic acid was “clinically significant,” whereas non-selective NSAIDs, COX-2-selective NSAIDs, intra-articular

Fig. 6

Ratios of the point estimates for topical NSAIDs (top panel), COX-2-selective NSAIDs (middle panel), and non-selective NSAIDs (bottom panel) relative to other nonsurgical therapies. Values of <1.0 indicate that the effect estimate for the respective NSAID was larger than the comparison treatment. *Ratio = 1.0. HA = hyaluronic acid, IA = intra-articular, MW = molecular weight, NSAID = nonsteroidal anti-inflammatory drug.

corticosteroids, and intra-articular hyaluronic acid were “possibly clinically significant.” Compared with a more conservative MCID of 0.50 SD unit, none of the treatments represented effect estimates that were “clinically significant”; only the effect sizes of non-selective NSAIDs and higher-molecular-weight intra-articular hyaluronic acid were “possibly clinically significant.”

In Figure 6, values of <1.0 indicate that the effect estimate of the respective NSAID therapy was larger than that of the comparison treatment. Intra-articular hyaluronic acid (regardless of molecular weight), intra-articular corticosteroids, and acetaminophen all had larger effect estimates than topical NSAIDs (Fig. 6, top panel). Compared with both COX-2-selective and non-selective NSAIDs, only higher-molecular-weight intra-articular hyaluronic acid had a larger

effect than the 2 forms of oral NSAID therapy (Fig. 6, middle and bottom panels).

Discussion

This systematic review confirmed the variability in the MCID for pain assessments used across guidelines and meta-analyses evaluating nonsurgical interventions for knee osteoarthritis. In some cases, the threshold for clinical significance was even inconsistent for a single scale (e.g., the WOMAC pain subscale or VAS for pain). The clinical significance associated with an effect estimate for a treatment in patients with knee osteoarthritis is dependent on which threshold is selected. If too low of an MCID is employed, an ineffective treatment may be determined to provide benefit. Alternatively, setting the MCID too high may result in rejecting treatments that are indeed efficacious. The findings

also demonstrate that treatment effects of a given therapy could be influenced by either clinical factors (e.g., hyaluronic acid molecular weight) or methodological (both study and statistical) factors. The comparison of the effect estimates of various pharmacological interventions versus a common comparator (e.g., placebo) showed considerable overlap. This similarity of treatment effect size across treatments raises questions as to the validity of and rationale for the heterogeneity of the recommendations assigned to some of these treatments, with certain knee osteoarthritis guidelines recommending for, and others against, the treatments that generate similar effect sizes. Such observations might explain, at least in part, why prior research has demonstrated conflicting treatment recommendations among the various knee osteoarthritis guidelines^{15,28} and further reinforce the contention that

the MCID should be used strictly as a supplementary tool when making treatment decisions.

One factor that could have altered these results and conclusions is that trial quality may have an impact on treatment effect estimates. As highlighted in Appendix D, the quality of evidence of the included pain outcomes was quite variable. If, for example, the authors of a given meta-analysis were to restrict their analysis to include only high-quality studies, the resulting effect size may very well be different from the effect calculated regardless of trial quality, which could then change the interpretation of clinical significance for the effect size. Another consideration that should be addressed is that the WOMAC pain scale was prioritized in this comparison. As noted in the results of the literature search, different scales have different MCIDs. If, for example, the VAS for pain had been prioritized instead of the WOMAC for this analysis, the effect sizes of the included therapies may have compared differently to the range of MCIDs reported for the VAS, which might (or might not) have changed the conclusions made about their clinical significance. An additional consideration for future research on knee osteoarthritis is the emergence of platelet-rich plasma (PRP) as a potential treatment option. This therapy has a small but growing body of evidence examining its effects in comparison with those of intra-articular saline solution as well as those of active comparators such as intra-articular hyaluronic acid. Current guidelines have not typically included PRP in their formal recommendations, perhaps because of the lack of a body of evidence to aid in decision-making, yet this body of evidence is continually growing and should be considered in future knee osteoarthritis investigations.

The authors of the included guidelines and meta-analyses often referred to the previous literature when selecting the most appropriate MCID for their research investigations. Historically, the MCID has been determined with one of a num-

ber of different methods, which can be categorized as expert-based, distribution-based, or anchor-based. An expert-based approach involves the development of a consensus panel to review and discuss the available data to determine the MCID, which may involve a voting procedure^{54,55}. A distribution-based MCID involves the use of statistical parameters to estimate thresholds of discrimination for changes in health, as based on the early work by Cohen⁵⁶ and Norman et al.⁵⁷. Anchor-based MCIDs, calculated by relating changes on a continuous outcome measure to changes in a patient's self-assessment of health status⁵⁸⁻⁶³, were common across the guidelines and meta-analyses included in this review; however, anchor-based MCIDs may differ for various reasons. For example, the 2 studies by Angst et al.^{64,65} both used a transition questionnaire to ask patients if their health was "much worse," "slightly worse," "equal," "slightly better," or "much better" relative to their baseline status, whereas Tubach et al. asked patients to assess their response to treatment on either a 5-point ("none," "poor," "fair," "good," or "excellent") or 15-point (ranging from "a very great deal worse" to "a very great deal better") Likert scale⁶⁶. Angst et al. defined the MCID for improvement as patients who stated that their health was "slightly better" relative to baseline, whereas Tubach et al. used the scores of 75% of the patients who deemed their response to treatment as "good."⁶⁴⁻⁶⁶ This example highlights the controversy on how much of a change in a patient's health status should be considered a "minimal" important difference, as the definition provided by Angst et al. appears to represent a smaller change than the criteria used by Tubach et al., which was, arguably, set too high⁶⁷. The MCID is recognized to be context-specific, and a patient's expectation may change depending on factors such as the type of treatment received, the time between outcome assessments, and the patient's age or other baseline characteristics^{67,68}. Variation in the patient populations and anchors used to determine these clinically significant thresholds may account for the wide range of MCIDs reported in the knee

