Clinical Practice Guideline for Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/ Pelvis Surgery

Review Period Report

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Overview of the Review Period

The reviews and comments related to this clinical practice guideline are reprinted in this document and posted on the AAOS website. All reviewers are required to disclose their conflict of interests.

Review Process:

AAOS contacted 9 organizations with content expertise to review a draft of the clinical practice guideline during the three-week peer review period in March 2021.

Additionally, the draft was also provided to members of the AAOS Board of Directors (BOD), members of the Council on Research and Quality (CORQ), members of the Board of Councilors (BOC), members of the Board of Specialty Societies (BOS) and members of the Committee on Evidence-Based Quality and Value (EBQV) for review and comment.

- Ten (10) individuals provided comments via the electronic structured peer review form. No reviewers asked to remain anonymous.
- All ten reviews were on behalf of a society and/or committee.
- The work group considered all comments and made some modifications when they were consistent with the evidence.

Reviewer Key

Each reviewer was assigned a number (see below). All responses in this document are listed by the assigned peer reviewer's number.

Table 1. Reviewer Key

Reviewer Number	Name of Reviewer	Society/ Committee Being Represented
1	William Hamilton	The Hip Society
2	Rachel Shakked	American Academy of Orthopaedic Surgeons
3	Emily Benson	American Academy of Orthopaedic Surgeons
4	Charles Hannon	American Academy of Hip and Knee Surgeons
5	Benjamin Miller	Committee on Evidence-Based Quality and Value, American Academy of Orthopaedic Surgeons
6	Matthew Austin	The Knee Society
7	Donald Hohman	American Academy of Orthopaedic Surgeons
8	Rebecca Johnson	American Society of Anesthesiologists
9	Glenn Wera	American Academy of Orthopaedic Surgeons
10	Matthew Abdel	Board of Directors, American Academy of Orthopaedic Surgeons

Reviewer Demographics

Table 2: Reviewer Demographics

Reviewer Number	Name of Reviewer	Primary Specialty	Work Setting
1	William Hamilton	Adult Hip	Academic Practice
2	Rachel Shakked	Foot and Ankle	Private Group or Practice
3	Emily Benson	Trauma	Academic Practice
4	Charles Hannon	Total Joint	Academic Practice
5	Benjamin Miller	Ortho/Oncology	Academic Practice
6	Matthew Austin	Total Joint	Private Group or Practice
7	Donald Hohman	Total Joint	Private Group or Practice
8	Rebecca Johnson	Other	Academic Practice
9	Glenn Wera	Total Joint	Non-Military Government or Public
10	Matthew Abdel	Adult Hip	Academic Practice

Reviewers' Disclosure Information

All reviewers are required to disclose any possible conflicts that would bias their review via a series of 10 questions (see Table 3). For any positive responses to the questions (i.e. "Yes"), the reviewer was asked to provide details on their possible conflict.

Table 3. Disclosure Question Key

Disclosure Question	Disclosure Question Details
A	A) Do you or a member of your immediate family receive royalties for any pharmaceutical, biomaterial or orthopaedic product or device?
B	B) Within the past twelve months, have you or a member of your immediate family served on the speakers bureau or have you been paid an honorarium to present by any pharmaceutical, biomaterial or orthopaedic product or device company?
C	C) Are you or a member of your immediate family a PAID EMPLOYEE for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier?
D	D) Are you or a member of your immediate family a PAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier?
E	E) Are you or a member of your immediate family an UNPAID CONSULTANT for any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier?
F	F) Do you or a member of your immediate family own stock or stock options in any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier (excluding mutual funds)
G	G) Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier?
H	H) Do you or a member of your immediate family receive any other financial or material support from any pharmaceutical, biomaterial or orthopaedic device and equipment company or supplier?
I	I) Do you or a member of your immediate family receive any royalties, financial or material support from any medical and/or orthopaedic publishers?
J	J) Do you or a member of your immediate family serve on the editorial or governing board of any medical and/or orthopaedic publication?

Table 4. Reviewer's Disclosure Information

Reviewer Number	Name of Reviewer	Disclosure Available via AAOS Disclosure System	A	B	C	D	E	F	G	H	I	J
1	William Hamilton	Yes										
2	Rachel Shakked	Yes										
3	Emily Benson	Yes										
4	Charles Hannon	Yes										
5	Benjamin Miller	Yes										
6	Matthew Austin	Yes										
7	Donald Hohman	Yes										
8	Rebecca Johnson	No	No	No	No	No	No	No	No	No	Yes	Yes
9	Glenn Wera	Yes										
10	Matthew Abdel	Yes										

Reviewer Responses to Structured Review Form Questions

All reviewers are asked 16 structured review questions which have been adapted from the Appraisal of Guidelines for Research and Evaluation (AGREE) II Criteria*. Their responses to these questions are listed on the next few pages.

Table 5. Reviewer Responses to Structured Review Questions 1-4

Reviewer Number	Name of Reviewer	1. The overall objective(s) of the guideline is (are) specifically described.	2. The health question(s) covered by the guideline is (are) specifically described.	3. The guideline's target audience is clearly described.	4. There is an explicit link between the recommendations and the supporting evidence.
1	William Hamilton	Neutral	Disagree	Disagree	Disagree
2	Rachel Shakked	Strongly Agree	Strongly Agree	Agree	Agree
3	Emily Benson	Agree	Agree	Strongly Agree	Agree
4	Charles Hannon	Agree	Agree	Agree	Agree
5	Benjamin Miller	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
6	Matthew Austin	Strongly Agree	Strongly Agree	Strongly Agree	Disagree
7	Donald Hohman	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
8	Rebecca Johnson	Agree	Agree	Disagree	Neutral
9	Glenn Wera	Agree	Agree	Agree	Agree
10	Matthew Abdel	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree

Table 6. Reviewer Responses to Structured Review Questions 5-8

Reviewer Number	Name of Reviewer	5. Given the nature of the topic and the data, all clinically important outcomes are considered.	6. The patients to whom this guideline is meant to apply are specifically described.	7. The criteria used to select articles for inclusion are appropriate.	8. The reasons why some studies were excluded are clearly described.
1	William Hamilton	Agree	Neutral	Agree	Neutral
2	Rachel Shakked	Strongly Agree	Disagree	Strongly Agree	Strongly Agree
3	Emily Benson	Agree	Strongly Agree	Agree	Strongly Agree
4	Charles Hannon	Strongly Agree	Neutral	Strongly Agree	Strongly Agree
5	Benjamin Miller	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
6	Matthew Austin	Disagree	Strongly Agree	Strongly Disagree	Disagree
7	Donald Hohman	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
8	Rebecca Johnson	Neutral	Neutral	Agree	Disagree
9	Glenn Wera	Agree	Agree	Agree	Agree
10	Matthew Abdel	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree

Table 7. Reviewer Responses to Structured Review Questions 9-12

Reviewer Number	Name of Reviewer	9. All important studies that met the article inclusion criteria are included	10. The validity of the studies is appropriately appraised.	11. The methods are described in such a way as to be reproducible	12. The statistical methods are appropriate to the material and the objectives of this guideline
1	William Hamilton	Neutral	Agree	Agree	Agree
2	Rachel Shakked	Strongly Agree	Strongly Agree	Strongly Agree	Neutral
3	Emily Benson	Strongly Agree	Agree	Strongly Agree	Strongly Agree
4	Charles Hannon	Strongly Agree	Agree	Strongly Agree	Strongly Agree
5	Benjamin Miller	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
6	Matthew Austin	Strongly Disagree	Strongly Disagree	Strongly Disagree	Disagree
7	Donald Hohman	Strongly Agree	Strongly Agree	Strongly Agree	Agree
8	Rebecca Johnson	Neutral	Agree	Neutral	Agree
9	Glenn Wera	Agree	Agree	Agree	Agree
10	Matthew Abdel	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree

Table 8. Reviewer Responses to Structured Review Questions 13-16

Reviewer Number	Name of Reviewer	13. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed.	14. Health benefits, side effects, and risks are adequately addressed.	15. The writing style is appropriate for health care professionals.	16. The grades assigned to each recommendation are appropriate.
1	William Hamilton	Neutral	Neutral	Disagree	Disagree
2	Rachel Shakked	Strongly Agree	Agree	Strongly Agree	Strongly Agree
3	Emily Benson	Agree	Agree	Strongly Agree	Agree
4	Charles Hannon	Strongly Agree	Agree	Agree	Strongly Agree
5	Benjamin Miller	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree
6	Matthew Austin	Strongly Disagree	Agree	Agree	Strongly Disagree
7	Donald Hohman	Strongly Agree	Agree	Agree	Agree
8	Rebecca Johnson	Disagree	Disagree	Agree	Disagree
9	Glenn Wera	Agree	Agree	Agree	Agree
10	Matthew Abdel	Strongly Agree	Strongly Agree	Strongly Agree	Strongly Agree

Would you recommend these guidelines for use in clinical practice?

