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AMERICAN ASSOCIATION OF
HIP AND KNEE SURGEONS
Clinical Practice Guideline

**Gabapentinoids in Total Joint Arthroplasty
March 2020**

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.

Acknowledgements:

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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