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

Clinical Practice Guideline

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Disclaimer

This clinical practice guideline (CPG) was developed by a physician volunteer clinical practice guideline development group based on a formal systematic review of the available scientific and clinical information and accepted approaches to treatment and/or diagnosis. This clinical practice guideline is not intended to be a fixed protocol, as some patients may require more or less treatment or different means of diagnosis. Clinical patients may not necessarily be the same as those found in a clinical trial. Patient care and treatment should always be based on a clinician's independent medical judgment, given the individual patient's specific clinical circumstances.

Disclosure Requirement

In accordance with AAOS policy, all individuals whose names appear as authors or contributors to this clinical practice guideline filed a disclosure statement as part of the submission process. All panel members provided full disclosure of potential conflicts of interest prior to voting on the recommendations contained within this clinical practice guideline.

Funding Source

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FDA Clearance

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First Edition

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SUMMARY OF RECOMMENDATIONS

Acupuncture

a) Limited evidence suggests that acupuncture may be used with standard treatment for improved pain scores; however, there were no significant differences in function.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

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b) Limited evidence suggests no significant difference in patient pain and function outcomes between auricular or other acupuncture and sham.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Acupressure

Limited evidence suggests that auricular acupressure may be used with standard treatment for opioid reduction and improved function; however, there was no difference in pain.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Compression

Limited evidence suggests no significant differences in pain or function with compression.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single

"Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Cryotherapy

Limited evidence suggests no significant difference in patient pain, function and opioid use between cryo-compression and control/ice/circulating water.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Early Mobilization

Limited evidence suggests no difference in patient pain, function and opioid use between earlier mobilization and standard treatment.

Strength of Recommendation: Limited.★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Massage

Massage may be used with standard treatment for improved pain outcomes.

Strength of Recommendation: Moderate ★★★☆
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Neuromuscular Electrical Stimulations

Neuromuscular electrical stimulation should be used with standard treatment to improve function, but no significant difference is seen in pain.

Strength of Recommendation: Strong ★★★★
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

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Transcutaneous Electrical Nerve Stimulation

Moderate evidence supports no significant difference in functional outcomes, pain or opioid use between transcutaneous electrical nerve stimulation and standard treatment or sham.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Peri-op Injections

Moderate evidence suggests no difference in patient outcomes between local and regional anesthesia for patients undergoing total knee and hip arthroplasty.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Peri-op Injections Total Shoulder Arthroplasty

Strong evidence supports the use of continuous regional anesthesia over local anesthesia in total shoulder arthroplasty to reduce pain and opioid use in the first 24hrs after surgery.

Strength of Recommendation: Strong ★★★★ (upgrade)
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Cognitive/Behavioral Treatment

Limited evidence suggests no difference in patient function or pain outcomes between cognitive behavioral therapy and standard treatment for patients undergoing total knee arthroplasty.

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Guided Relaxation Therapy

There is no significant difference in pain and opioid use outcomes between guided relaxation therapy and standard treatment.

Strength of Recommendation: Moderate ★★★☆

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Music Therapy

Music therapy might be used with standard treatment to decrease post-operative pain and opioid use.

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Patient Education

Limited evidence suggests patient education can be used to improve patient function and earlier cessation of opioid use.

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Virtual Reality

Limited evidence suggests no difference in patient outcomes between use of virtual reality and standard treatment.

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single

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"Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Intra-Articular Opioids vs NSAIDs

Limited evidence suggesting there is no difference in patient outcomes between intra-articular opioids and NSAIDs administered intraoperatively for post-operative pain control.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Opioid Combo/NSAID

Limited evidence suggests opioid/NSAID combination treatment may be used over NSAIDs to improve pain.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Fentanyl Patch vs Morphine

Limited evidence suggests no significant difference in patient outcomes between fentanyl patch and morphine.

Strength of Recommendation: Limited ★★☆☆
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Tramadol vs NSAID

Limited evidence suggests no significant difference in patient outcomes between tramadol and NSAIDs.

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Cox-2

Cox2 agents should be used to limit patient opioid consumption, improve pain and function; however, there is no difference in adverse events.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Oral Acetaminophen

There is no significant difference in pain intensity and opioid use between oral acetaminophen and intravenous acetaminophen.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Acetaminophen

Acetaminophen should be used to improve patient pain and decrease opioid use.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Acetaminophen/NSAID Combination Treatment

Acetaminophen/NSAID combination treatments may be used over NSAIDs for reduction in pain; however, no significant difference in reduction of opioid use.

Strength of Recommendation: Limited ★★☆☆ (downgraded)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

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Gabapentin

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.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

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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 of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Pregabalin

Moderate evidence suggests single or multi-dose pregabalin could be used to improve patient pain and opioid consumption outcomes; however, additional concerns for adverse events such as dizziness and sedation should be recognized with its use.

Strength of Recommendation: Moderate ★★★★ (downgrade)

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Ketamine

Strong evidence supports the use of intravenous ketamine in the peri-operative period to reduce opioid use in the first 24hrs after hip and knee arthroplasty.

Strength of Recommendation: Strong 

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Oral Relaxants

There is no significant difference in patient outcomes, pain intensity or opioid use between oral relaxants and placebo given postoperatively.

Strength of Recommendation: Moderate 

Description: Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

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Summary of Consensus Statement

There is no evidence or only conflicting supporting evidence for the following recommendations. In the absence of reliable evidence, the systematic literature review development group is making a recommendation based on their clinical opinion.

Anti-Depressants

In the absence of reliable evidence, it is the opinion of the workgroup that a recommendation for or against the use of duloxetine cannot be made given the limited evidence and safety concerns.

Strength of Recommendation: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

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INTRODUCTION

Overview

This Clinical Practice Guideline (CPG) is one of six funded by a Department of Defense grant to the METRC collaborative to evaluate the evidence regarding various aspects of recovery from injury to determine the most helpful recommendations for testing and treatment. This CPG evaluates therapeutic interventions for pain alleviation, improved function, and less opioid use after musculoskeletal injury or orthopaedic surgery.

The guideline is intended to be used by all qualified and appropriately trained providers and surgeons involved in alleviation of patient pain and improve function after musculoskeletal injury or orthopaedic surgery. It is also intended to serve as an information resource for decision makers and developers of practice guidelines and recommendations.

Goals and Rationale

This CPG is a systematic review of the available evidence regarding pain alleviation strategies after orthopedic injury and surgery intended to help improve care. The systematic review detailed herein was conducted between November 18th, 2019 and June 2nd, 2020 and demonstrates where there is evidence, where evidence is lacking, and what future research can target in order to improve comfort after orthopaedic injury and surgery.

Musculoskeletal care is provided in many different settings by many different healthcare providers. We created this guideline as an educational tool to guide qualified providers through a series of management decisions to improve the quality and efficiency of care. This guideline should not be construed as including all proper methods of care or excluding methods of care reasonably directed to obtain the same results. The ultimate judgment regarding any specific management must be made considering all circumstances presented by the patient and the needs and resources unique to the locality or institution. In addition, given the relative dearth of evidence on many questions, the working group would like all readers to use this CPG as a roadmap for future research. We hope you will be inspired to contribute to the evidence base by performing your own investigations and publishing them.

Intended Users and Patient Population

This guideline is intended to be used by orthopaedic surgeons and other clinicians caring for people recovering from orthopedic injury or surgery. Typically, orthopaedic surgeons will have completed medical training, a qualified residency in orthopaedic surgery, and some may have completed additional sub-specialty training. Other qualified healthcare professionals such as nurses, nurse practitioners, physician assistants, social workers, case managers, psychologists, and hand therapists who routinely treat this type of patient in various practice settings may also benefit from this guideline.

Appropriate strategies to alleviate pain and improve function after musculoskeletal injury and orthopaedic surgery assumes that decisions are predicated on the patient and / or the patient's qualified heath care advocate communicating with the clinicians caring for them regarding available options and interventions. Once the patient and or their advocate have been informed of available care options, and have discussed these options with their physician, with care taken to gently reorient common misconceptions about pain, an informed decision can be made. Clinician input based on knowledge and experience increases the probability of selecting a suitable intervention for each individual patient. This guideline is not intended for use as a benefits determination document.

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Etiology and Incidence

There are up to 2 million fractures a year in the United States. Several million elective orthopaedic procedures are done annually in the United States on both an inpatient and ambulatory level on patients of all demographics and across all age levels. Injury and surgery cause nociception, which is the pathophysiology of tissue damage.

Emotional and Physical Impact

The intensity of pain and magnitude of activity intolerance related to pain that a person experiences is related in part to the degree of nociception, and it is also closely tied to mental and social health. Alleviation of pain and activity tolerance while in pain are key aspects of recovery. Adequate comfort allows people to ambulate, do therapeutic exercises, and resume their usual life roles. Inadequate comfort can indicate important health opportunities. One can check for an adverse event such as compartment syndrome, infection, loosening of fixation, and others. In many cases there is a misinterpretation of the pain as indicating harm or damage. For others, the pain is tied to a sense of hopelessness or fear. Pain might be connected to prior psychological trauma and pain can be worse under stress such as job, financial, housing or other types of insecurity. Timely diagnosis and treatment of pain helps limit the potential for patients to develop a pain disorder. This means that pain continues to a be source of activity intolerance long after the body's healing is well established. People considering elective surgery can ready themselves for the recovery process. People who are injured must adapt to the unplanned circumstances.

Potential Benefits, Harms, and Contraindications

There is potential harm that can result from helping people get comfortable without diagnosing compartment syndrome, infection, loosening of implants and other problems. For instance, a regional anesthetic can mask the development of compartment syndrome.

There is potential that treating pain from a biomedical perspective (i.e. with pharmaceutical and physical interventions alone) will leave mental and social health opportunities undiagnosed and under-treated. Inadequate diagnosis and treatment of mental and social health opportunities increases the potential for iatrogenic harm, such as precipitation of an opioid misuse disorder, a persistent pain disorder, or prolonged work absence. In addition, treating pain without addressing underlying emotional or mental health disorders that can impact the pain experience results in these disorders (such as anxiety, depression, and PTSD) not being addressed, which carries its own risks, beyond issues related to pain and opioid use. Another potential harm is unnecessary secondary surgeries.

Another potential harm is misattribution of pain alleviation to an intervention when the changes were due to nonspecific effects (i.e. regression to the mean, the natural course of recovery, placebo and nocebo effects). This has the potential for contributing to unhealthy dependence on healthcare, financial harm, and psychological harm. Many of the things that bring comfort are active roles that an individual assumes. A potential benefit of this CPG is that it can help orient people to the external interventions that have a good balance of potential benefit to potential harm, direct them away from external interventions that may be distracting or unhealthy, which can then direct them to the active roles they can play in their own recovery.

Future Research

It would be counterproductive for the reader of this CPG to conclude that our understanding of these issues is solid and unlikely to evolve. While there was substantial evidence for some of the questions, most of the questions are still open to debate given the relatively small number of studies, the limited

quality of many of those studies, and the limited cumulative evidence. We hope that this CPG will inspire curiosity and creativity and serve as a call to action to produce more high-quality experimental data to help us understand how to help people recovering from surgery experience safe and effective pain alleviation.

Although there continues to be emerging research that indicates differences based on sex and gender in the pain experience and response to opioids, almost none of the studies included in this CPG disaggregated data based on sex or gender, potentially limiting the applicability of these recommendations. In addition, the experience of pain is impacted by multiple physiologic, psychologic, and cultural factors. Future research on pain and strategies to address pain should assess outcomes based on sex and gender, as well as race and ethnicity.

NOTES FROM THE WORKGROUP: Lessons learned, Potential Opportunities for Improvement

The workgroup took their responsibility to patients, clinicians, and society at large seriously. In the process we identified a few aspects of the CPG process that seemed to represent areas for discussion and potential evolution of the process. Since discussion in these areas felt constructive and integral to the final product, the workgroup felt that sharing them could improve the utility of this CPG and future CPGs.

The work group would like to be sure that readers understand that the current CPG process as developed and overseen by the AAOS Evidence Based Quality and Value Committee is a scientific experiment similar to a metanalysis. As with other scientific experiments there is a strict protocol to which the participants must adhere. Hypotheses (PICO questions) are developed by an interdisciplinary group of experts (the committee). Then AAOS staff gathers published studies, identifies those that qualify, evaluates the methodological quality of the studies, and then uses the qualifying studies to make recommendations. The wording of the recommendations and the rating of the strength of the evidence are codified by EBQV. The ability to downgrade or alter wording or ratings is similarly restricted by a set of rules. Our working group felt it was important to comment on a few aspects of this scientific experiment that we felt merited close attention of readers and potential evolution of the CPG procedures going forward.

First, the quality ratings of the studies are based almost entirely on reporting and do not account for the fact that studies published in low tier journals—some of which are relatively obscure—are likely of much lower quality, even if they pass all of our reporting and quality grades based on what is in the publication. Considerations of the rigor of peer review are important to the interpretation of both the primary evidence as well as this scientific experiment on which it is based. The workgroup understands that it is difficult to scientifically and fairly account for this. It is important that readers understand that many of the studies included are published in journals which we have limited knowledge of, and therefore are open to questions about their quality. Readers should keep this in mind as they interpret the CPG.

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METHODS

The methods used to perform this systematic review were employed to minimize bias and enhance transparency in the selection, appraisal, and analysis of the available evidence. These processes are vital to the development of reliable, transparent, and accurate clinical recommendations. To view the full AAOS clinical practice guideline methodology please visit https://www.aaos.org/additonalresources/ . This clinical practice guideline evaluates the association of pain management to patient outcomes. The AAOS approach incorporates practicing physicians (clinical experts) and methodologists who are free of potential conflicts of interest relevant to the topic under study, as recommended by clinical practice guideline development experts.[1]

This clinical practice guideline was prepared by the AAOS Pharmacology, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/Pelvis Surgery Guideline physician development group (clinical experts) with the assistance of the AAOS Clinical Quality and Value (CQV) Department (methodologists). To develop this clinical practice guideline, the clinical practice guideline development group held an introductory meeting on September 22, 2019 to establish the scope of the clinical practice guideline. As the physician experts, the clinical practice guideline development group defined the scope of the clinical practice guideline by creating PICO Questions (i.e. population, intervention, comparison, and outcome) that directed the literature search. The AAOS Medical Librarian created and executed the search (see Appendix III for search strategy).

Literature Searches

We begin the systematic review with a comprehensive search of the literature. Articles we consider were published prior to the start date of the search in a minimum of three electronic databases; PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. The medical librarian conducts the search using key terms determined from the guideline development group's PICO questions.
A CQV methodologist will review/include only primary literature but will supplement the electronic search with a manual search of the bibliographies of secondary literature sources, such as systematic reviews, as available. The methodologist will then evaluate all recalled articles for possible inclusion based on the study selection criteria and will summarize the evidence for the guideline work group who assist with reconciling possible errors and omissions.

A study attrition diagram is provided in the appendix of each document that details the numbers of identified abstracts, recalled and selected studies, and excluded studies that were evaluated in the CPG. The search strategies used to identify the abstracts is also included in the appendix of each CPG document.

Defining the Strength of Recommendation

Judging the quality of evidence is only a steppingstone towards arriving at the strength of a CPG recommendation. The strength of recommendation also takes into account the quality, quantity, and the trade-off between the benefits and harms of a treatment, the magnitude of a treatment's effect, and whether data exists on critical outcomes.

Strength of recommendation expresses the degree of confidence one can have in a recommendation. As such, the strength expresses how possible it is that a recommendation will be overturned by future evidence. It is very difficult for future evidence to overturn a recommendation that is based on many high quality randomized controlled trials that show a large effect. It is much more likely that future evidence

will overturn recommendations derived from a few small retrospective comparative studies. Consequently, recommendations based on the former kind of evidence are given a “strong” strength of recommendation and recommendations based on the latter kind of evidence are given a “limited” strength.

To develop the strength of a recommendation, AAOS staff first assigned a preliminary strength for each recommendation that took only the final quality and the quantity of evidence (see Table 1). The recommendations can be further downgraded or upgraded based on the GRADE and Evidence to Decision framework criteria described above.

Voting on Recommendations

The recommendations and their strength were voted on by the guideline development group members during the final meeting. If disagreement between the guideline development group occurred, there was further discussion to see whether the disagreement(s) could be resolved. Recommendations were approved and adopted in instances where a simple majority (60%) of the guideline development group voted to approve; however, the guideline development group had consensus (100% approval) when voting on every recommendation for this guideline. Any recommendation strength upgrade or downgrade based on the Evidence to Decision framework requires a super majority (75%) approval of the work group.

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Interpreting the Strength of Evidence

TABLE I. Level of Evidence Descriptions

Strength	Overall Strength of Evidence	Description of Evidence Quality	Strength Visual
Strong	Strong or Moderate	Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Or Rec is upgrade from Moderate using the EtD framework	
Moderate	Strong, Moderate or Limited	Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Or Rec is upgraded or downgraded from Limited or Strong using the EtD framework.	
Limited	Limited or Moderate	Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Or Rec is downgraded from Moderate using the EtD Framework.	
Consensus*	No Evidence	There is no supporting evidence, or higher quality evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.	

TABLE II. Interpreting the Strength of a Recommendation

Strength of Recommendation	Patient Counseling (Time)	Decision Aids	Impact of Future Research
Strong	Least	Least Important, unless the evidence supports no difference between two alternative interventions	Not likely to change
Moderate	Less	Less Important	Less likely to change
Limited	More	Important	Change possible/anticipated
Consensus	Most	Most Important	Impact unknown

Review Period

Following the final meeting, the CPG draft undergoes a 3-week review period for additional input from external content experts. Written comments are provided on the structured review form. All reviewers are required to disclose their conflicts of interest.

To guide who participates, the CPG work group identifies specialty societies at the introductory meeting. Organizations, not individuals, are specified.

The specialty societies are solicited for nominations of individual reviewers approximately six weeks before the final meeting. The review period is announced as it approaches, and others interested are able to volunteer to review the draft. The chairs of the guideline work group review the draft of the guideline prior to dissemination.

Some specialty societies (both orthopaedic and non-orthopaedic) ask their evidence-based practice (EBP) committee to provide review of the guideline. The organization is responsible for coordinating the distribution of our materials and consolidating their comments onto one form. The chair of the external EBP committees provides disclosure of their conflicts of interest (COI) and manages the potential conflicts of their members.

Again, the AAOS asks for comments to be assembled into a single response form by the specialty society and for the individual submitting the review to provide disclosure of potentially conflicting interests. The review stage gives external stakeholders an opportunity to provide evidence-based direction for modifications that they believe have been overlooked. Since the draft is subject to revisions until its approval by the AAOS Board of Directors as the final step in the guideline development process, confidentiality of all working drafts is essential.

