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Breaking Ground: 2025 Milestones in Cushing Syndrome and Looking Forward to 2026

Announcer:
You're listening to CME on ReachMD. This activity is the first in a series titled "The Cortisol Reports." This is episode one, titled "Breaking Ground: 2025 Milestones in Cushing Syndrome and Looking Forward to 2026." This episode is provided by Cornerstone Medical Education and the American Academy of CME, and is supported by an educational grant from Corcept Therapeutics.

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Dr. Hamrahian:
This is, CME on ReachMD, and I'm Dr. Amir Hamrahian. I am the Medical Director of the Comprehensive Adrenal Center at Johns Hopkins University, Associate Professor of Medicine, and I have, about, 25 years experience, taking care of patients with, Cushing syndrome.

Joining me to discuss, Cushing syndrome updates from 2025 and give us a look ahead at what's coming in 2026 is Dr. Deepak Bhatt. Dr. Bhatt, thanks for being here today.

Dr. Bhatt:
I'm Dr. Deepak Bhatt. I'm the Director of the Mount Sinai Fuster Heart Hospital and the Dr. Valentin Fuster Professor of Cardiovascular Medicine at the Icahn School of Medicine at Mount Sinai in New York.

Dr. Hamrahian:
So, Dr. Bhatt, let's jump right in. What can you tell us about the link, between hypercortisolism and difficult-to-control cardiometabolic conditions?

Dr. Bhatt:
I'd say, first of all, this is a fascinating area. It's evolved a lot since what a lot of us learned in medical school about Cushing syndrome and this idea of endogenous hypercortisolism being associated with a number of different disease states. Hypercortisolism is associated with lots of different comorbidities. So really lots of different potential manifestations of too much cortisol in the system. And while in the context of Cushing syndrome, this is very well appreciated, or at least some of it's well appreciated, these sorts of comorbidities can also occur with hypercortisolism when it isn't manifesting in the classic sort of moon facies or more extreme forms of hypercortisolism seen with Cushing syndrome.

If we look at some contemporary data, such as from the CATALYST trial, this was over 1,000 patients with an elevated hemoglobin A1c despite being on good diabetes therapy. In that population, what was found was a prevalence of hypercortisolism, that was really quite high. I'd say about a quarter of the patients, 23.8%, to be precise, had evidence of hypercortisolism as defined by a post-dexamethasone suppression test cortisol level of greater than 1.8 mcg/dL, so I've got to say that's a lot higher than I would have ever guessed or was ever taught in medical school. And that prevalence rose to over a third of patients if we're looking at folks that not only had difficult-to-treat diabetes but also resistant hypertension being treated with three or more antihypertensive drugs. So it is really eye-

opening, I think, just to understand how high the prevalence is, and that was nicely shown in the CATALYST study, which has now been published in *Diabetes Care*.

Well, what about resistant hypertension? Well, we already know from a number of studies and meta-analysis that cortisol excess is associated with high blood pressure and that elevated cortisol levels are particularly important when there are additional comorbidities, such as diabetic retinopathy, diabetic kidney disease. It turns out that in hypertensive patients with Cushing syndrome, specifically the conventional antihypertensives aren't effective until normal cortisol levels are achieved, so potentially, that may also apply to folks that don't have frank Cushing syndrome but still have elevated levels of cortisol that are contributing to resistant hypertension.

But what about contemporary data for difficult-to-control hypertension, or some would call it resistant hypertension? Well, data are coming soon. At the American College of Cardiology, there will be a late-breaker, the MOMENTUM trial, and this is a study that examined around 1,000 adults with resistant hypertension and then did the usual sorts of screening, consent, history, physical exam, a bunch of different labs, automated blood pressures. But then what's interesting and unique is that there was an overnight dexamethasone suppression test performed, 1 mg, and then the following morning, cortisol and other relevant labs were obtained. And then subsequently, in people that seem to have hypercortisolism, an even more extensive battery of testing, including more blood tests, things like ACTH, noncontrast CT scans, looking at the adrenals, that sort of thing is done. And the overall goal then is to find, within this 1,000 patients with resistant hypertension, what the prevalence is of hypercortisolism.

I'm really fortunate to be presenting these data as a late-breaking clinical trial at the upcoming American College of Cardiology sessions.

Well, with that, Dr. Hamrahian, perhaps you can remind us about the treatment landscape for Cushing syndrome going into this year and telling us about expanded indications that we saw.

Dr. Hamrahian:
The LINC6 trial is, an ongoing prospective observational phase 4 study. And, in 2025, as I mentioned, the two-year—the data was presented. The primary objective of the study is, to look at the long-term safety and tolerability of osilodrostat with the focus on hypercortisolism, adrenal hormone precursor accumulation, such as, 11-deoxycortisol, 11-deoxycorticosterone, and androgen levels, QT interval prolongation, and pituitary tumor enlargement, in patients with Cushing disease.

They look at the urinary free cortisol and late-night salivary cortisol at three months and six months that were recorded, in the meetings. The rate of the normalization of the urinary free cortisol was 73.9% at three months and 63% at six months, and the urine and the salivary cortisol normalization, bedtime salivary cortisol normalization was 56 and 30% at three and six months. As you know, the salivary cortisol is much difficult to, normalize, and that's why in most clinical studies the urinary free cortisol is used as an efficacy endpoint.

So based on this interim data, the FDA approved an expanded indication for osilodrostat in April of 2025 for the treatment of the endogenous hypercortisolism, including ACTH-dependent and ACTH-independent Cushing syndrome.

