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Insights into Inhaled Asthma Therapies: Uncovering Updates from NAEPP and GINA

Announcer:
You're listening to *Deep Breaths: Updates from CHEST* on ReachMD. This non-CME education was brought to you by CHEST and was sponsored by AstraZeneca. Your host is Dr. Demondes Haynes, who's a Professor of Medicine in the Division of Pulmonary and Critical Care at the University of Mississippi Medical Center in Jackson.

Dr. Haynes:

Welcome to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Demondes Haynes, and this is our third podcast in this series about asthma control. Today's discussion will focus on inhaled therapy and expert opinions on asthma treatment. And joining me to talk about this are Dr. Njira Lugogo and Dr. Neil Skolnik. Dr. Lugogo is a Clinical Professor of Internal Medicine in the Division of Pulmonary and Critical Care Medicine at the University of Michigan Health. Welcome to you, Njira.

Dr. Lugogo:

Thank you so much for having me.

Dr. Haynes:

And Dr. Skolnik is a Professor of Family and Community Medicine at the Sidney Kimmel Medical College of Thomas Jefferson University and the Associate Director of the Family Medicine residency program at Jefferson Health Abington. Neil, it's great to have you with us as well.

Dr. Skolnik:

Demondes, it's a pleasure to be here.

Dr. Haynes:

So starting with you, Neil, let's talk about short-acting beta agonists, or SABAs for short. Can you give us a quick review of how these work?

Dr. Skolnik:

It'd be my pleasure. Now, we all know that SABAs, short-acting beta agonists, treat symptoms by causing airway bronchodilation. They work by binding to the beta-2 adrenergic receptors. They produce smooth muscle relaxation through all these complicated mechanisms of increased production of cyclic AMP. But the reality is that SABAs have a good and bad aspect to them. They are very good for bronchodilation, they work quickly—within minutes—and they make patients generally feel a lot better with rapid onset. But that's a double-edged sword, which leads us, of course, to the bad aspect of SABAs. And that's that they don't address the underlying inflammation, so since patients feel better quickly, they often don't come into the office and ask for controller therapy so long as they're able to keep worse symptoms at least somewhat at bay.

The fact that this leads to adverse outcomes is something we've known for years. There was a classic paper by Sousa in *American Journal of Respiratory and Critical Care Medicine* way back in 1994 that showed that mortality risk increases after just 1 to 2 canisters of SABA use per month. Now subsequent studies, recently in the *European Respiratory Journal* 2020, showed that at just 3 to 5 canisters per year of albuterol use, we begin to see an increased risk of mortality, and at 6 to 10 canisters a year, the hazard ratio was 4.7. Now

that is mind-bogglingly high and pretty scary for something that patients reach for all the time thinking they're making their asthma better.

Dr. Haynes:

So with that in mind, let's turn to you, Njira. How do inhaled corticosteroids work in our asthma patients?

Dr. Lugogo:

So we all know that inhaled corticosteroids work by reducing airway inflammation. But what we may not think about or talk about is how inhaled corticosteroids accomplish the task of reducing airway inflammation and perhaps some new ways in which inhaled corticosteroids are working in patients with asthma. So in terms of anti-inflammatory therapy, inhaled corticosteroids have some early-onset effects that occur within minutes. These are so-called nongenomic effects. They work by decreasing bronchial vascular blood flow, reducing inflammatory mediators, and increasing beta-2 agonist bronchodilation. So that's something quite interesting, which is that medications that you're inhaling for anti-inflammatory therapy actually have a synergistic impact on bronchodilation. The inhaled corticosteroids themselves also have some mild bronchodilatory effects outside of beta agonists.

And then, there are late effects that occur within 4 to 24 hours that we call genomic effects. These include decreasing pro-inflammatory gene transcription, increasing anti-inflammatory gene transcription, which in turn down-regulates inflammation, airway edema, mucus hypersecretion, and mucus plugging, and also at the same time, increasing beta-2 receptor gene transcription, which is a critical component of making bronchodilators work better. And in fact, if you overuse SABAs, particularly as monotherapy, you get significant beta receptor downregulation, which makes the SABA medications ineffective. And so our inhaled corticosteroids are actually quite critical, both as anti-inflammatory therapies and in improving bronchodilation in patients that have asthma.

Dr. Haynes:

So Njira, what you just described really says or it makes it seem like that inhaled corticosteroids help our SABAs work better. Is that a good way to think about it?

Dr. Lugogo:

Absolutely. And there are studies that are out there where patients have been given short-acting beta agonists 4 times a day. For instance, the DENALI study was recently published, where they gave albuterol 4 times a day versus albuterol and budesonide 4 times a day versus budesonide 4 times a day. And what you saw by 12 weeks is a reduction in bronchodilation to ICS in the acute phase – 15 to 30 minutes after the medication was given – after the patients had been on albuterol 4 times a day for 12 weeks. And that's a way of demonstrating that there is beta receptor down regulation and that overusing this medication as monotherapy actually causes reduction in bronchodilation over time.

