**Medical Insider COPD Season 3**

**Elevating the use of inhalers: adherence in COPD**

Richard Russell: (00:00)

This podcast is intended for healthcare professionals outside of the United Kingdom and the United States of America only. Welcome to the Medical Insider COPD by Boehringer Ingelheim, a podcast offering a breath of fresh air to clinicians treating COPD across the globe. My name is Dr. Richard Russell. I'm a Consultant Chest Physician at Lymington New Forest Hospital, and a senior clinical researcher at the University of Oxford. I'm also the Editor-in-Chief of the *International Journal of COPD*. I'm delighted to be your moderating host for this season of Medical Insider COPD podcast. I'm here to bring you news and insights in COPD right from the source directly to you. Thank you for joining us today. Be sure to subscribe and follow Medical Insider COPD to ensure you do not miss any of the exciting podcasts in this series and in the series we've done already.

Today, we're going to delve into a publication, which I believe is well worth reading. It's a little bit of science entitled, ‘Necroptosis Signaling Promotes Inflammation, Airway Remodeling, and Emphysema in COPD’. It's just been published in the *American Journal of Respiratory and Critical Care Medicine*. I'm also going to be looking with you an emerging exciting topic in social media on COPD, particularly looking at vaccination for COVID and how COPD patients are dealing with that.

But first, I'm absolutely delighted to introduce today's special guest who is going to be here with me today to discuss the additions of adherence to COPD, professor Brad Drummond. Brad is an Associate Professor of Medicine at the University of North Carolina in Chapel Hill, ‘Go Tar Heels’. He trained in Texas, and then spent most of his time training further in higher research medicine in Johns Hopkins in Baltimore. He's a clinician and researcher and is really interested in translational medical research. So it's great to have to him talk today about adherence. Welcome Brad.

Brad Drummond: (02:03)
Thank you, Richard. It's great to be here. Uh, happy to contribute to the discussion about a very important topic.

Richard Russell: (02:08)
Excellent. Well, Brad, this is a topic which is very close to my heart too, and absolutely the critical key message for all of our patients and clinicians here today. So, I hope we can get some really good messages out for them. Let's start though, perhaps by talking about this word adherence, Brad, which is kind of got mixed up in some ways with adherence, compliance and authority kind of word. What do you think about that?

Brad Drummond: (02:32)
No, I fully agree. I think really you have to first understand what is meant by adherence. The WHO for example defines adherence as the extent to which a person's behavior corresponds with recommendations from healthcare providers. But I tend to simplify it down a bit. I tend to define adherence as, is what the patient doing consistent with what the patient and the provider have agreed upon to do.

Richard Russell: (02:55)
And what are the aspects of adherence that you think are really important?

Brad Drummond: (03:00)
I think the first recognition is that it's a longitudinal process and it's a longitudinal process that involves the provider and the patient relationship. And adherence really occurs across the time continuum. So, we think about adherence during the initiation phase when a patient's first taking their first dose, the implementation phase, the extent to which the patient's actual dosing corresponds to the regimen and the persistence phase, that is how long are they actually taking the medication from initiation to the last dose?

Richard Russell: (03:29)
Brad, we're going to focus clearly on therapies, inhaled therapies, particularly because we're respiratory physicians but adherence is not just about some medication, is it?

Brad Drummond: (03:38)
No, that's correct. There’s many factors that impacted here. It's about personal behavior, about relationships with providers. And I think it's important to really view adherence, not as a dichotomous variable, that's a yes or no sort of situation. It's very dynamic. Patients can be adherent 50% of the time to 50% of their medications, or they could be adherent 0% of the time to one of their medications. And so it's really a complex nomenclature. And the other important point is that adherence is not just about under-use. It's also about overuse of medications or misuse or using for example, inhalers in the wrong clinical situation.

Richard Russell: (04:12)
And is this a common problem? I think we sometimes assume it is a common problem, but we often ignore it. So what do you think, what does the data tell us about how common this issue is?

Brad Drummond: (04:22)
Yeah. The prevalence of adherence really depends on how you define adherence and, and in the literature, this can be defined as, a self-report, review of prescription fills, biochemical assessments, et cetera. But, you know, it's felt that, you know, as many as 10 to 20% of initial COPD inhaler prescriptions never reached the pharmacy. So right out of the gate, we're missing one out of five therapeutic interventions for a patient. And if you look at the literature, non-adherence probably ranges somewhere between 50 to 70% in COPD patients, depending upon how you define it. So, it's quite common.