The CPG is 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), and members of the Board of Specialty Societies (BOS) and members of the Committee on Evidence-Based Quality and Value (EBQV) for review and comment. The CPG is automatically forwarded to the AAOS BOD and CORQ so that they may review it and provide comment prior to being asked to approve the document. Members of the BOC and BOS are solicited for interest. If they request to see the document, it is forwarded to them for comment. Based on these bodies, over 200 commentators have the opportunity to provide input into each CPG.

The chairs of the guideline work group and the manager of the AAOS CQV unit drafts the initial responses to comments that address methodology. These responses are then reviewed by the chair and co-chair, who respond to questions concerning clinical practice and techniques. The Senior Manager of Clinical Quality and Value may provide input as well. All comments received and the initial drafts of the responses are also reviewed by all members of the guideline development group. All proposed changes to recommendation language as a result of the review period are based on the evidence. Final revisions are summarized in a report that is provided alongside the guideline document throughout the remainder of the approval processes and final publication.

The AAOS believes in the importance of demonstrating responsiveness to input received during the review process and welcomes the critiques of external specialty societies. Following final approval of the guideline, all individual responses are posted on our website http://www.aaos.org/quality with a point-by-point reply to each non-editorial comment. Reviewers who wish to remain anonymous notify the AAOS

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to have their names de-identified; their comments, our responses, and their COI disclosures are still posted.

The AAOS CPG Approval Process

This final clinical practice guideline draft must be approved by the AAOS Committee on Evidence Based Quality and Value Committee, and subsequently the AAOS Council on Research and Quality, and the AAOS Board of Directors. These decision-making bodies are described in the pharmacologic, physical and cognitive pain alleviation for musculoskeletal extremity/pelvis surgery CPG eAppendix. Their charge is to approve or reject its publication by majority vote.

Revision Plans

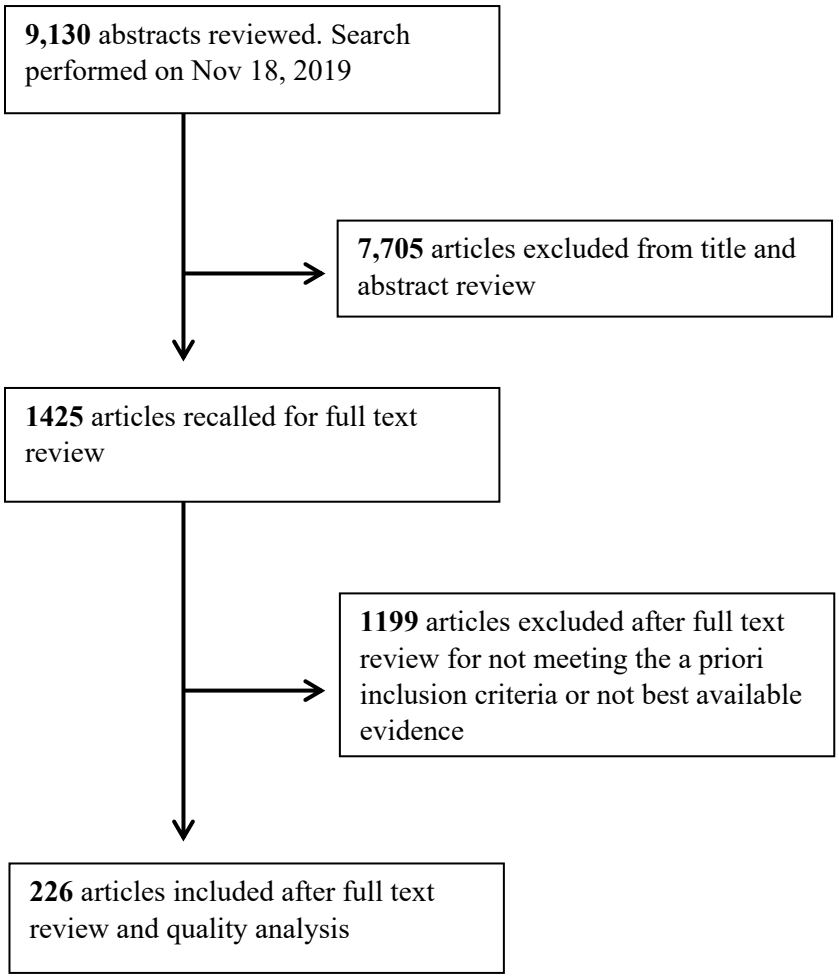
This clinical practice guideline represents a cross-sectional view of current treatment and may become outdated as new evidence becomes available. This clinical practice guideline will be revised in accordance with new evidence, changing practice, rapidly emerging treatment options, and new technology. This clinical practice guideline will be updated or withdrawn in five years.

CPG Dissemination Plans

The primary purpose of the present document is to provide interested readers with full documentation of the best available evidence for various procedures associated with the topic of this review. Publication of most clinical practice guidelines is announced by an Academy press release, articles authored by the clinical practice guideline development group and published in the Journal of the American Academy of Orthopaedic Surgeons, and articles published in AAOS Now. Most clinical practice guidelines are also distributed at the AAOS Annual Meeting in various venues such as on Academy Row and at Committee Scientific Exhibits. The final guideline recommendations and their supporting rationales will be hosted on www.OrthoGuidelines.org.

Selected clinical practice guidelines are disseminated by webinar, an Online Module for the Orthopaedic Knowledge Online website, Radio Media Tours, Media Briefings, and by distributing them at relevant Continuing Medical Education (CME) courses and at the AAOS Resource Center.

Study Attrition Flowchart



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RECOMMENDATIONS

Acupuncture

a) **Limited evidence suggests that acupuncture may be used with standard treatment for improved pain scores; however, there were no significant differences in function.**

b) **Limited evidence suggests no significant difference in patient pain and function outcomes between auricular or other acupuncture and sham.**

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

Three high quality (Crawford 2019, Wetzel 2011, Usichenko 2007) papers focusing on auricular acupuncture were evaluated. One paper showed improved pain with acupuncture versus sham; a second paper showed decreased opioid consumption with acupuncture versus sham; a third paper showed no difference.

One high quality (Petersen 2018) and one moderate (Mikashima 2012) quality papers evaluated acupuncture on various body areas and showed no difference or improvement in pain. One paper showed improved function after acupuncture, but the other showed no difference or slight improvement with standard care.

One high quality (Chen 2015) paper combined auricular and acupuncture on the body and compared it against sham acupuncture. The results showed an improvement in pain and decreased opioid use with fewer side effects in the acupuncture group.

The Acupuncture recommendation has been downgraded two levels because of inconsistent evidence.

Benefits/Harms of Implementation

Overall, effect size is limited with these studies, however the low cost and risk to the patient of acupuncture weigh positively in considering use of this physical treatment.

Cost Effectiveness/Resource Utilization

Minimal cost and resource utilization, however acupuncture-trained professional would have to be hired/available.

Acceptability

May have some challenge gaining acceptability in Western medicine, however acupuncture is more widely acknowledged as a reasonable medical treatment than in prior decades.

Feasibility

Most patients would have no limitation in receiving this treatment, however feasibility may be limited by the number of skilled acupuncture professionals available.

Future Research

Increased studies comparing auricular with other body acupuncture, better examination of pain and opioid consumption after these interventions, better examination of functional scores and outcomes after this intervention.

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Acupressure

Limited evidence suggests that auricular acupressure may be used with standard treatment for opioid reduction and improved function; however, there was no difference in pain.

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

Three high quality (Feng 2017, He 2013, Chang 2012) papers focusing on acupressure were evaluated. Two papers showed decreased opioid consumption and improved function with acupressure versus sham; one of these also showed improved pain and decreased side effects (nausea, vomiting, and dizziness) with acupressure versus sham. A third paper showed no difference in side effects with acupressure versus sham.

The Acupressure recommendation has been downgraded two levels because of inconsistent evidence.

Benefits/Harms of Implementation

Overall, effect size is limited with these studies, however the low cost and risk to the patient of acupressure weigh positively in considering use of this physical treatment.

Cost Effectiveness/Resource Utilization

Minimal cost and resource utilization, however acupressure-trained professional would have to be hired/available.

Acceptability

May have some challenge gaining acceptability in Western medicine, however acupuncture is more widely acknowledged as a reasonable medical treatment than in prior decades.

Feasibility

Most patients would have no limitation in receiving this treatment, however feasibility may be limited by the number of skilled acupressure professionals available.

Future Research

Increased studies with larger patient populations evaluating acupressure with better examination of pain and opioid consumption after these interventions, better examination of functional scores and outcomes after this intervention.

Compression

Limited evidence suggests no significant differences in pain or function with compression.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale
Three high quality studies (Grubhofer 2018, Snyder 2017, Pornrattanamaneewong 2019) and two moderate quality (Windisch 2011, Pornrattanamaneewong 2018) were evaluated with inconsistent results. In most cases, compression versus standard care showed no significant differences for pain or function. In one study, prolonged use of compression for six weeks had improved VAS and decreased DVT rate. A separate study had decreased opioid use on post-operative day one with compression.

The Compression recommendation has been downgraded two levels because of inconsistent evidence.

Benefits/Harms of Implementation
Overall, effect size is limited with these studies, however the low cost and risk to the patient of compression weigh positively in considering use of this physical treatment. A decreased rate of DVT could have a benefit to the patient.

Cost Effectiveness/Resource Utilization
Use of compression in these studies required a specific machine which itself would be a large cost if a treating facility had not already invested in these devices. Otherwise, resource utilization is low.

Acceptability
Compression is already widely used in hospitals and would have no concerns with acceptability.

Feasibility
Compression is already widely used in hospitals and would have no concerns with feasibility. For an extended use of compression (after discharge), feasibility would be more challenging to gain resources from payers to distribute portable devices.

Future Research
Increased studies with larger patient populations evaluating compression with better examination of pain and opioid consumption after these interventions, better examination of functional scores and outcomes after this intervention.

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Cryotherapy

Limited evidence suggests no significant difference in patient pain, function and opioid use between cryo-compression and control/ice/circulating water.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale
Nine high (Levy 1993, Schinsky 2016, Ivey 1994, Li 2016, Thijs 2019, Kullenberg 2006, Smith 2002, Sadoghi 2018, Park 2019) and seven moderate quality articles (Gibbons 2001, Karaduman 2019, Thienpont 2014, Bech 2015, Leegwater 2017, Dervin 1998, Su 2012, Pan 2015) were reviewed regarding cryotherapy. Of the five studies evaluating pain, three showed improved pain with cryotherapy and one of these also showed decreased opioid consumption. Of the seven studies evaluating function after cryotherapy, five showed improved range of motion with cryotherapy.

The Cryotherapy recommendation has been downgraded two levels because of inconsistent evidence.

Benefits/Harms of Implementation
Prolonged cryotherapy could potentially harm the patient with skin contact damage in certain sensitive population, but overall low risk intervention.

Cost Effectiveness/Resource Utilization
Use of a cryotherapy machine would be a large cost if a treating facility had not already invested in these devices. In addition, large cost for patient to take this device home if indicated. Potentially large resource utilization in donning/doffing if needing assistance from nursing.

Acceptability
Would require increased resource utilization which may have some concerns with acceptability.

Feasibility
For an extended use of cryotherapy (after discharge), feasibility would be more challenging to gain resources from payers to distribute portable devices.

Future Research
Increased studies with larger patient populations evaluating cryotherapy with better examination of pain and opioid consumption after these interventions, better examination of functional scores and outcomes after this intervention.

Early Mobilization

Limited evidence suggests no difference in patient pain, function and opioid use between earlier mobilization and standard treatment.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale
Twenty high quality (Christersson 2018, Sheps 2015, Bohl 2019, Paschos 2013, Jenssen 2018, Beaupre 2001, Aufwerber 2020, Kimmel 2012, Lehtonen 2003, Hagen 2020, Okamoto 2016, Schroter 2017, Aufwerber 2019, Keener 2014, Dehghan 2016, Iwakiri 2020, Sheps 2019, Mazzocca 2017, Smeeing 2018, Sherrington 2003) and thirteen moderate quality studies (Yashar 1997, Bennett 2005, Kumar 1996, Lee 2012, Johnson 1990, MacDonald 2000, Gross 2016, Liow 2002, De Roo 2015, Zhang 2017, Arndt 2012, Cuff 2012, Mortensen 1999, Suchak 2008) were reviewed. Most studies showed no significant difference in improvement in pain, patient reported outcomes or opioid use. Three high quality and one moderate quality studies showed worsened pain, while one high quality and one moderate quality study showed improved pain. Seven high quality and five moderate quality studies showed improved function, while two high quality and two moderate quality studies showed worsened function.

The Early Mobilization recommendation has been downgraded two levels because of inconsistent evidence.

Benefits/Harms of Implementation
Despite the large number of studies, only one showed significant negative adverse events for this intervention.

Cost Effectiveness/Resource Utilization
Potentially large resource utilization in delivering this level of care in the hospital setting

Acceptability
Would require increased resource utilization which may have some concerns with acceptability.

Feasibility
Intervention has been used extensively and is clearly feasible.

Future Research
Inconsistent results highlight the need for larger studies with an emphasis on heterogenous treatment effects.

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Massage

Massage may be used with standard treatment for improved pain outcomes.

Strength of Recommendation: Moderate 

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

One high quality (Pasyar 2018) and three moderate quality (Forward 2015, Eghbali 2010, Buyukyilmaz 2013) studies were reviewed. All studies showed improvements in pain. Only one study measured opioid use and did not report improvement, and no studies measured function.

Benefits/Harms of Implementation

No studies reported adverse events, but the level of risk associated with this intervention is low.

Cost Effectiveness/Resource Utilization

Potentially moderate to high resource utilization in delivering this level of care in the hospital setting.

Acceptability

Would require increased resource utilization and specialized staff which may have some concerns with acceptability

Feasibility

Intervention has been used extensively and is clearly feasible.

Future Research

Further research into the effect of this intervention on opioid use and function are needed, as well as cost effectiveness studies.

Neuromuscular Electrical Stimulation

Neuromuscular electrical stimulation should be used with standard treatment to improve function, but no significant difference is seen in pain.

Strength of Recommendation: Strong ★★★★

Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Two high quality (Stevens-Lapsley 2012, Feil 2011) and one moderate quality (Skowron 2019) study were reviewed. The two high quality studies showed improved function for Neuromuscular electrical stimulation (NMES) over standard of care, and one high quality study also showed improved function over Transcutaneous electrical nerve stimulation (TENS). The single moderate quality study showed decreased ROM and no change on QOL outcomes for NMES compared to standard treatment. Two studies (one high and one moderate quality) showed no changes in pain.

Benefits/Harms of Implementation

No studies reported adverse events and this technology is in widespread use. Risks appear to be low.

Cost Effectiveness/Resource Utilization

NEMS units are economical and may have low resource utilization in the hospital setting.

Feasibility

Intervention has been used extensively and is clearly feasible.

Future Research

Inconsistent results highlight the need for larger studies with an emphasis on heterogenous treatment effects. Further research into the effect of this intervention on opioid use and pain are needed, as well as cost effectiveness studies.

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Transcutaneous Electrical Nerve Stimulation

Moderate evidence supports no significant difference in functional outcomes, pain or opioid use between transcutaneous electrical nerve stimulation and standard treatment or sham.

Strength of Recommendation: Moderate  (downgrade)

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

Eight high quality (Kadi 2019, Gorodestskyi 2017, Ramanathan 2017, Feil 2011, Avramidis 2011, Izumi 2015, Forogh 2019, Rakel 2014) and three moderate quality (Goyal 2012, Lan 2012, Gorodetskyi 2010) studies were reviewed. Only one of these eleven studies reported improvements in function (over standard treatment), and two additional studies reported improvement in ROM. Only one moderate quality study reported reductions in opioid use. Three of nine studies reporting on pain outcomes showed improvement.

The Transcutaneous Electrical Nerve Stimulation recommendation has been downgraded one level because of inconsistent evidence.

Benefits/Harms of Implementation

No studies reported adverse events and this technology is in widespread use. Risks appear to be low.

Cost Effectiveness/Resource Utilization

Transcutaneous electrical nerve stimulation (TENS) units are economical and may have low resource utilization in the hospital setting.

Future Research

Inconsistent results highlight the need for larger studies with an emphasis on heterogenous treatment effects, particularly around pain outcomes and cost effectiveness studies.

Peri-op Injections

Moderate evidence suggests no difference in patient outcomes between local and regional anesthesia for patients undergoing total knee and hip arthroplasty.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale
Six high quality (Kuchalik 2017 (a), Kuchalik 2017 (b), Kuchalik 2013, Jules-Elysee 2015, Johnson 2017, Fahs 2018) total hip arthroplasty and twenty-six total knee arthroplasty (Tong 2018, Runge 2016, Zhou 2018, Kampitak 2018, Mayr 2019, Varshney 2019, Chaubey 2017, McDonald 2016, Tanikawa 2014, Fan 2016, McCarthy 2019, Safa 2014, Rizk 2017, Affas 2011, Meftah 2019, Sogbein 2017, Carli 2010, Chandy 2019, Chaumeron 2017, Tammachote 2013, Mahadevan 2012, Li 2017, Ukai 2020, Gi 2014, Uesugi 2014, Tanikawa 2017) showed no difference in patient outcomes.

The Peri-Op Injection recommendation has been downgraded one level because of inconsistent evidence.

Benefits/Harms of Implementation
Improved pain control can improve patient satisfaction and reduce patient morbidity by mitigating the systemic stress response. Reducing opioid use in the post-op period mitigates their well-known side-effects such as nausea/vomiting, respiratory depression, tolerance, etc. Local anesthetic systemic toxicity is always a concern when using local anesthetics. Proximal brachial plexus regional anesthesia may cause hemidiaphragm paresis which may not be tolerated in those with severe pulmonary disease.

Outcome Importance
Postoperative pain control is an important concern to patients, and when poorly managed is associated with delays in achieving functional milestones, greater opioid use, and increased morbidity. The US is in the midst of an opioid epidemic known to contribute to the development of hyperalgesia, tolerance, dependence, addiction, and abuse. Therefore, reducing opioid use is a national priority.

Cost Effectiveness/Resource Utilization
Bupivacaine and ropivacaine, the most used long-acting local anesthetics in regional anesthesia, are both inexpensive and available in generic formulations. The peri-operative use of continuous regional anesthesia requires the assistance of a qualified anesthesia provider, an infusion pump system, and close patient follow-up

Acceptability
Continuous regional anesthesia has been widely used for orthopaedic surgery patients for over 30 years.

Feasibility
Continuous regional anesthesia may not be available in smaller medical centers or ambulatory surgery centers.

