**Podcast Episode 5, Season 1 2020**

**Is two better than one? Early optimisation with dual bronchodilation in COPD**

Richard:

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 Southern Health, a senior clinical researcher at the University of Oxford. And I'm the clinical director of NHS England Southeast for respiratory medicine. I'm also the editor-in-chief of the international journal of COPD.

Richard:

And today it gives me great pleasure to be acting as your moderating host for this season of the Medical Insider COPD podcast series. I'm here to bring you news and insights in COPD right from the source directly to you. So, thank you for joining us today. Please watch out for Medical Insider COPD, and please join us for the whole series of podcasts which we're putting together.

Richard:

It gives me great pleasure today to introduce to you my friend and colleague, Professor Dave Singh. Professor Singh's going to talk to us today about the impact of bronchodilators and particularly their impact on early COPD. Professor Singh is a Professor of Respiratory Medicine and Pharmacology at the University of Manchester and is the Clinical Director of the Manchester Evaluation Unit. He's also a member of the Gold Scientific Committee. Dave, hello, and welcome to the podcast.

Dave:

Richard, hi. Good to talk to you today.

Richard:

So, Dave, we hear a lot about traits in COPD, and treatable traits is a very topical term. Can you unpack for us a bit how and when these things arise and how we should be picking them up in our patients?

Dave:

Yes. Treatable traits sounds complicated, but all these are, are problems that patients have. They're traits, they’re problems, and if you can treat them, then that's a treatable trait. So, for COPD, because it's a disease with many components, it's complex, patients can have many problems. So, this might give you a conceptual issue when you think, "Oh, well, how do I apply treatable traits to patients?" So, I want to simplify that. And one of the things we could do, particularly at the earlier stages of COPD, is focus on the dominant symptom that patients have, which is breathlessness and then that is going to be associated with problems in exercise performance or physical activity.

Richard:
Perhaps you could unpack for us a little bit about breathlessness and the impact that breathlessness has on patients and what happens, particularly in the early stages of COPD.

Dave:

Yeah. Important topic. So, we know patients tend to avoid doing activities in the earlier stages of COPD. Well, throughout the course of the disease. But in the earlier stages, we then have a difficulty finding out exactly how sick they are, because if you ask some of them, are you breathless? You may not uncover a great deal of symptoms, but what the patients are actually doing is avoiding certain physical tasks. So, this is where physical activity levels and exercise intolerance, whatever you want to call it is actually a key component of the earlier stages of COPD. And I think when we go through our little checklist of what we ask patients, how breathless are you, how far you can walk? Have a look, have they had exacerbations, et cetera? We've got to focus, as well, on what they can do in their daily living and what they're avoiding doing.

Richard:

So, do we ask the right questions, Dave, and what questions should we ask?

Dave:

Well, I think we sometimes miss it and we should be asking a personalized sort of question about what the patient does in their daily life and whether they're happy with their levels of activity. For example, some patients, they want to go to work. Some patients want to be completely independent and do their shopping. They may have lost that. For other patients it's just a matter of, can I get into the garden on a daily basis? And we need to understand that. And if our management strategy can then make sure that they maintain or even improve their physical ability to do those things, that's treatment success.

Richard:

And have any particular patients stuck in your mind that actually you've learned from in that way?

Dave:

Yes, absolutely. There is one patient I saw her a few years ago and he came to me in clinic having been admitted to intensive care unit and ventilated for a good few days with a pneumonia. And subsequently we'd done spirometry on him at discharge and repeated it and he had COPD with a long smoking pack year history. And his FEV1 was just below 50% predicted. And amazingly, his COPD had never been diagnosed before and he denied any symptoms when I sat opposite him. And I asked him, "Well, what about your job?" Because believe it or not, he works as a hospital porter, pushing patients around. And actually, that's when we uncovered, "Well, I use the lifts now. I don't pick up objects as heavy as I used to. I push the trolleys a bit slower." And nobody ever asked him about that. And his lung function had dropped to below 50% predicted.

