Acetaminophen in Total Joint Arthroplasty: The Clinical Practice Guidelines of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society

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Introduction

The American Association of Hip and Knee Surgeons (AAHKS), The American Academy of Orthopaedic Surgeons (AAOS), The Hip Society, The Knee Society and The American Society of Regional Anesthesia and Pain Medicine (ASRA) have worked together to develop evidence-based guidelines on the use of acetaminophen in primary total joint arthroplasty (TJA). The purpose of these guidelines is to improve the treatment of orthopaedic surgical patients and reduce practice variation by promoting a multidisciplinary evidenced-base approach on the use of acetaminophen following primary TJA.

The combined clinical practice guidelines are meant to address common and important questions related to the efficacy and safety of acetaminophen in primary TJA. Utilizing the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, the committee members completed a systematic review and meta-analyses to support the clinical practice guidelines.[1] For each question, we have provided a recommendation, assessed the strength of the recommendation, and elaborated on the rationale of the recommendation, which should be interpreted in accordance with the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*.[1] The current clinical practice guidelines were based on the available evidence, so future updates may become necessary as additional literature becomes available with future research.

Guideline Question 1:

For patients undergoing primary TJA, does perioperative intravenous (IV) or oral acetaminophen affect postoperative pain and/or opioid consumption?

Response/Recommendation:

Administration of IV or oral acetaminophen reduces pain and opioid consumption during the perioperative period of a primary TJA.

Strength of Recommendation: Moderate

Rationale:

We reviewed seventeen randomized clinical trials that represented the best available evidence including fifteen high quality and two moderate quality studies to assess the ability of IV or oral acetaminophen to reduce pain and/or opioid consumption during the perioperative period following TJA.[2-18] Among the included studies, eleven studies investigated IV acetaminophen compared to placebo, five studies investigated IV acetaminophen compared to oral acetaminophen, and three studies compared oral acetaminophen to placebo.[2-18] Despite the numerous high and moderate quality randomized clinical trials, only a limited amount of meta-analyses were able to be performed due to inconsistency in the reporting of outcomes and timepoints for reporting the outcomes.

Intravenous acetaminophen has been shown with limited heterogeneity in direct meta-analyses to demonstrate favorable reductions in postoperative pain and opioid

consumption compared to placebo. Among the studies reporting on postoperative pain, direct meta-analysis of IV acetaminophen demonstrated lower 6-hour sum of pain intensity differences (outcome is a four-point scale that summarizes the treatment benefit over a specific time period) and postoperative pain scores (i.e. visual analogue scale and numeric pain rating scale) between 24- and 48-hours compared to placebo following surgery. Additionally, direct meta-analysis of opioid consumption measured 24-hours following TJA had improved outcomes for IV acetaminophen compared to placebo.

Due to the lack of consistent outcomes, no meta-analysis could be performed comparing IV and oral acetaminophen. However, among the five high quality randomized clinical trials investigating the comparison of IV and oral acetaminophen, no difference was observed between the routes of administration to reduce postoperative pain and/or opioid consumption.[4, 9, 10, 14, 17] Similarly, no meta-analysis could be performed comparing oral acetaminophen and placebo. Only three high quality randomized studies were available to assess the ability of oral acetaminophen to reduce postoperative pain and/or opioid consumption compared to placebo.[6, 9, 16] Qualitative review of the available literature would suggest oral acetaminophen reduces postoperative pain and opioid consumption, but the results do not consistently favor oral acetaminophen over placebo at statistically significant levels.

Although IV acetaminophen has been shown to be superior to placebo and equivalent to oral acetaminophen with regards to reduction in postoperative pain and/or opioid consumption, the lack of overwhelming evidence supporting the superiority of oral acetaminophen compared to placebo has resulted in a downgrade of the recommendation from strong to moderate for oral acetaminophen. Furthermore, the strength of the

recommendation for IV acetaminophen was downgraded from strong to moderate due to concerns regarding the significantly higher cost of IV acetaminophen compared to oral acetaminophen. However, the US Food and Drug Administration has granted approval for marketing of a generic IV acetaminophen starting in December 2020, which is has the potential to dramatically reduce the cost and change the downgrade of the recommendation of IV acetaminophen.

Guideline Question 2:

For patients undergoing primary TJA, does acetaminophen after discharge affect postoperative pain and/or opioid consumption?

Response/Recommendation:

In the absence of reliable evidence, it is the opinion of the workgroup that oral acetaminophen may be used after discharge as part of a multimodal pain regimen, as it is a low-cost and low-risk treatment for pain after discharge from a primary TJA.

Strength of Recommendation: Consensus

Rationale:

Oral acetaminophen has widely been accepted as a safe, effective, and low-cost analgesic medication. Despite the numerous high and moderate quality randomized clinical trials investigating perioperative acetaminophen in the setting of a primary TJA, we lack specific evidence to guide a recommendation on the use of oral acetaminophen after discharge. As a result, we must rely on the available evidence regarding acetaminophen in the nonsurgical treatment of osteoarthritis and its use during the perioperative period of primary TJA to guide our recommendation. In the setting of nonsurgical treatment of osteoarthritis of the knee, direct meta-analysis of oral acetaminophen showed a significant improvement in pain and function compared to an oral placebo.[19] Lastly, the results from the current clinical practice guidelines has

shown the effectiveness of oral acetaminophen to reduce postoperative pain and opioid consumption during the inpatient period following primary TJA.

Although acetaminophen has not been proven to be effective in isolation for postoperative pain management following primary TJA, it has been demonstrated as an effective adjunct as part of a multimodal pain management protocol.[20] When used in conjunction with other non-opioid analgesic medications, patients experienced a decreased risk of medical complications.[20] Therefore, we can support the use of oral acetaminophen after discharge as part of a multimodal pain regimen.

Guideline Question 3:

For patients undergoing primary TJA, does perioperative acetaminophen compared to placebo have an increased risk of postoperative complications?

Response/Recommendation:

Administration of IV or oral acetaminophen does not increase the risk of complications following primary TJA.

Strength of Recommendation: Strong

Rationale:

Among the reviewed high and moderate quality randomized clinical trials, eleven studies reported on complications related to the administration of acetaminophen.[2-6, 12, 13, 15-18] Qualitative examination demonstrated no consistent difference between IV acetaminophen, oral acetaminophen, and placebo. Direct meta-analysis was only capable of being performed for IV acetaminophen, which showed no significant difference with regards to any complication (0.98 relative risk; 95% confidence interval of 0.83 to 1.16) or vomiting (1.16 relative risk; 95% confidence interval of 0.30 to 4.45). Therefore, IV and oral acetaminophen are considered to be safe analgesic medications to administer during the perioperative episode of a primary TJA.