Reviewer Number	Name of Reviewer	Would you recommend these guidelines for use in clinical practice?
1	William Hamilton	Would Not Recommend
2	Rachel Shakked	Recommend
3	Emily Benson	Recommend
4	Charles Hannon	Recommend
5	Benjamin Miller	Strongly Recommend
6	Matthew Austin	Would Not Recommend
7	Donald Hohman	Strongly Recommend
8	Rebecca Johnson	Recommend
9	Glenn Wera	Recommend
10	Matthew Abdel	Strongly Recommend

Reviewer Detailed Responses and Editorial Suggestions

Reviewer #1, William Hamilton, M.D

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: The response(s) below also includes all editing suggestions received from the Additional Comments section of the structured review form.
1	William Hamilton, M.D.	The Hip Society	A. In general, it would be helpful in reviewing the document to first see the PICO question that was used as the starting point for the final recommendation. Without knowing what question was being asked, it makes it somewhat difficult to judge the recommendation. B. I found the entire document lacking consistency and clarity. The recommendations should be looked at as a whole, there were some that contradicted each other. The rationale should be written in a consistent manner across the document and should support the recommendation being made. Many of the rationales written were vague and lacked details and therefore did not support the recommendation. Acupuncture: C. It is unclear the setting of the acupuncture studies (fracture surgery, arthroplasty, arthroscopy, etc), so it is therefore difficult to interpret whether this intervention would be applicable to any given surgeons practice. D. The 2 recommendations appear at first to contradict one another. Recommendation a) suggests evidence for improved pain scores with accupuncture, yet recommendation b) concludes the opposite. This leaves the reader wondering what the data shows and how it should be applied to one's practice. Acupressure: E. My impression is that most practicing Orthopedic surgeons would not appreciate/understand the difference between acupuncture and acupressure. I also think there is limited if any use of these modalities in the management of perioperative pain. F. Also, it's once again unclear the setting that these modalities were utilized (i.e. postsurgical pain, injury, or the treatment of a condition.). It would be difficult to implement this in practice without this context.

			Compression: G. Is compression being used as a modality to treat postoperative pain, reduce swelling from injury, etc? And what body part is being compressed? This may be much different if implemented with ankle surgery vs a pelvic fracture? Cryotherapy: H. The recommendation appears to compare cryo-compression and control/ice/circulating water. This once again makes interpretation difficult to interpret. Is this a comparison between cryo-compression and control (no cryo), or normal cryotherapy without compression? The rationale appears to be referencing studies that looked at cryotherapy, no mention of cryo-compression was made in the rationale. In reading the rationale- it appears that there were several studies that demonstrated the benefits of cryotherapy, some may have not shown a difference, but it makes me question why the strength of this recommendation was downgraded, when cryo appears to provide benefit, is widely used and believed to be of benefit. It's unclear why this was downgraded? It would be beneficial for the rationale to state why the strength was downgraded. I. In the cost effectiveness paragraph, it concludes that a large cost would be required for utilizing a machine or take-home device. Can't cryotherapy also be delivered with low cost over the counter solutions (ice bags, moldable ice packs, bag of frozen peas?) Early Mobilization: J. Once again it would be helpful to know what condition was being examined to answer this PICO question. K. I don't entirely understand the nature of the question, or the recommendation. Surgeons recognize the benefits of early mobilization, and it's not usually to reduce short term pain or opioid use, so why even bother asking a question like this? I would hesitate releasing a recommendation that questions the value of early mobilization when it has become the clear standard of care. L. Certainly, in hip and knee arthroplasty, the entire surgeon community has moved towards early mobilization, so it now represents the "standard" treatment. I see no value in this recommendation in the arthroplasty community, and in fact may cause a detriment to care. Massage M. What condition is massage being used to treat? Postoperative pain? I've never heard of the routine use of massage in this setting. I'd be cautious recommending the

			routine use of massage as it would have complicated ramifications for treatment and reimbursement following surgery. Neuromuscular EStim N. Same, would be helpful to know what condition the studies are studying TENS O. Same, would be helpful to know what condition the studies are studying Peri-op Injections P. This is the question and recommendation that I have the most trouble with of all listed, because it specifically references total hip and knee arthroplasty. It is very hard to follow, from the heading through the future research. I'm still not sure what is being recommended here. Q. The title of the section is peri-op injections, which for total hip and knee I interpret as a periarticular injection administered at the surgical site to reduce postoperative pain. There is ample evidence to demonstrate that these injections are helpful in reducing postoperative pain and opioid use in total hip and knee. R. However, the actual recommendation does not really discuss peri-articular injections, rather the benefits of local vs regional anesthesia. First, I am not aware of any surgeon performing total hip and knee replacements under local anesthesia. These surgeries are either performed under regional (Spinal/epidural) or general anesthesia. Various types of general anesthesia can be used, and regional nerve blocks can reduce postoperative pain. The rationale is so vague that it fails to explain what is being studied in the referenced studies. S. Second, I do not think it's appropriate to group THA, TKA, knee arthroscopy, ACLR, and shoulder arthroscopy together as they are quite different surgeries. T. Third, the primary purpose of peri-op injections is to reduce pain scores and opioid use, so the recommendation concluding that there is no difference in "patient outcomes" is vague, and in my field, not supported with our literature. U. Lastly, the rationale does not convey what was learned from the studies reviewed, it only says no difference in patient outcomes was shown. Only THA and TKA studies were included in the rationale, so how could ACLR, knee scope and shoulder arthroscopy be included? This rationale would need to be greatly expanded to specify what was being studied and the detailed findings of the studies. There is such

			heterogeneity of these studies that grouping them together as is done here and simply concluding that there are no differences in patient outcomes is non-sensical. V. This entire recommendation needs to be rewritten and clarified so it provides guidance to the practicing surgeon. Guided Relaxation Therapy W. This is one of the few sections where the actual procedure being studied is referenced in the rationale (joint arthroplasty- did not specify which joint) X. In the 3 studies referenced in the rationale, 2 of the 3 studies noted benefits of the relaxation therapy (decreased anxiety and better sleep, less pain). In a field void of well performed studies, it seems odd to make a moderate recommendation against a modality when 2 of the 3 available studies demonstrated some benefit. I recognize the CPG process and that this CPG is specifically targeting pain and opioid use. Y. One comment that I would note here is that many of the recommendations reference "standard treatment". It is quite vague what "standard treatment" means, especially in a guideline such as this. I assume it means- no relaxation therapy, but that doesn't mean the physician, nurses, and therapists aren't providing some form of relaxation through their words and actions? Music therapy Z. Would be more specific identifying what "musculoskeletal surgery" was studied in the rationale. Patient education AA. This rationale is written so the reader can interpret the findings in relation to the specific surgery that was performed. Each study referenced describes the surgery being performed, the intervention, and outcome. This format should be used more routinely in the rationale of the other recommendations. BB. For some of these recommendations, most notably this one, I'm left wondering why the committee decided to ask the specific question, and what benefit it might have to practicing surgeons? The conclusion also doesn't align with widely held beliefs within the medical community regarding the importance of patient education. Once again, I recognize the goal of the CPG is focused on pain and opioid use, but any sentiment discouraging patient education released by AAOS should be done with caution.

CC. Patient education and communication in the perioperative period are routinely hailed as paramount to achieving patient satisfaction and improved outcomes. Surgeons are constantly searching for new ways to improve communication and education to help patients through the surgical episode. Regular reviews of HCAHPS scores put communication and education as the most important factors to improving scores. More recent data (likely published after the period of review of this committee) shows education does improve the rates of opioid disposal.\

Virtual reality

DD. With so little data on this futuristic treatment modality, why choose to address it in this CPG? With so many recommendations combined with the paucity of data, this recommendation could be removed. Maybe this workgroup could add a section at the conclusion of the recommendations that summarizes the questions that were addressed, didn't have quality data to draw a conclusion, yet presents an opportunity for future research?

Intra-articular opioids vs NSAIDS

EE. The entire flow of these recommendations is hard to follow. Maybe they will be subject to reorganization, but there are so many esoteric recommendations on alternative treatments (acupressure, music therapy, relaxation treatment, etc) and then appears a recommendation on intra-articular injections. Its also a bit odd that the recommendations specifically studies intra-articular opioids vs NSAIDs, when there are many ingredients that surgeons use in peri-articular injections, why only compare these 2?

FF. The recommendation once again fails to specify several key points in the rationale that would be critical to the practicing surgeon in interpreting the data. What condition is being treated? What timeframe is being studied (pre-op, intraop, postop)? What joint is being studied?

GG. The recommendation discusses intra-articular opioids and NSAIDs. Is the NSAID also intra-articular, or only the opioid. There is data supporting the use of Toradol in peri-articular injections following total knee arthroplasty, so I'm not sure why that data was not examined.

HH. The Benefits/Harms section delves into all of the pain control modalities following total joint arthroplasty, but it appears that the recommendation was specifically asking whether opioids or NSAIDs are superior in the injection. This is another good example of why providing the PICO question that was posed may help interpret the data.

			Opioid combo vs NSAIDs II. It appears that this recommendation is suggesting that it is preferable to use oral opioids, and some combination of oral opioids, to REDUCE the use of NSAIDs? This approach is the exact opposite of what surgeons have been promoting for decades, that the use of peri-operative NSAIDs will help reduce the reliance on opioids. Personally I would eliminate this recommendation as it can only confuse surgeons who are providing proven multi-modal strategies for their patients. JJ. The rationale should better explain the study, the procedure being studied, and specify what opioid combination means. Tramadol combo vs NSAID KK. See above for rationale why this recommendation seems unneccesary. This is a very specific question comparing 2 commonly used medications that are used as part of surgeons multimodal strategy. There is only one study looking at the outcome, and it does not help surgeons in any way guide the treatment of their patients. LL. There appear to be too many recommendations that simply are not supported by studies and are not answering questions that surgeons have. Fentanyl patch vs Morphine MM. In what world are surgeons currently trying to decide between using a fentanyl patch and IV morphine to treat perioperative pain for our most commonly performed procedures. This document diminishes in relevance as it proceeds. With one moderate quality study on this question, AND the entire medical community moving away from the use of strong narcotics like these, I'd strongly recommend this recommendation be removed. Tramadol vs NSAID NN. It seems like this question was just addressed 2 recommendations before? This represents another very specific question that surgeons are not asking. Surgeons routinely use both Tramadol and NSAIDs in their multimodal strategies, so it's reasonable to ask what is the value of each individual ingredient in the cocktail, but I see no need to specifically compare 2 ingredients in the multi-modal pathway. Anti-depressants OO. Seems like this recommendation could also be eliminated due to the lack of data combined with the overwhelming number of recommendations being proposed. COX-2

PP. It feels as if the same workgroup did not function collaboratively on these recommendations, because at times they contradict one another. In the Opioid combo vs NSAIDs recommendation, the rationale suggests using the opioid combo medicine to reduce the use of NSAIDs, and in this recommendation, COX-2 usage is recommended to reduce the use of opioids. I believe the recommendations should act cohesively to provide guidance to practicing surgeons. In the event that available data is contradictory or prevents making cohesive recommendations, the workgroup should edit, modify, or eliminate certain questions to prevent this confusion.

