Dr. Mariam Hanna:
Hello, I'm Dr. Mariam Hanna, and this is the Allergist, a show that separates myth from medicine, deciphering allergies and understanding the immune system. I seem to capture the attention of physicians in the room when we talk about the Benadryl TikTok challenge, which surfaced in 2020. The challenge involved taking high doses of Benadryl, an over-the-counter allergy medication, to experience hallucinations—an idea that quickly spiraled out of control and resulted in multiple hospitalizations and a teenager losing their life. We each have our rant on antihistamines, the good ones, the bad ones, but today's guest is actually going to fill you with knowledge, skill, and passion on discussing today's topic: first-generation antihistamines. Allow me to introduce Dr. Stewart Carr. Dr. Carr is the Chief Medical Officer at Snow Asthma and Allergy in Abu Dhabi. Since 2019, he has spent 20 years in academic clinical allergy practice in the fair and beautiful city of Edmonton, Alberta, Canada, where he was an associate clinical professor at the University of Alberta. He is our past president of the CSACI, and his primary interests include pediatric asthma, food allergy, and eosinophilic esophagitis. And with that, I'd like to thank you so much for taking time out of your schedule to join us. Dr. Carr, welcome to the podcast.

Dr. Stuart Carr:
Thanks, Mariam. It's really great to be here, and I appreciate the invitation, and I'm very excited for our discussion today.

Dr. Mariam Hanna:
Okay, so we'll start with the basics. What are first-generation antihistamines, and how do they work pharmacologically?

Dr. Stuart Carr:
So first-generation antihistamines are really one of the oldest pharmacologic agents that we've had to treat allergic problems. They really started evolving in the 1940s, so we're really talking about a really old class of medications. Before that, we really didn't have a lot of treatments for allergic diseases, and as a new class of medications in the field, they really were effective at treating some of the symptoms that we commonly associate with allergies, especially the itching and the sneezing, the runny nose symptoms that most people with allergies are quite familiar with. There's a lot of old first-generation antihistamines. One like Benadryl, of course, is very well known in North America. Ones like Atarax, Chlor-Tripolon, the DimeTap, and triaminic family of cold and allergy medications like NyQuil. Here in my area in the UAE, I've learned a few new first-generation antihistamines that are popular like phenastilin chlorohistol. These are, again, really common medications, but they are very old, and for that reason, they were not subjected to the same sort of rigorous studies and approval processes that we're familiar with in more modern healthcare. How do they work? Well, I mean they really interact with the histamine receptor. They're not a histamine blocker. They're what's called an inverse agonist, which means that they actually do exert an effect on the histamine receptor. But what they do is they sort of induce the opposite effect that would happen if histamine was being released during an allergic reaction or allergic response. And by doing so, it means that they end up stabilizing

the inactive conformation of the histamine receptor. And this not only helps them work more effectively, but it may account for some of the anti-inflammatory effects that we see with higher doses of antihistamines, especially when we use the newer antihistamines at higher doses for problems like chronic urticaria.

Dr. Mariam Hanna:
Do the newer generations of antihistamines work slightly differently than these first-generation antihistamines?

Dr. Stuart Carr:
So their effect on the histamine receptor is really the same. The real difference is more in the sort of issues around that, like speed of onset, duration of action, and their ability to bind other receptors. One of the problems, of course, with the old first-generation antihistamines is that they really weren't very specific for the histamine receptor. They interact with many other human receptors, and that accounts for a lot of their side effects. In some cases, that also accounts for effects that people perceive as beneficial. For example, we'll talk more as we go about the anticholinergic effects, but with anticholinergic effects of old antihistamines, you get some beneficial symptom relief like runny nose, especially if it's for non-allergic reasons. So this helps explain why some people end up feeling like the old antihistamines may work better for them in certain situations.

Dr. Mariam Hanna:
That's a great point. Let's go to common indications for prescribing first-generation antihistamines in primary care. So not just allergy, but in the primary care world. What are some common indications that continue for these medications?