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Future Research

Local anesthetics have a key role in treating surgical pain. Future studies should explore novel local anesthetics and adjuvant agents that prolong the duration of pain relief, as well as motor-sparing regimens. These studies should also examine the optimal combination of both local and regional anesthetics versus either technique alone.

Peri-op Injections Total Shoulder Arthroplasty

Strong evidence supports the use of continuous regional anesthesia over local anesthesia in total shoulder arthroplasty to reduce pain and opioid use in the first 24hrs after surgery.

Strength of Recommendation: Strong ★★★★ (upgrade)
Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale
One high quality study (Panchamia 2019) demonstrated that a continuous interscalene brachial plexus catheter was associated with reduced pain and less opioid use thru noon on post-operative day 1 after Total Shoulder Arthroplasty.

One moderate quality study (Bjornholdt 2015) demonstrated that a continuous interscalene brachial plexus catheter was associated with reduced pain thru 8 hours post-operatively and less opioid use in the first 24 hours after Total Shoulder Arthroplasty.

The Peri-Op Shoulder Injection recommendation has been upgraded one level due to the large magnitude of treatment effects for the critical outcomes of pain and opioid consumption.

Benefits/Harms of Implementation
Improved pain control can improve patient satisfaction and reduce patient morbidity by mitigating the systemic stress response. Reducing opioid use in the post-op period mitigates their well-known side-effects such as nausea/vomiting, respiratory depression, tolerance, etc. Local anesthetic systemic toxicity is always a concern when using local anesthetics. Proximal brachial plexus regional anesthesia may cause hemidiaphragm paresis which may not be tolerated in those with severe pulmonary disease.

Outcome Importance
Postoperative pain control is an important concern to patients, and when poorly managed is associated with delays in achieving functional milestones, greater opioid use, and increased morbidity. The US is in the midst of an opioid epidemic known to contribute to the development of hyperalgesia, tolerance, dependence, addiction, and abuse. Therefore, reducing opioid use is a national priority.

Cost Effectiveness/Resource Utilization
Bupivacaine and ropivacaine, the most used long-acting local anesthetics in regional anesthesia, are both inexpensive and available in generic formulations. The peri-operative use of continuous regional anesthesia requires the assistance of a qualified anesthesia provider, an infusion pump system, and close patient follow-up

Acceptability
Continuous regional anesthesia has been widely used for orthopaedic surgery patients for over 30 years.

Feasibility
Continuous regional anesthesia may not be available in smaller medical centers or ambulatory surgery centers.

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Future Research

Local anesthetics have a key role in treating surgical pain. Future studies should explore novel local anesthetics and adjuvant agents that prolong the duration of pain relief, as well as motor-sparing regimens. These studies should also examine the optimal combination of both local and regional anesthetics versus either technique alone.

Cognitive/Behavioral Treatment

Limited evidence suggests no difference in patient function or pain outcomes between cognitive behavioral therapy and standard treatment for patients undergoing total knee arthroplasty.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale
One high quality (Riddle 2019) and one moderate quality study (Cai 2018) met inclusion criteria. Multiple studies of CBT are present in the orthopaedic literature; however, the lack of randomization and robust data analysis limit the current analysis to two studies. Furthermore, the various methods of CBT available and different methods of delivery make interpretation of the literature challenging.
One high quality study (Riddle 2019) demonstrated no differences in WOMAC scores among patients undergoing TKA for those who had or who had not received pain coping skills cognitive behavioral interventions. However, this study included only those patients with moderate to high levels of catastrophizing, an area not routinely measured among those undergoing musculoskeletal surgery.
One moderate quality study (Cai 2018) noted that patients with high levels of kinesiophobia undergoing TKA who were in the intervention arm experienced decreased pain and improved function, but noted decreased kinesiophobia, after surgery. However, this study is limited in its applicability, given the limitation of the patient population to only those with high levels of kinesiophobia, a characteristic not routinely measured in patients undergoing musculoskeletal surgery.

The Cognitive/Behavioral Treatment recommendation has been downgraded one level because of inconsistent evidence.

Benefits/Harms of Implementation
While cognitive behavioral therapy may be a promising non-pharmacologic modality to improve post-operative pain control and function, there is not enough evidence to recommend its use at this point. There are limited risks to using CBT, primarily emotional discomfort, although this may be more severe in some patients. Only one of the studies (Cai 2018) focused on differences in treatment efficacy between genders and found none, and none of the studies specifically evaluated the effect of education level on outcomes.

Cost Effectiveness/Resource Utilization
Costs and resource utilization depend on the method of CBT chosen. In some studies, noted above, CBT is performed by trained clinical psychologists, whereas in others physical therapists are trained in CBT techniques. The costs and use of resources may vary substantially depending on the method of delivery chosen.

If personnel other than behavioral health professionals are performing this intervention they would need to be identified and receive appropriate training. Presumably, they would be people already working with patients undergoing surgery, without need for additional hires. The availability and cost of this training is

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not known. However, once this training is received, this would seem to be a more cost-effective measure than pharmacologic options if training costs were offset by savings in other areas (e.g,, fewer opioids prescriptions, better function resulting in shorter lengths of stay).

Acceptability

CBT is receiving increased attention as a mechanism to improve pain and function. However, cost, resource utilization, and time management concerns may hinder the delivery of CBT to patients. The studies available for review were limited in either the patient population included (levels of kinesiophobia or pain catastrophizing) or because they were performed outside of the US. Given the significant cultural implications of pain expression and opioid use, it is difficult to extrapolate results found among patients in a different culture to patients from the broad range of backgrounds found in the US.

Feasibility

CBT may not be available to all patients due to limited access to or availability of behavioral health services, non-availability of CBT for outpatient surgical patients, and time constraints. Providing access to physical therapists and/or psychologist with training in CBT related to surgical outcomes may be challenging, especially in rural/frontier or smaller hospitals, where access to mental health services is already limited. While tele-mental health could be utilized for this, half of the US population does not have access to sufficient broad band internet access for this type of patient visit, and future studies would need to assess whether phone consultation in their circumstances is equivalent to in-person or virtual (audio and visual) interactions.

Future Research

Additional research is needed to better determine the impact of CBT on patient function and opioid use after musculoskeletal surgery. This would seem to be a promising non-pharmacologic intervention, given the significant impact of mental health on the pain experience and opioid use, but there is currently insufficient evidence to recommend its routine use. In addition, current evidence is limited to specific populations, and the efficacy of CBT has not been established for heterogeneous groups. While 2 of the included studies found no differences in outcome based on patient sex or gender, future studies should include this as a routine variable. Further research should investigate the effect of culture, education status, socioeconomic status, sex, gender, and other demographic variables on the efficacy of CBT after orthopaedic surgery. Furthermore, the optimal timing and method of delivery of CBT has not been established and merits further study.

Guided Relaxation Therapy

There is no significant difference in pain and opioid use outcomes between guided relaxation therapy and standard treatment.

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

Guided relaxation therapy includes progressive muscle relaxation and guided imagery with or without therapeutic touch. Three moderate quality studies (Forward 2015, Wang 2015, Lin 2012) met inclusion criteria.

In patients undergoing joint arthroplasty Lin et al (Lin 2012) found no differences in average pain score when comparing bed rest to relaxation interventions (in person and recorded), but patients in the intervention arm noted decreased anxiety and better sleep. Wang (2014) noted less pain after CPM use among patients receiving biofeedback, compared to control patients. However, no mention was made of differences in opioid use. Forward (2015) found no differences in reported pain or opioid use among patients receiving guided imagery or therapeutic touch, compared to patients receiving usual care.

Benefits/Harms of Implementation

There seem to be no obvious harms from use of these modalities, and, if future research supports its use, there is the potential benefit of improved patient outcomes and lower opioid use.

Cost Effectiveness/Resource Utilization

The interventions in the noted studies were provided by a variety of healthcare professionals and researchers. There would be costs associated with the use of this modality for initial and continued training of those involved, and these costs would need to be balanced with improvements in patient outcomes (and decreased lengths of stay) and opioid use.

Acceptability

Patients are accustomed to interventions or medications for pain control. There would need to be assessment of acceptance of these techniques among patients undergoing surgical treatment in the US. There would also need to be education among healthcare professionals in the US about the potential use and impact of these techniques.

Feasibility

Guided relaxation therapy may not be available to patients undergoing outpatient surgery or in locations where the availability of therapists/biofeedback machines are limited. The cost of these technique and need to have access to appropriately trained personnel could limit use of these modalities, especially in rural/frontier or smaller hospitals. Given the time constraints of those in most healthcare systems, finding the time needed for patient interaction with this type of intervention may be challenging. There would

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need to be more and better data on its effectiveness before most systems would invest the time and resources needed.

Future Research

The efficacy of guided relaxation therapy has not been established for heterogeneous groups, none of the studies reported results based on sex, and there was inconsistent reporting of what constituted "standard treatment. Further research should investigate the effect of culture, education status, socioeconomic status, sex, gender, and other demographic variables on the efficacy of guided relaxation therapy after orthopaedic surgery. Furthermore, the optimal timing and method of delivery of guided relaxation therapy has not been established and merits further study. Current studies in this area are limited to specific patient populations (e.g. patients using CPM after joint arthroplasty). Future studies should include patient undergoing a wider range of procedures. In addition, given the significant impact of cultural expectations, it is difficult to extrapolate results from other countries to the US. Additional studies would be required in the US, involving patients from a broad range of gender and racial/ethnic backgrounds, to determine applicability of this technique in the US. Given the limited access to needed resources to implement relaxation strategies, future research could also assess the impact of providing these virtually to patients in smaller hospitals.

Music Therapy

Music therapy might be used with standard treatment to decrease post-operative pain and opioid use.

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

Three moderate studies (Gallagher2018, McCaffrey 2004 and McCaffrey 2006) assessed the impact of use of music therapy after musculoskeletal surgery. The study by Gallagher also included use of relaxation and imagery strategies, making the impact of music therapy alone difficult to determine. The authors found no change in opioid or anti-emetic use of length of stay with the use of music therapy but noted decreased pain, anxiety, nausea, and mood up to POD 2 with the intervention. The studies by McCaffrey were designed to assess the impact of music therapy on cognitive function, with pain and function as secondary outcomes. The authors found that patients in the intervention arm demonstrated greater readiness to ambulate and less pain and opioid use, as well as higher satisfaction.

The Music Therapy recommendation has been downgraded one level because of feasibility issues.

Benefits/Harms of Implementation

The impact of MT on post-operative pain and function requires additional study but may be a useful addition to standard treatment. No potential harms were noted in either study, but this needs additional research.

Cost Effectiveness/Resource Utilization

Current studies of MT utilize either a board-certified music therapist (Gallagher) or CDs at the patient bedside. For hospitals not currently employing the former, this could be an added cost. CDs or other devices with recorded music could be costly, if they need to be replaced frequently. In-person therapists and biofeedback machines may present substantial cost and time barriers. The delivery of this therapy to outpatients remains to be studied.

Acceptability

Use of music for relaxation is accepted, but its use for pain control and improved function is less so. Acceptability would need to be evaluated in the setting of multi-patient rooms if the delivery method available did now allow for private sessions.

Feasibility

The ability to and cost of hiring a music therapist or train current healthcare professionals in this area could limit use of this technique, especially in rural/frontier or smaller hospitals. Hearing impaired patients may not benefit from pre-recorded relaxation sessions. MT is currently only studied in inpatients, although the listening only therapy may be available to outpatients as well.

Future Research

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

Music therapy may be a useful non-pharmacologic adjunct to improve post-operative pain and function. However, additional research is needed in this area. The impact of music therapy alone, without the addition of PMR and guided imagery, is needed to determine the relative impact of only music therapy. The first 2 modalities can be provided by other staff, without needing to have access to a music therapist, making the intervention less costly. If, however, the most important intervention is music therapy, the relative cost of hiring a therapist or training additional personnel in this technique (and accounting for the time that this would take from their usual duties) compared to usual care and any cost savings in terms of patient pain control and complications would need to be assessed. Additional research could also assess the impact of virtual or remote applications. Interventions for those deaf or hard of hearing also need to be evaluated. Sex-based differences in outcome need to be assessed.

Patient Education

Limited evidence suggests patient education can be used to improve patient function and earlier cessation of opioid use.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale
Patient education encompasses a broad range of topics and may be delivered in multiple ways. In addition, studies in this area used a wide variety of outcome measures, from pain scores, to opioid use, to measures of patient knowledge and self-efficacy, making the identification of consistent impact of this intervention challenging. One high quality study found improved pain scores, earlier discontinuation of opioids and decreased opioid consumption up to three months after rotator cuff repair in patients who received dedicated opioid education preoperatively compared to standard counseling (Syed 2018).
One high quality study (Riddle 2019) demonstrated that among patients with high catastrophizing scores undergoing TKA, training in pain coping skills or pre-operative arthritis education resulted in no differences in WOMAC scores or level of reported pain, compared to usual care. Given that this study focused only on those with high pain catastrophizing scores, the utility of this intervention for all patients undergoing TKA is unknown.

One high quality study (Huang 2017) found that patients undergoing empowerment education related to their THA allowed patients to become more knowledgeable about the procedure, developed greater self-efficacy had improved Tinetti Mobility scores, and improved SF-36 quality of life scores. No indication in this study regarding who provides this education.

One high quality study (Wong 1990) demonstrated that viewing a video, reviewing a handout and then frequent discussions with nurses after THA after anticipated changes in function led to no differences in function or psychosocial status, compared to controls, after surgery. This video was shown to patients at 6 days (and beyond) in the hospital after surgery. Given the current limited length of stay after THA, this study design has limited utility.

One high quality study (von Eck 2018) demonstrated improved satisfaction with recovery after knee or shoulder arthroscopic procedures among patients who underwent web-based education prior to and after surgery. However, the differences in satisfaction scores do not seem to be clinically significant.

One moderate quality study (van den Akker Scheek 2007) demonstrated that a 6-month home-based support program after THA and TKA had no impact on physical function or self-efficacy. A portion of the intervention included newsletters that were mailed to participants, but there is no indication that there was confirmation that patients receive or read these.

The Patient Education recommendation has been downgraded two levels because of inconsistent evidence.

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

Benefits/Harms of Implementation
There are no known harms from this intervention. These interventions may be of interest to patients interested in non-pharmacologic or non-invasive methods of pain control. These interventions also address function and self-efficacy, in addition to pain and opioid use. Providing education about opioids seems to impact amount and length of opioid use after surgery.

Cost Effectiveness/Resource Utilization
Costs and resource utilization vary with method of delivery. Web-based education platforms may require additional expertise to design and maintain the website. Education provided by dedicated clinical personnel may require additional staffing and training. Some of the interventions described involve extensive human resources in terms of home visits, frequent follow-up phone calls, teaching in patient education modules, etc. Additional research is needed to better determine the cost/benefit impact of this intervention.

Acceptability
Patient education is a well-accepted component of standard surgical practice. Specific to pain alleviation strategies, patients are accustomed to interventions or medications for pain control. There would need to be assessment of acceptance of these techniques among patients undergoing surgical treatment in the US. There would also need to be education among healthcare professionals in the US about the potential use and impact of these techniques.

Feasibility
Formalized patient education may require additional staffing, resources (websites, cellphone applications, etc.), and translating services. Patient's own education level may affect the success of patient education efforts. Given the human resources needed for this intervention, there may be limited options for this in small or rural hospitals. However, interactive telehealth could allow patient education classes to be taught over the internet, among different hospitals. Use of this modality for individual teaching in patient homes or using telemedicine, rather than in-person, for follow-up is limited to those with adequate access to broadband internet.

Future Research
The optimal delivery method and timing of patient education has yet to be determined and may be specific to the topic of interest. Social and demographic variables may influence the effect of patient education efforts. Further research should seek to determine the ideal timeline and delivery platform of patient education efforts, with sub-group analyses to determine if gender- and race/ethnicity-based differences affect the acceptance and outcomes of this intervention. Future research needs to focus on relative impact of specific interventions (e.g., teaching self-efficacy vs learning more about a procedure vs learning more about post-operative limitations vs learning more about opioids and addiction).

Virtual Reality

Limited evidence suggests no difference in patient outcomes between use of virtual reality and standard treatment.

Strength of Recommendation: Limited ★★☆☆ (downgrade)
Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale
Two moderate quality studies (Jin 2018 and Gianola 2020) addressed use of virtual reality. Jin et al utilized psychologic interventions, along with VR (simulated rowing), and found lower WOMAC scores up to 6 months and lower VAS scores up to 7 days among patients in the intervention group. However, the use of 2 modalities makes the effect of VR alone difficult to discern. Gianola found no differences in VAS, WOMAC, opioid use, knee range of motion, strength, or QoL but improve proprioception among patients who utilized VR, but the authors did not describe the intervention used.

The Virtual Reality recommendation has been downgraded one level because of feasibility and inconsistent evidence.

Benefits/Harms of Implementation
No benefits or harms were noted in either of the cited studies. However, there is insufficient evidence with this relatively new technology to understand potential risks.

Cost Effectiveness/Resource Utilization
The cost of VR was not discussed in either cited study. This will need additional evaluation, to assure that the cost of VR is offset by savings in terms of patient outcome (and length of stay) and opioid use.

Acceptability
While VR is used for recreation, its use in a medical setting is not widely discussed at this point. The acceptance of use of this technology among patients and surgeons will need additional input and research.

Feasibility
While VR is becoming more accessible, use may be limited in rural/frontier and smaller hospitals. In addition, training of healthcare professionals regarding the appropriate use of this technology may limit its translation into routine patient care.

Future Research
Virtual reality may prove to be an effective non-pharmacologic intervention to improve patient pain and function after musculoskeletal surgery. However, there is currently insufficient evidence to recommend its use. Further research is needed to identify the benefits, potentials harms, and associated costs with this modality. Research should include patients with a spectrum of genders and racial/ethnic backgrounds, to reflect the patient population in the US.

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

Intra-Articular Opioids vs NSAIDs

Limited evidence suggesting there is no difference in patient outcomes between intra-articular opioids and NSAIDs administered intraoperatively for post-operative pain control.

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

There are 2 moderate quality studies (Kim 2015, Sanel 2016) with inconsistent evidence suggesting no difference in outcomes in patients who receive intraarticular opioid versus NSAIDs.

The Intra-Articular Opioid vs NSAID recommendation has been downgraded one level because of inconsistent evidence.

