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

Dr. BobbieJean Sweitzer: Hello. I’m BobbieJean Sweitzer, Professor of Anesthesiology at Northwestern University and an Associate Editor for Anesthesiology and you are listening to an Anesthesiology podcast designed for physicians and scientists interested in the research that appears in our journal.

Today we are speaking with the author of a publication that will appear in the October 2018 issue of the journal. With us is Dr. Stavros G. Memtsoudis. Dr. Memtsoudis is a senior author of an article titled “Liposomal Bupivacaine Does Not Reduce Inpatient Opioid Prescription or Related Complications after Knee Arthroplasty.”

He is Professor of Anesthesiology in the Department of Anesthesiology at the Hospital for Special Surgery, Weill Cornell Medical College, New York, New York, and in the Department of Anesthesiology and Perioperative Medicine and Intensive Care Medicine at Paracelsus Medical University in Salzburg, Austria. Welcome, Dr. Memtsoudis.

Dr. Stavros Memtsoudis: Thank you for having me.

Dr. BobbieJean Sweitzer: So, what questions were you interested in addressing for this research endeavor?

Dr. Stavros Memtsoudis: We wanted to answer the question if liposomal bupivacaine was of benefit in reducing opioid prescriptions and related side effects as well lead to improved resource utilization amongst patients receiving knee arthroplasties, and specifically interested in the context of modern multimodal pain management including peripheral nerve blocks.

When we reviewed the literature in preparation for the study, we noticed that the RCTs, so the randomized control trials, on the topic were, number one, very limited and when they were done they were confined to single institutional data and the majority of them failed to actually find the benefit in total knee arthroplasty patients.

There were only a few that were positive studies, but when looking at those we saw that there were issues like non-equivalents between comparison groups as well as the fact that they did not really follow best practices in terms of comparing the liposomal bupivacaine in the context of multimodal analgesia including peripheral nerve blocks.

The other aspect, obviously, was that some of them seemed to be biased by conflicts of interest as it was industry-sponsored, but because we consider peripheral nerve blocks as the most effective ways of achieving pain control after knee replacements, we thought it would only be fair to compare liposomal bupivacaine in that context as it’s the true benchmark of something that we use now is better than something that we already have.

Dr. BobbieJean Sweitzer: So, was this actually a randomized controlled perspective trial?

Dr. Stavros Memtsoudis: No, it actually wasn’t. It was a retrospective observational study using population data that are collected from hundreds of hospitals throughout the United States. It’s in the context of the Premier database that we’ve used before. These studies have become very popular in recent years because they give us a glimpse into real-world practice without the confines of randomized controlled trials where we have strict inclusion and exclusion criteria.

But despite the large number of data, though, we always have to be aware of downsides as these database studies usually lack the ability to determine causality between interventions and outcomes and we have to basically look at plausibility of the results and keep in mind residual confounding.

Dr. BobbieJean Sweitzer: Yes, a couple of interviews ago, I believe, we interviewed a researcher who had used this Premier database. And I’m going to ask you a little about that a little bit later. For now, can you tell me a little more about what your specific primary and secondary outcomes were that you were looking for?

Dr. Stavros Memtsoudis: Yes. The primary outcome was inpatient opioid prescription. I have to very clearly state it’s prescription because with these data sets we don’t actually know how much patients consumed, but we can talk about it a little later. But we think that there’s a good correlation between what was built for opioids and what actually was consumed.

Then secondary outcomes were length and cost of hospitalization and opioid-related complications including respiratory GI complications, central nervous system events and genital/urinary adverse events.

I should mention while we’re talking about those complications that statistical significance in the outcomes is usually something that we define in the beginning in the methods of a paper and it can be easily achieved in large database research because even small differences tend to have reached traditional thresholds of statistical significance.

So, for this study and something that other researchers have developed in concept beforehand, we actually focused on something called “clinical meaningful difference.” So, we determined for opioid consumption this to be something around 15% for our study, although if you look at previous publications the recommendation is something like 25% but we chose to be a little bit more conservative and use 15% in order to not have too much bias in this selected threshold.

So, I just wanted to mention that because it’s important when we interpret the outcomes in this paper.

Dr. BobbieJean Sweitzer: You didn’t actually measure pain or pain scores, is that correct?

