Dr. James P. Rathmell: Alright, so the aim of this systematic review was to assess the analgesic efficacy and the adverse events associated with perioperative use of gabapentinoids in adult patients. What was the hypothesis for your study and actually how do you think about hypothesis testing when you’re designing a systematic review and meta analysis?

Dr. Alexis Turgeon: I think I’m first potentially biased because I was trained as an evidence-based scientist and researcher and for sure am always concerned when there’s a broad use of a drug or an intervention that is totally completely off-label; that was not designed for this purpose to start with. When we designed this study it was basically about questions that we were asked on the bedside by colleagues on why should we or shouldn’t we be using this drug for pain control in the acute care setting. And we hypothesized that the clinical effectiveness was definitely there, but potentially small and not clinically significant. But that was our main hypothesis to start with.

Dr. James P. Rathmell: Okay, so in essence you’ve hypothesized that gabapentin produces clinically meaningful pain reduction and the null hypothesis would reject — you would reject that if there were no clinical meaningful pain reduction. That’s how you’ve kind of set up the trial, correct?

Dr. Alexis Turgeon: Correct; exactly.

Dr. James P. Rathmell: Alright, so that term clinically meaningful is going to be very important. It’ll come up again as we discuss your findings. Walk us through how you conducted the systematic review and the meta analysis.

Dr. Alexis Turgeon: Yes, first I think it is teamwork. It needs several individuals. Although it may look like it’s simple work, it is not. It’s extremely time consuming and when we want to do something very exhaustive we need to do all the different steps that must be done in a correct manner. So a systematic review or a meta analysis is basically an extensive, exhaustive review of the literature surrounding a very specific question, which here was to look at the effect of gabapentinoids as compared to placebo, other analgesic regimen or usual care in randomized controlled trials.

So we looked at the main databases at Medline, EMBASE, Cochrane Central and Web of Science from their inception up to last year. And we retrieved all randomized controlled trials performed in adults undergoing elective or emergency surgery under any type of anesthesia. So there was no restriction for language, nor country of publication. We used the co-primary outcome as the main outcome, so our co-primary outcomes were postoperative acute pain at 6, 12, 24, 48 and 72 hours after surgery measured by any quantitative pain scale.

Secondary outcomes were postoperative subacute pain, post operative chronic pain, cumulative dose of opioids administered within 24, 48, 72 hours, persistent opioid use, also length of stay and incidence of adverse events such as dizziness, fall, ataxia, delirium, drug addiction, abuse, visual disturbance, respiratory failure and opioid related adverse events, and for sure postoperative nausea or vomiting.

So when we conduct such type of work we have reviewers that do the work completely independently. So we had three reviewers, three members of our team that assessed all the trials, extracted the data of eligible trials and also evaluated the risk of bias of the trial and disagreements were resolved by another reviewer.

So we looked at the risk of bias using the Cochrane risk of bias tool, and we measured the pain intensity using scores that we translated over a 100 point score, regardless of what the format of the scale was to start with. It was all converted. And we also looked, which is one of the, I think, important points of our work, we looked not only at how much or what the level of pain intensity or the amount of morphine that could be spared with the intervention, but we looked at whether this difference was clinically important or not between groups on acute pain intensity. And there’s been evidence in the literature that we need at least 10 points out of a 100 point scale to talk about the clinically important difference, and that a difference of 20 to 30 points represents an appreciable analgesic effect, and 50 points will be a more substantial effect.
For opioid dose we converted those into milligrams of morphine. We used random effect models, which are the usual outcome and statistic to pool data in meta analysis for dichotomous outcome and we used the inverse variance method for continuous data along with the Mantel-Haenszel one. So we presented our results using risk ratio.