Benefits/Harms of Implementation

Uncontrolled pain after total joint arthroplasty can lead to limited post-operative range of motion, poor functional outcomes, and patient's dissatisfaction. There are many analgesic modalities that can be used in the perioperative period, such as intravenous and oral opioids, epidural analgesia, and peripheral nerve blockade. Each method has its own risks and side effects, intravenous opioids cause nausea, vomiting, and urinary retention. Epidural analgesia is associated with urinary retention, respiratory depression, delayed ambulation and is complicated by perioperative thromboprophylaxis. Peripheral nerve blockade may cause muscle weakness resulting in delayed ambulation. There is also the risk of local anesthetic toxicity and nerve injury. Periarticular injection involves injection of a combination of analgesic drugs into the synovium, joint capsule, and subcutaneous tissues during orthopedic surgery. Periarticular injection after total joint arthroplasty has been reported to have good analgesic efficacy, cost-effectiveness, and few side effects. The main side effects are associated with local anesthetic toxicity. Adherence to dosing guidelines in conjunction with appropriate patient monitoring during and after injection will decrease the potential for harm.

Outcome Importance

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 has been shown to decrease opioid use.

Cost Effectiveness/Resource Utilization

Periarticular infiltration is generally performed by the surgeon during the procedure, which other than the medication costs, results in little added expense. It is recommended that these medications are prepared in a controlled, sterile manner. Intra articular opioids alone or in combination require chain of control processes to ensure there is no opioid misuse or abuse potential.

Acceptability

Surgeon training and acceptance of peri articular infiltration is increasing. Anesthesiologists are also learning how to incorporate peri articular infiltration into perioperative multimodal analgesic plans.

Feasibility

The inclusion of periarticular infiltration into practice is feasible. It will require surgeon education, pharmacy preparation of sterile combination of medications, and recognition of side effects associated with its use.

Future Research

Although the analgesic effect of various drug combinations for periarticular infiltration during orthopedic surgery has been well documented, the gold standard for drug combination has not yet been established. Future research should focus on the ideal combination and dose of medications.

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

Opioid Combo vs NSAID

Limited evidence suggests opioid/NSAID combination treatment may be used over NSAIDs to improve pain.

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

There is one high quality study (Bali 2016) showing limited significant difference in pain or opioid use between opioid combinations and NSAIDs.

The Opioid Combination/NSAID recommendation has been downgraded one level because of inconsistent evidence and the harm of opioids.

Benefits/Harms of *Implementation*

Multimodal analgesia incorporating oral opioids and NSAIDs is standard of care for managing orthopedic postoperative pain. Using a combination of oral opioids and NSAIDs will decrease parenteral opioid use and subsequently decrease opioid-related side effects, such as nausea, vomiting, and respiratory depression. There are no obvious harms to implementing this practice.

Outcome Importance

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.

Cost Effectiveness/Resource Utilization

Oral opioids and NSAIDs are commonly used and are both relatively inexpensive medications. Oral route of administration is significantly less expensive than parenteral medication administration.

Acceptability

Oral opioids and NSAIDs are both widely accepted medications for treating postoperative pain

Feasibility

This recommendation does not significantly change clinical practice as these medications are both widely used.

Future Research

Future research should focus on determining the most effective combination and dose of medications.

Tramadol Combo vs NSAID

Limited evidence suggests no difference in patient outcomes between tramadol combinations and NSAIDs.

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

One moderate quality study (Mochizuki 2016) looking at combo tramadol/acetaminophen vs NSAID in 1551 TKA patients demonstrated decreased VAS scores and independence from the need for walker in the tramadol/acetaminophen group.

Benefits/Harms of Implementation

Tramadol causes less respiratory depression, cardiac depression, dizziness, and drowsiness than morphine; therefore, it has been used as a first-line analgesic for postoperative pain. Combination therapy with acetaminophen and Tramadol results in less pain than when the medications are used alone.

Outcome Importance

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.

Cost Effectiveness/Resource Utilization

Tramadol is a centrally acting, oral analgesic that contains an opioid and is therefore considered a controlled substance. Side effects such as nausea, vomiting and dizziness are associated with Tramadol, although unlike other opioids, respiratory depression is rare.

Acceptability

Tramadol, acetaminophen and NSAIDs are all commonly used medications for postoperative orthopedic pain.

Feasibility

This recommendation does not significantly change clinical practice as all of these medications are widely used.

Future Research

Future research should focus on determining the most effective combination and dose of medications.

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

Fentanyl Patch vs Morphine

Limited evidence suggests no significant difference in patient outcomes between fentanyl patch and morphine.

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

One moderate quality study (Mattia 2010) compared fentanyl patch to MSO4 IV PCA. The authors concluded that the fentanyl patch and morphine IV PCA are both well tolerated and effective methods of pain control. Discontinuation rates and the incidence of adverse events were also evaluated.

Benefits/Harms of Implementation

All opioid medications are associated with similar side effects, consisting of nausea, vomiting, dizziness, and respiratory depression. Changing the route of administration from intravenous to an iontophoretic transdermal system (patch) eliminates some of the risks associated with intravenous administration and also allow for opioid administration after hospital dismissal.

Outcome Importance

In the setting of the current US opioid epidemic, the use of multimodal, non-opioid medications is the goal right now. Moving away from the routine use of opioids such as Fentanyl and Morphine has been a priority for surgeons, anesthesiologists and patients. The ability to provide opioid medications in the postoperative period without maintenance of intravenous access may be appealing as the number of ambulatory total joint arthroplasties increase.

Cost Effectiveness/Resource Utilization

There is limited evidence comparing cost of Morphine PCA to fentanyl patch, although removing the administration costs (pumps, tubing, nursing support, etc) is likely to make the fentanyl patch more cost-effective.

Acceptability

Iontophoretic transdermal systems have historically been used by physicians trained in chronic pain management. It is unlikely that orthopedic surgeons will be comfortable ordering and managing this route of opioid administration.

Feasibility

Both Fentanyl patch and Morphine PCA require significant physician oversight to prevent overdose or misuse. This makes both treatment options less feasible than multimodal oral analgesics.

Future Research

Future research should be focused on patients who may benefit from Fentanyl patch or Morphine PCA in the postoperative period such as chronic pain patients or those who have uncontrolled pain in the setting of aggressive multimodal oral analgesia.

Tramadol vs NSAID

Limited evidence suggests no significant difference in patient outcomes between tramadol and NSAIDs.

Strength of Recommendation: Limited ★★☆☆

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

There is one moderate quality study (Oh 2018) that compared cox-2 inhibitors, ibuprofen and tramadol. There was no significant difference in terms of pain intensity, incidence of adverse effects or dosage of rescue medications at 3 days or 2 weeks.

Benefits/Harms of Implementation

Tramadol is a centrally acting, oral analgesic that contains an opioid and is therefore considered a controlled substance. Side effects such as nausea, vomiting and dizziness are associated with Tramadol, although unlike other opioids, respiratory depression is rare. Traditional NSAIDs inhibit cyclooxygenase COX-1 and may inhibit platelet function or lead to gastrointestinal or renal toxicity. They have minimal side effects in most patients and are safe if avoided in patients considered high risk. Selective COX-2 inhibitors are thought to have fewer side effects. There have been some recent evidence to suggest that COX-2 medications may impair muscle regeneration or weaken tendon-bone healing.

Outcome Importance

In patients without significant kidney disease or gastrointestinal diseases in the setting of equal outcomes ibuprofen would be an inexpensive, easily obtainable option for postoperative pain control compared to Tramadol or COX-2 inhibitors. Targeting multiple pain pathways with multimodal analgesics including a combination of Tramadol and NSAIDs will decrease parenteral opioid use and side effects. In addition, using Tramadol in conjunction with NSAIDs may decrease the dose of Tramadol required, subsequently decreasing side effects.

Cost Effectiveness/Resource Utilization

Ibuprofen is an over the counter medication which is inexpensive and easily available to all patients. COX-2 inhibitors require a prescription and often require approval for insurance coverage. Tramadol is a controlled substance and requires a prescription.

Acceptability

Tramadol and NSAIDs are all commonly used medications for postoperative orthopedic pain.

Feasibility

This recommendation does not significantly change clinical practice as all of these medications are widely used.

Future Research

Future research should focus on determining the most effective combination and dose of medications.

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

Anti-Depressants

In the absence of reliable evidence, it is the opinion of the workgroup that a recommendation for or against the use of duloxetine cannot be made given the limited evidence and safety concerns.

Strength of Recommendation: Consensus ★☆☆☆

Description: Evidence there is no supporting evidence, or limited level evidence was downgraded due to major concerns addressed in the EtD framework. In the absence of reliable evidence, the guideline work group is making a recommendation based on their clinical opinion.

Rationale

There is lack of evidence for the use of duloxetine with only one moderate quality study (YaDeau 2016) included which demonstrated a reduction in opioid consumption but did not demonstrate an improvement in pain after surgery, the primary study outcome.

Benefits/Harms of Implementation

Reducing opioid use in the post-op period mitigates their well-known side-effects such as nausea/vomiting, respiratory depression, tolerance, etc. Pain and symptoms of depression/anxiety are well known to interact clinically such that it is difficult to treat pain when symptoms of depression/anxiety are poorly controlled, and vice versa. There is an FDA Black Box Warning on prescribing duloxetine to patients younger than 25 years old as there is an increased risk of suicidality in this population. Duloxetine may negatively interact with pre-existing therapies for those with mental health disease.

Outcome Importance

The US is in the midst of an opioid epidemic known to contribute to the development of hyperalgesia, tolerance, dependence, addiction, and abuse. Therefore, reducing opioid use is a national priority. Patients with mental health disease can face significant challenges in symptom control after surgery, and maintaining control is essential to pain management and functional improvement.

Cost Effectiveness/Resource Utilization

Duloxetine is a generic medication not requiring significant resources over other medications.

Acceptability

Some orthopaedic surgeons may be hesitant to prescribe duloxetine for pain given its use in anxiety and depression, concern for interference with pre-existing medications, or lack of clinical familiarity with medication treatments for mental health diseases.

Feasibility

Duloxetine is currently widely prescribed in the US and is FDA indicated for chronic musculoskeletal pain, fibromyalgia, diabetic peripheral neuropathic pain, generalized anxiety disorder, and major depressive disorder.

Future Research

Future pain outcomes should be investigated in patients with chronic pain, pre-operative opioid use, generalized anxiety disorder, major depressive disorder.

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

COX-2

Cox2 agents should be used to limit patient opioid consumption, improve pain and function; however, there is no difference in adverse events.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework

Rationale

There are eight high quality (Schroer 2011, Boonrioing 2010, Chen 2015, Xu 2018, Kahlenberg 2017, Mardani-Kivi 2013, Zhu 2018, Gong 2013) and four moderate quality studies (Ittichaikulthol 2010, Jianda 2016, Zhu 2014, Zhu 2016) that met inclusion criteria for this recommendation.

In a randomized double-blind placebo-controlled trial in patients undergoing TKA, Schroer et al (2011) studied celecoxib given twice daily for 6 weeks after discharge vs. placebo. Patients in the study group took significantly fewer opioids over the course of 12 months. Pain scores at rest and with activity were significantly lower in the celecoxib group out to 3 weeks after surgery, and pain scores at night were significantly lower out to 6 weeks after surgery. Patients in the celecoxib group had a significant increase in function across multiple patient reported outcome measures/functional domains (Knee Society Score – Function, Oxford, SF-12 – physical) at 6 weeks. No differences were noted in adverse events.

Boonriong et al (2010) evaluated preoperative celecoxib and placebo as one-time dose in patients undergoing anterior cruciate ligament reconstruction (ACLR). No significant differences were found between pain, narcotic use, or function between celecoxib and placebo. There were no other differences found to include adverse events between groups.

Chen et al (2015) evaluated patients after total hip arthroplasty receiving oral celecoxib preoperatively and postoperatively through day 5 vs placebo. Patients in the celecoxib group had improved VAS pain scores through 72 hours postop, but no difference in Harris Hip Scores. Patients in the celecoxib group were noted to ambulate more than 1 day earlier than the placebo group however the mean times to ambulation were 4.5 $\pm$1.2 days vs. 5.83 $\pm$2.04 days in the celecoxib vs. control group which calls into question the applicability of this outcome in most modern rapid recovery protcols. There were no differences in adverse events between groups.

Xu et al (2018) evaluated markers of inflammation in patients taking celecoxib with tramadol vs. tramadol alone after TKA. Indicators of aseptic inflammation (skin temperature, WBC, ESR and CRP) were all significantly reduced in the celecoxib group and Knee Society Scores were improved. Pain was not assessed.

Kahlenberg (2017) performed a randomized double-blind placebo-controlled trial evaluating preoperative celecoxib vs. placebo when given as 1 preoperative dose prior to hip arthroscopy. There were significant improvements in postoperative pain scores up to 2 hours after surgery. There were no differences noted in opioid consumption and small but not significant decreases in PACU time were found in the celecoxib group.

Mardani-Kivi (2013) performed a randomized triple blind placebo-controlled trial evaluating one dose of preoperative celecoxib vs. placebo for patients undergoing isolated ACLR or partial meniscectomy. Pain

scores were significantly lower in the celecoxib group for both ACLR and partial meniscectomy at 6 and 24 hours after surgery. Opioid usage was significantly less in the celecoxib group for partial meniscectomy at 6 and 24 hours and for the ACLR group at 6 hours. Function was not evaluated. There were no significant differences in adverse events.

Ittichaikulthol et al (2010) performed a randomized double-blind placebo-controlled trial in patients undergoing TKA/THA comparing 1 dose of preoperative celecoxib vs parecoxib vs placebo. Decreased opioid consumption was found in the first 24 hours in both celecoxib and parecoxib groups vs placebo. There were improved pain scores in the parecoxib group through 12 hours compared to both celecoxib and placebo but no difference in pain scores between celecoxib and placebo. Function was not assessed. There was less sedation in the parecoxib group but otherwise no difference in adverse events.

Jianda (2016) performed a randomized placebo-controlled trial looking at one dose of celecoxib preoperatively vs placebo in patients undergoing TKA. All patients received multimodal analgesia throughout hospital stay and the same postoperative discharge medications (to include celecoxib). Two-minute walking test at 3 days after surgery was better in the celecoxib group. Significant improvements in pain scores and decreased opioid consumption were found in the celecoxib group.
Zhu et al (2018) performed a randomized double-blind placebo-controlled trial evaluating the use of celecoxib in patients undergoing TKA. The primary outcome evaluated postoperative cognitive deficiencies, with pain scores evaluated as a secondary outcome. Postoperatively they noted statistically lower pain scores out to 7 days after surgery and less cognitive dysfunction in the celecoxib group.

Benefits/Harms of Implementation
Use of Cox-2 selective agents carries the risks associated with the known side effect profile of these medications, with the possible benefit of decreased gastrointestinal irritation and effect known to occur with non-cox-2 selective agents. Special caution should be exercised in patients with renal insufficiency and a known history of cardiovascular disease, as these medications may be contraindicated in this patient population.

Cost Effectiveness/Resource Utilization
Cox-2 agents may cost more than their non-selective counterparts, but as generic formulations come to market the differences in cost may gradually decrease.

Acceptability
The use of cox-2 selective agents is well accepted under conditions in which NSAIDs are typically used. Patients and clinicians should be aware of the potential risks of these medications and understand the presentation and treatment of potential adverse events.

Feasibility
As cox-2 selective agents become available in generic formulations, their availability to clinicians should become more common and encouraged.

Future Research
Cox-2 selective agents may play an important role in pain alleviation strategies after orthopaedic surgery. Further research into the ideal combination of medications to minimize opioid requirements and consumption after surgery are warranted. Future research should focus on non-arthroplasty surgery and evaluate outcomes and adverse events for longer periods to determine the safety of these medications in orthopaedic surgery patients' long term.

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

Oral Acetaminophen

There is no significant difference in pain intensity and opioid use between oral acetaminophen and intravenous acetaminophen.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

There are 2 high quality (Westrich 2019, Hickman 2018) 1 moderate quality studies (Politi 2017) and one low quality (Suarez 2018) showing no difference in pain scores or opioid use in patients receiving intravenous versus oral acetaminophen. There are 2 high quality studies showing no difference in adverse events between IV and oral acetaminophen.

Benefits/Harms of Implementation

Reducing opioid use in the post-op period reduces opioid-related side-effects such as nausea/vomiting, respiratory depression, opioid tolerance/abuse, etc. Acetaminophen is a well-accepted as a safe analgesic with minimal to no side effects in the vast majority of patients. The safety of oral and intravenous formulations is well established and widely accepted.

Outcome Importance

The US is in the midst of an opioid epidemic known to contribute to the development of hyperalgesia, tolerance, dependence, addiction, and abuse. Therefore, reducing opioid use is a national priority.

Cost Effectiveness/Resource Utilization

Oral acetaminophen is a widely available, inexpensive, generic, over the counter analgesic that does not require significant resources compared to opioids. Intravenous acetaminophen is much more costly than the oral route of administration with no difference in pain relief or side effects. If patients are able to take oral medications using acetaminophen po will result in decreased costs and similar analgesia.

Acceptability

Acetaminophen is widely accepted as an analgesic by orthopedic surgeons, anesthesiologists as well as patients. The tolerance of oral acetaminophen is extremely high with very few contraindications.

Feasibility

Acetaminophen is a widely used analgesic in the United States. Intravenous acetaminophen requires the presences of intravenous access but should be considered an excellent option for patients unable to take oral medications.

Future Research

It is well established that acetaminophen po vs. the intravenous route is similar in efficacy with regard to onset and pain relief. Future research should consist of analgesic combinations and the degree of opioid sparring. Future pain outcomes should be investigated in patients with chronic pain, pre-operative opioid use.

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

Acetaminophen

Acetaminophen should be used to improve patient pain and decrease opioid use.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

There is one high quality (Murata-Ooiwa 2017) and 2 moderate quality studies (Sinatra 2012, Takeda 2019) that demonstrate improved pain at rest in patients receiving acetaminophen. There are 3 high quality studies and 2 moderate quality studies demonstrating reduced opioid consumption in patients receiving acetaminophen.

Benefits/Harms of Implementation

Reducing opioid use in the post-op period reduces opioid-related side-effects such as nausea/vomiting, respiratory depression, opioid tolerance/abuse, etc. Acetaminophen is a well-accepted as a safe analgesic with minimal to no side effects in the vast majority of patients.

Outcome Importance

The US is in the midst of an opioid epidemic known to contribute to the development of hyperalgesia, tolerance, dependence, addiction, and abuse. Therefore, reducing opioid use is a national priority.

Cost Effectiveness/Resource Utilization

Acetaminophen is a widely available, inexpensive, generic, over the counter analgesic that does not require significant resources compared to opioids.

Acceptability

Acetaminophen is widely accepted as an analgesic by orthopedic surgeons, anesthesiologists as well as patients. The tolerance of acetaminophen is extremely high with very few contraindications.

Feasibility

Acetaminophen is a widely used analgesic in the United States.