Areas for Future Research:

Although we had numerous high and moderate quality randomized clinical trials to formulate the clinical practice guidelines on the use of acetaminophen, we were presented with limitations in the available literature. We suggest future research of acetaminophen focus on the oral route of administration during the perioperative period and after discharge from a primary TJA. We have robust literature consistently demonstrating IV acetaminophen is favored compared to placebo and no different compared to oral acetaminophen; however, the inconsistent outcomes of literature on oral acetaminophen compared to placebo limited our ability to provide a strong recommendation. As a result, additional high quality randomized clinical trials of oral acetaminophen compared to placebo would likely provide more consistent evidence for or against oral acetaminophen to strengthen the recommendation. Because acetaminophen has typically been prescribed as a fixed combination pill with an opioid, the literature investigating the isolated effect of oral acetaminophen with hip and knee patients in an outpatient setting has been focused on the nonsurgical management of osteoarthritis. Therefore, future research on the utilization of oral acetaminophen after discharge from a primary TJA would allow for an evidenced based recommendation in a future clinical practice guideline.

Peer Review Process:

Following the committee's formulation of the Clinical Practice Guideline draft, it underwent a peer review by the board of directors from AAHKS, ASRA, and the Hip and Knee Societies. The AAOS Evidence-Based Quality and Value Committee reviewed the Clinical Practice Guideline draft for endorsement. Additionally, the publication of the systematic review and meta-analysis on Acetaminophen in primary hip and knee arthroplasties that supported the formulation of the Clinical Practice Guideline has undergone peer review for publication.

FDA Clearance Statement:

Acetaminophen is a drug described in this Clinical Practice Guideline that has been approved by the Food and Drug Administration (FDA). The oral formulation has been approved for over the counter use. The intravenous formulation has been approved for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid medications, and fever reduction in adults and pediatric patients 2 years or older. Intravenous acetaminophen has an FDA block-box warning for risk of medication errors and hepatotoxicity. According to the FDA, it is the prescribing physician's responsibility to ascertain the FDA clearance status for all medications prior to use in a clinical setting.

Disclosure Requirement:

All authors or contributors to the Clinical Practice Guideline have provided a disclosure statement in accordance with the publicly available AAOS Orthopaedic Disclosure

Program. All authors and contributors attest none of the disclosures present are relevant to the Clinical Practice Guidelines.

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Gabapentinoids in Total Joint Arthroplasty: The Clinical Practice Guidelines of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society

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Introduction

The American Association of Hip and Knee Surgeons (AAHKS), The American Academy of Orthopaedic Surgeons (AAOS), The Hip Society, The Knee Society and The American Society of Regional Anesthesia and Pain Medicine (ASRA) have worked together to develop evidence-based guidelines on the use of gabapentinoids in primary total joint arthroplasty (TJA). The purpose of these guidelines is to improve the treatment of orthopaedic surgical patients and reduce practice variation by promoting a multidisciplinary evidenced-base approach on the use of gabapentinoids following primary TJA.

The combined clinical practice guidelines are meant to address common and important questions related to the efficacy and safety of gabapentinoids in primary TJA. Utilizing the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, the committee members completed a systematic review and meta-analyses to support the clinical practice guidelines.[1] For each question, we have provided a recommendation, assessed the strength of the recommendation, and elaborated on the rationale of the recommendation, which should be interpreted in accordance with the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*.[1] The current clinical practice guidelines were based on the available evidence, so future updates may become necessary as additional literature becomes available with future research.

Guideline Question 1:

For patients undergoing primary TJA, do perioperative gabapentinoids affect postoperative pain and/or opioid consumption?

Response/Recommendation:

In the perioperative period after primary TJA, gabapentinoids do not reduce postoperative pain, but pregabalin reduces opioid consumption.

Strength of Recommendation: Strong

Rationale:

We reviewed thirteen high quality prospective randomized controlled trials that represented the best available evidence to assess the efficacy of gabapentinoids in reducing postoperative pain and opioid consumption after TJA.[2–14] Among the included studies, seven studies investigated gabapentin compared to placebo and six studies investigated pregabalin compared to placebo.[2–14] Despite these high quality studies, only a limited amount of meta-analyses were performed due to inconsistency in outcomes reported and the timepoints at which these outcomes were reported.

Gabapentin did not have any impact on postoperative pain in the perioperative period at all time points after TJA compared to placebo in the seven high quality studies included. Five studies specifically evaluated pain scores within 3 days postoperatively and found there was no difference in pain scores between patients treated with gabapentin and patients treated with placebo.[4–6,9,12] Of the five studies reporting opioid consumption, one study reported

gabapentin reduced opioid consumption compared to placebo, while the other 4 studies found no difference.[4,5,9,11,12] Two of these studies were able to be included in a direct meta-analysis with limited heterogeneity, which determined gabapentin had no impact on morphine consumption measured at 72 hours postoperatively compared to placebo.[11,12] Direct meta-analyses evaluating complications associated with gabapentin compared to placebo found there was no difference in rates of nausea, vomiting, pruritus, dizziness, and sedation.

Pregabalin reduced opioid consumption, but did not show a consistently significant impact on postoperative pain compared to placebo in the perioperative period after primary TJA. Of the six studies included, five studies evaluated pain scores within 3 days postoperatively. Three of these studies found no difference in pain scores between placebo and pregabalin, while two studies found pregabalin reduced pain compared to placebo.[3,8,10,13,14] One study that demonstrated a favorable reduction in pain scores evaluated pregabalin for treatment of pain after total hip arthroplasty (THA) while the other study evaluated total knee arthroplasty (TKA) patients. Due to heterogeneity of the pain scores reported and the timepoints at which the pain scores were reported a direct meta-analysis was not able to be completed. However, a direct meta-analysis of four studies evaluating the efficacy of pregabalin on opioid consumption found that pregabalin moderately reduces opioid consumption compared to placebo after TJA.[3,8,10,13] Direct meta-analyses were performed to evaluate complications associated with pregabalin compared to placebo. There were no differences between pregabalin and placebo in rates of vomiting, pruritus, and dizziness. However, a direct meta-analysis of three studies evaluating sedation found that pregabalin moderately increases the risk of sedation compared to placebo after TJA. A direct meta-analysis of four studies evaluating nausea after TJA found pregabalin reduces the incidence of nausea compared to placebo.

Guideline Question 2:

For patients undergoing primary TJA, do gabapentinoids after discharge affect postoperative pain, opioid consumption, and/or the prevalence of postoperative neurogenic pain?

Response/Recommendation:

Pregabalin after discharge reduces postoperative pain, neuropathic pain, and opioid consumption after primary TJA, but gabapentin does not reduce pain or opioid consumption.

Strength of Recommendation: Strong

Rationale:

Six high quality studies evaluated the efficacy of post-discharge gabapentinoids on pain and opioid consumption after TJA.[2–4,7,9,13] Three of these studies evaluated gabapentin prescribed for 4 - 7 days after TKA. One study evaluated two weeks of pregabalin after TKA, one study evaluated 6 weeks of pregabalin after TKA, and one study evaluated one week of pregabalin after THA. Due to heterogeneity of outcomes reported, no meta-analyses were completed.