QQ. This specific COX-2 recommendation is reasonable. However, I question the final part of the sentence that says "there is no difference in adverse events". What does this mean? Is there no difference in adverse events compared to placebo? This is what the rationale suggests, in which case the COX-s agents would be considered very safe?!

RR. This is another rationale that is more explanatory than others and helpful to justify the recommendation. I would use this as a template to edit and augment others that are too vague and simplistic.

Oral Acetaminophen

SS. This is an example of a recommendation that would be helpful to practicing surgeons. I would be more specific in the wording of the recommendation, however. The use of "patient outcomes" is vague and could be replaced with pain scores and opioid use to better inform surgeons of the findings. I would prefer that the rationale be written in the same format as the COX-2 rationale so that it specifies which surgery is being studied, the timing of administration, and the outcomes being measured.

Acetaminophen

TT. This can be combined with the previous recommendation do make a 1a and 1b recommendation on acetaminophen. The recommendation is very vague and provides little help to practicing surgeons because it fails to identify the timeframe or setting that acetaminophen is helpful. If the workgroup intended this to be part of a perioperative protocol, part of a multi modal program, or used around the time of specific surgeries, I believe those findings should be stated in the recommendation.

UU. The rational should be structured to read like the COX-2 rationale, as this is vague and fails to inform the reader of the detailed findings of the study.

Acetaminophen/NSAID Combination Treatment vs NSAID

VV. I believe this document suffers from information overload with too many recommendations, and this is another one that could be removed. The guidelines have

			just finished showing that COX-2 meds and acetaminophen individually are helpful to reduce pain, so why have a guideline saying that the combination of the 2 is superior over just one? WW. It is now standard of care for surgeons in the arthroplasty community to be using these medications in combination. Gabapentanoids XX. This is an oddly worded combination of recommendations. The first sentence concludes that there is no difference between gabapentin and placebo, then says, "however", be concerned about side effects. It seems like this should say- gabapentin isn't better than placebo, "and" surgeons should be wary of the side effects. Pregabalin YY. Pregabalin is also a gabapentinoid medication, so could be combined with the previous recommendation on gabapentaniods. This recommendation appears appropriately worded. ZZ. The rational would benefit from more granularity explaining which surgery is being studied and more details on the intervention and outcomes. Ketamine AAA. This is a reasonable recommendation, but could use editing. Why use the word "Strong evidence" in the wording when the strength of recommendation takes care of that? BBB. The rationale should be expanded to better specify the details of the study. CCC. In the benefits/harm paragraph- are these findings associated with the referenced studies, or is this a commentary from the workgroup? Mentioning that long term Ketamine use leads to elevated liver enzymes and cystitis seems out of place in a recommendation that is discussing a single intraoperative use? DDD. Furthermore, in an effort lead by the AAHKS organization, where the AAOS team was utilized to query articles, a total of 6 high quality studies were found to evaluate intraoperative ketamine on opioid consumption after primary TJA (pending publication). It seems odd that only 2 studies were found in this effort? Oral Relaxants

			EEE. With only one study focused on the use of this medication after TKA and THA, and the known side effects, AND that this is not a medication that is mentioned as part of any standard multimodal program, this recommendation could be removed.

Workgroup Response to Reviewer #1

Dear William Hamilton, M.D.,

Thank you for your expert review of the Clinical Practice Guideline for Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/ Pelvis Surgery. We will address your comments by guideline section in the order that you listed them.

A. All PICO questions are presented in eAppendix 1.

B. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

C. The majority of the supporting evidence covered total knee arthroplasty, with one article including arthroscopy and anterior cruciate ligament repair.

D. All supporting evidence for this recommendation utilized auricular and acupuncture compared to a sham whereas recommendation A looks at acupuncture alone compared to a control.

E. Acupuncture and acupressure were included in the a priori scope as determined by the work group members.

F. All supporting evidence from this recommendation utilized total knee arthroplasty.

G. The majority of the supporting evidence covered total knee arthroplasty, with one article included hindfoot and ankle surgery.

H. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback. The recommendation was downgraded due to inconsistency in the findings.

I. This recommendation, and the supporting evidence, refer specifically to the use of cryotherapy machines.

J. The majority of the supporting evidence covered total knee arthroplasty, with eight articles including Achilles tendon rupture repair, ankle fracture, tibial shaft fracture, ankle surgery, shoulder arthroplasty, distal radius fracture, RC repair, radial head fracture.

K. Physical treatment options, to include early mobilization, was included in the a priori scope as determined by the work group.

L. Physical treatment options, to include early mobilization, was included in the a priori scope as determined by the work group.

M. The supporting evidence for this recommendation showed improved postoperative pain.

N. All supporting evidence for this recommendation covered total knee arthroplasty, knee arthroscopy, and ACL repair.

O. The majority of the supporting evidence covered total knee arthroplasty, with three articles including fracture around the hip, ACL repair, total hip arthroplasty, ankle fracture.

P. No response.

Q. This recommendation refers specifically to anesthesia.

R. The workgroup has added additional details to the rationale.

S. This recommendation has been rewritten; anterior cruciate ligament reconstruction and shoulder arthroscopy have been removed.

T. All patient outcomes were addressed (pain, opioid consumption and function) by the workgroup, and all showed no difference described in the rationale.

U. The recommendation has been edited; knee arthroscopy, ACL reconstruction, and shoulder arthroscopy have been removed.

V. The recommendation has been rewritten to clarify the specific outcomes and procedures.

W. No response.

X. All supporting evidence for this recommendation showed no difference in opioid use as well as no difference in pain; the workgroup opted against making a directional statement.

Y. The work group used the verbiage found in the supporting studies regarding standard treatment; a statement regarding inconsistency in reporting of what constituted standard treatment has been added to the Future Research section.

Z. This has been edited to clarify what was studied (i.e. elective hip, knee, and shoulder surgery).

AA. No response.

BB. The work group determined that patient education is relevant to pain alleviation and included it in the a priori scope of the guideline.

CC. No response.

DD. The supporting evidence was found in the search directed by the work group's PICO question regarding cognitive treatments.

EE. The recommendations are presented in the order by which the PICO questions were created. Additional attention to this order will be applied to future. Opioids vs NSAID was included in the scope included by the workgroup. Evidence for intra-articular injection of opioid vs NSAID was the only evidence that fit the inclusion criteria.

FF. All supporting evidence for this recommendation utilized TKA and arthroscopic meniscectomy both intraoperatively and postoperatively.

GG. All supporting evidence for this recommendation utilized intra-articular administration of either NSAID or opioid.

HH. All PICO questions are presented in eAppendix 1.

II. The recommendation is in favor of opioid combination (specifically naproxen sodium-codeine phosphate as examined in Bali, 2016) rather than opioid or NSAID in isolation.

JJ. No response.

KK. Opioid combination compared to NSAID was included in the a priori scope as determined by the work group members.

LL. No response.

MM. This analysis was included in the a priori scope as determined by the work group and the resulting evidence warranted a limited strength recommendation.

NN. All opioids were included in the a priori scope as determined by the work group.

OO. In the absence of reliable evidence, the work group felt it was important to make an expert opinion statement on the topic.

PP. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

QQ. The rationale has been edited to include more detail on the supporting studies.

RR. No response.

SS. This recommendation has been edited to specify the patient outcomes (i.e. pain scores and opioid use).

TT. All supporting evidence for this recommendation utilized preoperative, postoperative and intraoperative administration of acetaminophen.

UU. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

VV. Acetaminophen/NSAID combination was included in the a priori scope as determined by the work group members and a directional statement was warranted.

WW. Acetaminophen/NSAID combination was included in the a priori scope as determined by the work group members.

XX. The work group used a clause beginning with 'however' consistently across recommendations as applicable.

YY. No response.

ZZ. The rationale has been edited to include more detail on the supporting studies.

AAA. The use of the GRADE Evidence-to-Decision Framework may result in different strengths for level of evidence and strength of recommendation.

BBB. No response.

CCC. The benefits/harms paragraph has been edited.

DDD. The inclusion criteria for this guideline included 30 or more patients per group with outcome follow-up times of admission to 90 days.

EEE. Oral relaxants were included in the a priori scope as determined by the work group members and moderate evidence was found in support of a directional statement.

Reviewer #2, Rachel Shakked, M.D.