Richard:

I think it can be right in front of us. You're absolutely right. I also agree with you and we need to sometimes ask people what they were like one year ago, two years ago, because as you said, people do adapt, sadly, and change their lives to adapt to the breathlessness and the impact they're having.

Richard:

We treat with bronchodilators, Dave. Is one bronchodilator enough or should we also perhaps be using more than one bronchodilator because many still have symptoms, don't they?

Dave:

Yeah, this is very topical. And it's amazing to think actually, that dual bronchodilators only became available to us and to patients about five years ago, and they seem to have been here forever now and are part of our standard treatment. There's a very good case to start with two bronchodilators for many patients. So, when you look at the clinical trial data, two bronchodilators on average are better than one. When you look at responder rates, two are better than one. I guess a point to take and know is the data I'm talking about comes from clinical trials where by and large patients had FEV1 less than 80% predicted. And many of the studies were enriched for patients with slightly more breathlessness. So I think there's still a case that for patients with milder COPD and less symptoms you could start with one bronchodilator and if they remain steady, then that's fine. But I guess we come back to physical activity and trying to push patients to be as active as possible. And for most of them having two bronchodilators then would maximize their opportunity to do that.

Richard:

Now, you're a member of the GOLD scientific committee. GOLD influences a lot of what we do around the world and makes recommendations. Perhaps you can unpack for us some of the detail of what GOLD's saying, because GOLD is so much more than just a couple of figures, Dave, and I want to hear what you think about the detail of when we should use one bronchodilator, two bronchodilators, and what does GOLD say?

Dave:

Well as you know, Richard, GOLD splits into a set of recommendations for initial pharmacotherapy, the newly diagnosed patient, and then some follow-up recommendations. So, for a first prescription, a newly diagnosed patient, GOLD recommends that by-and-large a monotherapy for many patients would be reasonable and dual bronchodilator therapy would be for those patients who are more symptomatic, and it makes the suggestion of a CAT greater than 20. Now, while GOLD tries to base all of its recommendations, as far as possible, on evidence, the ABCD recommendations for newly diagnosed patients are more expert opinion because there's hardly any data from clinical trials on patients who are newly diagnosed.

Dave:

The data we have is mostly post hoc analysis pulling out patients, small groups of patients, from those RCTs who are treatment naive. So, when they entered the study they were actually not on inhaled corticosteroids, not on any other maintenance treatment. And for those patients, the data generally shows that two bronchodilators, as a population average, are better than one. So, these initial pharmacotherapy recommendations of GOLD, I think you have to adapt to the patient in front of you. They're not strict and robustly based on RCT evidence. Now for the follow-up recommendation, I think that's much clearer, the RCT evidence deals with that. And we should generally have a low threshold for stepping up from one to two.

Richard:

And I think what GOLD says is actually quite nice and clear, making some clear statements about, say for example, long-acting treatment is better than short-acting treatment. And as you've just said, in general, two treatments are better than one in the studies we've got. But what about the ATS guidance? What does that tell us about dual bronchodilators?

Dave:

The ATS guidance, well, I think it was very interesting. It was a robust methodology. You know this, there were six questions that were asked and one of them was about the relative merits of two versus one. It's a different methodology to GOLD and I've commented on how it was done properly and robustly. And it comes to the conclusion by pooling data from RCTs that meet certain quality criteria that across a range of metrics, lung function, symptoms, quality of life, two are better than one. And it ends quite rightly with a strong recommendation that two bronchodilators provide benefits compared to one.

Richard:

I guess we have to also bear in mind the local environment, the local cost, the local availability as well. And that's a consideration to put in to how we are going to treat COPD.

Dave:

Yeah, you're absolutely right, because with everything I've just said, occasionally people will ask me, they'll say, "Well, Dave, you've said all that. Why did GOLD write down that you could prescribe monotherapy?" And one of the reasons is exactly as you've said, Richard, that the availability of dual bronchodilators across the world and the cost within different payer systems varies. So that's one reason. The other reason is the one I came back to for those milder patients with less symptoms, there is less data. So, I think there's always the door open there that some patients would be fine with the monotherapy.