Richard Russell: (04:53)
And let's talk about the characteristics of patients or maybe, of inhalers, but how do we pick this up?

Brad Drummond: (04:59)
Yeah. So this is a very interesting topic of how do I, how do we identify patients who may be adherent or not adherent to their prescribed inhalers? And generally speaking, older age, when evaluated on its own is felt to be associated with better adherence. And interestingly in COPD, younger individuals may have less symptom burden, milder disease. So, they're less likely to be adherent. But we also know that older age is associated with comorbid conditions, polypharmacy, cognitive decline, and all of these things can impact or lead to poor adherence and poor inhaler technique. So it's a very complicated situation identifying patients.

Richard Russell: (05:34)
And do other things other than disease-related issues affect adherence and ability to adhere to therapy?

Brad Drummond: (05:42)
Absolutely. And, and this is where the comprehensive assessment of the patient is important. So, uh, certainly socioeconomic status or lack of insurance can impact behavioral changes that can relate to adherence. The patient provider relationship is an important predictor of adherence. So, continuity of care, explanation of rationale of therapies, all of those have been shown to increase adherence.

Richard Russell: (06:02)
And I'm certainly concerned about cost, and, cost must impact ability to, to pay for medication or need to pay for medication will certainly impact adherence.

Brad Drummond: (06:10)
For sure. So, patients who have a limited financial constraints may not fill medications, so they may have full non-adherence. And some may actually take medications, not as prescribed to sort of stretch out the link to the prescription. And that in itself is a definition of non-adherence.

Richard Russell: (06:25)
And that’s certainly something we are very aware of, I think, throughout the world, even in situations where cost is limited or minimal. What about the devices? Because we, you know, we're going to talk about inhalers, Brad, and you know, inhalers come in, all sorts of shapes and sizes. Some are easy to use, some are really difficult to use. What do you think about inhalers and inhaler technique and, and actually design of inhalers, does it help or even hinder adherence?

Brad Drummond: (06:47)
Yeah, you're absolutely right. Certainly, the design of an inhaler, both the steps required to effectively actuate the device or get the medication from the device into the lungs is quite important when we look at technique. You know, these inhalers are complicated, and patients may have multiple inhalers, which have different techniques and different timing of the day. And so those complexities can lead to non-adherence. We know that it's most important to personalise your prescription to the patient. So, what I mean by that is that showing the patients what these devices look like, discussing the benefits, the challenges of the different devices, because they all are unique and then understanding with the patient, what is most likely to be successful for their therapeutic plan.

Richard Russell: (07:25)
And I guess for the patient in front of us, we are the experts. And we've really got to know about the inhalers and know how to take them properly.

Brad Drummond: (07:33)
For sure. I think that, you know, individuals like myself and yourself who live in the pulmonary space everyday are probably very familiar with these medications. But our physicians who are really treating the majority of COPD in the primary care setting may not have the familiarity. And so, it is important to really understand the unique characteristics of these devices.

Richard Russell: (07:50)
Peak inspiratory flow, inspiratory flow capacity, and rate has been a big issue. And there's been many recent abstracts and publications about this. Does this impact device and ability to adhere to treatment?

Brad Drummond: (08:01)
Yeah, so at full confession, peak inspiratory flow is a, is a high area of interest from a research perspective in our institution here. And just to give a little brief background. So, the dry powder inhalers, the powder has to be dis-aggregated through a sufficient inspiratory flow to allow adequate distal lung deposition. And the way we, the way patients dis-aggregate that powder is through a sufficient inspiratory flow rate. And so, if a patient's not able to generate a sufficient inspiratory flow rate that, may impact the ability of that medication to get to the distal bronchioles of the lungs.

Richard Russell: (08:36)
So let's talk about the impact of this, Brad. If we get adherence right, then we will get some of the benefits or many of the benefits that we see in the clinical trials. But I'm assuming that if adherence is not right, we get none of those benefits.

Brad Drummond: (08:51)
I think that's a valid assumption. That's actually supported by the data. So, we know from the literature that poor adherence negatively impacts COPD exacerbation rates, quality of life and healthcare resources. And in a systematic review recently published, achieving adherence of at least 80% or higher is associated with lower hospital rates. If we look at large clinical trials, such as the TORCH study, which was over 6,000 COPD patients, there was individuals who demonstrated poor adherence to the study interventions had more severe exacerbations, they were more dyspnoeic, they had shorter time to first exacerbation. So clearly lack of adherence impacts clinical outcomes.