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: The response(s) below also includes all editing suggestions received from the Additional Comments section of the structured review form.
2	Rachel Shakked, M.D.	American Academy of Orthopaedic Surgeons	A. Overall objective is to evaluate the evidence for various methods to alleviate pain in the setting of orthopaedic injury and surgery as well as to identify areas where additional research is needed. Specifically, modalities will be assessed for their ability to alleviate pain, improve function, and reduce opioid consumption. B. Target audience is orthopaedic surgeons and "other qualified healthcare professionals". Consider providing specific examples of other qualified healthcare professionals. C. Some of the rationale could use a little more detail. D. Opioid use, functional outcome, and pain scores are appropriate outcomes to consider for this clinical practice guideline. E. Although the CPG states that this applies to patients after orthopaedic surgery or injury, certain questions, especially those regarding medication usage, apply to a specific subset of patients that should be further clarified. F. Statistical methods were not included. G. Some guidelines could expand on the side effects of the proposed intervention. H. Consider including a discussion that these are general recommendations and certain conditions may respond better to specific interventions than other conditions. For example, massage/acupuncture work better in terms of pain relief for low back pain than for an acute ankle fracture. I. Page 18 Line 463: consider changing "capability" to "function" J. Page 19 Lines 518-519: fix grammatical error K. Page 19 Lines 518-521: consider changing "people" to "patients"

			L. Page 20 Line 565: grammatical error M. Page 27 Line 765-766: grammatical error “compared with versus” N. Page 27 Line 742: Confusing to combine general and auricular acupuncture under one recommendation heading, but then discuss them separately in the rationale. Would consider dividing into another section or just make the recommendation for or against acupuncture in general without specifying auricular. O. Page 29 Line 792-793: Did all of the papers in the rationale review effects of auricular acupressure or general acupressure? If not specific to auricular acupressure, the recommendation should just state “acupressure” rather than “auricular acupressure” P. Page 33 Line 946: Recommendation only includes one of the goals of the CPG: pain level. Consider adding that no conclusion can be drawn about the effect of massage on function or opioid consumption. Q. Page 36 Line 1045: The rationale does not support the recommendation statement. TKA and THA articles are listed, but there is no discussion about knee arthroscopy, ACL reconstruction, and shoulder arthroscopy. Furthermore, I would have expected some of these studies to include post-op narcotic consumption. The recommendation could include a comment on opioid use. R. Page 38 Line 1087: Is there literature about single shot peripheral nerve blocks for TSA? Catheters are not always available at certain surgical sites, but single shot nerve blocks usually are available. S. Page 38 Line 1090: Consider changing this recommendation to moderate as there is only 1 high quality study and 1 moderate quality study. Otherwise, explain why there was no evidence for benefit of peripheral anesthesia in TKA, THA, knee arthroscopy, ACL reconstruction, and shoulder arthroscopy (previous recommendation on page 36) but there is benefit to peripheral anesthesia in TSA. T. Page 46 Lines 1347-1350: The Huang 2017 article discussion should address the purpose of this CPG – did the perioperative education affect pain scores, functional scores, or opioid consumption? U. Page 48 Line 1417-1422: Since this is a newer technology that is not widely utilized, consider a statement explaining how VR is utilized and how it is hypothesized to make a difference in orthopaedic patients.

			V. Page 49 Lines 1479-1480: The authors indicate that there is no difference in patient outcomes between opioid injection v. nsaid injection. In addition to this recommendation, consider the question of whether the literature supports intra-operative injection in general to reduce pain, improve function, and reduce narcotic consumption. W. Page 51 Line 1503: This guideline should be more specific. In isolation, it seems like it is an endorsement to use additional opioids. Typically a multimodal pain approach is better than opioids alone so the question here should actually be opioid v. opioid+NSAID. Furthermore, limiting opioids to the immediate post-operative period is ideal, so a multimodal approach to non-surgical orthopaedic pain should usually exclude opioids. X. Page 51 Lines 1510-1512: The rationale should include more detail. Y. Page 51 Line 1516: reword the sentence to avoid using the word "combination" twice. Z. Page 51 Lines 1517-1518: Should include NSAID side effects when discussing the harms of a multimodal pain program. AA. Page 52 Lines 1549-1551: Clarify which group showed decreased side effects and independence from the need for walker. BB. Page 52 Lines 1555: Avoid the phrase "it has been recommended" since this CPG is not recommending tramadol combination use over other modalities, like NSAIDs. CC. Page 53 Lines 1590-1591: Include the results of this study. DD. Page 54 Line 1627: The study result indicates no difference in pain level or opioid consumption. Consider editing the recommendation to reflect that. EE. Page 55 Lines 1682-1684: Include study results. FF. Page 56 Lines 1719-1720: Since this is a strong recommendation, consider a more specific statement including type of surgery for which it has been proven beneficial. Can eliminate the statement about adverse events – this can be addressed in the body of the recommendation.

			GG. Page 56 Lines 1743-1744: Would omit discussion of any differences between groups if statistical significance was not achieved. HH. Page 57 Line 1783: Cox-2 selective inhibitors are contraindicated in patients with cardiac history. This should be included as potential harm. II. Page 58 Lines 1810-1811: The studies show no difference in pain scores or opioid use. No mention is made of functional outcomes. Therefore, the recommendation should state that there is no difference in opioid requirement or pain scores between oral acetaminophen and IV acetaminophen. JJ. Page 66 Lines 2090-2091: The recommendation should read that there are no significant differences in patient outcomes, pain levels, or opioid use between oral relaxants and placebo

Workgroup Response to Reviewer #2

Dear Rachel Shakked, M.D.,

Thank you for your expert review of the Clinical Practice Guideline for Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/ Pelvis Surgery. We will address your comments by guideline section in the order that you listed them.

A. Thank you for your comments.

B. Additional information has been added to further define "other qualified healthcare professionals.

C. No response.

D. No response.

E. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

F. The structured review methodology applied to all recommendations is detailed in the Methods section.

G. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

H. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

I. Thank you for your comment. The draft has been modified.

J. Thank you for your comment. The draft has been modified.

K. Thank you for your comment. The draft has been modified.

L. Thank you for your comment. The draft has been modified.

M. Thank you for your comment. The draft has been modified.

N. All supporting evidence for this recommendation utilized auricular with acupuncture.

O. All supporting evidence for this recommendation utilized auricular acupuncture.

P. The work group elected to only include pain level in the recommendation.

Q. The recommendation has been edited; knee arthroscopy, ACL reconstruction, and shoulder arthroscopy have been removed.

R. All supporting evidence for this recommendation utilized local articular injection compared to nerve block.

S. This recommendation was upgraded from Moderate to Strong using the GRADE Evidence-to-Decision framework.

T. The discussion of the Huang 2017 article has been edited for clarity.

U. The work group elected to include the need for investigation into medical applications of virtual reality in both the acceptability and future research sections.

V. The scope of this recommendation was limited to articles containing opioid injections and NSAID and showed no difference in pain, opioid use and adverse events.

W. The structured review methodology as described in the methods section is applied to the a priori PICO questions as developed by the work group. These PICO questions did not include multimodal pain management.

X. The workgroup has added additional details to the rationale.

Y. Thank you for your comment. The draft has been modified.

Z. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

AA. The improvement group has been clarified in the rationale.

BB. Thank you for your comment. This sentence has been edited.

CC. Additional information has been added to the rationale.

DD. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

EE. Additional information has been added to the rationale.

FF. Majority of supporting evidence included TKA and THA patients, with one article looking at ACL repair. The workgroup didn't want to specifically state the type of surgery within the recommendation and described the surgery type within the rationale.

GG. The rationale has been edited.

HH. Additional information has been added to the potential harms section for this patient population.

II. No response.

JJ. The recommendation has been edited to state "…patient outcomes, pain levels, or opioid use…"

Reviewer #3, Emily Benson, M.D.

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: The response(s) below also includes all editing suggestions received from the Additional Comments section of the structured review form.
3	Emily Benson, M.D.	American Academy of Orthopaedic Surgeons	A. First of all I'd like to congratulate the group on the excellent effort and work done here. Here are my thoughts: B. A section on cannabis would be important considering the widespread and growing use of it in orthopedic patients. C. Many of the sections do not include any evidence or articles on orthopedic trauma patients, but yet recommendations are made that suggest an impact in these patients as well. It can be misleading to group elective patients in with trauma patients, such as in the section 1328 on patient education. It may be helpful whenever possible to make the distinction between elective and non-elective orthopedic surgery. D. Relatively little attention is given to opioids in this CPG in comparison to other modalities to treat pain, which is surprising considering our current national prescribing habits within our orthopedic community and our opioid epidemic. Is there a reason why there were no sections on duration of opioid treatment, risk of opioid dependence, incidence of overdose, etc? E. Short-acting opioids behave differently from sustained release opioids and have different side effects yet this CPG doesn't make the distinction. This may be beneficial to address. F. Regional anesthesia in fracture surgery is controversial and highly debated and would be great to be included in this CPG. You do include a section on elective surgeries and regional blocks, but not in fracture patients. G. Thank you!

Workgroup Response to Reviewer #3

Dear Emily Benson, M.D.,

Thank you for your expert review of the Clinical Practice Guideline for Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/ Pelvis Surgery. We will address your comments by guideline section in the order that you listed them.

A. Thank you for your comments.

B. Cannabis was not included in the scope of this guideline as defined by the work group.

C. The defined scope, and therefore the resulting literature search, included all musculoskeletal injuries, full details regarding the scope can be found in the Introduction as well as in eAppendix 1.

D. The workgroup opted not to make a statement on duration of opioid treatment, risk of opioid dependence, and incidence of overdose.

E. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

F. Perioperative injection treatment options were included in the a priori scope as determined by the work group.

G. Thank you.

Reviewer #4, Charles Hannon, M.D., M.B.A

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: The response(s) below also includes all editing suggestions received from the Additional Comments section of the structured review form.
4	Charles Hannon, M.D., MBA	American Academy of Hip and Knee Surgeons	A. I would like to commend the Development Group Members as well as the AAOS & METRC Staff for their fantastic work on this evidence-based clinical practice guideline on pharmacologic, physical, and cognitive pain alleviation for musculoskeletal extremity/pelvis surgery. The development of a clinical practice guideline requires significant time, energy, enthusiasm and collaboration and all involved should be congratulated. This clinical practice guideline will serve as a great resource for AAOS members to improve the quality of the care they provide their patients. Below, please see some suggestions for improvement or areas for clarification that will hopefully improve the guideline. Thank you for the opportunity to review the guidelines and congratulations on a job well done. General Comments: Scope B. Based on the introduction it is not explicitly clear if the recommendations included are for both nonoperative treatment of musculoskeletal injuries as well as post-operative treatment after surgery for musculoskeletal injuries (Lines 463 – 464, 549 - 552). In addition, it is unclear if the recommendations included are for acute pain from injury and surgery only or for chronic pain as well. I think it would be beneficial for the authors to be more specific in the introduction regarding the specific patient population the recommendations apply to. Providing some clarification regarding the intent and scope of the guideline will help readers better understand how to apply the recommendations. C. In addition, I recommend that the authors mention that all musculoskeletal injuries and surgeries were not studied for each treatment and that this limitation should be considered when interpreting the data and recommendations. Title D. The title of the clinical practice guidelines specifically refers to surgery, but throughout the introduction there is mention that this is also meant to serve treatment of injuries in addition to surgery. If it is meant to include treatment of musculoskeletal injuries as well you may consider changing the title to “Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/Pelvis Injury & Surgery”.

			Recommendations E. The recommendations are vague for many of the treatments listed and may not have broad evidence supporting their use for all musculoskeletal injuries & surgeries. For example, the cognitive/behavioral treatment recommendation states that there is "no difference in patient function or pain outcomes between cognitive behavioral therapy (CBT) and standard treatment." The two studies cited only study CBT in total knee arthroplasty patients (TKA). The authors may either consider specifying in the recommendation that this is for TKA patients or in the rationale mention that the findings on CBT in the TKA literature is being extrapolated to other musculoskeletal injuries & surgeries. A third option may be to include a limitations section at the beginning of the clinical practice guideline that discusses this. I would recommend one or more of these approaches be taken towards all of the recommendations. F. The term "standard treatment" is used as the comparison in the recommendations. Standard treatment is very different across all studies and is interpreted differently between providers. "Control" may be a better term to use in the recommendations. Rationales G. For several recommendations, the rationales were particularly vague. The injury or surgery context the treatments were studied in was not included for a majority of the rationales. I would recommend that the rationale for many treatments be expanded to include at the minimum the specific injuries or surgeries they were studied in because this is very valuable information for the reader. The cognitive/behavioral, patient education, & COX-2 rationales are great examples that provide helpful details and context for the readers. I felt that these rationales included enough information that allowed the reader to better understand how the data was interpreted and applied to make the recommendation and the strength of recommendation. H. Several of the recommendations were downgraded to a Limited strength despite several high-quality studies available. I think it would be very beneficial for readers to include in the rationale the reason why the recommendation was downgraded. Limitations I. Adverse events are mentioned in some of the recommendations, but not all. Unfortunately, in clinical practice guidelines including high quality studies such as this it is difficult to draw conclusions regarding the safety of a drug or treatment. In randomized controlled trials, there is significant heterogeneity and variability in the reporting of harm-related results particularly in the orthopedic literature (Goldhahn et al. JBJS 2009, Pitrou et al. Arch Intern Med 2009). It may be worth discussing this as a limitation in the introduction.

			Specific Comments J. Line 531 – Is underling supposed to be underlying? Acupuncture K. Lines 744 – 748 – For recommendation B, is this in auricular or other acupuncture alone or with standard treatment? Compression L. Line 837 – It is mentioned in the resource utilization section that all studies included in the rationale used a compression machine. It would be beneficial in the rationale to clarify that these studies evaluated the use of a compression machine and not compression with the use of wraps etc. M. Line 840 – Did this study compare compression alone versus standard care or standard care in addition to compression versus standard care alone? N. Given that compression with wraps etc. is often utilized as one of many approaches to reduce swelling and pain after musculoskeletal injury and surgery, I am concerned with a recommendation that says there are "no significant differences in pain or function with compression." Given the studies specifically evaluated compression machines maybe it is beneficial to specify "compression machines" in the recommendation itself. Cryotherapy O. Line 868 – "suggesting" should be changed to "suggests" Early Mobilization P. Lines 927 – While it does not directly address the PICO question, there are secondary benefits to early mobilization such as VTE prevention that may be considered in the use of early mobilization. Q. Similar to compression, I have concern with a recommendation against early mobilization. Early mobilization may not be beneficial for treatment after an ACL reconstruction or after fixation of a fracture, but is clearly beneficial after hip and knee arthroplasty. It may be beneficial in the rationale to explain that this recommendation may not apply to all orthopaedic injuries and surgeries. Neuromuscular Electrical Stimulation R. Line 955 – While the NEMS units themselves are economical, there is a significant cost in the outpatient setting in paying providers to administer the treatment. With regards to feasibility, there is also a need for appropriately trained personnel.

			S. Line 1001 – Strong recommendations typically imply that future research is not likely to change the recommendation. However, the future research section highlights the several major limitations of the current literature. Based on this section, the authors may want to consider downgrading this recommendation as I agree there are inconsistent results. Transcutaneous Electrical Nerve Stimulation T. Lines 1026 – Similar to NEMS, there is a significant cost in the outpatient setting in paying providers to administer the treatment. With regards to feasibility, there is also a need for appropriately trained personnel. Peri-Op Injections U. Line 1036 – What specific patient outcomes were listed? Previous recommendations specify functional outcomes, pain and opioid consumption. Specifically listing the outcomes analyzed would be beneficial. V. Line 1045 – Was the combination of local and regional anesthesia studied and compared to local and regional anesthesia alone? Cognitive/Behavioral Treatment W. Line 144 – I commend the authors for the detailed rationale. This very nicely summarizes the data included in the CPG. It provides important analysis of the data that better explains how the recommendation was formulated and how the strength of recommendation was chosen. Intra-Articular Opioids v. NSAIDs X. Line 1450 – I think the recommendation should specify this is referring to intra-articular opioids & NSAIDs administered intraoperatively for post-operative pain control. We don't want providers to misinterpret this recommendation to say they should be using intra-articular opioids for non-operative treatment of an injury or osteoarthritis. Opioid Combo v. NSAID Y. Line 1503 – It's unclear what is meant by opioid combination treatment. Does this refer to combinations with acetaminophen such Percocet and Norco or does this refer to opioids with NSAIDs. This should be clarified in the recommendation. Z. Previous limited recommendations in the clinical practice guideline are phrased "limited evidence suggests no difference in…." I recommend this verbiage be adopted for this limited recommendation.

			AA. Line 1517 – It may be beneficial to include that opioids should be used cautiously as they are associated with adverse events including, but not limited to nausea, vomiting, and respiratory depression. Tramadol Combo v. NSAID BB. Line 1541 - What specific outcomes were looked at in the one study included? It would be beneficial to specify if it is function, pain, or opioid consumption. Similar to the opioid combo treatment, I suggest this recommendation be more specific regarding "tramadol combinations." CC. Line 1550 – I recommend the authors format the rationale similarly to previous sections with complete sentences. Fentanyl Patch vs. Morphine DD. Line 1582 – What specific outcomes were looked at in the one study included? It would be beneficial to specify if it is function, pain, or opioid consumption. EE. Previous limited recommendations in the clinical practice guideline are phrased "limited evidence suggests no difference in…." I recommend this verbiage be adopted for this limited recommendation. FF. Line 1591 – More detail regarding the study included would be beneficial for readers. Tramadol vs. NSAID GG. Line 1627 - What specific outcomes were looked at in the one study included? It would be beneficial to specify if it is function, pain, or opioid consumption. HH. Previous limited recommendations in the clinical practice guideline are phrased "limited evidence suggests no difference in…." I recommend this verbiage be adopted for this limited recommendation. II. Line 1683 - More detail regarding the study included would be beneficial for readers. Oral Acetaminophen JJ. Line 1810 - What specific outcomes are referred to in "patient outcomes?" Previous recommendations have referred to function, pain and opioid consumption. I recommend the authors adopt similar verbiage and be more specific in this recommendation as well. Acetaminophen/NSAID Combination Treatment vs NSAID

			KK. Line 1895 - Previous limited recommendations in the clinical practice guideline are phrased "limited evidence suggests…." I recommend this verbiage be adopted for this limited recommendation. Gabapentinoids LL. Line 1933 – The workgroup may consider changing the title of the section to gabapentin as gabapentinoids refers to both pregabalin and gabapentin. The recommendations included in this section only refer to gabapentin and pregabalin has its own section. Ketamine MM. Line 2049 – Given the only two studies included are in hip and knee arthroplasty, the workgroup may consider replacing "…after surgery" in the recommendation with "after hip and knee arthroplasty."

Workgroup Response to Reviewer #4

Dear Charles Hannon, M.D., MBA,

Thank you for your expert review of the Clinical Practice Guideline for Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/ Pelvis Surgery. We will address your comments by guideline section in the order that you listed them.

A. Thank you for the positive feedback.

B. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

C. Additional detail has been added throughout the guideline regarding the applicable injuries and/or procedures.

D. The title of the guideline was determined by the work group.

E. Additional information has been added to the rationale specifying the patient population. The recommendation has also been edited to reflect the patient population found in the studies.

F. The work group mirrored the language (i.e. standard treatment) that was used in the supporting studies.

G. Recommendations and rationales have been edited following the Review Period as deemed necessary by the work group.

H. A sentence has been added to each upgraded or downgraded recommendation stating the reason for upgrade/downgrade as well as the strength of evidence.

I. The work group elected to include adverse events in the potential harms, benefits, and contraindications in a section of the Introduction.