Richard:

Thanks for that, Dave. Let's move on to talk about, the early COPD patient. There's been some really interesting data that I think is fairly compelling that loss of lung function occurs early in disease, not necessarily quite as much late. Can you unpack that for us a bit?

Dave:

Yeah. Actually, that type of data has been around for a long time and we're just seeing more and more of it. And you're right that the loss of FEV1 in GOLD stage one numerically is larger than in other GOLD stages. Why is this? Some people say it's a sort of numbers game that with bigger lung volumes at earlier stages you're more able to lose more. I think that holds a certain degree of sense. But also, many of the patients go through different stages. They go through stages of rapidly declining and then somehow there's stability. And then they might go through another phase. And I think a lot of that has to do with patient factors, environmental factors and our management. So, for example, treatment of co-morbidities, current smoking, physical activity, what inhalers they're on. So, these rates of decline are all modifiable, they're not always going to happen, despite what we do. And that again, raises the case for managing patients better at earlier stages of their disease.

Richard:

So, you're making a very strong case there, Dave, to one, let's try and diagnose these people as early as possible. Let's ask people different questions to actually pick out the impact of their disease and then intervene effectively. Dual bronchodilators would be part of that, do you think?

Dave:

Absolutely. As we discussed, they'd be a strong part of that. And you're absolutely right, the cornerstone to this is earlier diagnosis, but then taking it seriously, not looking at a patient who's FEV1 one is 90% and saying, "Oh, that's okay. We'll see you again in two years."

Richard:

Because we may actually have missed the boat and that would be very sad.

Richard:

Dave, you've been an investigator on studies which have particularly looked at specific outcomes, tying together lung function, breathlessness, exercise tolerance, and quality of life. Can you tell us about the impacts of bronchodilators, dual versus mono, in those kinds of studies and how we should look at those health impacts?

Dave:

Yes. Many of the randomized controlled trials for two bronchodilators versus one have shown very impressive effects on lung function. The earlier studies for some of the, what you call, patient reported outcomes, that's symptoms, quality of life, et cetera, the effects were maybe smaller than expected. But then when you re-analyse the studies in a different way and look at individual patients, so individual responder rates, you start to see a really significant benefit of two versus one. And there's another way to look at the data and that's to see how many patients you're stopping deteriorating. So, are patients dropping their lung function on an individual basis, are their symptoms deteriorating, are they having exacerbations? And again, a consistent pattern comes through.

Dave:

So, we need to have two ways of thinking about COPD. One, what can we improve? And two, can we stop worsening? Can we keep our patients stable? And that really has an eye on the long-term. We have an eye now on what we can do for symptoms and an eye on the long-term to at least keep our patient in the same place and not a worst place in the years to come. And you see that dual bronchodilators are holding patients steady. So, disease fluctuation, I think this is a relatively simple concept. If you get two bronchodilators, you're more likely to maintain airway tone, airway function, patients are less likely to have these disease fluctuations and remain stable over time, they're more able to remain active.

Richard:

And that actually may sound really simple, Dave, but actually when you unpack that and really think about what you're saying that is complex, but also so important. And I don't think we always take that seriously or pick up on it. And indeed, it's quite difficult to follow, perhaps.

Dave:

Well, it's future risk and doctors are used to thinking about future risk. Cardiovascular disease and primary care, secondary care, always thinking about future risk. And I'm just saying, let's do the same for COPD.

Richard:

I think that's really important. Let's talk about safety briefly, the studies you've done a real life as well as clinical trial data. Are there any concerns about safety of dual bronchodilators versus mono bronchodilator?

Dave:

Oh, well, that's something that I've had a keen interest on and kept a close eye on for patients in studies and looking at real world data. And it is remarkable. You look across the breadth of data that you see very little or nothing. And one of the points that people are keen on is to look at, well, in randomized control trials, maybe we haven't had the severest patients, maybe we've excluded patients with severe cardiovascular disease. And that's where you benefit from real world data. And again, in that scenario we don't see anything.

Richard:

Dave, that's been really insightful and really eye opening, some of the things you've said. Let's conclude though by putting you on the spot. There you are, you're a relatively young, healthy, patient with COPD who's getting some breathlessness, what treatments would you want as an initiation therapy?

