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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Shifting the Script: Personalizing Overactive Bladder Treatment in Complex Patients

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Dr. Rosenberg:
Hello. My name is Dr. Matt Rosenberg, and this is CE on ReachMD. So today I'm very, very happy to be joined by 2 people, Kennedy Koebbe and Dr. David Staskin. Kennedy, you've been working with me for a couple of years, and that's really why you're here today. And David, you've been a mentor of mine for years and really one of the experts in the field of OAB. So I'm excited to have you here.

So today we're going to be talking about OAB in general. We're going to talk about the limits with current treatments, especially low persistence with the antimuscarinics, as we know, and then we're going to talk about the differentiation between the beta-3 agonists and the antimuscarinics. So let's get started.

Kennedy, the first question is to you. Overactive bladder—you've been practicing as a nurse practitioner for several years, what kind of training did you get in the world of overactive bladder?

Ms. Koebbe:
Very generic training. I have my specialty in family nurse practitioner, therefore very much the old-school medications, starting with things like lifestyle modifications and then not a whole lot of specialty information or a whole lot of education on the newer options that are out there.

Dr. Rosenberg:
Interesting, because one of the feelings I've had for years—and David's known this—is that really the OAB belongs in the primary care office. This is what we do, what we should be treating, and, unfortunately, if we wait so long that a patient ends up in the urologist because they're in despair, we actually don't take care of them.

And so you and I've been working for a while; you know that I have a special interest in this, and how has that changed your mindset over a couple years, being exposed to the fact that primary care can be treating OAB?

Ms. Koebbe:
It's been extremely helpful working with you and all of your education on urology because, like you said, this is the time and the place to treat these people, in primary care, because we're the ones with our hands on these patients all the time, and it takes a lot to get them

into specialties, so very much it has been very eye opening to realize how much we can actually treat within primary care.

Dr. Rosenberg:
Well, good, and you feel comfortable now treating OAB in the practice. So let's actually start with a case. Let's play a little bit. Okay, now I'm going to throw some caveats or changes to this case a little bit, and then that's going to lead us to our specialist eventually.

So we have a 52-year-old woman coming into the office. She's on hormone therapy. She's reporting some brain fog, some memory issues. She's frustrated by her persistent urgency and frequency, which is disrupting her daily activities. She's already tried some behavioral therapy. She's limiting her coffee and her water intake. She doesn't drink fluids late into the evening. She actually got online and read about Kegel exercises, so she's tried that. All right? She comes in and talks to you. What are you going to do?

Ms. Koebbe:
So the first thing I'm going to do is discuss the specific lifestyle modifications with her, ensure that she knows what is containing caffeine, ensure that she knows that certain things, like chocolate, is containing caffeine.

Also, yes, stopping her fluids earlier in the day is important. However, setting a timeline, like stopping your fluids after 5 PM—that way she can look at that and see, "I've made these lifestyle modifications." Another thing is also pelvic floor therapy is a great option. It sounds like she's tried some of the at-home stuff. However, we could recommend that as well.

Dr. Rosenberg:
Okay, all right. Well, this is your first curve ball—what medical issues would you look for in her that could be kind of causing worsening of these symptoms?

Ms. Koebbe:
So first we're going to look at her medications and make sure that there's not anything that she is currently being treated for, for something else that's causing her to have increased urination, such as Lasix or certain diabetic medication. I know that she's doesn't have diabetes. However, there are off-label uses for things treated with Jardiance and things like that.

Okay, so after I assessed all of the medications, then we're going to do a physical exam. We're going to check for things such as a cystocele that could be causing this. We also could get an ultrasound to check for any anatomical changes that could be causing this as well.

Dr. Rosenberg:
Like a mass in the pelvis or something like that?

Ms. Koebbe:
Correct. Yeah.

Dr. Rosenberg:
But actually examining them, I'm glad you brought that up because so often we forget as clinicians we're laying our hands on patients, and just as you said, we're looking for, in her, any sort of vaginal abnormalities, a cystocele. You're looking for extremity issues like swelling. Maybe abdominal exam for pressure and things like that.