J. Thank you for your comment. The draft has been modified.

K. All supporting evidence for this recommendation combined auricular and acupuncture compared with sham acupuncture.

L. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

M. Supporting evidence included compression with standard of care compared to standard of care alone as well as studies which did not specify standard of care practices.

N. All supporting evidence for this recommendation included compression stocking, compression system, and bandage.

O. Thank you for your comment. The draft has been modified.

P. Outcomes apart from pain alleviation are not included in the scope of this guideline.

Q. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

R. Resource Utilization section addresses that utilization in hospital setting may have low resources.

S. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

T. The work group addressed cost in the Resource Utilization section.

U. The recommendation has been edited to specifically list pain or opioid use.

V. All supporting evidence for this recommendation compared local anesthesia to regional anesthesia. Complete details are shown in Appendix 2.

W. Thank you for the positive feedback.

X. Administered intraoperatively for post-operative pain control" has been added to the recommendation.

Y. Opioid combination was included in the scope of this guideline as defined by the work of Bali 2016 which looks at opioid with NSAID compared to NSAID.

Z. Limited evidence suggests" has been added to this recommendation.

AA. Additional information regarding adverse events has been added to the rationale.

BB. The primary endpoint was a comparison between the pain visual analog scale (VAS) change from baseline (PO day 2) and PO day 4, day 7, day 10, and day 14. The second endpoint was the number of days until the patient achieved independence from cane walking.

CC. Additional information has been added to the rationale.

DD. The supporting studies assessed patient global assessment of the method of pain control (a rating of 'good' or 'excellent' was considered as a success rating) and mean last pain intensity scores in the first 24 hours. Discontinuation rates and the incidence of adverse events were also evaluated.

EE. Limited evidence suggests" has been added to this recommendation.

FF. More detail regarding the study included has been added to the rationale.

GG. Visual analog scale (VAS) scores for pain intensity and satisfaction with medication, incidence of adverse effects, and use of rescue medication were recorded and compared between the 3 groups at 3 days and 2 weeks after surgery in the included study. Magnetic resonance and ultrasonography images of 82 patients were retrospectively reviewed at least 24 months after surgery, along with the range of motion and pain VAS and functional scores.

HH. Limited evidence suggests" has been added to this recommendation.

II. More detail regarding the study included has been added to the rationale.

JJ. The recommendation has been rewritten to specify the patient outcomes.

KK. This recommendation was downgraded to limited by the work group; the strength of evidence in support of this recommendation is moderate.

LL. This section has been renamed.

MM. The workgroup has taken this comment under consideration and made changes to the wording of the guideline based on this feedback.

Reviewer #5, Benjamin Miller, M.D., MS

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: The response(s) below also includes all editing suggestions received from the Additional Comments section of the structured review form.
5	Benjamin Miller, M.D., MS	Committee on Evidence-Based Quality and Value, American Academy of Orthopaedic Surgeons	A. Methodology is clear and the goals of the effort are detailed appropriately. B. The difference between "strength of evidence" and "strength of recommendation" is not clear throughout the document. For instance on the first recommendation, it appears that the strength of evidence is moderate, but the EtD framework was used to downgrade the strength of recommendation to limited. The way it is presented appears that the strength of evidence is limited, which is incorrect based upon the methodology. Please clarify and change document if warranted. C. Also I would recommend common language throughout the recommendations. The best presentation is "Limited/Moderate/Strong evidence suggests..." but not all recommendations follow this structure - that could easily be changed and would help with clarity. D. It would be helpful to specifically state in the rationale why each recommendation was downgraded when applicable.

Workgroup Response to Reviewer #5

Dear Benjamin Miller, M.D., MS,

Thank you for your expert review of the Clinical Practice Guideline for Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/ Pelvis Surgery. We will address your comments by guideline section in the order that you listed them.

A. Thank you for the positive feedback.

B. A sentence has been added to each upgraded or downgraded recommendation stating the reason for upgrade/downgrade as well as the strength of evidence.

C. Following the Review Period, multiple recommendations were edited for consistency.

D. The reason for downgrade has been added to all downgraded recommendations.

Reviewer #6, Matthew Austin, M.D.

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: The response(s) below also includes all editing suggestions received from the Additional Comments section of the structured review form.
6	Matthew Austin, M.D.	The Knee Society	A. The Knee Society appreciates the immense effort of the Workgroup and applauds their diligence in developing this Draft. The Knee Society also appreciates the opportunity to review the Draft and provide feedback. Please find a summary of our concerns below. Please note that our review specifically focuses on the Draft as it relates to the Knee Society. Overview B. The overarching challenge with this Draft is that the broad application of the Recommendations to the entirety of musculoskeletal extremity and pelvis surgery without specific literature support within each subspecialty is a difficult task. The Recommendations are formulated based upon grouping the studies under the umbrella of the entirety of musculoskeletal extremity and pelvis surgery. The strength of the evidence may be diminished when considering the dearth of high-quality studies within each subspecialty (shoulder, sports, arthroplasty, etc.) and may not justify the given Recommendation for a particular subspecialty. For example, the Recommendation supporting Massage (Strength: Moderate. 3/4) has a single, high-quality reference which focuses on foot massage in patients treated for tibial shaft fracture. The moderate quality papers were from Perm J (Impact Factor 0.94), Iran J Nurs Midwifery Res (Impact Factor 0.272) and Pain Manag Nurs (1.595). Therefore, we submit that the evidence referenced may not support the Moderate Strength Recommendation for the role of massage in the postoperative care of the total knee patient. Further examples are provided in the "Specific Concerns" section of the review. C. In addition, the Recommendations may want to state the timeframe for which the intervention may be useful. For example, during what time period does acupuncture improve pain scores (postoperative day 0 vs. postoperative day 1 vs. 2 weeks postoperatively)? For what timeframe does acupressure reduce opioid consumption? D. The AAOS may also want to review other similar Clinical Practice Guidelines (from AAOS, AAHKS and other specialty societies) that have recently been published as well as those in the developmental pipeline to identify and manage any conflicts within the different CPG's so as to avoid conflicting recommendations. This CPG crosses many subspecialties and may therefore have the increased potential for conflict.

Specific Concerns:
Early Mobilization

E. Recommendation: Limited evidence suggest no difference in patient pain, function and opioid use between early mobilization and standard treatment. Strength: Limited. 2/4.- Concern: The CPG does not state what would be considered "early" vs. "standard" mobilization. The workgroup may want to consider other potential benefits of early mobilization (decreased rates of VTE, decreased length-of-stay, etc.) that may be advantageous for the patient.

Massage

F. Massage may be used with standard treatment for improved pain outcomes. Strength: Moderate. 3/4. -Concerns: The recommendation is based upon a single high-quality reference which focuses on foot massage in patients treated for tibial shaft fracture. The moderate quality papers were from Perm J (Impact Factor 0.94), Iran J Nurs Midwifery Res (Impact Factor 0.272) and Pain Manag Nurs (1.595). There is concern that the Recommendation is not adequately supported by the literature. The Workgroup may want to reference the time frame for which massage may provide benefit. For example, what postoperative interval has massage been proven beneficial (immediately postop, postoperative day 1, etc.)? What specific areas are to be massaged (surgical site, periarticular musculature, etc.)?

G. Once again, as the Knee Society, we are focused on the applicability of these Recommendations to knee arthroplasty but it seems that the literature for the entirety of postoperative musculoskeletal care is assumed to provide evidenced-based treatment for specific subspecialties that have unique pathology and the response to the Recommended intervention may differ from subspecialty to subspecialty. What may work for tibial shaft fractures cannot be assumed to work for knee arthroplasty or shoulder arthroplasty.

Neuromuscular Electrical Stimulation

H. Neuromuscular electrical stimulation should be used with standard treatment to improve function, but no significant difference is seen in pain. Strength: Strong. 4/4. -Concerns: Only one of the high-quality studies (Stevens-Lapsley) involves patients undergoing total knee arthroplasty. The other two studies (one high, one moderate) were of arthroscopic patient cohorts. This is, once again, applying the entirety of the musculoskeletal literature and assuming it applies to a specific procedure. The Strength of recommendation is Strong and endorses the use of neuromuscular electrical stimulation. The evidence presented does not substantiate the Recommendation for patients undergoing knee arthroplasty. Furthermore, the timeframe for which the benefit of improved function for this intervention is not mentioned.

Peri-op Injections

I. Moderate evidence suggests no difference in patient outcomes between local and regional anesthesia for patients undergoing total knee and hip arthroplasty, knee arthroscopy, anterior cruciate ligament reconstruction, and shoulder arthroplasty. Strength: Moderate. 3/4. -Concerns: The topic of postoperative pain management is complex. The workgroup distills this topic into patient outcomes between local and regional anesthesia. However, even in a single subspecialty such as adult reconstruction, there are vast differences between total hip arthroplasty and total knee arthroplasty when it comes to pain management. Furthermore, there are high-quality studies in the hip and knee arthroplasty literature that demonstrate a synergistic effect between local AND regional anesthesia rather than each in isolation. In addition, there are a variety of techniques for perioperative analgesia that have a range of treatment effects and complications. For example, continuous regional anesthesia may provide improved pain scores in some studies but at the expense of delayed ambulation. Intrathecal morphine may provide improved pain scores but increase the incidence of opioid-related side effects. While we appreciate the attempt to provide guidance on this topic, the Recommendation, as it is currently constructed may not provide clinicians with the necessary information to achieve the goal of reducing opioid use in the perioperative period. We would recommend that the Workgroup review other CPG's that are in development in order to provide internal consistency within the CPG's.

Music Therapy

J. Music therapy might be used with standard treatment to decrease post-operative pain and opioid use. Strength: Limited. 2/4. -Concerns: The majority of the studies referenced the utility of music therapy in elderly patients undergoing hip and knee surgery. However, the patient population is not defined in the Recommendation nor is the timeframe that this type of therapy would provide benefit.