Dr. Stavros Memtsoudis: Correct. That is correct because we don’t have that level of detail in this database and that’s a common problem with clinical detail; it’s just not available and we have to take often surrogate markers for that, like opioid consumption – or prescription, I should say.

Dr. BobbieJean Sweitzer: So, can you tell us a little bit more about the population of patients, maybe the type of surgery or surgeries in this cohort group. Were these just total knee arthroplasties or primary or re-dos or…?

Dr. Stavros Memtsoudis: Yes. So, we actually wanted to level the playing field. So, we identified primary knee arthroplasty recipients that had surgery in the US amongst 500 hospitals and also limited to procedures that were done in hospitals that had a certain amount of procedures per year. So, we didn’t want to include hospitals that were doing them just once in a while.

And we also included just patients that had as part of their management a peripheral nerve block because, as I said before, we consider that as
Dr. BobbieJean Sweitzer: So, when you say peripheral nerve blocks, does it have to be the primary anesthetic or was it an adjunct or for postop analgesia or like regional, central neuraxial plus or general anesthesia plus peripheral or…?

Dr. Stavros Memtsoudis: Correct. So, they would have been basically adjuncts for pain management because the primary anesthetic was, in any one of these patients, either a general or a neuraxial anesthetic. So, peripheral nerve blocks were basically used for pain management here.

Dr. BobbieJean Sweitzer: Got it. So, how was the liposomal bupivacaine administered in this population? I understand it can be given intraarticular or in the peripheral nerve block, correct?

Dr. Stavros Memtsoudis: Yes. The reality is we don't actually know exactly how it was given; that piece of information is not available in the data set. We do know just the dose and that it was given, but during the time spent of the study, 2013 to 2016, only wound infiltration was actually approved by the FDA which does mean that it was not used off-label.

However, this was really of secondary concern to us because we thought that irrespective for how people choose to use liposomal bupivacaine, would it offer any advantage in the context of knee replacement with a peripheral nerve block?

So, while we don't have that level of detail, we weren't quite as concerned about not being able to tell specifically.

Dr. BobbieJean Sweitzer: And what percentage of patients received the liposomal bupivacaine?

Dr. Stavros Memtsoudis: It was about 1 in 5, so 21%, to be precise, of the overall cohort.

Dr. BobbieJean Sweitzer: Was there a variation among the different hospitals in the use of this drug? And if so, were there characteristics of those institutions with the highest and maybe the lowest utilization rates?

Dr. Stavros Memtsoudis: That was actually one of the very interesting findings of the study. There were tremendous differences in utilization patterns. So, amongst the 553 hospitals that were included, half of them never used liposomal bupivacaine while about 1/4th of the hospitals had utilization rates over 50%. And then there was specifically ten hospitals, about, that had utilization rates approaching 100%. So, everyone was getting them at that hospital.

However, even when restricting analysis to high-utilization hospitals—meaning those that had utilizations over 50%—we failed to identify any clinical significant impact on our primary outcome.

And while we don't have – really formally looked into the comparison of hospital characteristics that used or did not use liposomal bupivacaine, when you look at the patients in each group that did get the agent, it tended to be that hospitals that were smaller and those that were non-teaching institutions were more likely to administer liposomal bupivacaine.

Dr. BobbieJean Sweitzer: Did you see a regional variation?

Dr. Stavros Memtsoudis: No, this data set is purely US-based.

Dr. BobbieJean Sweitzer: Right. But, I mean, was it the East Coast, the West Coast, the Midwest.

Dr. Stavros Memtsoudis: We did not actually look at that. No. We did not look into that. Yes.

Dr. BobbieJean Sweitzer: So, can you speculate on maybe the factors that were driving this variation in use? Do you think it was patient or physician preference, surgeon, anesthesiologist or something else?

Dr. Stavros Memtsoudis: That was exactly the question that we asked ourselves. So, using some statistical methodology there we looked into how much in terms of hospital variables versus patient variables can explain the use of liposomal bupivacaine and we found that 79% of the variability of liposomal bupivacaine use was actually attributable to hospital factors. So, this suggests that protocols or routine practice were the most likely drivers for administration rather than patient-related factors or patients asking for it.

Dr. BobbieJean Sweitzer: And over time did you see an increasing or decreasing use of this drug?

