Host: Welcome to the *ANESTHESIOLOGY* journal podcast, an audio interview of study authors and editorialists.

Dr. James P. Rathmell: Hello, I'm Jim Rathmell, professor of anesthesia at Harvard Medical School and chair of the department of anesthesiology, perioperative and pain medicine at Brigham and Women's Hospital. I'm one of the executive editors for *ANESTHESIOLOGY*, and you're listening to an *ANESTHESIOLOGY* podcast that we've designed or physicians and scientists interested in the research that appears in the journal.

Today we're going to talk to the lead author of an original research article and an accompanying editorial view that appear in the July 2020 issue. With us today is Dr. Gisèle Pickering. Dr. Pickering is professor of medicine and clinical pharmacology at Clermont-Ferrand University Hospital and faculty of medicine in Clermont-Ferrand, France. Dr. Pickering is the first author of an article that appears in the July 2020 issue of the journal titled "Ketamine and Magnesium for Refractory Neuropathic Pain: A Randomized, Double-Blind, Crossover Trial." Dr. Pickering, thank you for joining us.

Dr. Gisèle Pickering: Hello, very pleased to participate in the discussion today.

Dr. James P. Rathmell: Also with us today is Dr. David Clark. Dr. Clark is professor of anesthesiology and vice chair for research in Stanford Medicine's department of anesthesiology, perioperative and pain medicine in Palo Alto, California. Dr. Clark wrote an editorial view that accompanies Dr. Pickering's research article titled "Ketamine for Chronic Pain: Old Drug New Trick."

Dr. J. David Clark: Thank you, I'm glad to be part of the conversation.

Dr. James P. Rathmell: Dr. Pickering, congratulations on completing a nicely designed study aimed at answering an important clinical question. Let's set the stage for listeners. Both ketamine and magnesium have analgesic effects in some settings. And we're seeing more and more use of these agents as low-dose intravenous infusions for the treatment of chronic pain in the outpatient setting, yet there's little evidence to support their utility in that setting. Can you explain what we knew about ketamine and magnesium as analgesics for treating chronic pain before you conducted your study?

Dr. Gisèle Pickering: Ketamine and magnesium have been used as analgesics for quite a number of years. And in fact, recent reviews have traced the poor to moderate level of evidence of ketamine analgesic effects in quite a number of randomized controlled trials. And it's specifically concerning neuropathic pain, which is a very bad type of pain that leads to quite a lot of impairment of quality of life. And it was the same for magnesium. Magnesium sulfate has been used as well quite a lot and it's been quite a lot of discussion of these analgesic effects. Finally, the combination of magnesium sulfate plus ketamine hasn't been really studied. So these three aspects have been quite poor in the literature so far, and that's what we knew about ketamine and magnesium before starting the study.

Dr. James P. Rathmell: Alright, so a lot of discussion in the literature; a lot of use out in the real clinical world, but really very little evidence to support that use in patients with chronic neuropathic pain. So you set out to determine what benefits, if any, follow short term infusions of ketamine with or without magnesium in patients with chronic pain. What was the hypothesis for your study when you began?

Dr. Gisèle Pickering: The hypothesis in the present trial with neuropathic pain patients was to look at IV ketamine, intravenous ketamine or intravenous ketamine plus magnesium on the pain relief that patients would get. The third point was to look at magnesium combined with ketamine would have an additive effect on pain relief, and also on other cognitive, emotional aspects.

Dr. James P. Rathmell: So you hypothesized that in patients with neuropathic pain, ketamine may provide pain relief and cognitive emotional benefit versus placebo, and that a combination with magnesium may have an additive effect over a five week observation period after the treatments. How was the study done?

Dr. Gisèle Pickering: The study was a randomized placebo controlled crossover double-blind clinical study. And patients after inclusion they received in random order by IV route either a placebo or ketamine or ketamine plus magnesium. And every 35 days they come back to the hospital every 35 days to have another injection; another infusion. And so we monitored the pain relief and quite a number of cognitive and emotional parameters during all this period.