Richard Russell: (09:28)
It's very honest if a study like TORCH actually to say that and sum up that patients were poorly adherence because that's very badly reported in studies. And we spend a lot of time when we're doing clinical trial studies, teaching patients to use inhalers and reinforcing that and making sure that they're using the right number of inhalers and we still get it wrong, which is rather sad. Good adherence though, Brad, makes a big difference.

Brad Drummond: (09:48)
Absolutely. So we do think that if you're able to achieve an adherence of 80% or higher to your prescribed medications, that you do have less symptom burden and fewer exacerbations. So, the converse of the poor adherence story is equally true that working on adherence is an important way to improve patient outcomes.

Richard Russell: (10:05)
So that really raises the question then, how do we do it? Well, how do you do it, Brad, in your practice? Because I think it's really important to learn from an expert. What do you do to detect or risk register, someone who might be poor adhere and what do you do about it?

Brad Drummond: (10:19)
It sounds silly, but the first thing you have to do is talk to the patient. I think you have to understand the patient's perspective on the role of inhalers, their accessibility to inhalers. And then I think you have to really educate the patient. You have to explain the purpose of medications. You have to explain the importance of adherence. You have to identify barriers that may be specific to that individual. And so that's really the first step. We use in our clinic, visual guides, basically laminated pictures of inhalers to help ensure that patients are taking what they think they're taking. We use educational videos. So, to work on inhaler technique in the clinic.

Richard Russell: (10:52)
And there's been a lot in the research world about digital devices, smart inhalers, do you think they can impact adherence?

Brad Drummond: (10:59)
The digital inhalers I think are, have a potential to impact adherence in COPD. Some of the devices are FDA approved at this point. But from my perspective, I do think they're still in the research space in COPD as their ability to impact disease outcomes. I think that there's a lot of potential for these devices to help provide real-time feedback to the patient and to the provider about their use, their technique. And that's really, I think, going to help improve our adherence in COPD.

Richard Russell: (11:26)
You mentioned the absolute importance of relationship and the fact that this is not a one shot. You can't do it in one sitting, you have to reinforce and grow the relationship of trust and understanding inhalers. You also mentioned the word personalisation. How can we personalise inhaler devices to specific patients? Do we do it by class? Or how do we do it?

Brad Drummond: (11:46)
I think you have to really uncouple the molecules that you're prescribing and the devices that you're prescribing. Because I do view these as unique entities and that's what makes perhaps pulmonary medicine exciting is we're prescribing not just a pill, we're prescribing a molecule and a device. And so my approach is to really think about what is the molecule or molecules you want to treat the patient with first, bronchodilator therapy, single or double, inhaled corticosteroid containing regimens, et cetera. And then think about what is the device that you think best matches that person's capability to obtain those molecules.

Richard Russell: (12:24)
So it's not simple. It actually takes several steps. And is there any good guidance because guidelines are beginning to recognise that adherence and actually technique for inhalers is absolutely essential. Where can we go for advice?

Brad Drummond: (12:33)
So certainly there are published guidelines, as you mentioned, for example, from a Global Initiative for Chronic Obstructive Lung Disease, are a nice resource. What's interesting is that a lot of the guidelines focus on thinking about adherence if a patient's not sufficiently controlled, but in fact, I think you need to think about adherence from day one, from the initiation phase. So that's an important point. But there's plenty of resources to help improve technique. The COPD Foundation has wonderful videos that are short and patient oriented. As I mentioned, there's plenty of resources to visual guides, placebo devices to help train patients in the clinic. So, there's a lot of resources out there. It takes a little bit of effort to get them, but once you've got them, you can use them every day in clinic.

Richard Russell: (13:08)
I think that's a really important piece of advice there, have multimodality, multichannel using YouTube, using online videos, but also using models and getting people to understand in a very practical, real way, how to use their inhalers. In a moment I’m going to be talking about this new scientific paper about necroptosis in COPD. But before then, I'm going to put you on the spot professor Drummond, can you give me three or four key takeaways for how we can look for adherence, improve adherence and practically improve the care of our patients?