Dr. Stuart Carr:
So I guess the obvious first answer is most commonly they're recommended for allergic problems, right? So again, whether it's a primary care physician or pharmacist, if patients have allergic rhinitis, hay fever symptoms, if they have hives, if they've had a history of food allergy, if they've got atopic eczema, atopic dermatitis, they're very often advised to try a first-generation antihistamine. They're the most commonly recommended medications for all of these allergic conditions at the primary care level.
But then there's a whole host of non-allergic sort of secondary indications for prescribing these or recommending these products. And one of the most common ones is poor sleep. They're often used as a temporary, hopefully temporary, relief for insomnia. Almost all of the over-the-counter sleep aids that you can find in the pharmacy, things like Unisom, they're all just repackaged first-generation antihistamines. Many of them are simply Benadryl with a different box. They're also commonly recommended or used for motion sickness. So, of course, in Canada, Gravol is a very well-known medication. It goes by the name Dramamine in the United States. And this is, again, basically Benadryl combined with a stimulant medication and again used to try to treat motion sickness, but in fact with very poor evidence of effectiveness. And that's something that again is grandfathered in because of the age of these products; they haven't necessarily been subjected to the kind of rigorous trials that would be required now in

order to get such an indication. They're often used just to treat nausea and vomiting apart from motion sickness, and there's even less good evidence for that. Although again, there are some specific agents like promethazine, which is often recommended as a treatment for the hyperemesis gravidarum of pregnancy. They occasionally are still being used to treat agitation with psychiatric disorders, nausea, and vomiting with chemotherapy or anesthesia agents. There are a few specific movement disorders where they're still used. They're often used to treat anxiety in some situations, serotonin syndrome, vertigo. The problem with a lot of those is that there are better options available, but again, these are historical uses of these medications.

Dr. Mariam Hanna:
Absolutely. We tend to get into this discussion in allergy when we have a blanket: "Let's get rid of all first-generation antihistamines forever," and then primary care uses them for other means, and then subspecialty care uses them quite routinely. And I don't think we realize that from the allergy side of things. Okay. This is not meant to be a trick question, sir, but Dr. Carr, when is Benadryl the first-line treatment for allergic reactions? I get this all the time in clinic. They use their second generation for their AR or their allergic rhinitis, but when it comes to having urticaria acutely with possible concern of an allergic reaction, Benadryl remains the first word that comes out of these parents' mouths or the children's mouths. Tthe short answer for me really is just never in my strong recommendation. And I think this goes back to what you were mentioning a moment ago, keeping in mind that there are non-allergic reasons that these medications are still used, but for allergic indications, there's really no advantage. There's no allergic situation where a first-generation antihistamine is the preferred or superior option to a modern second-generation antihistamine. If somebody is, of course, having a severe reaction, there's no role for an antihistamine as the first-line therapy anyway.
Epinephrine is the only appropriate treatment for a severe reaction such as anaphylaxis, but for mild acute allergic reactions, a faster-acting—and I emphasize that because a lot of people have the misconception that the first-generation antihistamines are very fast-acting when in fact they are not as fast-acting as modern second-generation antihistamines—a fast-acting, safer, modern second-generation antihistamine is simply going to give more bang for your buck across the board. And so there's really, again, no good situation where a first-generation antihistamine like Benadryl is the preferred first-line treatment for an allergic condition or acute reaction.

Dr. Mariam Hanna:
Okay, then let's talk about the side effects. Side effects of first-generation antihistamines that primary care providers should monitor for or counsel about. Which ones are big ones?