osteoarthritis literature. The anchor-based MCIDs used across these studies also represented populations of patients with conditions other than osteoarthritis (e.g., ankylosing spondylitis, low back pain, fibromyalgia, peripheral neuropathy, rheumatoid arthritis, rotator cuff disease, acute pain/trauma, endometriosis-associated pelvic pain)^{59,61-63,69-73}. A recent systematic review assessing the credibility of the MCID for patients with knee osteoarthritis suggested that the most credible estimates of the MCID were around 12 points for the WOMAC pain score, which is considerably lower than the 19.9-point VAS pain MCID referenced frequently in the assessed literature¹⁹. This range of credible MCIDs should be considered in the application of prior research findings, as clinical interpretation of the MCID may vary depending on the cutoff used. An MCID of 12 points on the VAS pain scale is a better representation of an appropriate MCID cutoff¹⁹. As the MCID for an outcome may be derived by evaluating a within-group change in health status relative to baseline, it is not clear that the same MCID is appropriate for between-group comparisons⁶⁷. For example, an SMD of 0.37 has been used for both within-group and between-group differences in pain scores. Also, although the VAS for pain commonly has been used as a pain scale in the knee osteoarthritis literature, it can be assessed under different scenarios (e.g., global pain, pain at rest, pain during activity), and, in many cases, the same MCID value is used for the VAS without this consideration. Using a single threshold as a marker for clinical significance also may be problematic⁶⁷. When an outcome is quantified on a continuous scale, the scores typically are averaged across all patients in the sample; therefore, if this average score (including its precision interval) does not exceed the MCID, then it would not be considered a clinically significant effect, which could potentially ignore a proportion of individual patients who did have a score greater than this value^{67,74}. When pooled effect estimates of a given intervention are inconsistent across guidelines and meta-analyses, the

inconsistency may be due to differences in search strategy, inclusion and exclusion criteria, selection of outcome measures (multiple scales are available that quantify the same outcome), or statistical analysis plan (e.g., the results of a pairwise meta-analysis versus a network meta-analysis or frequentist versus Bayesian approaches). For many nonsurgical interventions for knee osteoarthritis, recommendations for or against use vary across the knee osteoarthritis guidelines²⁸. In the present study, the effect estimates of treatments that have received less support in the guidelines had similar, if not greater, effect sizes than those that have been more commonly recommended. For example, as shown in Figures 5 and 6, the treatment effects of intra-articular hyaluronic acid, especially higher-molecular-weight formulations, were similar to, if not greater than, those of both non-selective and COX-2-selective NSAIDs. Relevant stakeholders must come to a consensus on a standard approach to determining the clinical significance of these therapies in order to ensure that patients are not limited in their treatment options prior to invasive surgical intervention.

The strengths of the current study were that a systematic and reproducible search was conducted within the most comprehensive electronic databases (PubMed/MEDLINE and Embase) and that a manual search for references that were not indexed in these databases was also performed. The most patient-important and most commonly assessed outcome among patients with knee osteoarthritis (i.e., pain) was examined. Meta-analyses and guidelines were only included if treatments were evaluated against a common comparator (placebo or control) in order to ensure comparability between studies when assessing the MCIDs and treatment effect sizes. One of the limitations of the present review was the inclusion of only studies that were published in English. It is unclear how the results might compare with the knee osteoarthritis literature in other countries, and it is possible that other reported MCIDs for this

patient population were missed. Only pain outcomes were examined; however, treatment decisions also may be based on other variables, such as costs and safety. Also, as only evaluations of nonsurgical therapies were included, it cannot be assumed that the results and conclusions of the literature search are also representative of a population of patients with knee osteoarthritis that requires surgical intervention. The comparison to published MCID values aimed to provide clinical insights into the treatment effects seen; however, the present study was limited by the inability to determine which of the published MCIDs is most appropriate to inform clinical significance within this patient population. For this reason, >1 MCID cutoff point was included in the comparison.

Conclusion

The review of the literature identified considerable variability in the MCIDs for pain assessments used across guidelines and meta-analyses evaluating nonsurgical interventions for knee osteoarthritis. Such a wide range of MCIDs may lead to conflicting treatment recommendations, potentially rejecting treatments that are efficacious or accepting treatments that are not effective for individuals in this patient population. Additional research is required to determine why certain pharmacological therapies are more consistently recommended in the knee osteoarthritis guidelines than others as the findings suggest substantial similarities in their effect estimates for pain outcomes. Relevant stakeholders must come to a consensus on a standard approach for determining the clinical significance of these therapies to ensure that patients are provided with all of the effective treatment options that may abrogate the need for invasive surgical intervention.

Appendix

Supporting material provided by the authors is posted with the online version of this article as a data supplement at [jbjs.org \(http://links.lww.com/JBJSREV/A480\)](http://links.lww.com/JBJSREV/A480)

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