This trail of evidence was evaluated using the grade approach, which allows to give us an idea of how strong we are about these results; how strong about the quality of the evidence that we observe. Also, which is another important aspect of our work, to limit the potentials for type one error and inform future research, we performed trial sequential analysis in our main analyses to look at whether there’s – where we are in the literature, so find whether additional studies would be required and if we have, let’s say, the sufficient power to measure what we are trying to measure. So it’s some sort of cumulative meta analysis with interim analyses giving us information on how we are exhaustive in the results that we obtain. So that’s basically the overview of the method that we use in our systematic review.

Dr. James P. Rathmell: So what did you learn?

Dr. Alexis Turgeon: We learned that there is, yes, a slightly lower postoperative pain intensity that was observed at 6, 12, 24 and 48 hours; not at 72. But that this effect was very small and not clinically significant, ranging below the minimal important difference of 10 points out of 100 for each time point. Recent recommendations suggest using several timing assessments like the ones used in the systematic review, as you know. It allows to avoid selective reporting or focusing on a single time point when there is no overall effect. So small effect observed, but not clinically significant.

And the effect was also not different with the type of drugs, whether it was gabapentin or pregabalin, and was consistent in all subgroup analyses. Trials at low risk of bias showed consistently no effect or a smaller effect on pain intensity compared to those with a high or unclear risk of bias. There was some statistical heterogeneity that was observed between trials that was partly attributable to the type of coanalgesia and the risk of bias, as mentioned. But the timing of the intervention, the time of pain assessment, the doses regimen, the type of comparator were not identified as factors contributing to the statistical heterogeneity. And exploratory analysis, additional subgroup analyses showed consistent findings, including surgeries potentially associated with pronociceptive mechanism.

So we also observed that several times the required information size was collected in our systematic review from the existing randomized controlled trial, which suggests that unnecessary trials were conducted over time and that no further study is required.

Dr. James P. Rathmell: So about as exhaustive as a meta analysis can get. This included 281 trials, a total of almost 25,000 patients. That’s a truly impressive data set and an enormous amount of work to combine in a meaningful way. And you found that the gabapentinoids, both gabapentin and pregabalin, compared to controls were associated with this small but not clinically meaningful decrease in pain. I believe it was an average of seven on a scale of zero to 100 at 48 hours after surgery, but after 72 hours subacute and chronic pain, no difference. And the gabapentinoids were associated with a decreased risk of postoperative nausea and vomiting, but with more dizziness and visual disturbances. So pretty significant side effects and a small drop in post operative nausea and vomiting.

So what do you conclude from your analysis? What’s the path forward here?

Dr. Alexis Turgeon: I think the small effect of this drug but no clinical significance, and our primary outcomes were acute pain, pain findings for subacute chronic pain, which is where people or most of the community would think that’s where the benefit would be. And also, importantly, a greater incidence of adverse events, namely dizziness and visual disturbance. And when major adverse events such as depression and addiction are unreported. So it means that we have a drug, an intervention that has a very small effect that is not clinically significant and that increases adverse events, and the major ones have never been very well evaluated so far. So it means in conclusion that these results are not supporting the routine use of gabapentin or pregabalin for the management of postoperative pain in adult patients. And also that additional trials evaluating the effect of perioperative use of gabapentinoids on postoperative acute pain intensity are not required.

Dr. James P. Rathmell: Dr. Kharasch, I want to turn to your editorial view. Now for listeners, the editorial is titled, “Perioperative gabapentinoids: defating the bubble.” You do a terrific job of putting the article in perspective. Perioperative use of gabapentinoids has become more and more common, despite conflicting studies and evidence of significant adverse effects. Can you walk us through the emergence of multimodal analgesia and early recovery after surgery, or ERAS programs, and the rationale for including perioperative gabapentinoids?