All right, let's say that everything was clear. All right? You've checked your labs. You probably checked for sugar to make sure she's not diabetic. You mentioned that. You've checked a urine and it's normal. You tell her, hey, I've looked at your insurance and they only want us to start with generics, and we're going to say that we've got to start with an antimuscarinic. Now here's the curve ball. She goes, "Well I was at this other clinic years before. I forgot to tell you this, but I had tried an antimuscarinic and I had dry mouth and dizziness." What are you going do?

Ms. Koebbe:
That is a very common side effect that we see with the antimuscarinics, so yeah, dry mouth and dizziness are what we do hear commonly. Also, big things we want to worry about in our patient population are constipation and even cognitive changes because those are things that we really don't want to mess around with, with our primary care population.

Dr. Rosenberg:
Yeah, we really don't, do we? I mean how many times have we looked on Epocrates, and unfortunately the patients are very savvy and, especially with electronic records, and they're coming in and saying, “Hey what about some of these side effects with that?”

So next what class would you go to?

Ms. Koebbe:
Well, one of the things that I've had really good success with is the beta-3 class.

Dr. Rosenberg:
Okay, I'm going to stop you. I’m going to bring Dr. Staskin in because Dave is really one of the world's experts on the beta-3s. So Dave, give us a pearl. Teach me what I need to know.

Dr. Staskin:
Well, first of all, I mean just to clarify the symptoms we're treating, urgency with frequency. Frequency means also getting up at night—nocturia—and the patient may or may not actually have urge incontinence, so it's sort of urgency with or without incontinence. And you see this—these OAB symptoms that we've been referring to—in both male and female patients.

And the antimuscarinic drug class that you were talking about actually works by sort of inhibiting bladder contraction, works on the muscarinic receptors of the bladder. The beta-3s work by relaxing the bladder, meaning it stimulates the bladder during bladder storage to hold more urine. So what we're really doing is directing a little bit more towards the storage phase where the symptoms are, and we're also using a class of medications that aren't associated with inhibition of the bladder contracting and a decreased incidence of urinary retention.

Dr. Rosenberg:
For those of you just tuning in, you’re listening to CE on ReachMD. I’m Dr. Matt Rosenberg and here with me today is Dr. David Staskin and Ms. Kennedy Koebbe. We’re here discussing recent advances in the management of OAB.

Dave, you were very involved with really pivotal studies on this, as in the key trials on mirabegron and vibegron. Can you talk about those studies for me?

Dr. Staskin:
Well, again, there are 2 agents, the generic name for them, mirabegron and vibegron. And as you start to look at it, mirabegron was the first one that was developed. Now, vibegron was developed, and it's interesting, there's a beta-3 receptor—there's just what we're talking about—a beta-3 agonist and a beta-1 receptor, which is the blood pressure heart rate receptor. So I give beta-blockers for hypertension and you'd like to stimulate beta-3 and not stimulate beta-1.

Interestingly enough, when vibegron was developed, mirabegron was about, in units, 600:1 beta-3 to beta-1, and vibegron is 9500, so we were very excited to put the drug to the clinical test and see whether there were differences there.

There were 2 major studies. One was called EMPOWUR. This involved male and female patients, 15% men. They had classic OAB symptoms, which we talked about—urgency, frequency with or without urge incontinence, and getting up at night. We measured all of these things in EMPOWUR and showed that there was a statistical improvement over placebo and there was an active control, tolterodine. And the drug not only beat the placebo in everything that we measured but actually numerically—it was not run against as a statistical comparison—but did better, numerically better than tolterodine at every point that we measured, no matter what the patient's age, no matter the severity of their disease, no matter what we looked at. So we were very, very pleased with the initial study.

The second idea, though, was, since the drug had seemed to perform so well, especially in men in the study, was to do a study where you treated men who were treated for their BPH with an alpha-blocker—and possibly an ARI in combination but at least on an alpha-blocker—but had persistent symptoms of OAB.

Now we don't have a lot of time to go into BPH and its evaluation, but everybody knows a woman comes into the office, frequency,

urgency, getting up at night, she has OAB. And a man comes in with frequency, urgency, and getting up at night and he gets an alpha-blocker. And a lot of these men aren't obstructed to begin with, and especially if they've responded with improved flow and bladder emptying with an alpha-blocker.