Qualitative review of the three studies that evaluated treatment with gabapentin for less than 7 days after TKA found that it had no impact on postoperative pain in all three studies.[4,7,9] One of these studies evaluated chronic and neuropathic pain at 3 – 4 years postoperatively and found no effect of gabapentin compared to placebo.[7] Only one study evaluated opioid consumption after discharge and found there was no difference in opioid consumption at 6 days postoperatively between gabapentin and placebo.[9]

There were two pregabalin studies that evaluated pain scores between 3 days and 1 week postoperatively and one that evaluated pain scores at 3 months and 6 months postoperatively. All three of these studies found favorable reductions in pain scores with pregabalin compared to placebo.[2,3,14] Two of these studies evaluated opioid consumption after discharge.[2,3] Buvanendran et al. found no difference in opioid use at 6 months postoperatively between patients who received pregabalin and placebo. However, they did find that rates of neuropathic pain were lower in patients who received pregabalin compared to placebo. [2] Clarke et al. found at 1 week postoperatively patients who received pregabalin consumed fewer opioids than patients who received placebo.[3]

Guideline Question 3:

For patients undergoing primary TJA, is there a difference in efficacy between low- and high-dose gabapentinoids in reducing postoperative pain, opioid consumption, and/or postoperative complications?

Response/Recommendation:

There is no difference in postoperative pain, opioid consumption, or complications between low-dose and high-dose gabapentinoids. However, the use of gabapentinoids may lead to increased risk of confusion among elderly patients and respiratory depression with concurrent use of opioids.

Strength of Recommendation: Moderate

Rationale:

Three high quality studies evaluated the difference in dosing of gabapentinoids and their effects on postoperative pain, opioid consumption, and complications after primary TJA.[7,9,13] Two studies evaluated high- and low-doses of gabapentin while one study evaluated high- and low-doses of pregabalin. Both studies that evaluated gabapentin found that there was no difference in pain scores between high- and low-dose gabapentin.[7,9] One of these studies also evaluated opioid consumption and found there was no difference in opioid consumption between high- and low-dose gabapentin groups.[9]

One study directly compared 75 mg of pregabalin twice a day for 6 weeks compared to 150 mg of pregabalin twice a day for 6 weeks postoperatively.[13] The study found no difference

in opioid consumption or complications between the two doses except for constipation which was more frequent in the low-dose group.

The strength of recommendation is moderate given there is only one high quality study comparing high- and low-dose pregabalin, and studies comparing gabapentin to placebo found no difference in postoperative pain and opioid consumption with a lack of consistency in measures/scales for these high priority outcomes. It is the opinion of the workgroup that gabapentinoids be used cautiously especially when given concurrently with opioids or used in the elderly given pregabalin is associated with increased risk of postoperative sedation. Recent publications by the Food and Drug Administration (FDA) and other surgical subspecialties have highlighted these concerns regarding respiratory depression with concurrent use of opioids and gabapentinoids.[15–18] A recent database study by Ohnuma et al. also found a dose-dependent association with gabapentinoids and postoperative pulmonary complications after total hip and knee arthroplasty.[19] It is the opinion of the workgroup that pregabalin may cause increased sedative effects in the elderly and should be used with caution in this population. Given the limited high quality evidence evaluating safety and dosage, it is the consensus of this group that when gabapentinoids are utilized after primary TJA, the lowest clinically efficacious dose should be used to minimize the risk of complications.

Areas for Future Research:

The thirteen high quality prospective randomized controlled trials demonstrate that pregabalin is effective in reducing postoperative pain and opioid consumption after primary TJA. However, there is a lack of evidence regarding the most efficacious and safe dosage, frequency, and duration of treatment. Further research is needed to determine when pregabalin treatment should begin, how much and how often it should be given as well as how long patients should take it after primary TJA.

While thirteen high quality prospective randomized controlled trials were included no study directly compared pregabalin to gabapentin and placebo. In all of the studies included, different multimodal analgesics and anesthetic regimens were utilized limiting the interpretation and generalization of the results. Thus, a well-designed, powered, prospective randomized controlled trial with three groups directly comparing gabapentin to pregabalin and placebo should be performed to better understand the differences in efficacy between pregabalin and gabapentin. In addition, high quality studies are necessary to better understand the complications associated with gabapentinoids, such as respiratory depression, particularly when utilized with opioids. This study should include patients of all ages including the elderly to better understand the side effect profile of these drugs among all primary TJA patients.

Peer Review Process:

Following the committee's formulation of the Clinical Practice Guideline draft, it underwent a peer review by the board of directors from AAHKS, ASRA, and the Hip and Knee Societies. The AAOS Evidence-Based Quality and Value Committee reviewed the Clinical Practice Guideline draft for endorsement. Additionally, the publication of the systematic review and meta-analysis on Gabapentinoids in primary hip and knee arthroplasties that supported the formulation of the Clinical Practice Guideline has undergone peer review for publication.

Disclosure Requirement:

All authors or contributors to the Clinical Practice Guideline have provided a disclosure statement in accordance with the publicly available AAOS Orthopaedic Disclosure Program. All authors and contributors attest none of the disclosures present are relevant to the Clinical Practice Guidelines.

FDA Clearance Statement:

Gabapentinoids are a class of drugs described in this Clinical Practice Guidelines that has been approved by the FDA for various prescription uses including neuropathic pain associated with diabetic peripheral neuropathy, management of postherpetic neuralgia, adjunctive therapy for seizures, fibromyalgia, and management of neuropathic pain associated with spinal cord injury. The use of gabapentinoids for treatment of acute postoperative pain is not an indication approved by the FDA and thus the recommendations listed above are for off-label use. The FDA does recommend that gabapentinoids be used with caution when combined with other central nervous system depressants such as opioids and in patients with underlying respiratory depression as the

co-use of opioids and gabapentinoids may further exacerbate respiratory depression and increase the risk of opioid overdose and death.[18] In addition, there are reports of gabapentinoid abuse. According to the FDA, it is the prescribing physician's responsibility to ascertain the FDA clearance status for all medications prior to use in a clinical setting.

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We would like to thank AAHKS for providing the funding and administrative support. We would like to thank Jayson Murray, Kyle Mullen, Francisco Casambre and Vidya Visvabharathy from the AAOS Department of Research, Quality, and Scientific Affairs for their assistance with the analysis and guidance. Lastly, we thank the leadership of the AAHKS, AAOS, ASRA, and the Hip and Knee societies for help with organizational support.