Future Research

Superiority to placebo is well established. Future research should consist of analgesic combinations and the degree of opioid sparring. Future pain outcomes should be investigated in patients with chronic pain, pre-operative opioid use.

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

Acetaminophen/NSAID Combination Treatment vs NSAID

Acetaminophen/NSAID combination treatments may be used over NSAIDs for reduction in pain; however, no significant difference in reduction of opioid use.

Strength of Recommendation: Limited ★★☆☆ (downgrade)

Description: Evidence from one or more "Low" quality studies with consistent findings or evidence from a single "Moderate" quality study recommending for or against the intervention. Also, higher strength evidence can be downgraded to limited due to major concerns addressed in the EtD Framework.

Rationale

One high quality study (Thybo 2019) and one moderate quality study (Gupta 2016) evaluated the effect of combination acetaminophen with NSAID vs. NSAID alone. In a multi-center study evaluating morphine use after THA, the authors noted statistically significant reductions in morphine usage in the combination group vs. NSAIDs alone, however this did not meet the pre-defined MCID of 10mg (Thybo 2019).
A moderate quality study evaluating combination therapy after TKA or THA found significantly lower pain scores up to day 3 and decreased opioid consumption in the combination ibuprofen/acetaminophen group vs. ibuprofen alone (Gupta).

The Acetaminophen/NSAID Combination recommendation has been downgraded one level because of inconsistent evidence.

Benefits/Harms of Implementation

Potential harms are related to the risk profile of the individual medications. Combination therapy does not offer additional risk of harm to the medications given in isolation.

Cost Effectiveness/Resource Utilization

There are minimal additional costs associated with this intervention. The use of acetaminophen and NSAIDs are commonplace and most medications are now generic. Combination therapy does not require a novel combination medication.

Acceptability

No anticipated issues. Patients and clinicians should be aware of the presenting signs and treatments required for adverse events related to both classes of medications.

Feasibility

Both acetaminophen and NSAIDs are used commonly and are readily available in most pharmacies.

Future Research

The ideal combination and dosing strategy are unclear at this point. Future research should focus on identifying the most efficacious and safest combination medication strategy and expand studies to include orthopaedic surgery patients undergoing non-arthroplasty procedures.

Gabapentin

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 of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Four high level studies (Lunn 2015; Paul 2013; Paul 2015; Clarke 2014) evaluated multi-dosed perioperative oral gabapentin. Lunn 2015 looked at high dose (1300mg/d) and low dose (900mg/d) gabapentin protocol consisting of a single preoperative dose through 7 days post operatively in TKA. Sleep quality was better in the first 48 hrs. in both gabapentin groups, but no differences were seen in overall pain (only VAS pain at rest) or morphine used. Furthermore, dizziness was more frequently observed in both gabapentin groups leading the authors to conclude that gabapentin may have a limited role in multimodal TKA pain control and should not be recommended as standard of care. The CPG group agrees with the authors of these studies that routine clinical use of gabapentin should be avoided outside of controlled clinical research scenarios allowing for gabapentin's potential use in future multimodal pain regimens.

Paul evaluated pre- (600mg) and post-operative (200mg TID) gabapentin in both TKA (2013) and THA (2015) and found no differences in pain, ROM, morphine consumption, satisfaction, or length of stay in either cohort. It is worth noting that Paul 2013 did not use any femoral or adductor canal nerve blocks and but did utilize post-operative PCA and spinal anesthesia.

Clarke 2014 utilized a PCA, spinal anesthesia, femoral and sciatic nerve blocks in addition to 600mg pre- and 200mg TID post-operative gabapentin (or placebo) for 4 days in a TKA population. The gabapentin group used significantly less morphine in the first 24 hrs. and increased in hospital knee ROM (secondary outcomes). No differences were seen in pain or physical function at 4 days, 6 wks., and 3 months after surgery (WOMAC score was primary outcome). The placebo group had significantly more nausea and pruritus (possible opioid side effect) compared to the gabapentin group on POD 1 and dizziness on POD 3.

Two high quality studies (Clarke 2009; Panah Khahi 2012) looked at single dose gabapentin given either before or after surgery. Clarke (2009) looked at single dose gabapentin (600 mg) either before or after THA and found no difference in pain scores or morphine consumption. Similarly, Panah Khahi (2012) looked at single dose gabapentin (300 mg) following ORIF of a tibia fracture and found no difference in pain or morphine consumption.

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Feasibility
Gabapentin is FDA off label use for perioperative pain.

Future Research
Research would benefit from further well-constructed trial looking at gabapentin in the TKA population in the presence of adductor canal blocks, dosed both pre-and post-operatively in a variety of patient populations beyond TJA, and with studies powered for primary outcomes looking at pain, narcotic use, adverse events, sleep quality, and function.

Pregabalin

Moderate evidence suggests single or multi-dose pregabalin could be used to improve patient pain and opioid consumption outcomes; however, additional concerns for adverse events such as dizziness and sedation should be recognized with its use.

Strength of Recommendation: Moderate ★★★☆ (downgrade)
Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale
Single Dose:
Lee (TKA & THA) 43 min, Omara (femur fracture with intramedullary nail) 140 min, Sebastian ("lower limb orthopedic surgeries") 70 min, Ahn (arthroscopic shoulder surgery) decreased incidence at 24 hr (40% vs. 13%) and 48 hr (40% vs. 10%) of rescue IV ketorolac in control vs. pregabalin group respectively. Line 2000 – Lee, Omara, Sebastian – same study population as above for line 1997. Lee regression of sensory & motor block was 15 min and 11 min longer for pregabalin, respectively; Omara regression of sensory & motor block was 14 min and 15 min longer for pregabalin, respectively; Sebastian regression of sensory block was 20 min longer for pregabalin. For Rahat the population was "orthopedic surgeries for tibial fractures" and the "duration for analgesia" was 148 min longer for the pregabalin group.

Three high quality (Lee, 2018; Omara, 2019; Sebastian, 2016) studies and one moderate quality (Rahat, 2018) study found an increased duration of spinal anesthetic. Omara and Lee also found an increased duration of motor block.

Lee, Ahn, Omara population groups (orthopaedic surgeries) are all the same as previously listed. The only new study is Akhavanakbari with a study population only detailed as "lower limb orthopedic surgery.

Three high quality studies (Lee, 2018; Ahn, 2016; Akhavanakbari, 2013) found improved pain scores on VAS or NRS.

Omara (2019) found sleep quality was improved in the first 24 hours as a secondary outcome.

Significant side effects included dizziness (Rahat, 2018, Akhavanakbari, 2013; Sebastian, 2016), sedation (Sebastian, 2016; Lee, 2018), hypotension (Sebastian, 2016), and blurred vision (Lee, 2018).

Multi-dose:
Two high quality studies (Clarke, 2015; Cho, 2019) and one moderate quality study (Eskander, 2013) of multi-dose pregabalin found that pain was lower on post-op day 7 by numerical rating scale, 14 days by visual analogue scale (VAS), and through 8 hours by VAS in TKA, ACL, and shoulder arthroscopy cohorts respectively. However, pain in the Clarke study in a TKA population was a secondary outcome measure.

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One high quality study (Buvanendran, 2015) suggests improvement in neuropathic pain at 3 and 6 months (primary measure) and sleep quality in the first 24 hours (secondary measure) with multi-dose pregabalin in a TKA population.

Two high quality studies (Buvanendran, 2015; Singla, 2015) suggest multidose pregabalin may increase ROM in the first 30 and 3 days respectively (secondary measures) in a TKA population.

Two high quality (Clarke, 2015; Singla, 2015) studies in TKA populations and one moderate quality (Eskandar 2013) study in shoulder arthroplasty found a decrease in opioid consumption within the first week in pregabalin groups on secondary measures.

One high quality study (Yik, 2019) found no difference in any primary (morphine equivalents) or secondary (VAS, ROM, KSS, WOMAC, SF-36) measures in a TKA population.

The Pregabalin recommendation has been downgraded one level because of inconsistent evidence.

Feasibility
Pregabalin is NOT FDA approved for perioperative use.

Future Research
The literature would benefit from high level studies addressing outcomes on function, standardization of dosing (timing, strength and duration), as well has having non-industry backed studies as 3 studies (Bhuvanendran, 2010; Clarke, 2015; Signla, 2015) with supportive findings disclosed industry support. Many of the statistically significant findings in support of pregabalin were in secondary measures. These findings need to be replicated in studies powered with these outcomes as primary measures.

Ketamine

Strong evidence supports the use of intravenous ketamine in the peri-operative period to reduce opioid use in the first 24hrs after hip and knee arthroplasty.

Strength of Recommendation: Strong ★★★★

Description: Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention. Also requires no reasons to downgrade from the EtD framework.

Rationale

Two high quality studies (Remerand 2009, Cengiz 2014) demonstrated that peri-operative intravenous ketamine was associated with less morphine use in the first 24 hours after THA & TKA respectively.

Benefits/Harms of Implementation

Reducing opioid use in the post-op period mitigates their well-known side-effects such as nausea/vomiting, respiratory depression, tolerance, etc. Ketamine can produce many side-effects however they are mostly associated with anesthetic-level dosing. Low-dose, i.e. sub-anesthetic, ketamine used as an adjunct pain medicine has been associated with vivid dreams and hallucinations.

Outcome Importance

The US is in the midst of an opioid epidemic known to contribute to the development of hyperalgesia, tolerance, dependence, addiction, and abuse. Therefore, reducing opioid use is a national priority.

Cost Effectiveness/Resource Utilization

Ketamine is an inexpensive, generic medication on the WHO Model List of Essential Medicines, 21st List (2019). The peri-operative use of ketamine requires the assistance of a qualified anesthesia provider.

Acceptability

Ketamine is already widely used as an adjunctive pain medicine for patients undergoing surgery.

Feasibility

Intravenous ketamine can be easily administered by intermittent manual bolus, gravity infusion, or mechanical pump infusion.

Future Research

Ketamine is an NMDA receptor antagonist, and the NMDA receptor is the nexus of pathways leading to hyperalgesia from poorly controlled pain and opioid use. Future studies should explore longer term outcomes associated with the perioperative use of ketamine such as the development of chronic pain, persistent opioid use, and opioid use disorder.

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Oral Relaxants

There is no significant difference in patient outcomes, pain intensity or opioid use between oral relaxants and placebo given postoperatively.

Strength of Recommendation: Moderate ★★★☆

Evidence from two or more "Moderate" quality studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.

Rationale

One high quality article (Skrejborg 2020) evaluated the use of an oral relaxant (Chlorzoxazone) compared to placebo, administered for the first 7 days after TKA or THA. No significant differences were found in pain after a 5-minute walk on POD 1 or pain at rest during the first 24 hours after surgery. No significant differences were found in Oxford Hip Score or Oxford Knee Score at 7 days or 12 months after surgery. There were also no significant differences found in opioid consumption during the first 7 days after surgery or for side effects, such as fatigue, dizziness, nausea, or vomiting while hospitalized after surgery.

Benefits/Harms of Implementation

While there are multiple potential side effects of relaxants, such as drowsiness, dizziness, lightheadedness, headaches, and gastrointestinal upset, none were identified in this study. These should be evaluated in any future research in this area. In addition, this study did not assess for differences based on patient sex or gender, so differences in potential harms among sexes is not known.

Cost Effectiveness/Resource Utilization

While approved in the US and available for relatively low cost, the lack of efficacy noted in this study does not support the use of Chlorzoxazone for this indication, and the additional cost is not offset by lower use of opioids.

Acceptability

Chlorzoxazone is also approved for use in the US but based on one-high quality study, does not seem to improve post-operative pain or function or lower opioid use.

Feasibility

Chlorzoxazone appears to be a readily available medication in the US, but additional research is needed to determine if this, or other oral relaxants, given during the perioperative period have significant benefit in terms of pain, opioid use, or function, before recommending their routine use.

Future Research

With the need to decrease opioid prescribing and the trend of shorter hospital stays, use of non-opioid oral medications after TKA and THA to improve patient function with lower risks of side effects needs additional investigation. This could include the use of oral muscle relaxants. Given the differences in nociception and pharmacokinetics ***and*** pharmacodynamics among the sexes, future research on the use of relaxants in this setting should include assessments of outcomes based on patient sex.

APPENDICES

Appendix I: References for Included Literature

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Appendix II: PICO Questions Used to Define Literature Search

1. In adult (>17) patients being surgically treated for musculoskeletal extremity/pelvis conditions, do physical treatment options (Cryotherapy, TENS, motion, etc.) improve patient outcomes?

2. In adult (>17) patients being surgically treated for musculoskeletal extremity/pelvis conditions, do peri-operative injection treatments improve patient outcomes?

3. In adult (>17) patients being surgically treated for musculoskeletal extremity/pelvis conditions, do cognitive/behavioral treatment options improve patient outcomes?

4. In adult (>17) patients being surgically treated for musculoskeletal extremity/pelvis conditions, do opioids improve patient outcomes?

5. In adult (>17) patients being surgically treated for musculoskeletal extremity/pelvis conditions, do anti-depressant improve patient outcomes?

6. In adult (>17) patients being surgically treated for musculoskeletal extremity/pelvis conditions, do NSAIDs improve patient outcomes?

7. In adult (>17) patients being surgically treated for musculoskeletal extremity/pelvis conditions, does acetaminophen improve patient outcomes?

8. In adult (>17) patients being surgically treated for musculoskeletal extremity/pelvis conditions, do acetaminophen/NSAID combination treatments improve patient outcomes?

9. In adult (>17) patients being surgically treated for musculoskeletal extremity/pelvis conditions, do gabapentins improve patient outcomes?

10. In adult (>17) patients being surgically treated for musculoskeletal extremity/pelvis conditions, does ketamine improve patient outcomes?

11. In adult (>17) patients being surgically treated for musculoskeletal extremity/pelvis conditions, do muscle relaxants/anxiolytics improve patient outcomes?

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Appendix III: Literature Search Strategy

Appendix: Literature Search Strategies by Database

Database: PubMed
Interface: NCBI (https://www.ncbi.nlm.nih.gov/pubmed)
Date Last Searched: June 2, 2020

LINE	SEARCH SYNTAX
1	"Orthopedic Procedures"[Mesh:NoExp] OR ("Arthroplasty"[mh] NOT ("Total Disc Replacement"[mh] OR "Arthroplasty, Replacement, Finger"[mh])) OR "Cementoplasty"[Mesh:NoExp] OR "Arthrodesis"[Mesh:NoExp] OR "Amputation"[mh] OR ("Bone Lengthening"[mh] NOT ("Orthognathic Surgical Procedures"[mh] OR "Mandible"[mh] OR mandible[tiab] OR mandibular[tiab])) OR "Acetabuloplasty"[mh] OR "Arthroscopy"[mh] OR "Fracture Fixation"[mh] OR "Limb Salvage"[mh] OR "Meniscectomy"[mh] OR "Osteotomy"[Mesh:NoExp] OR "Synovectomy"[mh] OR "Tendon Transfer"[mh] OR "Tenodesis"[mh] OR "Tenotomy"[mh] OR "Ulnar Collateral Ligament Reconstruction"[mh] OR "Fasciotomy"[mh] OR orthopedic*[tiab] OR orthopaedic*[tiab] OR arthroplast*[tiab] OR hemiarthroplast*[tiab] OR arthroscop*[tiab] OR osteotomy[tiab] OR osteotomies[tiab] OR osteoplasty[tiab] OR chondroplasty[tiab] OR osteochondroplasty[tiab] OR tenotomy[tiab] OR tenotomies[tiab] OR tenodesis[tiab] OR meniscectomy[tiab] OR synovectomy[tiab] OR tenosynovectomy[tiab] OR tendoscopy[tiab] OR arthroereisis[tiab] OR fixat*[tiab] OR arthrodesis[tiab] OR salvag*[tiab] OR amputat*[tiab] OR acetabuloplasty[tiab] OR "hip replacement"[tiab] OR "hip replacements"[tiab] OR "knee replacement"[tiab] OR ("joint replacement"[tiab] NOT temporomandibular[tiab]) OR "ankle replacement"[tiab] OR "shoulder replacement"[tiab] OR "elbow replacement"[tiab] OR "femoral replacement"[tiab] OR "ankle fusion"[tiab] OR (release[tiab] AND "carpal tunnel"[tiab]) OR resurfacing[tiab] OR hemipelvectomy[tiab] OR repair*[tiab] OR reconstruct*[tiab] OR Latarjet[tiab] OR Ilizarov[tiab] OR "open reduction"[tiab] OR microfracture[tiab] OR arthrotomy[tiab] OR fasciotomy[tiab] OR nailing[tiab] OR plating[tiab] OR ((surgery[tiab] OR surgical[tiab] OR surgically[tiab] OR operative*[tiab] OR perioperative*[tiab] OR "peri operative"[tiab] OR "peri operatively"[tiab] OR preoperative*[tiab] OR "pre operative"[tiab] OR "pre operatively"[tiab] OR postoperative*[tiab] OR "post operative"[tw] OR "post operatively"[tiab] OR intraoperative*[tiab] OR "intra operative"[tiab] OR "intra operatively"[tiab]) AND (fractur*[tiab] OR avuls*[tiab] OR injur*[tiab] OR "Fractures, Bone"[Mesh:NoExp] OR "Fracture Dislocation"[mh] OR "Fractures, Avulsion"[mh] OR "Fractures, Closed"[mh] OR "Fractures, Comminuted"[mh] OR "Fractures, Compression"[mh] OR "Fractures, Malunited"[mh] OR "Fractures, Multiple"[mh] OR "Fractures, Open"[mh] OR "Fractures, Spontaneous"[mh] OR "Fractures, Stress"[mh] OR "Fractures, Ununited"[mh] OR "Intra-Articular Fractures"[mh] OR "Osteoporotic Fractures"[mh] OR "Periprosthetic Fractures"[mh] OR "Wounds and Injuries"[Mesh:NoExp] OR "Athletic Injuries"[mh] OR "Blast Injuries"[mh] OR "Crush Injuries"[mh] OR "Amputation, Traumatic"[mh] OR "Multiple Trauma"[mh] OR "Shock, Traumatic"[mh] OR "Soft Tissue Injuries"[mh] OR "Sprains and Strains"[mh] OR "Tendon Injuries"[mh] OR "War-Related Injuries"[mh] OR "Ankle Fractures"[mh] OR "Humeral Fractures"[mh] OR "Radius Fractures"[mh] OR "Shoulder Fractures"[mh] OR "Ulna