So we included these men in a study, both a 12-week and a 1-year study, just like the EMPOWUR trial, and saw the same excellent result compared to placebo, this time for all the symptoms that we've talked about. In addition, we did bladder function studies and showed that there was no effect on flow, no effect on bladder contractility, and then an improvement in these symptoms and no increase in residual urine. So we weren't affecting bladder contractility, but we were improving their OAB symptoms. We were very, very pleased with both the 12-week and the 1-year results in that study.

Dr. Rosenberg:
Dave, that was a great summary of those studies. I appreciate that and especially coming from you, having been so intimately involved with those.

But, Kennedy, I'm going to get back to you now. We're with this 52-year-old woman. She's tried the antimuscarinics. What are you going to do at this point?

Ms. Koebbe:
At that point I would start a beta-3.

Dr. Rosenberg:
Okay, makes sense. Okay, here's the curve ball. She's got hypertension. Does that worry you?

Ms. Koebbe:
So in this case I would start the vibegron to help with that hypertension.

Dr. Rosenberg:
Okay, all right. Well, let's change that again. Let’s say she's older now. I mean, given her history—now she's 74—what would you do now?

Ms. Koebbe:
At that point, I would not be starting an antimuscarinic on her. A beta-3 would be the way to go due to the setup.

Dr. Rosenberg:
I wouldn't have started that in the beginning. I think with that age, we would have just gone straight to a beta-3 given the data.

But we're kind of scratching at the surface here a little bit. Dave, the differences between vibegron and mirabegron—help me with this.

Dr. Staskin:
Well, it's interesting, Matt, because I think that I probably think about this the way you do in primary care. I mean, if you prefer a pill that can be crushed, you would probably prefer vibegron.

As Kennedy had mentioned, the blood pressure issue, these drugs are good with patients that have controlled hypertension, but there have been some patients because of the beta-3/beta-1 difference so that there is a hypertension thing, to take blood pressures intermittently over the course of treatment if a patient stays on it for the mirabegron but not the vibegron.

I'll ask you whether it's important for you with drug–drug interactions at CYP2D6 in your practice. Mirabegron is metabolized by CYP2D6 and vibegron not to any clinically significant degree by CYP3A4. So if you have a patient that's on antidepressants or some other medication that uses the CYP2D6 pathway, that’d probably make a difference to you.

But neither are really recommended in hepatic failure, but in patients with some mild to moderate renal failure, vibegron in the package insert is not limited but mirabegron is.

So there are some differences. If you say to me can you tell me there's a specific difference in study data, I could give you the standard academic answer, which is there's never been a head-to-head study, so we don't have efficacy difference, but we do have differences in the molecules and the effect that they have on patients.

Dr. Rosenberg:
Dave, you hit something very important there, which is CYP2D6, but I'm going to throw something else out there too, which is the average 80-year-old patient—which is the median age for us—is on 8 or more medications.

So Kennedy, we're seeing this patient in there and we—yes, CYP2D6 is a narrow pathway, CYP3A4 is much wider, so we get nervous about that. So that is a concern.

And the other concern we have—let's go back to the antimuscarinics a little bit and some of those cognitive changes. We're all familiar with, in primary care, the Beers list and the—basically that's the "do not use this in the elderly population" list, and unfortunately all the antimuscarinics are on that.

So really understanding the drugs and the makeup and the comorbidities associated with our patients is very, very important.

Kennedy, now I'm going to throw another curve ball to you. All right? Our 52-year-old woman became 74 and now she's becoming a 72-year-old guy, all right, changing the case out. All right, this patient is now on tamsulosin and dutasteride. He was seeing us or another primary, doesn't matter—comes in and says, "My flow is good but I'm just still rushing to the bathroom all the time and I really don't like it very much," right? What do we do? What would you do? Are you going to call me? Are you going to Dave? Are you going to start some treatment. What do you want to do?

Ms. Koebbe:
Yeah, so this is actually something that I have learned a lot since working in our office, that OAB is very undertreated in the male population.

So very much his symptoms are consistent with OAB. Previously, I would have probably at that point referred to urology. At this point, now I know that if we start a beta-3 on this patient they may have benefit.