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Nonsteroidal Anti-Inflammatory Drugs in Total Joint Arthroplasty: The Clinical Practice Guidelines of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society

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Introduction

The American Association of Hip and Knee Surgeons (AAHKS), The American Academy of Orthopaedic Surgeons (AAOS), The Hip Society, The Knee Society and The American Society of Regional Anesthesia and Pain Medicine (ASRA) have worked together to develop evidence-based guidelines on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in primary total joint arthroplasty (TJA). The purpose of these guidelines is to improve the treatment of orthopaedic surgical patients and reduce practice variation by promoting a multidisciplinary evidenced-base approach on the use of NSAIDs following primary TJA.

The combined clinical practice guidelines are meant to address common and important questions related to the efficacy and safety of NSAIDs in primary TJA. Utilizing the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, the committee members completed a systematic review and meta-analyses to support the clinical practice guidelines.[1] For each question, we have provided a recommendation, assessed the strength of the recommendation, and elaborated on the rationale of the recommendation, which should be interpreted in accordance with the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*.[1] The current clinical practice guidelines were based on the available evidence, so future updates may become necessary as additional literature becomes available with future research.

Guideline Question 1:

For patients undergoing primary TJA, do oral NSAIDs administered either immediately preoperatively and/or in the early postoperative period, affect postoperative pain and/or opioid consumption?

Response/Recommendation 1A:

An oral NSAID administered either preoperatively and/or in the early postoperative period reduces pain and opioid consumption following primary TJA.

Strength of Recommendation 1A: Strong

Response/Recommendation 1B:

Administration of an oral selective clyclooxygenase-2 (COX-2) NSAID immediately preoperatively, compared to early postoperative administration, provides improved postoperative pain control and reduced opioid consumption following primary TJA.

Strength of Recommendation 1B: Moderate

Rationale:

We reviewed seventeen randomized clinical trials that represented the best available evidence including nine high quality and eight moderate quality studies to assess the effectiveness of selective COX-2 (includes selective [i.e. Celecoxib] and preferential [i.e. Meloxicam] COX-2 inhibitory agents) and non-selective (COX-1 and -2 inhibitory agents) oral NSAIDs to reduce pain and/or opioid consumption postoperatively following TJA.[2-18] Among the included studies comparing either a selective and/or

non-selective NSAID to placebo, ten studies investigated a selective NSAID and five studies investigated a non-selective NSAID.[2-5, 7-15, 17] Similar to other topics within the clinical practice guidelines, only a limited amount of meta-analyses was able to be performed due to inconsistency in the reporting of outcomes and timepoints for reporting the outcomes.

Oral NSAIDs demonstrated with limited heterogeneity in direct meta-analysis to reduce opioid consumption and sum of pain intensity differences (outcome is a four-point scale that summarizes the treatment benefit over a specific time period) compared to placebo. When direct meta-analysis was performed individually for primary total hip and knee arthroplasty, opioid consumption was lower when patients were administered preoperative and/or postoperative oral NSAIDs. Combined analysis of primary hip and knee arthroplasties demonstrated similar results favoring reduced opioid consumption and improved sum of pain intensity differences for oral NSAIDs compared to placebo.

Due to a lack of consistent outcomes, no direct or network meta-analysis could be performed comparing selective or non-selective NSAIDs. However, qualitative analysis of selective and non-selective oral NSAIDs consistently demonstrate an overwhelmingly significant response of a reduction in postoperative pain and opioid consumption for both types of NSAIDs. Three studies have directly compared selective and non-selective oral NSAIDs, which showed no significant difference in the outcomes of postoperative opioid consumption or pain scale.[13, 18] Similarly, no direct or network meta-analysis could be performed to investigate preoperative verses postoperative dosing of oral NSAIDs. Among the studies comparing a selective NSAID to placebo, three studies included preoperative dosing, four studies included postoperative dosing, and four studies included

both preoperative and postoperative doses.[2, 3, 5, 7-9, 11-14] The studies comparing a non-selective NSAID to placebo included four studies utilizing postoperative dosing and one study utilizing both preoperative and postoperative doses.[4, 10, 13, 15, 17] However, one high quality study comparing preoperative and postoperative administration of a single dose of a selective NSAID showed a reduction in opioid consumption with the preoperative administration of the oral selective NSAID.[12]

Guideline Question 2:

For patients undergoing primary TJA, do oral NSAIDs administered after discharge affect postoperative pain and/or opioid consumption?

Response/Recommendation 2A:

Administration of an oral selective COX-2 NSAID after discharge reduces pain and opioid consumption during the six-week period following a primary total knee arthroplasty (TKA).

Strength of Recommendation 2A: Moderate

Response/Recommendation 2B:

In the absence of reliable evidence, it is the opinion of the workgroup that oral selective COX-2 NSAIDs may be used after discharge as part of a multimodal pain regimen to reduce postoperative pain and opioid consumption in patients undergoing primary total hip arthroplasty (THA).

Strength of Recommendation 2B: Consensus

Rationale:

Despite the numerous high and moderate quality randomized clinical trials investigating administration of oral NSAIDs during the perioperative period, such as preoperatively or during the postoperative admission, we lack the same level of evidence to evaluate the use of oral NSAIDs after discharge. Because of concerns regarding the safety of non-selective oral NSAID administration for an extended duration and lack of

specific evidence for non-selective oral NSAIDs after discharge, the workgroup has elected to only make a recommendation regarding the use of selective oral NSAIDs after discharge from a primary TJA.

Similar to the administration of oral selective COX-2 (includes selective [i.e. Celecoxib] and preferential [i.e. Meloxicam] COX-2 inhibitory agents) NSAIDs during the perioperative period, such as preoperatively or during the postoperative admission, utilization of an extended duration of oral selective COX-2 NSAIDs reduces the postoperative pain and opioid consumption. A single high quality study investigating the administration of an oral selective COX-2 NSAID compared to placebo for six-weeks provides overwhelming evidence favoring oral selective COX-2 NSAID use following a primary TKA.[19] Because we lack similar evidence after a primary THA, the workgroup provides a consensus recommendation favoring the administration of an oral selective COX-2 NSAID after discharge from primary THA. Furthermore, the inclusion of an oral NSAID as a component of a postoperative multimodal pain management protocol following primary TJA has demonstrated a reduction in pain, opioid consumption, and the risk of opioid-related adverse effects, such as respiratory depression, nausea/vomiting, sedation, or urinary retention.[20] Therefore, we can support the use of oral selective COX-2 NSAIDs after discharge from a primary TJA as part of a multimodal pain regimen.

Guideline Question 3:

For patients undergoing primary TJA, does intravenous (IV) ketorolac administered preoperatively, intraoperatively, or early postoperatively affect postoperative pain and/or opioid consumption?

Response/Recommendation 3A:

Administration of IV ketorolac preoperatively, intraoperatively, or within 24 hours postoperatively reduces pain and opioid consumption postoperatively (within the first 48 hours) following primary TJA.

Strength of Recommendation 3A: Strong

Response/Recommendation 3B:

Low-dose (15 mg) and high-dose (30 mg) administration of IV ketorolac immediately postoperatively are equivalent at reducing pain and opioid consumption postoperatively (within the first six hours) following primary TJA.