Dr. James P. Rathmell: Now I want you to pause a bit here and explain the triple crossover paradigm of saline, ketamine and ketamine plus magnesium infusions that were used and how that triple crossover paradigm allowed you to gain enough statistical power to conduct the study using just 20 patients with chronic neuropathic pain.

Dr. Gisèle Pickering: In fact we included 23 patients, but indeed the sample was of 20 patients that we analyzed. And how we designed the study was that we had quite a number of studies before in our center where we had quite – unpublished studies as well, and we calculated the requisite sample size that was estimated from a pilot study as well as from papers in the literature. And in fact, we arrived to this number of 20 patients, and it's a study with a statistical power of 90%, which is quite good for a randomized clinical trial.

Dr. James P. Rathmell: And it's important for listeners to understand that that triple crossover paradigm allows each patient to serve as their own control. And as long as there's no carryover of the treatment effect from one period to the other, it allows you to reduce the noise in the system dramatically and increase the power, and you can get very powerful studies with a very small number of patients. So Dr. Pickering, what'd you find?

Dr. Gisèle Pickering: What we found was that we had no effect of either the ketamine or ketamine plus magnesium in terms of pain relief over the 35 days after infusions. And it was quite a surprise in a way because some patients responded, but the main effect of the 20 patients they showed no affect. So that was the third finding. And the second one was that we had absolutely no additional secondary health related, emotional, sleep, quality of life improvement in the three arms. And then the point was that adding magnesium did not add anything to pain relief. So these findings were surprising in a way because there has been quite a lot of discussion in the literature, but at the same time, methodologically it was quite well done.

Dr. James P. Rathmell: So I want to go over your findings just one more time for listeners. Daily pain intensity was not significantly different between the three groups over 35 days. There were no significant differences in emotional, sleep and quality of life measures, and during placebo, ketamine and ketamine magnesium infusions, 10%, 20% and 35% of patients respectively reported at least one adverse event. What were the limitations of your study?

Dr. Gisèle Pickering: Well, there were a few limitations. I mean one was probably that the dose we used was quite low, although the dose that is commonly use in pain clinics that was 0.5 mg/k. And we had no (inaudible) effect five weeks. Although after the first week it seemed to have a slight decrease of pain for the patients. So one of the limitations might be that the dose of ketamine was a bit low.

The second one was that patients were all ketamine naïve. So we selected them so that they did not know what was the effect of ketamine. And obviously it's quite difficult to have a good type of blinding for these patients because it's difficult to achieve with ketamine because we know there are quite a number of known side effects. And we used real placebo, which was saline. In many papers if they used a positive placebo like midazolam or clonidine to effect blinding. So we had the results, but at the same time the placebo effect we got was maybe poorly estimated in the study just because it's naïve patients. So these are the main limitations that I could underline. Although the dose itself and the number of patients are always the things that we could improve.

Dr. James P. Rathmell: So what do you think the take-home message is for practicing pain specialists?

Dr. Gisèle Pickering: So for practicing pain specialists I think everywhere in the world, I mean we use a lot of ketamine. In Europe we use quite a

lot of ketamine for chronic pain patients. There is no consensus of use. There's been quite a lot of discussion about how do use ketamine. What we got from this paper is that we can say that one infusion of 0.5 mg/k ketamine is not efficient for chronic pain relief, although a number of patients seemed to be improved and there is some degree of pain relief. The second point is that there is no additive effect of magnesium when it's added to ketamine on pain relief. So these are the main two take-home messages I think that would be important for pain specialists.

Dr. James P. Rathmell: Dr. Clark, I want to turn to your editorial view titled "Ketamine For Chronic Pain: Old Drug, New Trick." You do a terrific job of putting the article in perspective. Ketamine's a pretty common pharmacologic tool for anesthesiologists. It was first approved as an anesthetic in 1970. Can you start by walking us through some of the more recent findings about ketamine's utility in treating other problems like depression and reducing chronic postoperative pain?