Dave:

Well, it will come as a shock as a non-smoker. So, once I've gotten over that, depending on my symptoms and my level of lung function, I would want to optimize what I can do. And if that means an earlier intervention with a dual bronchodilator, I would want that. I would want to keep as active as possible, because physical activity, in the whole population, it's linked to long-term outcomes. And that's the same for COPD, and that's best to achieved to maintain that with a dual bronchodilator.

Richard:

You've hit on a particular word there. I think optimize is so important. And the idea that we need to hold onto a therapy until things are getting worse, you've actually debunked that myth as well very effectively this morning.

Dave:

Yeah, absolutely. Early optimization is something that we miss in COPD. We seem to always have this stepwise approach which in many cases is allowing a period of time for patients to deteriorate, and you may not get that back.

Richard:

In a moment I'm going to move on to discuss a new publication in the world of COPD, looking at the effect of home pulmonary rehabilitation. But I need to formally thank my friend, my colleague, Professor Dave Singh. Thank you for joining me today.

Dave:

Very enjoyable discussion, Richard, as always. Thanks for having that discussion with me.

Richard:

So now let me unpack for you an important paper that's just been published in the International Journal of COPD, volume 15, page 2505-14. This is by Gephine et al from Lille. It's entitled the long-term effectiveness of home pulmonary rehabilitation in older people. The questions they asked, which are really important is does rehabilitation work in the home setting? Are the benefits sustained? And is there a difference in age benefit and in their outcomes? So, what this group did was take patients with COPD and rehabilitate them for 90 minutes, once a week, for eight weeks in their own homes. They had 341 patients under 70 and 139 patients over 70, and they reviewed them for up to 14 months.

Richard:

So, what were their results? The older patients had more oxygen needs and more co-morbidities at baseline. They had a longer sit to stand test and also shorter shuttle walk testing. But interestingly, they responded just the same way as the younger patients. 88% of under seventies responded, 70% of over seventies responded, and they got the same degree of benefits, and these benefits were maintained at 14 months. Interestingly, given the face-to-face nature of this study, completion rates were very high. 93% and 86% of patients respectively by age completed the study, showing that actually clearly home rehabilitation is very effective and acceptable to our patients, which was great.

Richard:

So, what's the take home message? Well, rehabilitation works. No question about that, we know that. Home rehabilitation is also very effective. The benefits are certainly maintained over time and older patients respond just the same as younger. But this is very labour intensive, and in this post-COVID world, where actually doing face-to-face rehabilitation may be more difficult, perhaps we also need to know about the effectiveness of virtual rehabilitation in the home setting. I'm sure there's more data to come. And now we're moving on to my delve into social media.

Richard:

The world of COPD has been busy at the moment because of World COPD on 18th November, and also has been particularly worried about air pollution and biomass fuels. So, what's social media saying about biomass fuels? Well, in Korea, they're certainly concerned about the use of indoor briquettes burning for fuel. This of course will affect women as much indoor biomass does. Wood burning stoves are certainly a problem in rural India and China, and there has been concern in similar places before with dung burning. This seems to be a rural problem, but interestingly on social media, there seems to be solutions. Their outcome's clearly changing with the use of eco stoves, which are now being rolled out across the developing countries, and also liquid petroleum gas stoves, which are also much cleaner.

Richard:

Issues of biomass and air pollution are not just a problem in the developing world. A recent study published in 2017, and also now common on social media, has shown that wood-burning in Europe contributes to 51% of the production of all PM2.5's. Now PM2.5's are those particles in the air which contribute to airway inflammation. So, this is bad for our lungs and the study estimates that this is contributing to the excess deaths of 790,000 people in Europe. So, this is a big issue. Clearly on social media, we need to take this forward. It's a hot topic, both for those people inside their homes and in pollution outside their homes. There are solutions and we need to grasp them and publicize them for everybody.

Richard:

And as we finish this podcast, it just leaves me to thank my colleague and friend, Professor Dave Singh for his contribution today. And also, I hope you will join me in looking forward to the next edition of Medical Insider COPD podcast. Thank you for joining me today