Strength of Recommendation 3B: Moderate

Rationale:

We reviewed seven randomized clinical trials that represented the best available evidence including four high quality and three moderate quality studies to assess the ability of IV ketorolac to reduce postoperative pain and/or opioid consumption following TJA.[21-27] Qualitative analysis consistently demonstrated statistically favorable outcomes for IV ketorolac compared to placebo regarding the reduction in postoperative

pain and opioid consumption with no significant increase of medical complications such as adverse events, nausea/vomiting, blood loss, pruritus, urinary retention, or respiratory depression. Despite the high and moderate quality randomized clinical trials, only direct meta-analysis of opioid consumption could be performed due to inconsistency in the reporting of pain outcomes and timepoints for reporting the outcomes. The direct meta-analysis of opioid consumption significantly favored IV ketorolac compared to placebo with limited heterogeneity.

Among the included studies, the total dosage of IV ketorolac administered to patients ranged between 15 mg and 150 mg given within the first 24 hours after surgery.[21-27] However, only one high quality study compared low- and high-doses of IV ketorolac, which demonstrated no difference between a single postoperative dose of 15 mg or 30 mg of IV ketorolac.[27] Although no difference was observed between the low- and high-dose treatments, 15 mg and 30 mg IV ketorolac doses are still considered relatively low-doses compared to the other published doses of IV ketorolac. Therefore, the lack of an observed difference could simply be the result of not having a large enough difference between the dose amounts to observe a dose response. Despite the potential for reduced postoperative pain and opioid consumption with higher IV ketorolac doses, the workgroup suggests the use of minimally effective doses to diminish the risk of medical complications such as acute kidney failure.

Guideline Question 4:

For patients undergoing primary TJA, do NSAIDs given preoperatively, intraoperatively, or postoperatively compared to placebo have an increased risk of postoperative medical complications?

Response/Recommendation:

Oral or IV NSAIDs administered preoperatively, intraoperatively, or postoperatively do not appear to increase the risk of medical complications following primary TJA; however, providers should consider patient comorbidities, the type of NSAID administered, dose, and duration of administration.

Strength of Recommendation: Limited

Rationale:

Among the reviewed high and moderate quality randomized clinical trials comparing perioperative oral NSAIDs and placebo, twelve studies reported on medical complications related to the administration of NSAIDs.[2-5, 7-9, 11-15] Qualitative examination demonstrated no consistent difference between oral selective COX-2 (includes selective [i.e. Celecoxib] and preferential [i.e. Meloxicam] COX-2 inhibitory agents) NSAIDs, oral non-selective (COX-1 and -2 inhibitory agents) NSAIDs, and placebo with the exception of a lower incidence of postoperative fever with patients receiving an oral NSAID. Direct meta-analysis was capable of being performed comparing various complications between perioperative NSAIDs and placebo, which

showed no significant difference with regards to any adverse event (0.93 relative risk; 95% confidence interval of 0.85 to 1.02), vomiting (0.82 relative risk; 95% confidence interval of 0.52 to 1.31), nausea (0.84 relative risk; 95% confidence interval of 0.68 to 1.04), blood loss (-0.23 standard mean difference; 95% confidence interval of -0.54 to 0.08), pruritus (1.73 relative risk; 95% confidence interval of 0.96 to 3.13), urinary retention (1.24 relative risk; 95% confidence interval of 0.34 to 4.59), and sedation (0.46 relative risk; 95% confidence interval of 0.16 to 1.26). Similar to oral NSAIDs, direct meta-analysis of medical complications between IV ketorolac and placebo were not significant with regards to any adverse events (0.94 relative risk; 95% confidence interval of 0.59 to 1.50), nausea (0.89 relative risk; 95% confidence interval of 0.70 to 1.12), vomiting (0.73 relative risk; 95% confidence interval of 0.47 to 1.14), blood loss (-0.14 standard mean difference; 95% confidence interval of -0.46 to 0.17), pruritus (0.50 relative risk; 95% confidence interval of 0.22 to 1.12), urinary retention (0.75 relative risk; 95% confidence interval of 0.43 to 1.32), or respiratory depression (-0.05 standard mean difference; 95% confidence interval of -0.28 to 0.18).

Despite the evidence favoring oral and IV NSAIDs in the qualitative and quantitative analysis of numerous high and moderate quality studies to reduce postoperative pain and opioid consumption, the gastrointestinal and renal safety profile of oral and IV NSAIDs have not been thoroughly studied in patients following primary TJA. Although nausea and vomiting were frequently reported among the studies, more severe complications including upper gastrointestinal bleeding and acute renal failure were not reported. It is possible the lack of reporting an upper gastrointestinal bleed is due to the rarity of the complication. As a result, clinicians should consider the safety of

perioperative NSAIDs as it relates to severe gastrointestinal and renal failure complications. Therefore, the work group downgraded the recommendation strength by only assigning a limited strength to the recommendation.

Areas for Future Research:

While the best available evidence included numerous high and moderate quality randomized clinical trials, we were still presented with limitations of the literature in the formulation of the clinical practice guidelines on the use of NSAIDs following primary TJA. We suggest future research on perioperative administration of NSAIDs focus on determining the optimal timing of the dosage and type of NSAID (selective or non-selective) to reduce the postoperative pain and/or reduction in opioid consumption. Because the current literature only has a single study investigating the use of a selective NSAID after discharge of a primary TKA, additional research is still necessary. We suggest future research focus on the use of selective NSAIDs after discharge of primary hip and knee arthroplasties. If future research has been able to demonstrate the safe utilization of extended non-selective NSAIDs following primary TJA, then we would suggest the inclusion of non-selective NSAIDs in future research following discharge from primary TJA. Although we have robust literature to favor the effectiveness of IV ketorolac, we lack evidence to support the appropriate dosage that weighs the need to achieve adequate pain control while avoiding the risks of higher doses. The workgroup believes the largest impediment to wider adoption of NSAIDs relates to concerns surrounding the gastrointestinal and renal safety of the broad use of medications such as preoperative and postoperative oral NSAIDs with IV ketorolac, IV corticosteroids, and DVT prophylaxis of aspirin. As a result, we suggest continued monitoring for adverse events as NSAIDs become more widely adopted following primary TJA.

Peer Review Process:

Following the committee's formulation of the Clinical Practice Guideline draft, it underwent a peer review by the board of directors from AAHKS, ASRA, and the Hip and Knee Societies. The AAOS Evidence-Based Quality and Value Committee reviewed the Clinical Practice Guideline draft for endorsement. Additionally, the publication of the systematic review and meta-analysis on NSAIDs in primary hip and knee arthroplasties that supported the formulation of the Clinical Practice Guideline has undergone peer review for publication.