Dr. Stuart Carr:
Sure. So probably the most important one, certainly the one that gets the most attention, is sedation. So the first-generation antihistamines readily cross the blood-brain barrier. And when they interact with histamine receptors in the central nervous system, that's what leads to sedation.
But a lack of overt sedation doesn’t necessarily rule out impairment. And we know from very well-designed and well-controlled studies that first-generation antihistamines decrease reaction time, they impact information processing and learning. And in one really elegant study out of the

UK, they looked at teenagers writing their end-of-year exams during their allergy season. So these were people with seasonal hay fever, and with seasonal hay fever alone, there was a 40% increased chance of a poor performance compared to their midwinter exams, but that went up to 70% if they were being treated with a first-generation antihistamine. So you feel tired and you'll fall asleep faster when you take an old first-generation antihistamine like Benadryl.
But what we didn't really understand until the last, I would argue maybe 15 years or so, maybe a little longer, is that they then delay and disrupt the onset of REM sleep. So you fall asleep, but you don't get a restful and rejuvenative sleep. And of course, it's during those deep sleep cycles where we do a lot of our information processing from the previous day. And in young children, this is very important to their learning and development by having this disrupted sleep quality. Of course, then a lot of people will notice that they wake up feeling fatigued and describe symptoms similar to a hangover effect with these antihistamines in the morning. The first-generation ones, also interact with many other receptors, and the muscarinic receptor, which is responsible for the anticholinergic side effects, results in very well-known effects that most doctors are pretty familiar with: constipation, dry mouth, urinary retention, increased heart rate, and at high doses we get into these delirium and even potentially movement disorders and some very serious potential adverse effects. They also interact with serotonin receptors that cause increased appetite and weight gain, and they have a significant effect on the cardiac ion channels, which can increase the QT interval and result in ventricular arrhythmias.

Dr. Mariam Hanna:
The sedation part is sometimes still desired by primary care as well as dermatology for patients dealing with atopic dermatitis as an aid for those that are having a lot of difficulty falling asleep. Is there evidence that works?

Dr. Stuart Carr:
So again, yes, there's evidence that it does decrease sleep latency. So again, somebody who is itchy or suffering that way may fall asleep faster. But again, what we're now doing is giving them a bad sleep. And in the words of the sadly and very traumatic in the allergy world, recently deceased Dr. Marcus Maurer he always said, "Don't give a bad antihistamine masking as a sedative." If a person truly needs help with their sleep, then give them a proper sedative.

Dr. Mariam Hanna:
Perfect. What about the anticholinergic side effects of helping with that non-allergic rhinitis? Non-allergic rhinitis drives some absolutely bonkers, and there's very limited terms of medications that work. Do we have medications that work better for non-allergic rhinitis other than an anticholinergic orally?

Dr. Stuart Carr:
Yeah. So in fact, we have topical anticholinergics, and really that's what we should be aiming for, just like we do when we're using topical steroids compared to systemic steroids, which are riddled with very significant adverse effects. In their topical formulation, they have an excellent safety profile, and it's very much the same with the anticholinergics. So instead of exposing someone to dry mouth and urinary retention and other potentially life-threatening adverse

effects from anticholinergics, and then long-term effects we'll talk about when we talk about their effects on the elderly population, topical anticholinergics are tremendously effective at decreasing rhinorrhea and postnasal drip and are widely available.

Dr. Mariam Hanna:
Beautiful. Okay, then let's move on to our special populations. I may have caused my kid to go into delirium as an infant, giving them a dose of Benadryl to finally knock them out to sleep. It didn't work, and he sang me songs all night. So maybe that's my inner reason for going delirious when patients mention Benadryl. But tell me, what kind of things should we be considering in pediatric populations around high doses of first-generation antihistamines?

Dr. Stuart Carr:
In young children, there are a lot of reasons they may be at increased risk. One of them for sure is that their blood-brain barrier is less well-developed. It's more permeable in infancy and early childhood, and for that reason, these drugs will pass through into the central nervous system much more readily and at a higher level than in older children or adults. And that's just going to accentuate this sedative adverse effect, which may be very detrimental, especially if these are being used, for example, to prevent nausea or vomiting. And by sedating the child, they may now not drink enough fluid and increase their risk for dehydration. But children in that age group are also at higher risk for anticholinergic effects.
They may also have paradoxical responses, which sounds like maybe what happened with your child, where they can become agitated and hyperactive. And interestingly, literally today I saw a notification of a publication of a Korean study that showed that using first-generation antihistamines during illnesses in young children increased the risk of seizure by 15%. Kids two and under, and by about 10% in older kids. But obviously, seizure risk is highest during illnesses in very young children, and first-generation antihistamines as a co-factor that I was completely unaware of, despite sharing your passion for dissuading people from using these products for frankly decades. I feel like a broken record half the time going through my spiel, but to learn that there's a significantly increased risk for febrile seizure was quite an alarming finding.