Intra-articular Opioids vs. NSAIDs

K. Limited evidence suggesting there is no difference in patient outcomes between intra-articular opioids and NSAIDs. Strength: Limited. 2/4. -Concerns: The Recommendation does not seem to mirror the spirit written in the Rationale. In particular, the Outcome Importance, which states "Opioid-related side effects such as dizziness, nausea and vomiting can result in delayed ambulation and subsequently delay discharge from the hospital. Using a combination of periarticular local anesthetics, opioids, NSAIDs, and other agents have been shown to decrease opioid use." This important statement is supported by the evidence in the literature but is lost in the actual Recommendation itself. We are aware of the process that the CPG must follow, however, the Recommendation as written may fail to improve patient care if the provider does not read the document beyond the Summary. Thus, an opportunity to improve patient care may be lost.

Opioid Combo vs. NSAID

L. Opioid combination treatment may be used over NSAIDs to improve pain. Strength: Limited. 2/4. -Concerns: The Recommendation lacks clarity in intent. As with the previous Recommendation concerning Intra-articular Opioids vs. NSAIDS, The Recommendation does not seem to mirror the spirit written in the Rationale. In particular, the Outcome Importance, which states "Targeting multiple pain pathways with multimodal analgesics including oral opioids and NSAIDs will decrease parenteral opioid use and side effects. In addition, it may decrease the amount of NSAIDs needed which could decrease the risks associated with NSAID use, such as renal and GI dysfunction." This important statement is supported by the evidence in the literature but is lost in the actual Recommendation itself. We are aware of the process that the CPG must follow, however, the Recommendation as written may fail to improve patient care if the provider does not read the document beyond the Summary. Thus, an opportunity to improve patient care may be lost.

Tramadol Combo vs. NSAID

M. Limited evidence suggests no difference in patient outcomes between tramadol combinations and NSAIDs. Strength: Limited. 2/4. -Concerns: The Recommendation lacks clarity in intent. In particular, the Outcome Importance, which states "Targeting multiple pain pathways with multimodal analgesics including tramadol, acetaminophen and NSAIDs will decrease parenteral opioid use and side effects. In addition, using tramadol in conjunction with acetaminophen may decrease the dose of tramadol required, subsequently decreasing side effects." This important statement is supported by the evidence in the literature but is lost in the actual Recommendation itself. We are aware of the process that the CPG must follow, however, the Recommendation as written may fail to improve patient care if the provider does not read the document beyond the Summary. Thus, an opportunity to improve patient care may be lost.

Fentanyl Patch vs. Morphine

N. There is no significant difference in patient outcomes between fentanyl patch and morphine. Strength: Limited. 2/4. -Concerns: This Recommendation is based only upon one moderate quality study. However, in arthroplasty, the majority of the community has moved away from both extended release opioids and patient-controlled anesthesia towards multimodal, opioid-sparing analgesia. For this reason, the Recommendation may not have clinical relevance to knee arthroplasty patient.

Tramadol vs. NSAID

O. There is not significant difference in patient outcomes between tramadol and NSAIDs. Strength: Limited. 2/4.-Concerns: This Recommendation is based only upon one moderate quality study that compared cox-2 inhibitors, ibuprofen and tramadol. However, in arthroplasty, the majority of the community has moved towards multimodal, opioid-sparing analgesia. The question may be not whether one modality works better than another in isolation rather it is whether a combination of modalities works better than one in isolation.

			Gabapentinoids P. a. There is no significant difference in patient outcome between multi-dose gabapentin and placebo; however, additional concerns for adverse events such as sedation and respiratory depression should be recognized with its use. b. There is no significant difference in patient outcome between single-dose gabapentin and placebo; however, additional concerns for adverse events such as sedation and respiratory depression should be recognized with its use. Strength: Strong. 4/4. -Concerns: We would ask the Workgroup to consider rewording the Recommendations. We pose the question that if there is no significant difference in outcomes between the treatment and the placebo and the treatment carries the risk of adverse events what is the benefit to the patient of the treatment? We would recommend that the workgroup review other recently published CPG's and those that are in development in order to provide internal consistency within the CPG's. We have a similar concern for the Pregabalin Recommendation. Ketamine Q. Strong evidence supports the use of intravenous ketamine in the peri-operative period to reduce opioid use in the first 24hrs after surgery. Strength: Strong. 4/4. -Concerns: The study by Remerand was published in 2009, prior to the adoption of rapid recovery techniques. The THA patients all underwent general anesthesia and had morphine PCA pumps, which is not reflective of current practice. We were unable to access the Cengiz paper which was published in J Coll Physicians Surg Pak (Impact Factor 0.42). In addition, the side effects of vivid dreams and hallucinations are not trivial and may delay discharge which is important with both hip and knee arthroplasty being taken off the CMS Inpatient Only list of procedures. We appeal to the workgroup to reconsider this Recommendation. R. The Workgroup was challenged by the methodology which explored individual comparisons that may miss the "big picture" gleaned from the evidence on the topic of perioperative pain management for the arthroplasty patient. A clinically relevant question for those caring for arthroplasty patients may not be whether one modality works better than another in isolation (opioid combo vs. NSAID, tramadol vs. NSAID, fentanyl patch vs. morphine, etc.) but whether a combination of modalities works better than one in isolation (i.e. multimodal vs. opioid only). There is a significant volume of high-quality evidence in the arthroplasty literature that indicates a multimodal approach to pain management improves outcomes and may reduce opioid-related side effects as compared to opioid only programs. This is an important question that may be worth exploring for the Workgroup.

Workgroup Response to Reviewer #6

Dear Matthew Austin, M.D.,

Thank you for your expert review of the Clinical Practice Guideline for Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/ Pelvis Surgery. We will address your comments by guideline section in the order that you listed them.

A. Thank you for your review.

B. The a priori scope of all musculoskeletal injuries and surgeries was applied to each PICO questions as determined by the work group; the resulting strength of recommendation was then downgraded as appropriate and at the discretion of the work group when results were inconsistent.

C. Due to the high volume of supporting literature, and the inclusion criteria allowing for follow-up times from admission to 90 days, the work group elected to comment on follow-up times within the rationales.

D. While the scope of AAOS-published guidelines typically ensures that recommendations will not overlap directly, this unique grant-funded project's expansive scope introduces the potential for future overlap. It will require diligence in future project planning to ensure the Academy is not releasing conflicting recommendations.

E. Outcomes apart from pain alleviation are not included in the scope of this guideline.

F. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

G. No response.

H. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

I. The work group has modified this recommendation to specify the patient outcomes as pain and opioid use. The work group has also highlighted in the rationale the need for future research to examine the optimal combination of both local and regional anesthesia.

J. The supporting evidence included hip, knee, and shoulder surgery.

K. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

L. The recommendation language has been edited for clarity.

M. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

N. Opioid combo compared to NSAID was included in the a priori scope as determined by the work group members.

O. The work group highlighted the need for future research examining the most effective combination and dose of medications.

P. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording to the recommendation, but has added a sentence to the rationale based on this feedback.

Q. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

R. The structured review methodology as described in the methods section is applied to the a priori PICO questions as developed by the work group. These PICO questions did not include mulimodal pain management.

Reviewer #7, Donald Hohman, M.D.

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: The response(s) below also includes all editing suggestions received from the Additional Comments section of the structured review form.
7	Donald Hohman, M.D.	American Academy of Orthopaedic Surgeons	A. highly relevant. B. well organized.

Workgroup Response to Reviewer #7

Dear Donald Hohman, M.D.,

Thank you for your expert review of the Clinical Practice Guideline for Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/ Pelvis Surgery. We will address your comments by guideline section in the order that you listed them.

A. Thank you for the positive feedback.

B. Thank you for the positive feedback.

Reviewer #8, Rebecca Johnson, M.D.

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: The response(s) below also includes all editing suggestions received from the Additional Comments section of the structured review form.
8	Rebecca Johnson, M.D.	American Society of Anesthesiologists	A. Page 19, Lines 523-526: RE: "There is potential harm that can result from helping people get comfortable without diagnosing compartment syndrome, infection, loosening of implants or other problems. For instance, a regional anesthetic can mask the development of compartment syndrome."-COMMENT: This statement is controversial and not built upon a solid evidenced-based background. In certain situations, regional anesthesia use may even assist with diagnosis as breakthrough pain from a critical rise in intracompartmental pressure will still be expected to occur in the presence of the sensory block from a peripheral nerve block. A comfortable patient that then experiences pain may trigger the surgeon to evaluate the compartment closer. The sentence perpetuates a myth that regional anesthesia is known to delay diagnosis and treatment of compartment syndrome. Considering this supportive material is in the introductory part of this important document, it will be crucial that non evidenced-based materials be omitted or placed in a fairer context. Please consider another example for your statement and remove the sentence, "For instance, a regional anesthetic can mask the development of compartment syndrome." B. Page 36 Peri-op Injections. COMMENT: This recommendation is quite general with inclusion of total knee and hip arthroplasty, knee arthroscopy, anterior cruciate ligament reconstruction and shoulder arthroscopy. Whereas, there is a separate and unique recommendation provided (page 38) for Peri-op injections Total Shoulder Arthroplasty. The evidence on page 36-38 is primarily science from total joint arthroplasty in total hip and total knee arthroplasty populations. Perhaps it would make more sense to break these recommendations differently. I would suggest Peri-op Injections Total Joint Arthroplasty and Peri-op Injections Arthroscopy instead? C. Page 38 Peri-op Injections Total Shoulder Arthroplasty. COMMENT: Consider re-evaluating the Strength of Recommendation: Strong. Based on what is provided on page 38, the rating of 'Strong' requires evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. This recommendation appears to be based upon only one "High" quality study (Panchamia 2019) and the strength of recommendation may be better classified as 'Moderate,' similar to the 'Moderate' strength provided on Page 36. Alternately, please provide the rationale for upgrading from 'Moderate' using the EtD framework and place this information on page 38.