Disclosure Requirement:

All authors or contributors to the Clinical Practice Guideline have provided a disclosure statement in accordance with the publicly available AAOS Orthopaedic Disclosure Program. All authors and contributors attest none of the disclosures present are relevant to the Clinical Practice Guidelines.

FDA Clearance Statement:

Non-selective NSAIDs are a class of drugs described in this Clinical Practice Guideline that has been approved by the Food and Drug Administration (FDA) for various prescription uses including relief of symptoms associated with osteoarthritis, inflammatory arthritis, primary dysmenorrhea, bursitis, tendonitis, and acute gout flares based on the individual drug. Additionally, oral formulations have been approved for over the counter use. Meloxicam is a preferential COX-2 inhibitory agent that has been FDA approved for relief of symptoms associated with osteoarthritis and rheumatoid

arthritis. Celecoxib is the only highly selective COX-2 inhibitory agent available on the US market, which has FDA approval for the management of acute pain as well as relief of symptoms associated with osteoarthritis, inflammatory arthritis, and primary dysmenorrhea. All NSAIDs carry the FDA's block-box warning for an increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke) and serious gastrointestinal events (including bleeding, ulceration, and perforation of the stomach or intestines). According to the FDA, it is the prescribing physician's responsibility to ascertain the FDA clearance status for all medications prior to use in a clinical setting.

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Opioids

Opioids in Total Joint Arthroplasty: The Clinical Practice Guidelines of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society

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Introduction

The American Association of Hip and Knee Surgeons (AAHKS), The American Academy of Orthopaedic Surgeons (AAOS), The Hip Society, The Knee Society and The American Society of Regional Anesthesia and Pain Medicine (ASRA) have worked together to develop evidence-based guidelines on the use of opioids in primary total joint arthroplasty (TJA). The purpose of these guidelines is to improve the treatment of orthopaedic surgical patients and reduce practice variation by promoting a multidisciplinary evidenced-base approach on the use of opioids following primary TJA.

The combined clinical practice guidelines are meant to address common and important questions related to the efficacy and safety of opioids in primary TJA. Utilizing the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, the committee members completed a systematic review and meta-analyses to support the clinical practice guidelines.[1] For each question, we have provided a recommendation, assessed the strength of the recommendation, and elaborated on the rationale of the recommendation, which should be interpreted in accordance with the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*.[1] The current clinical practice guidelines were based on the available evidence, so future updates may become necessary as additional literature becomes available with future research.

Guideline Question 1:

For patients undergoing primary TJA, does preoperative opioid use affect patient reported outcomes, patient satisfaction, complications, opioid consumption after surgery, and/or risk for chronic opioid use?

Response/Recommendation:

Preoperative opioid use is associated with inferior patient reported outcomes, increased opioid consumption after surgery, an increased risk for chronic opioid use, and an increased risk of complications after TJA.

Strength of Recommendation: Moderate

Rationale:

We reviewed fourteen studies that evaluated the influence of preoperative opioid use on outcomes after TJA.[2–15] All studies were assessed as low quality and thus a limited amount of meta-analyses were performed due to inconsistency in outcomes reported and the timepoints at which these outcomes were reported.

Nine studies evaluated the effects of preoperative opioid use on patient reported outcomes.[2,5–11,15] Seven studies found that when compared to opioid naïve patients, patients taking preoperative opioids had inferior patient reported outcome scores in all outcomes measured.[2,5–8,11,15] Three of these studies were included in a direct meta-analysis with limited heterogeneity, which found that preoperative opioid use is associated with inferior pain scores postoperatively compared to opioid naïve patients (0.52 standard mean difference; 95%

confidence interval 0.28 to 0.76).[5,9,15] Two studies found mixed effects of preoperative opioid use on patient reported outcome scores. Hansen et al. found that preoperative opioid users had no difference in patient reported outcome scores, but had significantly decreased range of motion following total knee arthroplasty (TKA) compared to opioid naïve patients.[9] Manalo et al. found no difference in range of motion after TKA or the University of California Los Angeles (UCLA) activity scores, but inferior visual analogue scores (VAS) among patients taking preoperative opioids compared to opioid naïve patients.[10]

Opioid consumption after TJA among patients taking opioids preoperatively was evaluated by seven studies.[2,4–7,9,14] All seven studies found that patients taking opioids preoperatively consume significantly more opioids after TJA compared to opioid naïve patients. Seven studies evaluated chronic opioid use and found that preoperative opioid use is a major risk factor for chronic opioid use after TJA.[4,6–8,12–14] Due to heterogeneity of the timepoints at which opioid consumption were reported, a direct meta-analysis was not able to be completed.

Five studies compared complication rates after TJA between patients taking opioids preoperatively and opioid naïve patients.[5–9] Three studies found that complications were more frequent among patients who took opioids preoperatively, while two studies found no difference between opioid naïve patients and patients that took opioids preoperatively. Three studies found no difference in reoperation rates while one study found increased reoperation rates among patients taking opioids preoperatively.[5–8] It is the opinion of the workgroup that it is likely these studies were underpowered to detect differences in reoperation and revision rates between the two groups. The current literature suggests that complications are more common among patients taking opioids preoperatively, but is inconclusive regarding reoperation and revision rates.

While all studies included are of limited quality, the workgroup upgraded this recommendation from limited to moderate. This recommendation was upgraded due to the consistency among a large number of low quality studies and the importance of reducing opioid use in light of the current opioid epidemic.

Guideline Question 2:

For patients undergoing primary TJA who consume opioids preoperatively, does reducing opioid consumption prior to surgery affect patient reported outcomes and/or opioid consumption after surgery?

Response/Recommendation:

Reduction of opioid use prior to TJA may lead to improved patient reported outcomes after TJA compared to patients who do not reduce opioid consumption prior to surgery.

Strength of Recommendation: Limited

Rationale:

One low quality study evaluated the influence of reducing preoperative opioid use on patient reported outcome scores and opioid consumption after TJA.[10] In their retrospective case control study, Nguyen et al. found that patients on chronic opioids prior to TJA who reduced their opioid consumption by more than 50% prior to surgery had significantly better patient reported outcome scores after TJA compared to patients who did not reduce their opioid intake prior to surgery. The percent change of improvement in patient reported outcome scores was similar to a control group of opioid naïve patients. Based on this low-quality evidence and the evidence presented above that demonstrates that patients on preoperative opioids have inferior outcomes compared to opioid naïve patients, it is the opinion of the workgroup that reduction of preoperative opioid use may lead to improved patient reported outcomes after TJA. This

recommendation was upgraded from consensus to recommendation given the importance of reducing opioid use in light of the current epidemic.

Guideline Question 3:

For patients undergoing primary TJA, does an opioid administered immediately prior to surgery affect postoperative pain, opioid consumption, and/or complications after surgery?

Response/Recommendation:

An opioid administered immediately prior to surgery reduces postoperative pain and opioid consumption within the first 72 hours after TJA, but may increase the risk of complications, such as respiratory depression or sedation, especially if combined with other opioids administered intraoperatively or postoperatively.