Dr. J. David Clark: Well, ketamine is a tremendously interesting drug with a long history, and it always seems to be finding its way into a clinic with a new potential indication. As you know, the drug has been used as an anesthetic induction agent and (inaudible) analgesic. It's proven its value in managing postoperative pain in patients as well. But as you say, there are a few new uses that it may have, one of which is to potentially reduce chronic or persistent postoperative pain.

And there there have been a number of studies in different types of surgical models showing on the whole that there may be a modest to moderate reduction in the incidence of chronic pain after certain types of surgery. Even there we're perhaps not entirely certain of the effects or the dosing regime or the particular type of surgery in which it might be most useful. But that research goes on. And currently I would point out there's a large trial being done in New Zealand and Australia enrolling thousands of patients that will hopefully give us definitive evidence one way or another on its ability to reduce chronic pain.

On the other side of things, the drug has begun to be used as an antidepressant. So while we in anesthesia think of ketamine as an analgesic drug, people who study mood disorders and other types of psychiatric disease are aware of neuroplasticity contributing to conditions like depression in an NMDA receptor mediated way. So because of that hypothesis, psychiatrists infused ketamine in patients with depression, and it was seen very reproducibly that some patients with depression would have a reduction in the severity of their depression that could last anywhere from several days to perhaps two weeks. And because of that, one of the enantiomersive ketamine, esketamine, was developed as an antidepressant and that now has received FDA approval and is being used.

Dr. James P. Rathmell: Well before Dr. Pickering's study, the one we're discussing today, what did we know about the utility of low dose ketamine infusion for treating refractory chronic neuropathic pain?

Dr. J. David Clark: Frankly what we knew was a little confusing and contradictory, which was one of the beauties of the study, then, that Dr. Pickering performed. What we had was evidence both suggesting slight utility and some suggesting really very little utility in the setting of neuropathic pain. In Dr. Pickering's study a very carefully characterized population of patients was recruited and they were treated using this very powerful triple crossover design. So I think what we know now is much better how ketamine might work in these patients.

Dr. James P. Rathmell: And tell us how does Dr. Pickering's study modify our understanding of the usefulness of the treatment?

Dr. J. David Clark: Well I think Dr. Pickering's data shows us very clearly that ketamine has a very limited and perhaps no utility in a general sense for patients for chronic neuropathic pain, if your goal is to reduce pain for 35 days, which was the time period chosen by Dr. Pickering for her primary endpoint. I think the data by virtue of using the triple crossover, using ketamine and the combination of ketamine and magnesium, really allow us more confidence in reaching that conclusion.

Dr. James P. Rathmell: Well rather than just simply calling for additional research, you set out a number of steps that you think we should take as pain practitioners when deciding if and when to use ketamine for treating chronic pain. Can you walk us through your recommendations?

Dr. J. David Clark: I will do that. I did try to resist the typical conclusion that simply more research is needed, and attempted to initiate a further conversation about exactly what it is that we want to know if we are to pursue ketamine as an analgesic drug for chronic pain. First of all, I suggest that we need to know much more about possible side effects and complications of use. No one supposes that single infusions or even multiple infusions of ketamine will cure chronic pain. Therefore, if we start on the road of giving these infusions, we should probably understand what it means to commit a patient to having many infusions of the drug. We simply have a very poor idea of what the rates of cardiovascular side effects, of psychiatric side effects, hepatic toxicity, urologic toxicity or even potentially causing a substance use disorder might be. There I think we need more information. We need that for ourselves and to provide to our patients in selecting how they'd like to be treated.

Another is we need to decide what would constitute an adequate response to justify repeating the infusion. Is it okay to repeat an infusion of ketamine if a patient has a small amount of pain relief for a week, or do we have a standard that requires really a much more robust response that would be reasonable to require, given a certain level of toxicity and expense?