Dr. Stavros Memtsoudis: As of 2016, we actually saw a rapid increase in the utilization. So, in 2013 it was about 7% and then by the time we got to 2016 it was one in 4, so 26%. So, there was a rapid increase. I don't have any recent data, but I can only assume that trend may have continued.

Dr. BobbieJean Sweitzer: So, remind me, when was this drug approved for use in the US?

Dr. Stavros Memtsoudis: I believe it was in 2013.

Dr. BobbieJean Sweitzer: And can you account for the fact or did the price get a lot better or there was a paper that came out that drove…?

Dr. Stavros Memtsoudis: I think it was marketed very well. When it first came out, hope was that this drug would prolong analgesia at the site of surgery because 72 hours of action and I think that sounded very appealing to a lot of surgical settings. And it was also of interest because it could be easily administered by surgeons at the end of surgery and send patients home with this prolonged pain relief.

So, I think that that hope or that marketing was very successful. But studies supporting all this really took a while to come out and this is basically one of them.

Dr. BobbieJean Sweitzer: So, I recall that you've determined the use of opioids based on whether a patient was actually billed for an opioid and I think you mentioned before about the prescriptions, that you weren't sure how. But were you able to track, at least, opioid use in the hospital?

Dr. Stavros Memtsoudis: So, to be precise, we cannot fully be sure that patients actually took the medication; that's a limitation of the database and that's one that we commonly discuss in these types of papers. However, there are a number of factors that mitigate this issue in my view.

So, number one is both groups would be equally exposed to this type of bias. So, the group that got liposomal bupivacaine versus the other one, there's no reason to really believe that one would be treated differently than another in terms of coding or billing.

And secondly, a patient does not usually get billed for an ordered substance; it only gets really billed when it gets dispensed by the pharmacy and then, logically, the pharmacy only dispenses medications when the patients are about to take them.

So, therefore, we believe that there's at least a high correlation between billed items and those consumed in the setting. So – but as mentioned, we cannot be 100% sure that prescription equals consumption.
Dr. BobbieJean Sweitzer: Sure, but that makes sense what you said, both of those factors.

So, I suspect that there was a wide range of different opioids that patients were prescribed and likely took while in the hospital. How did you manage this to arrive at comparisons?

Dr. Stavros Memtsoudis: A common way of dealing with this type of issue is to use tools that allow us to convert different opiates into oral morphine equivalents. So, again, to level the playing field. We can also take into account the root of administration because that's recorded in the data set, so we can convert IV to PO in those cases. And there was specific tools that we used that are available online for the study and then mentioned in the manuscript.

Dr. BobbieJean Sweitzer: So, I think you mentioned this a bit and I think there's several different studies in various patient populations. Some of them, as you mentioned, have problems perhaps with methodology or bias. But some show encouraging results and others show very limited benefit. Can you just sort of maybe go through that a bit more now specifically what you think maybe is the likelihood of the most common reasons why we're seeing this variation in reports?

Dr. Stavros Memtsoudis: Right. Number one, you have to look at the setting. There are certain patient groups and surgical settings that show benefit and I think they're like superficial surgeries where the liposomal bupivacaine can report into the skin or wound and provide a good pain relief. But when you look specifically at total knee arthroplasty studies, there are about, I'd say, a maximum of 20 on this topic with less than a handful showing benefit.

And all of the ones that show benefit are, number one, relatively small. And the common criticism of those is that they're virtually all industry-sponsored. They may also not compare the use of liposome bupivacaine to state-of-the-art alternatives like multimodal regimens including peripheral nerve blocks.

So, I think those factors kind of spurred us and others to look into these comparisons on a population basis.

Dr. BobbieJean Sweitzer: Yes, I think often the devil's in the details. We try to extrapolate something from one very, very different population or circumstance to…

Dr. Stavros Memtsoudis: Correct.

Dr. BobbieJean Sweitzer: Yes. I know that the plastic surgeons seemed to be excited proponents of use of this and I can see where as you mentioned like the superficial, mainly the pain is from a different mechanism than a joint and where maybe peripheral nerve blocks aren't being used, you can see a difference in analgesia.

Dr. Stavros Memtsoudis: Agreed, yes.