Dr. Evan Kharasch: The history of enhanced recovery after surgery, sometimes called ERAS as well as multimodal analgesia, is about a two decade old story. And to compress this down, the concept of enhanced recovery after surgery, or ERAS, was started by a group of surgeons in Europe. And they recognized that certain things that were being done in the care of surgical patients did not necessarily need to be done, and in fact they may have been less than helpful and at times even harmful. They put forth a number of recommendations as far as patient care spanning the time from preadmission through the perioperative period and through the postoperative period; most of them having to do with surgical care. There were about 20 items that were deemed to be in need of reform from things like not fasting patients preoperatively and feeding them earlier postoperatively, increased mobilization, not using drains and nasogastric tubes, early mobilization, the use of epidural anesthesia for abdominal surgery, as well as not using excessive amounts of opioids postoperatively that would cause ileus.

Part of that was the concept of multimodal analgesia, and that concept had to do with the idea of not using just one drug for the treatment of postoperative pain, such as opioids, but rather using several drugs together in combination to treat postoperative pain. The idea around multimodal analgesia is that by combining drugs they would have an additive effect on pain relief, but hopefully not an equally additive effect on side effects, or that they might have synergistic effect on pain relief but only additive effect on side effects.

And a couple of things happened over the course of those two decades. One is that the concept of avoiding excessive amounts of opioids to the point of causing ileus and side effects somehow morphed into the concept of restricting opioids to treat pain. The other thing that happened is that in the very aggressive pursuit of multimodal analgesia, investigators tested their multimodal regimens for effectiveness on relieving pain or reducing the need for other analgesics, but they never really tested the other aspect of multimodal analgesia, which was examining whether side effects were reduced.

Dr. James P. Rathmell: Now before Dr. Turgeon’s study what was the evidence of benefit and the evidence of risk for the gabapentinoids used perioperatively? And how did their use become so common?

Dr. Evan Kharasch: The evidence of benefit was initially looking at the very early postoperative period; just a few hours after surgery. And there was evidence for about a 30% reduction in either opioid use or pain. Some later studies looked at a period of just a few days postoperatively and there was some lesser evidence for the degree of clinical effectiveness. And as studies started to look at longer periods of time, the evidence for benefit declined even more.

There was almost no evidence, or no evaluation, of side effect profiles. One of the earliest studies that looked at the question of side effects was only published just a few years ago that looked at the interaction between opioids and gabapentinoids and asked the question if we are using gabapentinoids to try and reduce opioid dose in order to limit opioid side effects, just what is the influence of the combination of gabapentinoids and an opioid on opioid related side effects.

And my attention was drawn to this question when I was asked to write an editorial about one of the earliest studies, also published in Anesthesia, which evaluated this question. And the investigators looked at the influence of opioids alone, gabapentinoids alone and
opioids and gabapentinoids in combination on respiratory depression. And what they found was that gabapentinoids alone had minimal effect, opioids, as they are well-known to do, decreased ventilation, but the combination decreased ventilation even more than opioids alone. So if the intent of combining drugs was to diminish side effects, what these investigators found was that the side effects were actually increased. But this research was done more than a decade after clinicians started using these drugs in combination.

The use of gabapentinoids became more common for reasons that appear to be multi-factorial. One was that this coincided with the emphasis on enhanced recovery after surgery and the emphasis on multimodal analgesia. There weren’t new drugs introduced into the specialty that could enable this, so clinicians started looking outside of traditional anesthetic drugs for things that might be used in an ERAS protocol. This coincided with the use of many drugs, often in combinations of four, five and six drugs, together in multimodal cocktails.

So it was the push towards multimodal analgesia. It was the push towards enhanced recovery. Much later came the problem of opioid overuse in outpatients, which then stimulated renewed interest and a desire by anesthesiologists, for reasons that are a little bit unknown, to restrict opioid use in the operating room even more. Other elements which contributed to some of this enthusiasm was emphasis on outpatient surgery, emphasis on reducing opioids and a desire overall for anesthesiologists to do something to try and treat postoperative pain, or in fact do anything to try and reduce postoperative pain and opioid use.