Dr. Mariam Hanna:
It is alarming. Yeah. The infants, they often say this is the only one that says that between six months and two years of age we can use it because of that box label. But this is particularly the population we are even more concerned about and even supported by this study.

Dr. Stuart Carr:
And that also depends on which country you're in. For example, in Australia, you cannot give any product containing a first-generation antihistamine to children under two, and you're not to use any cough and cold medications containing a first-generation antihistamine under age six. So their label indication is completely different than the ones that we're accustomed to in North America. So again, the labels are a useful tool, but they don't necessarily always reflect the most current and best evidence. And for example, they certainly don't reflect this study that just came across my desk this morning.

Dr. Mariam Hanna:
Absolutely. Okay. Moving on to the next category of special populations in the elderly. What are they at higher risk for? What should we consider here?

Dr. Stuart Carr:
So there's a couple of issues with the elderly that are really important. I mean, first of all, first-generation antihistamines will have more risk for drug interactions than modern second-generation antihistamines. And of course, many elderly patients are already on a number of different medications. And the last thing we want to do is interact with the medications that they're already taking. So that's number one. But more importantly, we've learned frighteningly over the last maybe 20 years that the regular or long-term use of first-generation antihistamines because of their anticholinergic effects significantly increases the risk for developing dementia and Alzheimer's as well. Additionally, acutely, if using these products in elderly patients, they may have anxiety, confusion, and sort of delirium at a much higher rate than in non-elderly adults. So the problem with these medications is, again, they're often used to treat things like agitation and anxiety, for lack of a better word.
They're often used as a drug of convenience.

Dr. Mariam Hanna:
I'm going to bring up another at-risk population. So our oncology patients do end up on a lot of medications, and they're typically prescribed an antihistamine cocktail as pre-medication. Is there a way to have meaningful impact in that specialty?

Dr. Stuart Carr:
Yeah, it's a great question, Mariam, and I think it feeds into a larger question as well, which is the fact that first-generation antihistamines are still predominantly used in the inpatient setting in hospitals—not just in oncology, but just on the general wards, in surgical suites, and in the emergency room. And a lot of that is because up until recently, the only parenteral preparations that were available to treat either allergic reactions or to try to premedicate before transfusions or chemotherapy, if parenteral treatment was needed, were first-generation antihistamines. And recently, a second-generation antihistamine has become available and been approved by the FDA—cetirizine in a parenteral formulation. I actually am not sure yet if it's available in Canada, but it has been approved by the FDA, it is available now in the United States. It's not available where I am, but I feel like that may be a game-changer because unfortunately, and if we think back to our own training, whenever somebody was having an allergic response in the hospital, or a risk for allergic symptoms, or had pruritus or something that we may consider an antihistamine for, the default position in the hospital was simply Benadryl.
And because that was the one that was available, that's what we used predominantly. And what that did is it fostered a mindset, an understanding amongst trainees, and this includes all the physician trainees, nursing trainees, pharmacy trainees, basically everyone who spends time in the hospital setting, to assume that this must be the good one. "This is the one we use in the hospital, this is the one we use when things are going bad, this is the one we use in a crisis. This must be the good one." And patients have that same perspective. "But Doc, when I went to the emergency, they gave me a shot of Benadryl. Isn't that the good one?" Well, it was the one