Obviously, we would do the same workup that we talked about with the female, with the lifestyle changes, with the ultrasound of their abdomen as well. However, we do those workups before we get to the point where we're on 2 medicines for BPH anyways, so at that point I would say a beta-3 is exactly what this patient needs.

Dr. Rosenberg:
Fantastic. David, what do you think?

Dr. Staskin:
Well, again, beta-3 is with a low incidence of causing bladder problems, meaning bladder weakness. Again, very little effect in the urodynamic study on bladder contractility or flow and also showing good emptying.

So the real question is, if a man comes in and he was 40 and had great flow and felt he emptied his bladder and he had frequency, urgency, and getting up at night, it would be silly to treat him with an alpha-blocker for outflow obstruction.

For a man in the COURAGE study who was treated with an alpha-blocker, and potentially with combination therapy, who still had frequency and urgency, we have a study, a drug-labeled study, that shows that urgency—and this is the only drug that's approved for urgency, the vibegron in its package insert—that urgency, frequency, nocturia, and urge incontinence all improve.

And then the third category, which was not in the study, would be men who had prostate surgery for outlet obstruction and now have a great flow but may have even had frequency and urgency before they had their outlet procedure and may or may not have been significantly obstructed. And these men are also, for their OAB symptoms with good flow and good bladder emptying, are really candidates to treat their OAB symptoms.

Dr. Rosenberg:
Dave, fantastic. Tell me the differences in the drugs. Is it their approval data? What do we have there?

Dr. Staskin:
Well, like I said, there's no head-to-head study. The beta-3s, I think, are much better drugs, obviously for male and female patients for the reasons we've discussed. I don't think there's any question.

We pointed out some differences between the 2 beta-3s which may be important to prescribers. But I think through the experience of mirabegron, which has been on the market for multiple years now, and vibegron, also for a significant period of time, that it's really opened up a whole new avenue for approaching both the male and female patients either with new or persistent OAB symptoms.

Dr. Rosenberg:
That's great. Thank you.

David, thank you for saying that. And by the way, vibegron is really the only medication that's indicated for men who were pharmacologically treated for their BPH and still have those symptoms of lower urinary tract symptoms such as for OAB. So you're absolutely correct on that and I appreciate that.

Kennedy, I know you had some thoughts on actually patients and adherence and compliance with medications. Can you share that with me?

Ms. Koebbe:
Yeah, I just really appreciate the fact that you touched on medication interactions, on the route that patients are able to take these medications, and all the different things that are really important to us in primary care. We are always dealing with different things such as the route that patients are able to take it. So this will help with the adherence and everything of being able to use these medications.

Dr. Rosenberg:
Yeah. And in terms of talk about crushability or with food or things like that, what kind of effect does that have on compliance?

Ms. Koebbe:
Pretty much any of our patients at this point could be taking that because they either have an oral route that they can take crushed medications or they have a PEG tube or any route that makes it very flexible in the adherence section.

Dr. Rosenberg:
And, Kennedy, I'm going to ask you one final question. I certainly appreciate everything you've been saying today. What would you tell your colleagues in training?

Ms. Koebbe:
I think that it is really important to continue to do continuing education and find mentors who are so knowledgeable in these areas because it really does help keep things in primary care and help with referral process and not having to send out for things and it's been amazing.

Dr. Rosenberg:
And, Dave, you've heard this from me 1,000 times—that most people suffer from OAB in silence. When you go into a supermarket and there's an aisle of continence pads and people find that normal, the bottom line is that is not normal and they don't know it's not normal. And the problem is if we don't, in primary care, tell them this, they're not going to go on their own to a specialist, and that's unfortunate. That's why we're so key on this, and telling patients what is normal will help them see what is abnormal.

And for us as physicians to be teaching those who work with us, our APPs, to identify this—because for me, having you, Kennedy, and our other APP is so vital because you interact with the patients differently. And together as a team we bring them up. And I really do believe that if primary care gets hold of this and we all talk to our patients about this we can serve them that much better.

Anyhow, with that in mind that's really all the time we have today. Dave, any last comments.

Dr. Staskin:
Well, thank you for inviting me.

Dr. Rosenberg:
I appreciate you so much for everything you've taught me and for everything you taught the group today. Kennedy, like always, you're amazing. I appreciate everything you're doing. And with the group, with our audience, thank you for your time today.

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