Strength of Recommendation: Strong

Rationale:

We reviewed six studies that compared the influence of an opioid administered pre-emptively immediately prior to TJA to placebo on postoperative outcomes after TJA.[16–21] Five studies are high quality and one is moderate quality. Three studies evaluated transdermal fentanyl patches placed 10 – 12 hours prior to surgery, one study evaluated intramuscular morphine, one study evaluated oral morphine, and one study evaluated intravenous morphine. A very limited amount of meta-analyses was performed due to inconsistency in outcomes reported and the timepoints at which these outcomes were reported.

All six studies reported visual analogue pain scores (VAS) within 72 hours after TJA after administration of an opioid pre-emptively prior to TJA. Four of the high quality studies found that an opioid administered pre-emptively prior to surgery resulted in lower VAS scores

within 72 hours after TJA compared to placebo.[16–19] Three of these studies evaluated transdermal fentanyl and the fourth study evaluated intramuscular morphine. The two remaining studies, which evaluated intravenous morphine and oral morphine, found no difference in VAS scores compared to placebo.[20,21]

All six studies evaluated opioid consumption within 72 hours after TJA. Five of the six studies found that administration of an opioid pre-emptively prior to TJA resulted in lower morphine consumption after TJA compared to placebo.[16,18–21] The other study found no difference in opioid consumption after TJA when comparing pre-emptive opioid administration to placebo.[17] Only one study evaluated range of motion after TJA and found no difference amongst patients who received a pre-emptive opioid prior to TJA compared to placebo.[16] Three studies included a direct meta-analysis with moderate heterogeneity found that patients who received an opioid preemptively prior to surgery had decreased opioid consumption compared to placebo (-1.51 standard mean difference; 95% confidence interval -2.37 to -0.64).

Direct meta-analyses were performed to compare rates of nausea, vomiting, and urinary retention. The direct meta-analyses found no difference between patients who received a pre-emptive opioid prior to TJA and placebo in rates of nausea (0.88 relative risk; 95% confidence interval 0.62 to 1.25), vomiting (0.60 relative risk; 95% confidence interval 0.33 to 1.10), and urinary retention (1.08 relative risk; 95% confidence interval 0.34 to 3.40). Four studies evaluated sedation and respiratory depression and found no difference between pre-emptive opioids and placebo.[16,17,19,21] However, it is the opinion of the workgroup that when combined with other opioids administered during the perioperative period, such as intraoperatively or postoperatively, opioids administered prior to surgery may increase the risk of complications including respiratory depression and sedation.

Guideline Question 4:

For patients undergoing primary TJA, do opioids administered intraoperatively affect postoperative pain, opioid consumption, and/or complications?

Response/Recommendation:

An opioid administered intraoperatively reduces opioid consumption, but does not affect postoperative pain within 72 hours after surgery. An opioid administered intraoperatively may increase the risk of complications, such as respiratory depression or sedation, especially if combined with other opioids administered preoperatively or postoperatively.

Strength of Recommendation: Moderate

Rationale:

We reviewed two high quality studies that evaluated the influence of an opioid administered intraoperatively during primary TJA on postoperative pain, opioid consumption, and complications.[22,23] Given the differences in outcome measures utilized and the timepoints at which were measured at no meta-analyses could be performed.

Both studies evaluated postoperative opioid consumption after administering an intraoperative opioid during primary TJA. They both found that administering an intraoperative opioid reduced postoperative opioid consumption compared to placebo within the first 72 hours after surgery.[22,23] These two studies also evaluated VAS pain scores and found no difference between patients who received an intraoperative opioid and placebo within the first 72 hours postoperatively. Similarly, there was no difference in the rates of nausea or vomiting between

patients who received intraoperative opioids and those who received placebo. However, it is the opinion of the workgroup that when combined with other opioids administered preoperatively or postoperatively, opioids administered during surgery may increase the risk of complications including respiratory depression and sedation. Given there is not significant evidence on the risk of complications associated with intraoperative opioid use we downgraded this recommendation from a strong recommendation to a moderate recommendation.

Guideline Question 5:

For patients undergoing primary TJA, do opioids administered after surgery affect postoperative pain, opioid consumption, patient reported outcome scores, and/or complications?

Response/Recommendation:

Scheduled opioid administration without multimodal analgesia within 72 hours after primary TJA reduces the need for additional opioid pain medications for breakthrough pain and may reduce postoperative pain within 72 hours after surgery, but providing scheduled opioids is discouraged. Scheduled opioid administration postoperatively may increase the risk of complications, such as respiratory depression and sedation, especially if combined with other opioids administered during the perioperative period.

Strength of Recommendation: Moderate

Rationale:

Nine studies including six high quality studies and three moderate quality studies evaluated the influence of postoperative opioids on outcomes after primary TJA. A limited number of direct meta-analyses were performed due to inconsistency in outcomes reported and the timepoints at which these outcomes were reported.

Eight studies evaluated the postoperative consumption of opioids for breakthrough pain either delivered orally or with patient controlled analgesia between patients who received scheduled opioids postoperatively and patients who received placebo. All eight studies found that the administration of scheduled opioids postoperatively reduced the consumption of opioids

for breakthrough pain.[24–31] Two studies were included in a direct meta-analysis with moderate heterogeneity and found that patients who were administered scheduled opioids postoperatively routinely required less opioids for breakthrough pain compared to placebo (-0.54 standard mean difference; 95% confidence interval of -0.92 to -0.15).

All nine studies evaluated postoperative pain and reported mixed results.[24–32] Three studies reported no difference in pain control between patients who received scheduled opioids postoperatively and placebo.[25,26,31] Three studies reported mixed results where some pain measures were improved among patients who received opioids scheduled postoperatively while others pain parameters were no different between these patients and placebo.[28,29,32] The final three studies found that opioids administered after primary TJA reduce postoperative pain compared to placebo.[24,27,30]

Direct meta-analyses evaluating complications associated with postoperative opioid use compared to placebo found no differences between the two groups in rates of respiratory depression (-0.17 standard mean difference; 95% confidence interval of -0.45 to 0.10), pruritus (1.01 relative risk; 95% confidence interval of 0.70 to 1.47), nausea (1.30 relative risk, 95% confidence interval of 1.03 to 1.65), vomiting (1.10 relative risk; 95% confidence interval of 0.69 to 1.74), confusion (1.82 relative risk; 95% confidence interval 0.35 to 9.49), dizziness (1.50 relative risk; 95% confidence interval 0.60 to 3.71), headache (0.69 relative risk; 95% confidence interval 0.30 to 1.59), and constipation (1.71 relative risk; 95% confidence interval 0.82 to 3.59). While the current literature does not demonstrate significant differences in rates of adverse events, it is the opinion of the workgroup that opioids pose significant risks to patients when not safely administered. The cumulative dose of opioids administered as well as the timing between opioid doses must be carefully monitored in TJA patients. Patients who receive excess opioid

pain medication are at significant risk for adverse events such as sedation and respiratory depression. It is the recommendation of the workgroup that extended release opioids should be avoided to help mitigate this risk. In addition, it is the opinion of the workgroup that the lowest clinically effective dose of opioids be prescribed and administered to patients to help curb these adverse events in addition to the risk for chronic opioid dependence. Given the inconsistency in results with regards to postoperative pain as well as complications associated with postoperative opioid use this recommendation was downgraded from strong to moderate.