So there became a lot of exuberance, if you will, about the use of gabapentinoids, but without the underlying clinical evidence. So what this study by Dr. Turgeon and colleagues does is bring additional light to the fundamental question of how we evaluate the clinical effectiveness of drugs in terms of meeting their intended goals of treating pain, but at the same time without increasing side effect or hopefully by decreasing side effects.

What they learned was that the weight of evidence is that gabapentinoids’ reduction of pain is small in degree and short-lived in longevity, but was accompanied by substantial side effect. They reinforced a number of other studies that have asked a similar question in the past five years, but they did it at a scale that was unprecedented. Their results also coincide with understanding by United States Food and Drug Administration that the side effects of gabapentinoids, particularly in the perioperative period, are much greater than were previously appreciated. Food and Drug Administration recently, in late 2019, issued warnings about the respiratory adverse effect of gabapentinoids. They’re requiring the manufacturers of gabapentinoids to put these warnings in their package labels as well as to do new clinical trials, particularly of gabapentinoids in combination with opioids to assess the risks of respiratory depression.

So we do now have a much better understanding of the risks and benefits of gabapentinoids in the perioperative period, and what we’ve learned over the course of the past several years is that the evidence of their benefit has been declining, while the evidence of their risk has been growing.

**Dr. James P. Rathmell:** In your editorial you tell readers this: “The analysis was well executed; the number of patients robust; the quality of evidence properly evaluated; the results clearly presented and the conclusion is well supported and unambiguous.” The final section of your editorial is titled evidence of action, and you explain that over the past two decades evidence of benefit from routine perioperative administration of gabapentinoids has diminished while evidence of harm has increased. That’s what you just told us in the last section. Is there sufficient evidence at this point to abandon their use altogether in the perioperative realm? And if so, how do we move these findings out into widespread changes in actual practice?

**Dr. Evan Kharasch:** If our goal as clinicians is to practice evidence-based medicine, the best evidence that we have now, as was summarized very eloquently by Dr. Turgeon and his co-authors, is that the routine use of perioperative gabapentinoids for the treatment of postoperative pain in adults is not supported. There was not evidence of benefit in subpopulations as well, and their other important observation is that conducting even more clinical trials to try and evaluate or perhaps develop evidence of benefit is not likely to produce that benefit.

So what we can do with this evidence is to harness the enthusiasm that led to the widespread use of gabapentinoids to redirect that enthusiasm to revising and refining our clinical practice and using the evidence that has been developed to treat patients in a more informed way. And that would suggest that we not continue to use gabapentinoids perioperatively on adults on a routine basis.

**Dr. James P. Rathmell:** Not a lot of room for interpretation there, [laughs] absolutely. Dr. Turgeon, what comes next for you and your research team?

**Dr. Alexis Turgeon:** I think what comes next comes with what Dr. Kharasch just mentioned. It’s all about implementing this information and transferring this information to the bedside, but also the societies that develop and are developing guidelines on acute pain management. And that’s a different kind of work, but it’s extremely important to make sure that the implementation is out there after that kind of work.

**Dr. James P. Rathmell:** Terrific. I hope today’s discussion will lead many of you who are listening to read this new article and the editorial review that appear in the August 2020 issue of ANESTHESIOLOGY, where you can learn much more about the perioperative use of gabapentinoids. Dr. John Wunderer from Vanderbilt and I also created an infographic that appears in the same issue. It’s titled, “Seeing the forest for the trees: reconsidering perioperative gabapentinoids,” where we summarize the major findings of this study. Drs. Turgeon and Kharasch, thank you very much for joining me today and for the terrific explanations.

**Dr. Evan Kharasch:** Thank you very much for the opportunity to participate in this conversation and discussion.

**Dr. Alexis Turgeon:** Thank you very much, Dr. Rathmell, for this great discussion, and also to Dr. Kharasch and his colleagues for this great summary and the editorial that is associated with our work. Thanks very much.

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