D. Page 51 Opioid Combo vs NSAID AND Page 53 Fentanyl Patch vs Morphine. Benefit/Harms of Implementation. COMMENT: The evidence is building to support the need for perioperative management strategies (i.e., regional and neuraxial anesthesia, intravenous local anesthesia, and nonopioid medications) [doi: 10.1213/ANE.0000000000002458] that reduce the risk of chronic opioid use following surgery not promote the use of opioid therapies. Additional messaging in these recommendations should include suggestions for developing opioid stewardship programs and even consider providing specific text recommendations/guidance for short-term opioid use and tapering off of opioids after orthopedic surgery [https://doi.org/10.1016/j.mayocp.2019.11.019]. Consider inclusion of CDC guidelines: https://www.cdc.gov/acute-pain/postsurgical-pain/index.html

E. Page 52 Tramadol Combo vs NSAID AND Page 54 Tramadol vs NSAIDS. COMMENT: Please consider revising these recommendations based on recent studies demonstrating prolonged opioid use with tramadol compared to oxycodone [https://www.bmj.com/content/365/bmj.l1849]. Further, tramadol's more benign profile and "first-line" analgesic designation should be reconsidered. Not unlike other prodrugs that require conversion, tramadol metabolizes to O-desmethyltramadol and in some "ultrarapid metabolizers" there will be quite potent clinical manifestations of extreme sleepiness, confusion, or respiratory depression that warrants stressing this drug similar to the section on Gabapentinoids (Page 61-62) and Pregabalin (page 63-63) and include a disclaimer for recommendations for Tramadol likewise, ". . .;however, additional concerns for adverse events such as dizziness and sedation should be recognized with its use."

COMMENT ON THE OVERALL STRUCTURE AND CONTENT OF THE GUIDELINE:

F. There is inconsistent language and presentation of the recommendations throughout suggesting the group took a "divide and conquer" approach. For example, page 66, "Oral Relaxants" recommendations emphasize a point that studies did not assess for differences based on sex or gender. "So differences in potential harms among the sexes is not known." This is true; however, that would be a universal finding and likely a "Benefits/Harms of Implementation" for all recommendations and would be better placed in advance of the recommendation section and not hidden in just this one section.

G. Respectfully, the better sections in this document (e.g., Cognitive/Behavioral Treatment, Guided Relaxation Therapy, Patient Education) follow an approach providing depth with literature cited examples to support the strength of recommendation provided within the 'Rationale' and a thoughtfully strong 'Future Research' sections. The same amount of depth is absent in other sections. I would highly suggest revising the comprehensive document following standardized examples the mimic Gabapentinoids (page 61-62) and Pregabalin (page 63-64). The authors of these pages should be commended and emulated.

			H. THANK YOU VERY MUCH FOR ALLOWING ME TO REVIEW THIS IMPORTANT WORK. I. I would recommend more strongly with minor revision. Thank you very much for including input and for allowing me an ability to participate in the creation of this important work.

Workgroup Response to Reviewer #8

Dear Rebecca Johnson, M.D.,

Thank you for your expert review of the Clinical Practice Guideline for Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/ Pelvis Surgery. We will address your comments by guideline section in the order that you listed them.

A. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

B. Following the Review Period, this recommendation was revised by the work group to only state total hip and knee arthroplasty.

C. This recommendation was upgraded from Moderate to Strong using the GRADE Evidence-to-Decision framework.

D. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

E. The study referenced did not meet the inclusion criteria of being a randomized controlled trial.

F. Differences based on sex and gender is detailed in the future research section of the Introduction.

G. Additional information has been added to the rationale.

H. Thank you for your comments.

I. Thank you for the feedback.

Reviewer #9, Glenn Wera, M.D.

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: The response(s) below also includes all editing suggestions received from the Additional Comments section of the structured review form.
9	Glenn Wera, M.D.	American Academy of Orthopaedic Surgeons	A. Line 328 oral versus IV acetaminophen. I found a few articles online which support this finding/recommendation that there is no published difference. This is very informative and may help clarify industry bias and physician lore which may perceive one treatment as superior. B. Line 354 gabapentinoids. I have the clinical impression that there is little benefit based on our institutional experience but have seen concerns about sedation and mental status changes. This information is helpful in making care paths. C. Line 372 single dose pregabalin. Again I have a strong clinical impression that this findings is correct and our institutional order sets reflect this finding. D. Line 546 reword to "This CPG is not a fixed consensus". E. More information is needed on Liposomal Bupivicaine. F. More information is needed on type of anesthetic at the time of surgery. For example, pain control is expected to be better after total knee arthroplasty in cases where a neuraxial anesthetic was used. G. Line 1271: Although music therapy has been researched in various settings such as the cast room, its importance to readers likely remains limited. H. 1326: I urge caution in stating that there is little evidence that patient education can be used to improve function and earlier cessation of opiod use. This suggests a major failure in the profession. While there may minimal evidence in this CPG, a statement stating the need for more information is needed here. I. 1580: The topic of fentanyl patch is probably not really relevant in this era of the opioid crisis. It is probably not applicable to orthopedic surgeons and therefore may be removed from the CPG. Fentanyl is not part of any of the leading multimodal analgesic cocktails etc in current practice.

			J. 1582: No difference between fentanyl patch and morphine cannot be a correct conclusion based on addiction risk, pharmacokinetics, or delivery method. I suggest removal of fentanyl from the discussion. K. 1719: Cox2 agents such as celecoxib seem to be supported by this manuscript. However one major justification for this drug is minimization of bleeding and gastro-intestinal side effects. I could not tell from the manuscript if these issues along with nephrotoxicity were evaluated. L. Additional information about the type of anesthesia performed at surgery as well as regional blockade (adductor canal blocks etc) would strengthen this CPG.

Workgroup Response to Reviewer #9

Dear Glenn Wera, M.D.,

Thank you for your expert review of the Clinical Practice Guideline for Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/ Pelvis Surgery. We will address your comments by guideline section in the order that you listed them.

A. Thank you for the positive feedback.

B. Thank you for the positive feedback.

C. Thank you for the positive feedback.

D. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

E. The workgroup has taken this comment under consideration but ultimately opted not to make any changes to the wording of the guideline based on this feedback.

F. The type of anesthesia performed at surgery is detailed in full in the evidence tables found in Appendix 2.

G. The strength of recommendation was downgraded to limited due to feasibility.

H. The work group opted to downgrade this recommendation due to inconsistency in the findings of the supporting evidence. Supporting evidence found both improvement and no significant change in patient outcomes, the need for future research in this area is highlighted in the rationale.

I. Evidence warranting a directional statement was found during the systematic search based on the work group's PICO questions.

J. Supporting evidence found both improvement and no significant change in patient outcomes; future research in this area is needed to make a directional recommendation.

K. Gastro-intestinal side effects were discussed by the work group but the evidence didn't warrant a directional statement.

L. The type of local and regional anesthesia for patients undergoing surgery is detailed in the complete evidence tables found in eAppendix 2.

Reviewer #10, Matthew Abdel, M.D.

Reviewer Number	Reviewer Name	Society or committee you are representing	Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline: The response(s) below also includes all editing suggestions received from the Additional Comments section of the structured review form.
10	Matthew Abdel, M.D.	Board of Directors, American Academy of Orthopaedic Surgeons	A. Well done!

Workgroup Response to Reviewer #10

Dear Matthew Abdel, M.D.,

Thank you for your expert review of the Clinical Practice Guideline for Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/ Pelvis Surgery. We will address your comments by guideline section in the order that you listed them.

A. Thank you for the positive feedback.

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Appendix A – Structured Review Form

Review Questions (REQUIRED)

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
1. The overall objective(s) of the guideline is (are) specifically described.	○	○	○	○	○
2. The health question(s) covered by the guideline is (are) specifically described.	○	○	○	○	○
3. The guideline's target audience is clearly described.	○	○	○	○	○
4. There is an explicit link between the recommendations and the supporting evidence.	○	○	○	○	○
5. Given the nature of the topic and the data, all clinically important outcomes are considered.	○	○	○	○	○
6. The patients to whom this guideline is meant to apply are specifically described.	○	○	○	○	○
7. The criteria used to select articles for inclusion are appropriate.	○	○	○	○	○
8. The reasons why some studies were excluded are clearly described.	○	○	○	○	○
9. All important studies that met the article inclusion criteria are included.	○	○	○	○	○
10. The validity of the studies is appropriately appraised.	○	○	○	○	○
11. The methods are described in such a way as to be reproducible.	○	○	○	○	○
12. The statistical methods are appropriate to the material and the objectives of this guideline.	○	○	○	○	○
13. Important parameters (e.g., setting, study population, study design) that could affect study results are systematically addressed.	○	○	○	○	○
14. Health benefits, side effects, and risks are adequately addressed.	○	○	○	○	○
15. The writing style is appropriate for health care professionals.	○	○	○	○	○
16. The grades assigned to each recommendation are appropriate.	○	○	○	○	○

Please provide a brief explanation of both your positive and negative answers in the preceding section. If applicable, please specify the draft page and line numbers in your comments. Please feel free to also comment on the overall structure and content of the Guideline:

Would you recommend these guidelines for use in clinical practice? (REQUIRED)

- ○ Strongly Recommend
- ○ Recommend
- ○ Would Not Recommend
- ○ Unsure

Additional Comments regarding this clinical practice guideline?