Brad Drummond: (13:40)
Absolutely. So, number one, you have to realise that adherence is a complicated matter, and it involves the patient, the device, and the relationship with the provider. Number two, poor adherence is clearly associated with poor outcomes. So, thinking about adherence early is important. And finally individualising therapies can help enhance adherence and improve patient outcomes. And so that's what we can really do to help maximise our patient's symptom burden in COPD.

Richard Russell: (14:07)
Professor Drummond, I've enjoyed this enormously. I particularly love the switch there from actually thinking of adherence not just as a failure thing and not just when people fail, but from the very beginning. And I think that's a really important take home message for even experienced clinicians out there. Think of it at the very beginning and keep it on your mind at every single moment. Professor Drummond, thank you very much for joining us today on the Medical Insider COPD podcast. I look forward to speaking to you and seeing you again very soon.

Brad Drummond: (14:35)
Thank you very much. I really enjoyed this conversation. It was wonderful.

Richard Russell: (14:44)
In a moment, I'm going to unpack for you an important issue in the social media world of COPD patients. But before I do that, I want to talk to you about an interesting and new scientific paper in COPD. This has just been published in the Blue Journal, the *American Journal of Respiratory Critical Care Medicine*. Online right now, June 16, 2021. It's by Zhe et al., and entitled ‘Necroptosis Signaling Promotes Inflammation, Airway Remodeling, and Emphysema in COPD’.

Richard Russell: (15:13)
So, what's this all about? Well, necroptosis is cell death. When cells die in this way they release inflammation, and this inflammation can lead to emphysema, so may have an important role to play in the production of COPD. And what's really exciting is if we can change this, and block this particular type of cell death, then maybe we can have new treatments for COPD to prevent emphysema. So, this group from Australia and Belgium, have investigated some important proteins in the cell death pathway, which leads to emphysema, both in humans and also in some mice models which I'll explain about. They looked at two proteins, RIPK3, which is a signal in cell death, and also the MLKL terminal protein in cell death progression. They measured this in lung tissue of humans and also by using knockout mice which can't make these proteins and exposing these mice to cigarette smoke media such that they present with emphysema, they can see where these proteins were important in the production of emphysema.

Richard Russell: (16:16)
So, what did they find? Well in humans, certainly MLKL was elevated in people with emphysema but RIPK3 was not. And actually, if this protein was elevated then, particularly with cigarette smoke media, there was an increase in necroptosis, leading to emphysema. And if you had a knockout mice which could not make the MLKL, then it did not develop emphysema. So, there is a clear message here. That actually this protein and this pathway for necroptosis may be really important in the production of emphysema both in mice and potentially in humans. So, the race is on now to develop new drugs and inhibitors of the MLKL pathway which hopefully will reduce the production of emphysema. Obviously, we need to stop our patients smoking but when will we give these drugs? Can we give them as early as possible to stop this disease which does relentlessly progress from progressing and thus stop the production of emphysema in our COPD patients?

Richard Russell: (17:18)
So, I hope you've enjoyed the Podcast so far that focused on adherence and also this new science. I'm now going to talk about an important piece from social media. This is a little controversial but one which is really important to our patients. I'm going to talk about a vaccination for COVID. This is an issue for our patients, and there're lots of concerns on social media about the safety and necessity of vaccination for COPD patients. There's very little actually about the risk of COVID which is disappointing. When there's a debate though many patients on social media, particularly those individuals that have had COVID, say that vaccination is essential and this is supported by patient groups such as #COPD, The COPD Foundation, who say that vaccination is absolutely essential.

So, how do we respond to this? I think we need to be very clear and offer help, and advice, and support for our patients. Clearly lay out the risk and benefits of vaccination for COVID-19. The benefits are a reduction in COVID transmission, reduction in COVID infection, reduction long COVID, and importantly a reduction hospitalisations and mortality. Of course, there are some risks which go with it and perhaps COVID vaccination should not be recommended for everybody, but we need to be honest and open with our patients.

I hope you've enjoyed today's Medical Insider COPD Podcast. I've had a great time talking to Brad Drummond about adherence in COPD, which is absolutely critical to care, and then I've opened a little paper for you which is a piece of science which may lead to new insights and new treatments for COPD, and finally I'd love you to think about vaccination for patients, how we advise them, and give them clear messages. I look forward to you joining me next time on Medical Insider COPD Podcast.