we had that we could give a shot of. I'm hoping—and maybe I'm naive—but I'm hoping that with the development of parenteral cetirizine, a second-generation antihistamine, which has a much better safety profile and a better benefit profile, I'm hoping that may shift over the next couple of generations, but this is not going to happen overnight.
There are very few situations where patients can't take an oral antihistamine. And they have rapid absorption, excellent bioavailability, and instead of giving patients a sedating medication that will make them drowsy, dry mouth, and these other effects we talked about above and beyond treatments that are also causing unfavorable adverse effects, I'd so much rather give them a safer, very effective, but non-drowsy, non-impairing antihistamine in those scenarios. So we have to keep working on that. We have to try to keep fighting the good fight. And if we get parenteral cetirizine in Canada, which I assume will happen, that could be a game-changer.

Dr. Mariam Hanna:
Fight the good fight. I like that. Any recent changes in guidelines nationally or internationally that you can point us to on the use of first-generation antihistamines or any other safety warnings or publications that you want to bring up with today's episode?

Dr. Stuart Carr:
Yeah, so I mean, the first guideline that I saw that really took this issue on straight up and not diplomatically was the guidelines, which is the allergic rhinitis and its impact on asthma guidelines. This is the big document through the World Health Organization that focuses on managing allergic rhinitis. And over a decade ago, they bluntly said, "There is no role for first-generation antihistamines in the treatment of allergic rhinitis or allergic conjunctivitis, that you should only be using second-generation antihistamines." The international chronic urticaria guidelines have followed up on that and have made the same blunt statement. They've also said, "There is no role for using first-generation antihistamines in the treatment of chronic urticaria, and again, we should only be using second-generation antihistamines for this problem." I mentioned already that in Australia in 2020, their government issued a statement that no children under age two should receive any product containing a first-generation antihistamine for any indication, and that children under age six should not be receiving cold or flu medications that contain a first-generation antihistamine. They've also strongly discouraged their use as a sleep or behavior aid in children. And of course, the Canadian Society of Allergy published a position statement in 2019 highlighting the increased risk of not only adverse effects like we mentioned but increased risk of death from accidents, overdoses either intentionally or unintentionally, or cardiac events with first-generation antihistamines. And that second-generation antihistamines are really the preferred treatment for both allergic rhinitis and urticaria, and that first-generation antihistamines should only be used as a last resort and should be kept behind the counter. Now again, some of these things haven't occurred, but these are just some of the efforts that have been made to modify that. My strong opinion is there is no allergic condition where first-generation antihistamines are the preferred choice or offer any advantage over second-generation antihistamines other than side effects.

Dr. Mariam Hanna:

What more can we say on top of that? Alright, time to wrap up and ask today's allergist, Dr. Stuart Carr, for his top three key messages to impart to patients and physicians on today's topic: first-generation antihistamines. Dr. Carr, over to you.

Dr. Stuart Carr:
So I guess it's always hard to boil something like this down to just a few things. I think one of the things we mentioned before, but I think is worth reiterating, is that antihistamines should not be the first-line treatment for a severe allergic reaction, and that first-generation antihistamines are not superior to second-generation antihistamines for acute mild allergic reactions. For another point, I would say again that we don't want to try to take advantage of their side effects when those side effects are both unpredictable and not easily controlled, and we now understand may carry extra baggage. And then I guess my last point would simply be, don't give up on the fight. This is a conversation that I have with patients almost on a daily basis, as I'm sure you do, and as much as I said, it might sound like a broken record, I really don't back off anymore. I don't cave in and allow my patients, "Okay, if you want to use that at night, if you want to take Axs to help you sleep," I will constantly tell them that we're probably not doing a good enough job of treating this problem, for example, with the itch with eczema. We need better anti-inflammatory treatment of their skin rather than a sedating antihistamine. So don't cave in, keep fighting that fight, and try to get your patients into a place where they're taking a safer, more effective product.

Dr. Mariam Hanna:
Thank you, Dr. Carr, for joining us on today's episode of The Allergist.

Dr. Stuart Carr:
It's been a pleasure.

Dr. Mariam Hanna:
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