	Fractures"[mh] OR "Arm Injuries"[mh] OR "Hip Injuries"[mh] OR "Leg Injuries"[mh] OR "Shoulder Injuries"[mh] OR (strain*[tiab] AND (Tendons[mh] OR "Muscle, Skeletal"[mh] OR muscle*[tiab] OR tendon*[tiab])) OR tear[tiab] OR tears[tiab] OR tearing[tiab] OR torn[tiab] OR trauma[tiab] OR traumatic[tiab] OR (ruptur*[tiab] AND (Tendons[mh] OR tendon*[tiab] OR "Ligaments, Articular"[mh])) OR wound*[tiab])
2	"Extremities"[mh] OR "Bones of Lower Extremity"[mh] OR "Bones of Upper Extremity"[mh] OR "Hip Joint"[mh] OR "Knee Joint"[mh] OR "Anterior Cruciate Ligament"[mh] OR "Posterior Cruciate Ligament"[mh] OR "Collateral Ligaments"[mh] OR "Ankle Joint"[mh] OR "Tarsal Joints"[mh] OR "Shoulder Joint"[mh] OR "Acromioclavicular Joint"[mh] OR "Sternoclavicular Joint"[mh] OR "Elbow Joint"[mh] OR "Wrist Joint"[mh] OR "Carpal Joints"[mh] OR "Achilles Tendon"[mh] OR "Hamstring Tendons"[mh] OR "Rotator Cuff"[mh] OR "Ankle Fractures"[mh] OR "Humeral Fractures"[mh] OR "Radius Fractures"[mh] OR "Shoulder Fractures"[mh] OR "Ulna Fractures"[mh] OR "Arm Injuries"[mh] OR "Hip Injuries"[mh] OR "Leg Injuries"[mh] OR "Shoulder Injuries"[mh] OR extremity[tiab] OR extremities[tiab] OR limb[tiab] OR "long bone"[tiab] OR "long bones"[tiab] OR leg[tiab] OR hip[tiab] OR pelvic[tiab] OR acetabulum[tiab] OR acetabular[tiab] OR femoroacetabular[tiab] OR labral[tiab] OR knee[tiab] OR femur[tiab] OR femoral[tiab] OR trochanter*[tiab] OR intertrochanter*[tiab] OR subtrochanter*[tiab] OR pertrochanter*[tiab] OR tibia[tiab] OR tibial[tiab] OR hamstring[tiab] OR (quadriceps[tiab] AND (tendon[tiab] OR ruptur*[tiab])) OR ("rectus femoris"[tiab] AND (tendon[tiab] OR strain*[tiab] OR ruptur*[tiab])) OR patella[tiab] OR patellar[tiab] OR patellofemoral[tiab] OR "anterior cruciate"[tiab] OR ACL[tiab] OR "posterior cruciate"[tiab] OR menisc*[tiab] OR ankle[tiab] OR Achilles[tiab] OR subtalar[tiab] OR hindfoot[tiab] OR calcaneal[tiab] OR talus[tiab] OR talar[tiab] OR tarsometatarsal[tiab] OR Lisfranc[tiab] OR malleolus[tiab] OR malleolar[tiab] OR foot[tiab] OR arm[tiab] OR forearm[tiab] OR shoulder[tiab] OR glenohumeral[tiab] OR glenoid[tiab] OR "rotator cuff"[tiab] OR acromioclavicular[tiab] OR subscapularis[tiab] OR supraspinatus[tiab] OR humerus[tiab] OR humeral[tiab] OR (pectoralis[tiab] AND (tendon[tiab] OR "Rupture/surgery"[Mesh:NoExp])) OR biceps[tiab] OR triceps[tiab] OR clavicle[tiab] OR elbow[tiab] OR elbows[tiab] OR radius[tiab] OR radial[tiab] OR ulna[tiab] OR ulnar[tiab] OR olecranon[tiab] OR wrist[tiab] OR carpal[tiab] OR Colles*[tiab] OR Monteggia*[tiab] OR Torus[tiab] OR scaphoid[tiab] OR "total joint"[tiab] OR THA[tiab] OR TKA[tiab]
3	#1 AND #2
4	Cryotherapy[mh] OR Ice[mh] OR "Hot Temperature/therapeutic use"[mh] OR "Electric Stimulation Therapy"[mh] OR "Early Ambulation"[mh] OR "Acupuncture Therapy"[mh] OR Massage[mh] OR "Motion Therapy, Continuous Passive"[mh] OR cryotherapy[tiab] OR cryotherapies[tiab] OR "cold therapy"[tiab] OR ice[tiab] OR cooling[tiab] OR warming[tiab] OR heating[tiab] OR TENS[tiab] OR NMES[tiab] OR ((electric[tiab] OR electrical[tiab]) AND stimulat*[tiab]) OR electrostimulation[tiab] OR electrotherapy[tiab] OR "nerve stimulation"[tiab] OR "muscle stimulation"[tiab] OR ((early[tiab] OR accelerated[tiab] OR immediate[tiab]) AND (ambulat*[tiab] OR walking[tiab] OR mobilization[tiab] OR mobilisation[tiab] OR motion[tiab] OR weightbearing[tiab] OR "weight bearing"[tiab] OR rehabilitation[tiab])) OR acupuncture[tiab] OR pharmacoacupuncture[tiab] OR

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	acupotomy[tiab] OR auriculotherapy[tiab] OR "dry needling"[tiab] OR massag*[tiab] OR "continuous passive motion"[tiab]
5	"Anesthesia, Conduction"[mh] OR "nerve block"[tiab] OR "nerve blocks"[tiab] OR "nerve blockade"[tiab] OR "nerve blockades"[tiab] OR IPACK[tiab] OR "plexus block"[tiab] OR "plexus blocks"[tiab] OR "plexus blockade"[tiab] OR "plexus blockades"[tiab] OR "neuraxial block"[tiab] OR "neuraxial blocks"[tiab] OR "neuraxial blockade"[tiab] OR "neuraxial blockades"[tiab] OR "adductor canal block"[tiab] OR "adductor canal blocks"[tiab] OR "adductor canal blockade"[tiab] OR "fascia iliaca compartment block"[tiab] OR "fascia iliaca compartment blocks"[tiab] OR "fascia iliaca compartment blockade"[tiab] OR "fascia iliaca block"[tiab] OR "fascia iliaca blocks"[tiab] OR "fascia iliaca blockade"[tiab] OR "paravertebral block"[tiab] OR "paravertebral blocks"[tiab] OR "paravertebral blockade"[tiab] OR "paravertebral blockades"[tiab] OR "spinal anaesthesia"[tiab] OR "spinal anesthesia"[tiab] OR "spinal anaesthetic"[tiab] OR "spinal anaesthetics"[tiab] OR "spinal anesthetic"[tiab] OR "spinal anesthetics"[tiab] OR "spinal analgesia"[tiab] OR "subarachnoid block"[tiab] OR "subarachnoid anesthesia"[tiab] OR "subarachnoid anaesthesia"[tiab] OR "epidural anaesthesia"[tiab] OR "epidural anesthesia"[tiab] OR "regional anesthesia"[tiab] OR "regional anesthetic"[tiab] OR "regional anaesthesia"[tiab] OR "regional anaesthetic"[tiab] OR "local anesthesia"[tiab] OR "local anesthetic"[tiab] OR "local anesthetics"[tiab] OR "local anaesthesia"[tiab] OR "local anaesthetic"[tiab] OR "local anaesthetics"[tiab] OR "peri-articular infiltration"[tiab] OR "periarticular infiltration"[tiab] OR "peri-articular injection"[tiab] OR "peri-articular injections"[tiab] OR "periarticular injection"[tiab] OR "periarticular injections"[tiab] OR "interscalene block"[tiab] OR "interscalene blocks"[tiab] OR "interscalene blockade"[tiab] OR "infiltration anesthesia"[tiab] OR "infiltration analgesia"[tiab] OR "infiltrative analgesia"[tiab] OR "lidocaine"[tiab] OR "ropivacaine"[tiab] OR "bupivacaine"[tiab] OR "ketorolac"[tiab] OR "tromethamine"[tiab] OR "epinephrine"[tiab] OR "nerve catheter"[tiab] OR "nerve catheters"[tiab] OR "perineural catheter"[tiab] OR "perineural catheters"[tiab]
6	"Adrenal Cortex Hormones"[mh] OR "adrenal cortex hormones"[tiab] OR corticosteroid*[tiab] OR "cortico steroid"[tiab] OR corticoid*[tiab] OR cortisone[tiab] OR prednisone[tiab] OR prednisolone[tiab] OR methylprednisolone[tiab] OR triamcinolone[tiab] OR dexamethasone[tiab] OR glucocorticoid*[tiab] OR cortisone[tiab] OR hydrocortisone[tiab] OR betamethasone[tiab] OR budesonide[tiab] OR mineralocorticoid*[tiab]
7	"Anti-Inflammatory Agents, Non-Steroidal"[mh] OR "Cyclooxygenase 2 Inhibitors"[mh] OR "non-steroidal anti-inflammatory agent"[tiab] OR "nonsteroidal anti-inflammatory agents"[tiab] OR meloxicam[tiab] OR Mobic[tiab] OR naproxen[tiab] OR Aleve[tiab] OR ibuprofen[tiab] OR Advil[tiab] OR flurbiprofen[tiab] OR ketorolac[tiab] OR Toradol[tiab] OR "COX-2 inhibitor"[tiab] OR "COX-2 inhibitors"[tiab] OR "COX2 inhibitor"[tiab] OR "COX2 inhibitors"[tiab] OR "cyclooxygenase 2 inhibitor"[tiab] OR "cyclo oxygenase inhibitor"[tiab] OR celecoxib[tiab] OR Celebrex[tiab] OR diclofenac[tiab] OR misoprostol[tiab] OR sulindac[tiab] OR

	ketoprofen[tiab] OR tolmetin[tiab] OR etodolac[tiab] OR fenoprofen[tiab] OR piroxicam[tiab] OR indomethacin[tiab] OR nabumetone[tiab] OR aspirin[tiab] OR etoricoxib[tiab]
8	"Injections, Intra-Articular"[Mesh:NoExp] OR inject*[tiab] OR infiltration*[tiab] OR "intra articular"[tiab] OR intraarticular[tiab] OR "peri articular"[tiab] OR periarticular[tiab]
9	((#6 OR #7) AND #8) OR #5
10	Psychotherapy[mh] OR "Patient Education as Topic"[mh] OR "Health Education"[mh] OR psychotherapy[tiab] OR psychotherapies[tiab] OR psychotherapeutic[tiab] OR ((cogniti*[tiab] OR behavior*[tiab] OR behaviour*[tiab]) AND (therapy[tiab] OR therapies[tiab] OR treatment*[tiab] OR intervention*[tiab])) OR (CBT[tiab] NOT ("cord blood transplantation"[tiab] OR "carotid body tumor"[tiab] OR "cortical bone trajectory"[tiab] OR "cortical bone thickness"[tiab] OR "computer based training"[tiab])) OR ("virtual reality"[tiab] AND (therapy[tiab] OR therapies[tiab] OR treatment*[tiab] OR intervention*[tiab] OR rehabilitation[tiab])) OR "mirror therapy"[tiab] OR "visual feedback"[tiab] OR "mirror feedback"[tiab] OR ((sensorimotor[tiab] OR "sensori motor"[tiab] OR "sensory"[tiab]) AND (feedback[tiab] OR training[tiab] OR rehabilitation[tiab])) OR (music[tiab] AND (therapy[tiab] OR therapies[tiab] OR treatment*[tiab] OR intervention*[tiab])) OR "guided imagery"[tiab] OR "motor imagery"[tiab] OR Reiki[tiab] OR hypnosis[tiab] OR mindfulness[tiab] OR meditat*[tiab] OR education*[ti] OR teaching[ti]
11	Narcotics[mh] OR Tramadol[mh] OR narcotic*[tiab] OR opioid*[tiab] OR opiate*[tiab] OR papaver*[tiab] OR oxycodone[tiab] OR Oxycontin[tiab] OR "Oxy-ER"[tiab] OR "Oxy-CRF"[tiab] OR "OxyIR"[tiab] OR "Oxy-IR"[tiab] OR Percodan[tiab] OR Percocet[tiab] OR Roxicet[tiab] OR hydrocodone[tiab] OR dihydrocodeinone[tiab] OR Vicodin[tiab] OR Vicoprofen[tiab] OR Norco[tiab] OR Lortab[tiab] OR Lorcet[tiab] OR oxymorphone[tiab] OR Opana[tiab] OR morphine[tiab] OR Kadian[tiab] OR Avinza[tiab] OR "MS Contin"[tiab] OR Duramorph[tiab] OR Roxanol[tiab] OR codeine[tiab] OR fentanyl[tiab] OR Duragesic[tiab] OR Actiq[tiab] OR Sublimaze[tiab] OR hydromorphone[tiab] OR Dilaudid[tiab] OR meperidine[tiab] OR Demerol[tiab] OR tramadol[tiab] OR Ultram[tiab] OR buprenorphine[tiab] OR propoxyphene[tiab] OR Darvocet[tiab] OR Omnopon[tiab] OR methadone[tiab] OR Dolophine[tiab] OR Methadose[tiab] OR suboxone[tiab] OR nalbuphine[tiab] OR propoxyphene[tiab] OR pentazocine[tiab]
12	"Antidepressive Agents"[mh] OR "Serotonin and Noradrenaline Reuptake Inhibitors"[mh] OR "Monoamine Oxidase Inhibitors"[mh] OR "Serotonin Uptake Inhibitors"[mh] OR "Dopamine Uptake Inhibitors"[mh] OR antidepressant[tiab] OR antidepressants[tiab] OR "anti depressant"[tiab] OR "anti depressants"[tiab] OR SNRI*[tiab] OR (serotonin[tiab] AND (norepinephrine[tiab] OR noradrenaline[tiab] OR antagonist[tiab]) AND inhibitor*[tiab]) OR duloxetine[tiab] OR desvenlafaxine[tiab] OR levomilnacipran[tiab] OR venlafaxine[tiab] OR nefazodone[tiab] OR trazodone[tiab] OR SSRI*[tiab] OR (selective[tiab] AND serotonin[tiab] AND inhibitor*[tiab]) OR citalopram[tiab] OR escitalopram[tiab] OR fluoxetine[tiab] OR fluvoxamine[tiab] OR paroxetine[tiab] OR sertraline[tiab] OR vilazodone[tiab] OR (monoamine[tiab] AND oxidase[tiab] AND inhibitor*[tiab]) OR MAOI[tiab] OR MAOIs[tiab] OR

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	isocarboxazid[tiab] OR phenelzine[tiab] OR tranylcypromine[tiab] OR NDRI*[tiab] OR (norepinephrine[tiab] AND dopamine[tiab] AND inhibitor*[tiab]) OR bupropion[tiab] OR amitriptyline[tiab] OR clomipramine[tiab] OR desipramine[tiab] OR doxepin[tiab] OR imipramine[tiab] OR nortriptyline[tiab] OR protriptyline[tiab] OR trimipramine[tiab] OR amoxapine[tiab] OR maprotiline[tiab] OR mirtazapine[tiab] OR vortioxetine[tiab]
13	"Acetaminophen"[mh] OR acetaminophen[tiab] OR paracetamol[tiab] OR Tylenol[tiab] OR propacetamol[tiab]
14	"Pregabalin"[mh] OR "Gabapentin"[mh] OR gabapentin[tiab] OR gabapentinoid*[tiab] OR Neurontin[tiab] OR Gralise[tiab] OR Horizant[tiab] OR pregabalin[tiab] OR Lyrica[tiab]
15	Ketamine[mh] OR ketamine[tiab] OR Ketalar[tiab] OR Ketaject[tiab] OR katamine[tiab] OR Calipsol[tiab] OR Calypsol[tiab] OR Imalgene[tiab] OR Kalipsol[tiab] OR Ketanest[tiab] OR Vetalar[tiab] OR Ketamin[tiab] OR Ketamina[tiab]
16	"Neuromuscular Agents"[mh] OR "Succinylcholine"[mh] OR "Rocuronium"[mh] OR "Mivacurium"[mh] OR "Pancuronium"[mh] OR "Benzodiazepines"[mh] OR "Hydroxyzine"[Mesh:NoExp] OR "muscle relaxant"[tiab] OR "muscle relaxants"[tiab] OR abobotulinumtoxinA[tiab] OR baclofen[tiab] OR Botox[tiab] OR carisoprodol[tiab] OR chlorzoxazone[tiab] OR cyclobenzaprine[tiab] OR Dantrium[tiab] OR dantrolene[tiab] OR Dysport[tiab] OR Flexeril[tiab] OR incobotulinumtoxinA[tiab] OR Lioresal[tiab] OR metaxalone[tiab] OR methocarbamol[tiab] OR Myobloc[tiab] OR Norflex[tiab] OR onabotulinumtoxinA[tiab] OR orphenadrine[tiab] OR Parafon[tiab] OR rimabotulinumtoxinB[tiab] OR Robaxin[tiab] OR Skelaxin[tiab] OR tizanidine[tiab] OR Xeomin[tiab] OR atracurium[tiab] OR cisatracurium[tiab] OR mivacurium[tiab] OR pancuronium[tiab] OR rocuronium[tiab] OR succinylcholine[tiab] OR vecuronium[tiab] OR Norgesic[tiab] OR quazepam[tiab] OR chlordiazepoxide[tiab] OR flurazepam[tiab] OR alprazolam[tiab] OR diazepam[tiab] OR oxazepam[tiab] OR clonazepam[tiab] OR estazolam[tiab] OR clorazepate[tiab] OR triazolam[tiab] OR lorazepam[tiab] OR temazepam[tiab] OR clobazam[tiab] OR midazolam[tiab] OR Doral[tiab] OR Valium[tiab] OR Versed[tiab] OR hydroxyzine[tiab]
17	(1990:3000[pdat]) AND English[la]
18	(2000:3000[pdat]) AND English[la]
19	(2005:3000[pdat]) AND English[la]
20	(2010:3000[pdat]) AND English[la]
21	"randomized controlled trial"[pt] OR "Randomized Controlled Trials as Topic"[mh] OR "random allocation"[mh] OR random*[tiab]

22	MEDLINE[tiab] OR (systematic*[tiab] AND review*[tiab]) OR "meta analysis"[tiab] OR "meta-analysis"[pt] OR systematic review[pt]
23	#21 or #22
24	("animals"[mh] NOT "humans"[mh]) OR "cadaver"[mh] OR cadaver*[tiab] OR "in vitro"[tiab] OR animal*[ti] OR dog[ti] OR dogs[ti] OR canine[ti] OR horse[ti] OR horses[ti] OR equine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rabbit[ti] OR rabbits[ti] OR sheep[ti] OR porcine[ti] OR pig[ti] OR pigs[ti] OR rodent*[ti] Or monkey*[ti] OR ((comment[pt] OR editorial[pt] OR letter[pt] OR "historical article"[pt]) NOT "clinical trial"[pt]) OR abstracts[ti] OR editorial[ti] OR reply[ti] OR commentary[ti] OR letter[ti] OR address[pt] OR news[pt] OR "newspaper article"[pt] OR pmcbook OR "case report"[ti] OR "case reports"[pt]
25	((Infant[mh] OR Child[mh] OR pediatric*[ti] OR paediatric*[ti] OR child[ti] OR children[ti]) NOT (Adult[mh] OR Adolescent[mh] OR Adult[ti]))
26	#24 OR #25
27	((#4 OR #10) AND #3) AND #17
28	(#9 AND #3) AND #18
29	((#12 OR #14 OR #15 OR #16) AND #3) AND #19
30	((#7 OR #11 OR #13) AND #3) AND #20
31	((#27 OR #28 OR #29 OR #30) AND #23) NOT #26