Dr. Haynes:

For those just tuning in, you're listening to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Demondes Haynes, and today I'm speaking with Drs. Njira Lugogo and Neil Skolnik about inhaled therapies for asthma. Now, I think that discussion about inhaled therapy is a good segue to talk about expert opinions on the treatment of asthma. So coming back to you, Neil, can you talk a little bit about the focus updates from NAEPP from 2020?

Dr. Skolnik:

Of course. I had the privilege of serving on the expert working group 4 that helped put together the guidelines, and we did a comprehensive, in-depth review of SMART therapy. Based on that comprehensive evidence review commissioned by the NAEPP as well as metanalysis published in *JAAM* in 2018 and updated in 2022, it is clear that SMART therapy decreases exacerbations by about 30 percent when compared to continuing the same dose of ICS/LABA and by a little over 20 percent when compared to a higher dose of ICS/LABA. And that's why SMART therapy using inhaled budesonide/formoterol is recommended as the preferred therapy for steps 3 and 4 for patients with moderate to severe persistent asthma.

Dr. Haynes:

Thanks so much for that, Neil. So Njira, what does GINA 2023 tell us about asthma treatment?

Dr. Lugogo:

GINA 2023 is very clear in one aspect. The strategy is to pair anti-inflammatory with fast-acting relievers, regardless of asthma severity. The patients that have relatively limited symptoms take ICS fast-acting reliever, be it formoterol or albuterol, for rescue or when they

have acute symptoms. And the patients that have relatively more active disease and require twice daily treatment take ICS/formoterol for maintenance and reliever, or in the absence of ICS/formoterol therapy, take other maintenance therapies, either with vilanterol or salmeterol, with ICS albuterol rescue therapy. And so what GINA is really focused on now is empowering clinicians by giving them various tracks to follow to prioritize risk mitigation by giving anti-inflammatory therapies anytime a fast-acting reliever is used.

And more importantly, a fundamental change has been made in the last few years, which is that SABA-only treatment is no longer recommended. And so despite having patients that maybe have relatively few symptoms, when those patients have symptoms – they have inflammation and bronchoconstriction – they need to be treated with an ICS fast-acting reliever therapy, either in the form of maintenance and reliever therapy or what we now call AIR, which is anti-inflammatory reliever therapy. And, you know, we really are trying to accomplish something big here. We have so many good drugs, and as Neil mentioned in the earlier podcasts, we have patients that are still dying of asthma. Yet, we've had in our hands a therapy that significantly reduces the risk of dying. In fact, if you fill more than 6 canisters a year of ICS and use them, your mortality goes down 50 percent. And he just shared some very concerning details about how using high doses of SABA can increase mortality and asthma exacerbations.

So we really need to embrace a new paradigm where we just simply do not give patients with asthma monotherapy with short-acting beta agonists anymore, and we really need to be sure in the event that you are providing patients with any kind of SABA therapy in the context of underlying maintenance therapy that they are actually adherent with their maintenance therapies.

Dr. Haynes:

Njira, thanks so much for those comments. And as we come to the end of today's program, Neil, can you share some key takeaways from our discussion today?

Dr. Skolnik:

If I think of three key points, the first is that inflammation is critical to the development of exacerbations. We've known for years that it was a critical part of control. We've now learned that it is a critical part of ongoing exacerbations. That's point number one. Number two – prior to an exacerbation, there is a window of opportunity where patients have increased symptoms, and their peak flow begins to go down, and they begin to use their albuterol more often for relief of symptoms, which leads to important point number 3 – that the use of ICS/SABA instead of albuterol alone leads to a substantial decrease in the likelihood of someone going on from that window of opportunity where they're seeing increase in symptoms on to a full blown exacerbation. So we have an opportunity to be part of a new paradigm of rescue therapy where we use ICS/SABA as the standard of rescue therapy, and by so doing, we can reduce the likelihood of patients having asthma exacerbations.

Dr. Haynes:

Neil, thanks for recapping all of that for us. And with those key takeaways in mind, I want to thank my guests, Dr. Njira Lugogo and Dr. Neil Skolnik, for joining me to discuss inhaled therapies for the treatment of asthma. Njira and Neil, it was great speaking with you both today on this third podcast.

Dr. Skolnik:

Well, it was great speaking with you as well.

Dr. Lugogo:

Thank you so much.

Announcer:
This has been *Deep Breaths: Updates from CHEST* on ReachMD. This non-CME education was brought to you by CHEST and was sponsored by AstraZeneca. To access this and other episodes in this series, visit *Deep Breaths: Updates from CHEST* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!