Dr. BobbieJean Sweitzer: So, I wanted to come back a little bit about this Premier health care database. I know that big data and people talking about using databases and some of these are for billing purposes, others are for quality or about even looking at comparisons between hospitals. Can you give us a little bit more information about this database?

Dr. Stavros Memtsoudis: Yes. So, particularly, Premier is a commercially available database—so it's not a government-sponsored data set—that collects administrative and billing data from hundreds of hospitals throughout the United States and entries represent approximately 20% of all hospitalizations.

Now, unlike some government-sponsored data sets like the National Hospital Discharge Survey which is administered by the CDC for example, it is, strictly speaking, not nationally representative because it's rather a convenient sample of participating institutions that basically provide their data and then can use it to get reports back for quality measures or billing questions.

Nevertheless, it has been used for a multitude of population-based projects resulting in high-impact publications that inform a lot of readers on important topics including perioperative outcomes in public health. And we recently have had an interest in the field of (sounds like pharmacology) projects related to pain management and some of them have actually been published in this very journal.

And it basically shows the breadth of information that can be gathered from these type of data sets, in particular Premier, because of the ability to really get into the billing items that encompass drugs and devices, which is very rare with other data sets.

Dr. BobbieJean Sweitzer: Are there disadvantages of utilizing billing data and researching a clinical question?

Dr. Stavros Memtsoudis: Oh, absolutely. And I think anyone who interprets these studies needs to be aware of them. First, the large sample size allows for the analysis of low-incidence outcomes; however, the issue is that we cannot really determine any kind of causal relationships. The best we can do is determine associations between interventions and outcomes.

However, then, when you look a potential mechanism that can explain why we see what we see, then you can take the next step and use plausibility to make sense of the data. However, that still doesn't mean that it's the last word in a particular research field. So, therefore, I always view these database studies and the results that we gather from them as primary hypothesis-generating and allowing us to really get a glimpse of real-world practice and see what is actually going on so then we can go ahead and ask those questions of why.

Randomized controlled trials are not always possible to answer these questions, but at least we can then go and follow up with mechanistic studies to prove that those plausible explanations truly can be backed up with mechanisms that we can study.

Dr. BobbieJean Sweitzer: But you would think that if you did design a randomized controlled trial, maybe it would benefit knowing this to better design or decide what your specific question or hypothesis would be.

Dr. Stavros Memtsoudis: Absolutely, because often when designing randomized controlled trials we don't exactly know what the important observations or questions are because we basically start from scratch; we have one outcome that we usually chose and that may be the wrong one to look at or these data sets really inform us what variables may be important to consider as well.

So, I definitely agree with you that they're very helpful in designing randomized control trials with the information that we get from them.

Dr. BobbieJean Sweitzer: So, did you have to use any special statistical analyses for this study? And if so, why?

Dr. Stavros Memtsoudis: Well, advanced statistical methodology is needed for these type of studies. And that field of methodology and statistics is evolving just as much as the medical field. And so, our team of biostatisticians always strives to use the most appropriate and state-of-the art approaches when it comes to these analyses.

So, for example, for this study we used something called multi-level regression approaches which take into account individual hospital-related...
aspects. It has also become common practice in database research to per-
form something called sensitivity analysis. So, that describes the use of
different methodologies or analyses of subgroups within the data set to
make sure that the results are not just influenced by the choice of statistical
technique that we chose.

So, for example, sometimes you chose a regression analysis and you
back it up with a matched approach to make sure that no matter what
technique you use, your results or conclusions stay the same. And often we
will also look into subgroups to make sure that the choice of population
does not cause us to draw false conclusions.

So, in this study, for example, we performed several sensitivity analy-
ses to look into the effect of liposomal bupivacaine in high-utilization
versus low-utilization hospitals, those receiving general versus neuraxial
anesthesia and also to assess if the definition of comorbidity burden would
affect outcomes.

For us it was good to see that none of them actually did affect our
conclusions which increased the confidence and the robustness of our re-

Dr. BobbieJean Sweitzer: Did you find that there was any benefit of the
liposomal bupivacaine subgroup of patients or…?

Dr. Stavros Memtsoudis: Using the predefined criteria for clinical signifi-
cance, we did not find liposomal bupivacaine to add any value in terms of
reducing opioid prescription, opioid-related complications or resource
utilization. Although some of the outcomes may have reached statistical
significance, we did not really see what we were looking for in terms of
clinical significance.