Database: Embase
Interface: Elsevier (https://embase.com)
Date Last Searched: June 2, 2020

LINE	SEARCH QUERY
1	orthopedic surgery'/de OR ('amputation'/exp NOT ('thumb amputation'/de OR 'finger amputation'/de)) OR 'bone resection'/de OR 'bone transplantation'/exp OR 'cartilage transplantation'/exp OR 'cementoplasty'/de OR ('distraction osteogenesis'/de NOT ('mandible'/de OR mandible:ti,ab OR mandibular:ti,ab OR 'maxilla'/de OR maxilla:ti,ab OR maxillary:ti,ab OR maxillomandibular:ti,ab OR 'temporomandibular joint disorder'/de OR temporomandibular:ti,ab OR 'orthognathic surgery'/exp OR orthognathic:ti,ab OR maxillofacial:ti,ab OR alveolar:ti,ab)) OR 'fasciotomy'/de OR 'foot surgery'/de OR 'fracture treatment'/de OR 'fracture fixation'/exp OR 'fracture reduction'/de OR 'hemipelvectomy'/de OR 'joint surgery'/de OR 'arthrodesis'/de OR 'ankle arthrodesis'/de OR 'subtalar arthrodesis'/de OR 'arthrolysis'/de OR 'arthroplasty'/de OR 'ankle arthroplasty'/exp OR 'elbow arthroplasty'/exp OR 'replacement arthroplasty'/de OR 'hemiarthroplasty'/exp OR 'total arthroplasty'/exp OR 'arthroscopic surgery'/exp OR 'arthrotomy'/de OR 'bursectomy'/de OR 'capsular release'/de OR 'chondroplasty'/exp OR 'leg lengthening'/de OR 'ligament surgery'/exp OR 'limb salvage'/de OR 'open reduction

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	(procedure)'/exp OR 'osteotomy'/de OR 'femur intertrochanteric osteotomy'/de OR 'femur osteotomy'/de OR 'fibula osteotomy'/de OR 'fibulotibial osteotomy'/de OR 'pelvis osteotomy'/de OR 'tibia osteotomy'/de OR 'tibia proximal osteotomy'/de OR 'tendon surgery'/exp OR 'hip surgery'/exp OR 'joint capsulotomy'/de OR 'knee surgery'/exp OR 'shoulder surgery'/exp OR 'synovectomy'/de OR orthopedic*:ti,ab OR orthopaedic*:ti,ab OR arthroplast*:ti,ab OR hemiarthroplast*:ti,ab OR 'hemi arthroplast*':ti,ab OR arthroscop*:ti,ab OR osteotomy:ti,ab OR osteotomies:ti,ab OR osteoplasty:ti,ab OR chondroplasty:ti,ab OR osteochondroplasty:ti,ab OR tenotomy:ti,ab OR tenotomies:ti,ab OR tenodesis:ti,ab OR meniscectomy:ti,ab OR synovectomy:ti,ab OR tenosynovectomy:ti,ab OR tendoscopy:ti,ab OR arthroereisis:ti,ab OR fixat*:ti,ab OR arthrodesis:ti,ab OR salvag*:ti,ab OR amputat*:ti,ab OR acetabuloplasty:ti,ab OR (((hip OR knee OR joint OR ankle OR shoulder OR elbow OR femoral) NEAR/3 replacement*):ti,ab NOT temporomandibular:ti,ab) OR (ankle NEAR/3 fusion):ti,ab OR (release NEAR/3 'carpal tunnel'):ti,ab OR resurfacing:ti,ab OR hemipelvectomy:ti,ab OR repair*:ti,ab OR reconstruct*:ti,ab OR Latarjet:ti,ab OR Ilizarov:ti,ab OR 'open reduction':ti,ab OR microfracture:ti,ab OR arthrotomy:ti,ab OR fasciotomy:ti,ab OR nailing:ti,ab OR plating:ti,ab OR ((surgery:ti,ab OR surgical:ti,ab OR surgically:ti,ab OR operative*:ti,ab OR perioperative*:ti,ab OR 'peri operative':ti,ab OR 'peri operatively':ti,ab OR preoperative*:ti,ab OR 'pre operative':ti,ab OR 'pre operatively':ti,ab OR postoperative*:ti,ab OR 'post operative':ti,ab OR 'post operatively':ti,ab OR intraoperative*:ti,ab OR 'intra operative':ti,ab OR 'intra operatively':ti,ab) AND (fractur*:ti,ab OR injury/de OR 'avulsion injury'/exp OR 'blast injury'/de OR 'battle injury'/de OR 'crush trauma'/de OR 'limb injury'/exp OR 'multiple trauma'/de OR 'musculoskeletal injury'/exp OR 'pelvis injury'/exp OR 'ligament rupture'/de OR 'tendon rupture'/de OR 'sport injury'/de OR 'traumatic amputation'/de OR 'traumatic shock'/exp OR wound/de OR (strain*:ti,ab AND (tendon/de OR 'skeletal muscle'/exp OR muscle*:ti,ab OR tendon*:ti,ab)) OR tear:ti,ab OR tears:ti,ab OR tearing:ti,ab OR torn:ti,ab OR trauma:ti,ab OR traumatic:ti,ab OR (ruptur*:ti,ab AND (tendon/de OR tendon*:ti,ab OR 'joint ligament'/exp)) OR wound*:ti,ab))
2	limb'/de OR 'upper limb'/exp OR 'lower limb'/exp OR 'bones of the extremities'/de OR 'bones of the arm and hand'/de OR 'arm bone'/exp OR 'carpal bone'/exp OR 'bones of the leg and foot'/de OR 'leg bone'/exp OR 'tarsal bone'/exp OR 'long bone'/exp OR 'acromioclavicular joint'/de OR 'ankle'/exp OR 'elbow'/de OR 'tarsal joint'/exp OR 'carpal joint'/de OR 'hip'/exp OR 'joint capsule'/de OR 'joint cavity'/de OR 'ankle lateral ligament'/de OR 'collateral ligament'/exp OR 'knee ligament'/exp OR 'knee'/exp OR 'knee meniscus'/de OR 'patellofemoral joint'/de OR 'radioulnar joint'/de OR 'shoulder'/exp OR 'sternoclavicular joint'/de OR 'subchondral bone'/de OR 'subtalar joint'/de OR 'wrist'/de OR 'tendon'/de OR 'achilles tendon'/de OR 'hamstring tendon'/de OR 'quadriceps tendon'/de OR 'rotator cuff'/exp OR 'limb injury'/exp OR extremity:ti,ab OR extremities:ti,ab OR limb:ti,ab OR 'long bone':ti,ab OR 'long bones':ti,ab OR leg:ti,ab OR hip:ti,ab OR pelvic:ti,ab OR acetabulum:ti,ab OR acetabular:ti,ab OR femoroacetabular:ti,ab OR labral:ti,ab OR knee:ti,ab OR femur:ti,ab OR femoral:ti,ab OR trochanter*:ti,ab OR intertrochanter*:ti,ab OR subtrochanter*:ti,ab OR pertrochanter*:ti,ab OR tibia:ti,ab OR tibial:ti,ab OR hamstring:ti,ab OR (quadriceps:ti,ab AND (tendon:ti,ab OR ruptur*:ti,ab)) OR ('rectus femoris':ti,ab AND (tendon:ti,ab OR strain*:ti,ab OR ruptur*:ti,ab)) OR patella:ti,ab OR

	patellar:ti,ab OR patellofemoral:ti,ab OR 'anterior cruciate':ti,ab OR ACL:ti,ab OR 'posterior cruciate':ti,ab OR menisc*:ti,ab OR ankle:ti,ab OR Achilles:ti,ab OR subtalar:ti,ab OR hindfoot:ti,ab OR calcaneal:ti,ab OR talus:ti,ab OR talar:ti,ab OR tarsometatarsal:ti,ab OR Lisfranc:ti,ab OR malleolus:ti,ab OR malleolar:ti,ab OR foot:ti,ab OR arm:ti,ab OR forearm:ti,ab OR shoulder:ti,ab OR glenohumeral:ti,ab OR glenoid:ti,ab OR 'rotator cuff':ti,ab OR acromioclavicular:ti,ab OR subscapularis:ti,ab OR supraspinatus:ti,ab OR humerus:ti,ab OR humeral:ti,ab OR (pectoralis:ti,ab AND (tendon:ti,ab OR ruptur*:ti,ab)) OR biceps:ti,ab OR triceps:ti,ab OR clavicle:ti,ab OR elbow:ti,ab OR elbows:ti,ab OR radius:ti,ab OR radial:ti,ab OR ulna:ti,ab OR ulnar:ti,ab OR olecranon:ti,ab OR wrist:ti,ab OR carpal:ti,ab OR Colles*:ti,ab OR scaphoid:ti,ab OR 'total joint':ti,ab OR THA:ti,ab OR TKA:ti,ab
3	#1 AND #2
4	cryotherapy'/exp OR 'ice'/de OR 'thermotherapy'/exp OR 'electrostimulation'/de OR 'ambulation'/de OR 'acupuncture'/exp OR 'massage'/exp OR 'neuromuscular electrical stimulation'/de OR 'transcutaneous electrical nerve stimulation'/de OR 'nerve stimulation'/de OR 'muscle excitation'/de OR 'passive movement'/de OR cryotherapy:ti,ab OR cryotherapies:ti,ab OR 'cold therapy':ti,ab OR ice:ti,ab OR cooling:ti,ab OR warming:ti,ab OR heating:ti,ab OR ((electric OR electrical) NEAR/3 stimulat*):ti,ab OR electrostimulation:ti,ab OR electrotherapy:ti,ab OR 'nerve stimulation':ti,ab OR 'muscle stimulation':ti,ab OR ((early OR accelerated OR immediate) NEAR/3 (ambulat* OR walking OR mobilization OR mobilisation OR motion OR weightbearing OR 'weight bearing' OR rehabilitation)):ti,ab OR acupuncture:ti,ab OR pharmacoacupuncture:ti,ab OR acupotomy:ti,ab OR auriculotherapy:ti,ab OR "dry needling":ti,ab OR massag*:ti,ab OR ('continuous passive' NEXT/1 (motion OR movement)):ti,ab
5	nerve block'/exp OR 'local anesthesia'/exp OR 'regional anesthesia'/exp OR 'spinal anesthesia'/exp OR 'periarticular drug administration'/exp OR 'nerve block*':ti,ab OR 'adductor canal block*':ti,ab OR 'ipack':ti,ab OR 'fascia iliaca compartment block*':ti,ab OR 'fascia iliaca block*':ti,ab OR 'plexus block*':ti,ab OR 'neuraxial block*':ti,ab OR 'paravertebral block*':ti,ab OR 'regional an$esthetic$':ti,ab OR 'regional an$esthesia':ti,ab OR 'local an$esthesia':ti,ab OR 'local an$esthetic$':ti,ab OR 'peri-articular infiltration':ti,ab OR 'periarticular infiltration':ti,ab OR 'peri-articular injection$':ti,ab OR 'periarticular injection$':ti,ab OR 'interscalene block*':ti,ab OR 'infiltration an$esthesia':ti,ab OR 'infiltration analgesia':ti,ab OR 'infiltrative analgesia':ti,ab OR 'infiltrate analgesia':ti,ab OR 'lidocaine':ti,ab OR 'ropivacaine':ti,ab OR 'bupivacaine':ti,ab OR 'ketorolac':ti,ab OR 'tromethamine':ti,ab OR 'epinephrine':ti,ab OR 'anesthetic catheter'/exp OR ((nerve OR perineural OR epidural) NEAR/4 catheter$):ti,ab OR 'lidocaine'/exp OR 'ropivacaine'/exp OR 'bupivacaine'/exp OR 'ketorolac'/exp OR 'trometamol'/exp OR 'epinephrine'/exp OR ((spinal OR subarachnoid OR intradural OR intrathecal OR epidural) NEAR/3 (an$esthesia OR an$esthetic$ OR analges* OR block* OR inject*)):ti,ab
6	corticosteroid'/exp OR corticosteroid*:ti,ab OR corticoid*:ti,ab OR 'adrenal cortex hormone$':ti,ab OR prednisone:ti,ab OR methylprednisolone:ti,ab OR triamcinolone:ti,ab OR glucocorticoid*:ti,ab OR cortisone:ti,ab OR hydrocortisone:ti,ab OR

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	dexamethasone:ti,ab OR prednisolone:ti,ab OR betamethasone:ti,ab OR budesonide:ti,ab OR mineralocorticoid*:ti,ab
7	nonsteroid antiinflammatory agent'/exp OR 'cyclooxygenase 2 inhibitor'/exp OR 'non-steroidal anti-inflammatory agent':ti,ab OR 'nonsteroidal anti-inflammatory agents':ti,ab OR meloxicam:ti,ab OR mobic:ti,ab OR naproxen:ti,ab OR aleve:ti,ab OR ibuprofen:ti,ab OR advil:ti,ab OR flurbiprofen:ti,ab OR ketorolac:ti,ab OR toradol:ti,ab OR 'cox-2 inhibitor$':ti,ab OR 'cox2 inhibitor$':ti,ab OR 'cyclooxygenase 2 inhibitor':ti,ab OR 'cyclo oxygenase inhibitor':ti,ab OR celecoxib:ti,ab OR celebrex:ti,ab OR diclofenac:ti,ab OR misoprostol:ti,ab OR sulindac:ti,ab OR ketoprofen:ti,ab OR tolmetin:ti,ab OR fenoprofen:ti,ab OR piroxicam:ti,ab OR etodolac:ti,ab OR indomethacin:ti,ab OR nabumetone:ti,ab OR aspirin:ti,ab OR etoricoxib:ti,ab
8	intrarticular drug administration'/exp OR 'periarticular drug administration'/exp OR inject*:ti,ab OR infiltration*:ti,ab OR 'intra articular':ti,ab OR intraarticular:ti,ab OR 'peri articular':ti,ab OR periarticular:ti,ab
9	((#6 OR #7) AND #8) OR #5
10	psychotherapy'/exp OR 'patient education'/exp OR 'Reiki'/de OR 'meditation'/exp OR psychotherapy:ti,ab OR psychotherapies:ti,ab OR psychotherapeutic:ti,ab OR ((cogniti* OR behavior* OR behaviour*) NEXT/1 (therapy OR therapies OR treatment* OR intervention*)):ti,ab OR (CBT:ti,ab NOT ('cord blood transplantation':ti,ab OR 'carotid body tumor':ti,ab OR 'cortical bone trajectory':ti,ab OR 'cortical bone thickness':ti,ab OR 'computer based training':ti,ab)) OR ('virtual reality':ti,ab AND (therapy:ti,ab OR therapies:ti,ab OR treatment*:ti,ab OR intervention*:ti,ab OR rehabilitation:ti,ab)) OR (mirror NEXT/3 (visual OR therapy OR feedback)):ti,ab OR ((sensorimotor OR 'sensori motor' OR 'sensory') NEXT/2 (feedback OR training OR rehabilitation)):ti,ab OR (music NEXT/1 (therapy OR therapies OR treatment* OR intervention*)):ti,ab OR 'guided imagery':ti,ab OR 'motor imagery':ti,ab OR Reiki:ti,ab OR hypnosis:ti,ab OR mindfulness:ti,ab OR meditat*:ti,ab OR education*:ti OR teaching:ti
11	narcotic agent'/exp OR 'narcotic analgesic agent'/exp OR narcotic*:ti,ab OR opioid*:ti,ab OR opiate*:ti,ab OR papaver*:ti,ab OR oxycodone:ti,ab OR Oxycontin:ti,ab OR 'Oxy-ER':ti,ab OR 'Oxy-CRF':ti,ab OR 'OxyIR':ti,ab OR 'Oxy-IR':ti,ab OR Percodan:ti,ab OR Percocet:ti,ab OR Roxicet:ti,ab OR hydrocodone:ti,ab OR dihydrocodeinone:ti,ab OR Vicodin:ti,ab OR Vicoprofen:ti,ab OR Norco:ti,ab OR Lortab:ti,ab OR Lorcet:ti,ab OR oxymorphone:ti,ab OR Opana:ti,ab OR morphine:ti,ab OR Kadian:ti,ab OR Avinza:ti,ab OR 'MS Contin':ti,ab OR Duramorph:ti,ab OR Roxanol:ti,ab OR codeine:ti,ab OR fentanyl:ti,ab OR Duragesic:ti,ab OR Actiq:ti,ab OR Sublimaze:ti,ab OR hydromorphone:ti,ab OR Dilaudid:ti,ab OR meperidine:ti,ab OR Demerol:ti,ab OR tramadol:ti,ab OR Ultram:ti,ab OR buprenorphine:ti,ab OR propoxyphene:ti,ab OR Darvocet:ti,ab OR Omnopon:ti,ab OR methadone:ti,ab OR Dolophine:ti,ab OR Methadose:ti,ab OR suboxone:ti,ab OR nalbuphine:ti,ab OR propoxyphene:ti,ab OR pentazocine:ti,ab