Third, I think we need to decide how we're going to approach the issue of dosing. Dr. Pickering's data and other data in the field really suggested very low doses in the half milligram per kilogram area, while probably on the safe end of the spectrum, are not likely very effective for the treatment of neuropathic pain and perhaps other types of pain for which ketamine might be used. How then do we select a dose? Do we start at a low dose and work our way up towards some of the higher doses that have been used? Or is it going to be necessary really to use ketamine very aggressively, if at all?

And finally, it's concerning that in our communities we see so-called ketamine clinics popping up. These are clinics that will look at your medical or psychological condition and infuse ketamine, generally for cash, often costing from several hundred to several thousand dollars per infusion. Yet these drugs are often used a la carte; it's the only treatment that you get. We've learned over decades in the field of chronic pain management that our results are best when we use so-called multidisciplinary approaches. Yes, pharmacological agents may have a role, but so, too, would physical ones that attempt to maintain or improve a person's functional status, psychological interventions that may improve a person's ability to manage their own pain, and perhaps alternative methods that use approaches not commonly employed by the normally trained physician, also with the goal of reducing pain in these chronic pain patients.

Dr. James P. Rathmell: Sage advice. So Dr. Pickering, what comes next for you and your research team?

Dr. Gisèle Pickering: In France we are continuing our program on NMDA antagonists. We've been working for a number of years on ketamine, of course, and also on related to ketamine with memantine, dextromethorphan or magnesium. We're still convinced that these drugs acting on the NMDA receptors are quite interesting for pain relief, however, as mentioned Dr. Clark, quite difficult to use them safely. And our concern as well is on safety and of course efficacy. And we plan to look more closely on ketamine responders and try to identify responding factors in order to identify early patients who could respond to ketamine. Because we see quite a lot of patients. We don't have the ketamine clinics in Europe, but we have quite a number of pain clinics with patients coming with repeated doses of IV ketamine, and we don't really know what's happening in the long term. So it's important for us as well to focus on the safety and the efficacy of repeated doses of ketamine and to identify as well which dose we should give, the frequency, the speed of the infusion and so on.

So these points are very important for a future study that we are starting to set up with quite a lot of pharmacokinetics and as well the metabolism of ketamine. We're very interested as well on real life data. And we have a study going on at the moment with almost 600 patients that we follow for one year after ketamine infusion—one or several ketamine

infusions—in order to look at the benefit/risk ratio of ketamine in these patients; not only on pain relief, but also on cognition, emotion, quality of life and addiction as well, because we don't talk enough of the addictive effect of ketamine and why patients require to take ketamine quite often.

So these are the two main things that we are focusing on; trying to set up and to find the ketamine responders and to identify these patients and to try to reach a consensus. Because so far in Europe and also in America and also worldwide, I mean we are very poor at having a consensus on the use of ketamine in chronic pain patients. There has been quite a number of papers, very interesting papers, but some conflicting results as well. So what we plan to do now is try always to optimize these NMDA antagonist treatments with efficacy and of course look at the side effects. I agree with the cardiovascular side effects are really poorly looked after as well as the neuropathic side effects as well. And more generally all the misuse of ketamine in these chronic pain patients that have very often a number of comorbidities and are really usually vulnerable, and sometimes fragile persons.

Dr. James P. Rathmell: Excellent. Keep up the good work. We desperately need the type of research that you're doing to answer the questions and learn better how to use ketamine in treating chronic pain.

I hope today's discussion will lead many of you listening to read this new article and the editorial view that appear in the July 2020 issue of *ANESTHESIOLOGY*, where you can learn much more about the use of low dose ketamine and magnesium infusions for the treatment of chronic neuropathic pain.

Dr. Jon Wanderer from Vanderbilt University and I also created an infographic that appears in the same issue titled "Ketamine for Neuropathic Pain: An Infusion of Relief?," and that ends with a question mark. In the infographic we summarize the major finding of Dr. Pickering's study. Drs. Pickering and Clark, thank you very much for joining me today and for the terrific explanations.

Dr. Gisèle Pickering: Thank you very much, and thank you to Dr. Clark as well.

Dr. J. David Clark: Thank you very much. I appreciate being a part of the conversation.

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