Dr. BobbieJean Sweitzer: Were you able to look at the group of patients
and separate them between those having general versus centroneuraxial
and whether the liposomal bupivacaine had a difference in those two
groups or was there not enough information to do that?

Dr. Stavros Memtsoudis: Actually that was one of our sensitivity analyses
and I have to say one of the nice things about the peer review because this
was actually brought up by one of the reviewers. And we found that a
higher proportion of patients receiving general anesthesia actually received
liposomal bupivacaine compared to the group that received neuraxial an-
esthesia.

But results were similar in the primary analysis, compared to the
primary analysis, although the effect of liposomal bupivacaine was more
pronounced in the general anesthesia subgroup. However, that did not
reach clinical significance.

Dr. BobbieJean Sweitzer: So, you said that this was raised in – during
the peer review process?

Dr. Stavros Memtsoudis: Yes. So, this was a suggestion of one of the
reviewers who thought that it would be important to look into the dif-
fences between patients that had neuraxial versus general anesthesia and
that’s exactly what we did.

Dr. BobbieJean Sweitzer: So, a little shout out to thank all those peer
reviewers. Sometimes those of us…

Dr. Stavros Memtsoudis: Exactly.

Dr. BobbieJean Sweitzer: Right. We think it’s just a hurdle to get over,
We sort of dread getting back those reviews, but I think they spend a lot
of time and volunteer and they often make our studies better.

Dr. Stavros Memtsoudis: Exactly.

Dr. BobbieJean Sweitzer: So, was there a difference in length of stay or
cost of care between the patients receiving and not receiving the liposomal
bupivacaine?

Dr. Stavros Memtsoudis: No. When peripheral nerve blocks were used
as we defined our cohort, there was no clinically significant difference
between those in whom liposomal bupivacaine was used or not.

Dr. BobbieJean Sweitzer: Now, I don’t recall, you may have mentioned
this already, but did you look at complication rates and if there was an
impact on that?

Dr. Stavros Memtsoudis: Yes, we did and there was, again, no difference
in the odds for complications between the two groups.

Dr. BobbieJean Sweitzer: So, a lot of no difference, it sounds like. So, it’s
been around for a while now. What do we know from other studies about
this drug? Like, is – and maybe it’s an unfair question to ask you, but do
you think there is, perhaps, some evidence that the utility of this drug in
certain patients or why do we use this drug still? Why is it still with us?

Dr. Stavros Memtsoudis: In all fairness, I don’t want to make this sound
that this study encompasses all patients and can be extrapolated to all
settings. So, in all fairness, there may be situations in patients in whom
liposomal bupivacaine has benefits. Our results just don’t support routine
use in the total knee arthroplasty at this time.

And, as you know, the FDA recently expanded the approved use
to upper extremity nerve blocks. So, perhaps in that setting we will find
some benefits. But the problem is always that the evidence always lags
behind the launch of these drugs and often it takes years for us to identify
which particular patient and what particular setting may be benefitting
from such an approach.

But again I think it’s important in the whole process to have a very
balanced approach to these type of evaluations because there are those that
are industry-sponsored and those that are investigator-driven and don’t have
funding from industry; not that industry funding is always a bad thing, but
I think it needs to be taken into account when interpreting these studies.

And unfortunately as soon as industry-sponsored studies are re-
viewed, there’s always like this higher level of threshold that’s kind of be-
ing expected for them to show a benefit and they’re always being viewed a
little bit differently. However, one has to really look at the entire literature
on a topic which may take a while to produce.

But then again, studies like this which look into the question in a
database context or a population-based context then can really brush aside
all these little issues that have come up with randomized controlled trials,
how they’ve been designed and let us look into what happens when this
drug is actually being used in a real-world setting: Does it reduce length of
stay? Does it reduce opioid consumption? Does it reduce complications?

Dr. BobbieJean Sweitzer: So, I hope today’s discussion will interest many
of our listeners and lead you to read this important article to learn more.
Thank you, Dr. Memtsoudis for discussing your work with us today. You
are a prolific researcher and author; I’ve read so many of your articles and
I do wish you well as you continue your efforts to enhance the practice of
anesthesiology and strive to improve the care of our patients.

Dr. Stavros Memtsoudis: Thank you very much.

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