Guideline Question 6:

For patients undergoing primary TJA, does the number of opioid pills prescribed at the time of discharge affect postoperative pain, opioid consumption, opioid refills, number of unused opioid pills, and/or complications including chronic opioid dependence?

Response/Recommendation:

Prescribing lower quantities of opioid pills at discharge may lead to equivalent patient reported outcomes, pain relief, reduced opioid consumption, and fewer unused opioid pills after TJA.

Strength of Recommendation: Moderate

Rationale:

One high quality study evaluated the influence of the number of opioid pills prescribed at discharge after TJA on patient reported outcome scores, pain control, and opioid consumption after TJA.[33] In their prospective blinded randomized controlled trial, Hannon et al. found that patients who received 30 oxycodone immediate release pills (OxyIR) as opposed to 90 pills had equivalent patient reported outcome scores and significantly fewer unused pills at 6 weeks postoperatively. Patients who received 90 OxyIR pills had on median 73 unused pills while patients who received 30 OxyIR pills had on median 15 unused pills. Opioid consumption within 6 weeks after surgery was equivalent between the two groups, however regression analysis determined that being prescribed 90 OxyIR pills was independently associated with taking more oxycodone pills. Given the risks associated with diversion of unused opioid pills, it is the opinion

of the workgroup that patients be prescribed the fewest number of opioid pills possible without jeopardizing pain control and clinical outcomes after TJA.

Guideline Question 7:

For patients undergoing primary TJA, does tramadol affect postoperative pain, opioid consumption, and/or postoperative complications and how does its efficacy compare to other opioid medications?

Response/Recommendation:

Tramadol administered within 24 hours after surgery may reduce postoperative pain and opioid consumption after TJA within 72 hours after surgery, but may be associated with adverse events such as dizziness and dry mouth.

Strength of Recommendation: Moderate

Rationale:

Three studies evaluated the effects of tramadol on postoperative pain, opioid consumption, and complications after primary TJA**.** One high quality study compared the use of tramadol versus a placebo for treatment of pain after TJA.[34] Another high quality study compared tramadol to placebo and to paracetamol with codeine.[35] One additional high quality study compared tramadol to other opioid medications for treatment of pain after TJA. There were mixed results among all studies on the effects of tramadol on pain, patient-reported outcome scores, opioid consumption and adverse events after TJA.

Both studies that compared tramadol to a non-opioid control found that there was no difference in pain relief between the control and tramadol.[34,35] However, each study found different results with regards to opioid consumption. Stiller et al. found that intravenous tramadol

100 mg/mL administered every 6 hours for 24 hours after surgery led to 31% lower morphine consumption in TKA patients measured via a morphine patient controlled analgesia (PCA) device.[34] Stubhaug et al. found that after THA the addition of either 50 mg or 100 mg oral tramadol did not result in any change in opioid consumption when compared to placebo.[35] When compared to paracetamol with codeine, both 50 mg and 100 mg oral tramadol resulted in less efficacious pain relief and opioid consumption. Pang et al. found that tramadol reduced opioids administered via a patient controlled analgesic device compared to placebo.[36]

Adverse events including dizziness, dry mouth, and nausea were more common among patients who received tramadol compared to placebo. A direct meta-analysis of two studies found that rates of dry mouth (1.97 relative risk; 95% confidence interval 1.04 to 3.75) and dizziness (1.50 relative risk; 95% confidence interval 1.12 to 2.00) were more common among patients who took tramadol compared to placebo.[35,36]

Given the conflicting evidence with regards to opioid consumption, the fact that two studies evaluated intravenous tramadol which is not approved by the Food and Drug Administration in the United States, and that there was inconclusive evidence comparing the efficacy of tramadol to other opioids the strength of the recommendation was downgraded to moderate.

Areas for Future Research:

The best available evidence includes high and moderate quality data, however there remain many limitations in the formulation of the clinical practice guidelines on the use of opioids after primary TJA. Given the poor outcomes after primary TJA among patients who take chronic opioids prior surgery, we recommend future research on innovative and effective ways at reducing chronic opioid use prior to TJA. Future research should evaluate whether reducing chronic preoperative opioid use leads to improved postoperative outcomes including postoperative pain, opioid consumption, opioid dependence, and functional outcomes.

Opioids administered during the perioperative period (e.g. immediately preoperatively, intraoperatively, and postoperatively) reduce the need for additional opioid consumption and postoperative pain. However, there is significant heterogeneity in the route, dose, frequency, and type of opioids administered in the current literature. For example, in the studies reporting on opioids administered preoperatively, most investigate transdermal fentanyl while only two other studies evaluate intravenous and oral opioids. In addition, many of the studies included did not utilize a multimodal analgesic regimen. Future research should focus on determining the role of opioids in a modern multimodal anesthesia and analgesia protocol after TJA. This would include determining what opioids should be administered, the route, dose, frequency, and duration of treatment. Future research should also focus on how many pills should be prescribed after discharge and ways to help patients wean from taking opioids after surgery.

With the advent of the opioid crisis in the United States, tramadol has been considered a safer alternative to other traditional opioid pain medications for treatment of postoperative pain. However, there remains limited literature on its efficacy in a modern multimodal analgesia protocol. Future research is warranted to determine the type of tramadol that should be

administered (e.g. immediate v. extended release), the dosage, frequency, and duration of treatment. In addition, there is a paucity of literature on oral tramadol, which requires further study. Further investigation is also warranted into the side effects associated with tramadol use and whether these side effects are further compounded when traditional opioids are also administered.

Peer Review Process:

Following the committee's formulation of the Clinical Practice Guideline draft, it underwent a peer review by the board of directors from AAHKS, ASRA, and the Hip and Knee Societies. The AAOS Evidence-Based Quality and Value Committee reviewed the Clinical Practice Guideline draft for endorsement. Additionally, the publication of the systematic review and meta-analysis on opioids in primary hip and knee arthroplasties that supported the formulation of the Clinical Practice Guideline has undergone peer review for publication.

Disclosure Requirement:

All authors or contributors to the Clinical Practice Guideline have provided a disclosure statement in accordance with the publicly available AAOS Orthopaedic Disclosure Program. All authors and contributors attest none of the disclosures present are relevant to the Clinical Practice Guidelines.

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