Dr. Bhatt:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Deepak Bhatt, and today I'm speaking with Dr. Amir Hamrahian about recent and future updates in Cushing syndrome. We spoke a bit earlier about what's coming in 2026 and the changing landscape of Cushing syndrome treatment from 2025. Now, let's keep digging into what happened in 2025.

Dr. Hamrahian, relacorilant received a decision from the FDA. Let's review that drug's profile and updates.

Dr. Hamrahian:
Happy to. So relacorilant, is an investigational, selective glucocorticoid receptor modulator, that is designed to, decrease the excess cortisol activity at the glucocorticoid receptor and to treat manifestation of the endogenous hypercortisolism. It's highly selective, to the glucocorticoid receptor with no activity at the progesterone, mineralocorticoid, or androgen receptors. It is structurally different than the nonselective glucocorticoid receptor antagonist mifepristone, so really, we cannot say that these are sisters, in other words. So by being selective, at the receptor, it avoids, unwanted off-target progesterone receptor effects, such as endometrial hypertrophy and vaginal bleeding that we see with mifepristone. And because of a lack of increase in ACTH and no clinically, and no significant increase in cortisol levels, it does not cause hypokalemia, one of the things that we carefully monitor in patients, with mifepristone. And also, it does not appear to causing adrenal insufficiency or QT interval prolongation, pending the peer-reviewed, publications on this drug.

I would like to just briefly mention that, the, the QT interval prolongation may happen with some of the medication we have for Cushing syndrome, and our pharmacy team can play a very significant role in this aspect. We many times, because of being busy with our clinics, and sometimes, you know, the patient may be started on medication by another physician, we may miss some potential important drug interactions that can increase the risk of, for example, QT interval prolongation, and we get a call, e-mail, message from

our pharmacy team that, there is such a problem and, for example, this patient started on a medication that may also interact with this drug. So that is a very important, kind of, aspect of our team management of the patients

The GRACE had a two-phase, the open-label phase and have a placebo phase. And the, the patients went on an open-label phase and had their medication dose from 100 to 400 mg per day adjusted based on the response, and what we saw that, —at the end of the open-label phase, there was a significant decrease in systolic and diastolic blood pressure in the patients who were on relacorilant. And then after the, the open-label phase, the patients, went to a withdrawal phase, and that was for 12 weeks, where, about half of the patients, who qualified based on the predefined criteria, they stayed on the relacorilant, and the other half, they went on placebo. And we saw that the patients who was on the relacorilant continued to have their blood pressure controlled with no significant difference, but the patients who went on placebo had a significant increase in their blood, pressure levels. In this, placebo-controlled randomized withdrawal phase, the patients with hypertension continued on relacorilant at about six times—I mean exactly 5.9 times more likely to maintain hypertension response. The same thing also was seen with the glycemic measure.

I want to mention this, that it's important to know that, when you start from a lower hemoglobin A1C, usually the response magnitude is less, and in this population of the patients in the GRACE, the hemoglobin A1C was 6.7% at baseline, so most patients had relatively good, good control.

The adverse events was mostly mild to moderate, grade 1 or 2, and mostly was kind of, consistent with the glucocorticoid withdrawal syndrome, such as, pain in extremities, nausea, back pain, fatigue, arthralgia, headache, dizziness, paresthesia, et cetera. There were few, severe or medically significant adverse events, and there was no, red flag, from safety profile of the medication compared to what we have known about relacorilant in the past.

The FDA issued a complete response letter that, they needed additional evidence of effectiveness, for a favorable benefit-risk assessment. So based on the latest information I have, Corcept plans to meet with the FDA this year to determine, the path forward.

Dr. Bhatt:
Very interesting. So, Dr. Hamrahian, what other emerging agents did we learn about?

Dr. Hamrahian:
Atumelnant, can be used in ACTH-dependent Cushing syndrome. So this is a once-daily oral, nonpeptide, first-in-class, competitive and selective ACTH receptor antagonist. The primary results from the phase 1B/2A study was presented at the Endocrine Society in 2024, and it showed promising results, results regarding the effectiveness of the drug. In this, at least, preliminary report of a small number of patients, all the patients normalized their urinary free cortisol. They had improvement in their symptoms, and there was a good tolerability. Most adverse events, was related to the development of the adrenal insufficiency, and when the hydrocortisone was added as a kind of a block and replace approach, they mostly improved.

Another important, drug, category to look for are the 11 beta-HSD1 inhibitors, that at least there are a couple of agents that are being evaluated, for patients with, endogenous, and maybe even there is a role for them in exogenous, Cushing syndrome. So, how do they work? They work by blocking the cortisone to cortisol, conversion in peripheral tissues, liver muscle adipose tissue, allowing the local effect of the cortisol to decrease but at the same time maintaining the systemic cortisol necessary for, homeostasis so, potentially, they do not cause adrenal insufficiency. We had the, data was presented from the RESCUE trial—during the Endocrine Society in 2025. This is the use of the clofutriben, for patients with endogenous ACTH-dependent Cushing syndrome. So the investigators reported that at week 6, three out of the eight patients taking clofutriben and zero out of six patients on placebo normalized the urinary free cortisol without suppressing cortisol level to the levels that may indicate adrenal insufficiency, which, all the patients had a level more than 10 mcg/dL of the morning serum cortisol level, so demonstrating that there was no signs, clinically or biochemically, of adrenal insufficiency.

Dr. Bhatt:
It was really a pleasure having this conversation with you. I learned a lot from hearing your thoughts on this evolving field. Thank you so much. I hope the audience also enjoyed it.

Dr. Hamrahian:
The same for me. Thank you so much.

Announcer:
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