12	antidepressive agent'/exp OR 'serotonin noradrenalin reuptake inhibitor'/exp OR 'monoamine oxidase inhibitor'/exp OR 'serotonin uptake inhibitor'/exp OR 'dopamine uptake inhibitor'/exp OR antidepressant$:ti,ab OR "anti depressant$":ti,ab OR SNRI*:ti,ab OR (serotonin NEAR/4 inhibitor*):ti,ab OR duloxetine:ti,ab OR desvenlafaxine:ti,ab OR levomilnacipran:ti,ab OR venlafaxine:ti,ab OR nefazodone:ti,ab OR trazodone:ti,ab OR SSRI*:ti,ab OR citalopram:ti,ab OR escitalopram:ti,ab OR fluoxetine:ti,ab OR fluvoxamine:ti,ab OR paroxetine:ti,ab OR sertraline:ti,ab OR vilazodone:ti,ab OR (monoamine NEAR/3 inhibitor*):ti,ab OR MAOI$:ti,ab OR isocarboxazid:ti,ab OR phenelzine:ti,ab OR tranylcypromine:ti,ab OR NDRI*:ti,ab OR bupropion:ti,ab OR amitriptyline:ti,ab OR clomipramine:ti,ab OR desipramine:ti,ab OR doxepin:ti,ab OR imipramine:ti,ab OR nortriptyline:ti,ab OR protriptyline:ti,ab OR trimipramine:ti,ab OR amoxapine:ti,ab OR maprotiline:ti,ab OR mirtazapine:ti,ab OR vortioxetine:ti,ab
13	paracetamol'/exp OR 'propacetamol'/exp OR acetaminophen:ti,ab OR paracetamol:ti,ab OR propacetamol:ti,ab OR tylenol:ti,ab
14	pregabalin'/exp OR 'gabapentinoid'/exp OR 'gabapentin'/exp OR pregabalin:ti,ab OR gabapentinoid*:ti,ab OR gabapentin:ti,ab OR Lyrica:ti,ab OR Neurontin:ti,ab OR Gralise:ti,ab OR Horizant:ti,ab
15	ketamine'/exp OR ketamine:ti,ab OR katamine:ti,ab OR ketalar:ti,ab OR ketaject:ti,ab OR calipsol:ti,ab OR calypsol:ti,ab OR imalgene:ti,ab OR kalipsol:ti,ab OR ketanest:ti,ab OR vetalar:ti,ab OR Ketamin:ti,ab OR Ketamina:ti,ab
16	muscle relaxant agent'/exp OR 'suxamethonium'/exp OR 'rocuronium'/exp OR 'mivacurium'/exp OR 'pancuronium'/exp OR 'benzodiazepine derivative'/exp OR 'hydroxyzine'/exp OR 'muscle relaxant':ti,ab OR 'muscle relaxants':ti,ab OR abobotulinumtoxinA:ti,ab OR baclofen:ti,ab OR Botox:ti,ab OR carisoprodol:ti,ab OR chlorzoxazone:ti,ab OR cyclobenzaprine:ti,ab OR Dantrium:ti,ab OR dantrolene:ti,ab OR Dysport:ti,ab OR Flexeril:ti,ab OR incobotulinumtoxinA:ti,ab OR Lioresal:ti,ab OR metaxalone:ti,ab OR methocarbamol:ti,ab OR Myobloc:ti,ab OR Norflex:ti,ab OR onabotulinumtoxinA:ti,ab OR orphenadrine:ti,ab OR Parafon:ti,ab OR rimabotulinumtoxinB:ti,ab OR Robaxin:ti,ab OR Skelaxin:ti,ab OR tizanidine:ti,ab OR Xeomin:ti,ab OR atracurium:ti,ab OR cisatracurium:ti,ab OR mivacurium:ti,ab OR pancuronium:ti,ab OR rocuronium:ti,ab OR succinylcholine:ti,ab OR vecuronium:ti,ab OR Norgesic:ti,ab OR quazepam:ti,ab OR chlordiazepoxide:ti,ab OR flurazepam:ti,ab OR alprazolam:ti,ab OR diazepam:ti,ab OR oxazepam:ti,ab OR clonazepam:ti,ab OR estazolam:ti,ab OR clorazepate:ti,ab OR triazolam:ti,ab OR lorazepam:ti,ab OR temazepam:ti,ab OR clobazam:ti,ab OR midazolam:ti,ab OR Doral:ti,ab OR Valium:ti,ab OR Versed:ti,ab OR hydroxyzine:ti,ab
17	[1990-3000]/py AND [english]/lim
18	[2000-3000]/py AND [english]/lim
19	[2005-3000]/py AND [english]/lim
20	[2010-3000]/py AND [english]/lim

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21	randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'randomization'/de OR random*:ti,ab,kw
22	systematic review'/exp OR 'meta analysis'/exp OR ((systematic* NEAR/2 review*):ti,ab,kw) OR 'meta analys*':ti,ab,kw
23	#21 or #22
24	abstract report'/de OR abstracts:ti OR 'book'/de OR 'editorial'/de OR 'editorial':it OR editorial:ti OR 'note'/de OR 'note':it OR 'letter'/de OR 'letter':it OR letter:ti OR reply:ti OR commentary:ti OR 'case study'/de OR 'case report'/de OR 'chapter':it OR 'conference paper'/exp OR 'conference paper':it OR 'conference abstract':it OR 'conference review':it OR 'cadaver'/de OR 'in vitro study'/exp OR cadaver*:ti,ab OR 'in vitro':ti,ab OR 'animal experiment'/exp OR animal$:ti OR dog:ti OR dogs:ti OR canine:ti OR horse$:ti OR equine:ti OR mouse:ti OR mice:ti OR rat:ti OR rats:ti OR rabbit:ti OR rabbits:ti OR sheep:ti OR porcine:ti OR pig:ti OR pigs:ti OR rodent$:ti OR monkey$:ti
25	('Juvenile'/exp OR p$ediatric*:ti OR child:ti OR children:ti) NOT ('adult'/exp OR 'adult*':ti)
26	#24 OR #25
27	((#4 OR #10) AND #3) AND #17
28	(#9 AND #3) AND #18
29	((#12 OR #14 OR #15 OR #16) AND #3) AND #19
30	((#7 OR #11 OR #13) AND #3) AND #20
31	((#27 OR #28 OR #29 OR #30) AND #23) NOT #26

Database: Cochrane Central Register of Controlled Trials (CENTRAL)
Interface: Wiley (https://www.cochranelibrary.com/central)
Date Last Searched: June 2, 2020

LINE	SEARCH QUERY
1	(orthopedic* OR orthopaedic* OR arthroplast* OR hemiarthroplast* OR arthroscop* OR osteotomy OR osteotomies OR osteoplasty OR chondroplasty OR osteochondroplasty OR tenotomy OR tenotomies OR tenodesis OR meniscectomy OR synovectomy OR tenosynovectomy OR tendoscopy OR arthroereisis OR fixat* OR arthrodesis OR salvag* OR amputat* OR acetabuloplasty OR (((hip OR knee OR joint OR ankle OR shoulder OR elbow OR femoral) NEAR/3 replacement*) NOT temporomandibular) OR (ankle NEAR/3 fusion) OR (release NEAR/3 "carpal tunnel") OR resurfacing OR hemipelvectomy OR repair* OR reconstruct* OR Latarjet OR Ilizarov OR "open reduction" OR microfracture OR arthrotomy OR fasciotomy OR nailing OR plating OR ((surgery OR surgical OR surgically OR operative* OR perioperative* OR "peri operative" OR "peri operatively" OR preoperative* OR "pre operative" OR "pre operatively" OR postoperative* OR "post operative" OR "post operatively" OR intraoperative* OR "intra operative" OR "intra operatively") AND (fractur* OR avuls* OR injur* OR (strain* AND (muscle* OR tendon*)) OR tear OR tears OR tearing OR torn OR

	trauma OR traumatic OR (ruptur* AND (tendon* OR ligament OR ligaments)) OR wound*))):ti,ab
2	(extremity OR extremities OR limb OR "long bone" OR "long bones" OR leg OR hip OR pelvic OR acetabulum OR acetabular OR femoroacetabular OR labral OR knee OR femur OR femoral OR trochanter* OR intertrochanter* OR subtrochanter* OR pertrochanter* OR tibia OR tibial OR hamstring OR (quadriceps AND (tendon OR ruptur*)) OR ("rectus femoris" AND (tendon OR strain* OR ruptur*)) OR patella OR patellar OR patellofemoral OR "anterior cruciate" OR ACL OR "posterior cruciate" OR menisc* OR ankle OR Achilles OR subtalar OR hindfoot OR calcaneal OR talus OR talar OR tarsometatarsal OR Lisfranc OR malleolus OR malleolar OR foot OR arm OR forearm OR shoulder OR glenohumeral OR glenoid OR "rotator cuff" OR acromioclavicular OR subscapularis OR supraspinatus OR humerus OR humeral OR (pectoralis AND (tendon OR ruptur*)) OR biceps OR triceps OR clavicle OR elbow OR elbows OR radius OR radial OR ulna OR ulnar OR olecranon OR wrist OR carpal OR scaphoid OR "total joint" OR THA OR TKA):ti,ab
3	#1 AND #2
4	cryotherapy:ti,ab OR cryotherapies:ti,ab OR "cold therapy":ti,ab OR ice:ti,ab OR cooling:ti,ab OR warming:ti,ab OR heating:ti,ab OR ((electric OR electrical) NEAR/3 stimulat*):ti,ab OR electrostimulation:ti,ab OR electrotherapy:ti,ab OR "nerve stimulation":ti,ab OR "muscle stimulation":ti,ab OR ((early OR accelerated OR immediate) NEAR/4 (ambulat* OR walking OR mobilization OR mobilisation OR motion OR weightbearing OR "weight bearing" OR rehabilitation)):ti,ab OR acupuncture:ti,ab OR pharmacoacupuncture:ti,ab OR acupotomy:ti,ab OR auriculotherapy:ti,ab OR "dry needling":ti,ab OR massag*:ti,ab OR ("continuous passive" NEXT/1 (motion OR movement)):ti,ab
5	((nerve NEXT/1 block*) OR IPACK OR (plexus NEXT/1 block*) OR (neuraxial NEXT/1 block*) OR ("adductor canal" NEXT/1 block*) OR ("fascia iliaca compartment" NEXT/1 block*) OR ("fascia iliaca" NEXT/1 block*) OR (paravertebral NEXT/1 block*) OR "regional anesthesia" OR "regional anesthetic" OR "regional anaesthesia" OR "regional anaesthetic" OR "local anesthesia" OR "local anaesthesia" OR "local anesthetic" OR "local anesthetics" OR "local anaesthetic" OR "local anaesthetics" OR (articular NEXT/2 (infiltration OR injection OR injections)) OR "periarticular infiltration" OR "periarticular injection" OR "periarticular injections" OR (interscalene NEXT/1 block*) OR "infiltration anesthesia" OR "infiltration analgesia" OR "lidocaine" OR "ropivacaine" OR "bupivacaine" OR "ketorolac" OR "tromethamine" OR "epinephrine" OR ((nerve OR perineural OR epidural) NEAR/4

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	catheter*)):ti,ab OR ((spinal OR subarachnoid OR intradural OR intrathecal OR epidural) NEAR/3 (an?esthesia OR an?esthetic? OR analges* OR block* OR inject*)):ti,ab
6	("adrenal cortex hormones" or corticosteroid* or corticoid* or prednisone or methylprednisolone or triamcinolone or dexamethasone or glucocorticoid* or cortisone or hydroxortisone or prednisolone or betamethasone or budesonide or mineralocorticoid*):ti,ab
7	("non-steroidal anti-inflammatory agents" OR "nonsteroidal anti-inflammatory agents" OR meloxicam OR Mobic OR naproxen OR Aleve OR ibuprofen OR Advil OR flurbiprofen OR ketorolac OR Toradol OR "COX-2 inhibitor" OR "COX-2 inhibitors" OR "COX2 inhibitor" OR "COX2 inhibitors" OR "cyclooxygenase 2 inhibitor" OR "cyclo oxygenase inhibitor" OR celecoxib OR Celebrex OR diclofenac OR misoprostol OR sulindac OR ketoprofen OR tolmetin OR etodolac OR fenoprofen OR piroxicam OR indomethacin OR nabumetone OR aspirin OR etoricoxib):ti,ab
8	(inject* OR infiltration* OR "intra articular" OR intraarticular OR "peri articular" OR periarticular):ti,ab
9	((#6 OR #7) AND #8) OR #5
10	psychotherapy:ti,ab OR psychotherapies:ti,ab OR psychotherapeutic:ti,ab OR ((cogniti*:ti,ab OR behavior*:ti,ab OR behaviour*:ti,ab) AND (therapy:ti,ab OR therapies:ti,ab OR treatment*:ti,ab OR intervention*:ti,ab)) OR (CBT:ti,ab NOT ("cord blood transplantation":ti,ab OR "carotid body tumor":ti,ab OR "cortical bone trajectory":ti,ab OR "cortical bone thickness":ti,ab OR "computer based training":ti,ab)) OR ("virtual reality":ti,ab AND (therapy:ti,ab OR therapies:ti,ab OR treatment*:ti,ab OR intervention*:ti,ab OR rehabilitation:ti,ab)) OR "mirror therapy":ti,ab OR "visual feedback":ti,ab OR "mirror feedback":ti,ab OR ((sensorimotor:ti,ab OR "sensori motor":ti,ab OR "sensory":ti,ab) AND (feedback:ti,ab OR training:ti,ab OR rehabilitation:ti,ab)) OR (music:ti,ab AND (therapy:ti,ab OR therapies:ti,ab OR treatment*:ti,ab OR intervention*:ti,ab)) OR "guided imagery":ti,ab OR "motor imagery":ti,ab OR Reiki:ti,ab OR hypnosis:ti,ab OR mindfulness:ti,ab OR meditat*:ti,ab OR education*:ti OR teaching:ti
11	(narcotic* OR opioid* OR opiate* OR papaver* OR oxycodone OR Oxycontin OR "Oxy-ER" OR "Oxy-CRF" OR "OxyIR" OR "Oxy-IR" OR Percodan OR Percocet OR Roxicet OR hydrocodone OR dihydrocodeinone OR Vicodin OR Vicoprofen OR Norco OR Lortab OR Lorcet OR oxymorphone OR Opana OR morphine OR Kadian OR Avinza OR "MS Contin" OR Duramorph OR Roxanol OR codeine OR fentanyl OR Duragesic OR Actiq OR Sublimaze OR hydromorphone OR Dilaudid OR meperidine OR Demerol OR tramadol OR Ultram OR buprenorphine OR propoxyphene OR Darvocet OR Omnopon OR methadone OR Dolophine OR Methadose OR suboxone OR nalbuphine OR propoxyphene OR pentazocine):ti,ab

12	(antidepressant OR antidepressants OR "anti depressant" OR "anti depressants" OR SNRI* OR (serotonin NEAR/4 inhibitor*) OR duloxetine OR desvenlafaxine OR levomilnacipran OR venlafaxine OR nefazodone OR trazodone OR SSRI* OR citalopram OR escitalopram OR fluoxetine OR fluvoxamine OR paroxetine OR sertraline OR vilazodone OR (monoamine NEAR/3 inhibitor*) OR MAOI OR MAOIs OR isocarboxazid OR phenelzine OR tranylcypromine OR NDRI* OR bupropion OR amitriptyline OR clomipramine OR desipramine OR doxepin OR imipramine OR nortriptyline OR protriptyline OR trimipramine OR amoxapine OR maprotiline OR mirtazapine OR vortioxetine):ti,ab
13	acetaminophen:ti,ab OR paracetamol:ti,ab OR propacetamol:ti,ab OR tylenol:ti,ab
14	(pregabalin OR gabapentinoid* OR gabapentin OR Lyrica OR Neurontin OR Gralise OR Horizant):ti,ab
15	(ketamine OR katamine OR ketalar OR ketaject OR calipsol OR calypsol OR imalgene OR kalipsol OR ketanest OR vetalar OR Ketamin OR Ketamina):ti,ab
16	("muscle relaxant" OR "muscle relaxants" OR abobotulinumtoxinA OR baclofen OR Botox OR carisoprodol OR chlorzoxazone OR cyclobenzaprine OR Dantrium OR dantrolene OR Dysport OR Flexeril OR incobotulinumtoxinA OR Lioresal OR metaxalone OR methocarbamol OR Myobloc OR Norflex OR onabotulinumtoxinA OR orphenadrine OR Parafon OR rimabotulinumtoxinB OR Robaxin OR Skelaxin OR tizanidine OR Xeomin OR atracurium OR cisatracurium OR mivacurium OR pancuronium OR rocuronium OR succinylcholine OR vecuronium OR Norgesic OR quazepam OR chlordiazepoxide OR flurazepam OR alprazolam OR diazepam OR oxazepam OR clonazepam OR estazolam OR clorazepate OR triazolam OR lorazepam OR temazepam OR clobazam OR midazolam OR Doral OR Valium OR Versed OR hydroxyzine):ti,ab
17	"conference abstract":pt OR abstracts:ti OR editorial:ti OR reply:ti OR commentary:ti OR letter:ti OR cadaver*:ti,ab 'in vitro':ti,ab OR animal*:ti OR dog:ti OR dogs:ti OR canine:ti OR horse:ti OR horses:ti OR equine:ti OR mouse:ti OR mice:ti OR rat:ti OR rats:ti OR rabbit:ti OR rabbits:ti OR sheep:ti OR porcine:ti OR pig:ti OR pigs:ti OR rodent?:ti OR monkey?:ti
18	([mh Infant] OR [mh Child] OR (pediatric* OR paediatric* OR child OR children):ti) NOT ([mh Adult] OR [mh Adolescent] OR adult*:ti)
19	#17 OR #18
20	((#4 OR #10) AND #3) NOT #19 *with Publication Year from 1990 to 2020, in Trials*
21	(#9 AND #3) NOT #19 *with Publication Year from 2000 to 2020, in Trials*
22	((#12 OR #14 OR #15 OR #16) AND #3) NOT #19 *with Publication Year from 2005 to 2020, in Trials*
23	((#7 OR #11 OR #13) AND #3) NOT #19 *with Publication Year from 2010 to 2020, in Trials*
24	#20 OR #21 OR #22 OR #23

View background material via the Pain Alleviation CPG eAppendix 1
View data summaries via the Pain Alleviation CPG eAppendix 2

LETTERS OF ENDORSEMENT FROM ORGANIZATIONS

Orthopaedic Trauma Association
Education ▪ Research ▪ Advocacy
9400 W. Higgins Road, Suite 305, Rosemont, IL 60018-4975
Phone: (847) 698-1631 ▪ www.ota.org ▪ OTA@ota.org

Kaitlyn S. Severino, MBA, CAE
Director,
Department of Clinical Quality and Value

Dear Ms. Severino,

The OTA has voted to endorse the AAOS Clinical Practice Guideline for Pharmacologic, Physical, and Cognitive Pain Alleviation for Musculoskeletal Extremity/Pelvis Surgery. This endorsement implies permission for the AAOS to officially list our organization as an endorser of this appropriate use criteria and reprint our logo in the introductory section of the appropriate use criteria review document.

Sincerely,

Heather A. Vallier, MD

OTS President

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View data summaries via the Pain Alleviation CPG eAppendix 2

SOMOS
Society of Military Orthopaedic Surgeons

September 20, 2021

Kaitlyn S. Sevarino, MBA, CAE
Director,
Department of Clinical Quality and Value

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Sincerely,

Sincerely,

Jonathan F. Dickens

Jonathan F. Dickens, MD
President
Society of Military Orthopaedic Surgeons