Transcript January 2023 podcast Let's talk e-cigarettes

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> Music Intro.
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> If asking your mate down the pub about vaping. Here's what they probably say. No one agrees if it's safer on not so, you might as well smoke anyway. Now what your mate needs is a Cochrane review all the facts have been checked at least twice. They find there's a lot that the experts agree on and might give you different advice.

NL: Hi, I'm Nicola Lindson

JHB: and I'm Jamie Hartman-Boyce.

NL: We're both researchers based at the University of Oxford, where we work with the Cochrane tobacco addiction group. Welcome to this edition of let's talk e-cigarettes. This podcast is a companion to a research project being carried out at the University of Oxford, where every month we search the e-cigarette research literature to find new studies. We then use these studies to update our Cochrane systematic review of e-cigarettes for smoking cessation. This is called a living systematic review. In each episode, we start by going through the studies we have found that month and then go into more detail about a particular study or topic related to e-cigarettes.

JHB: Happy 2023 everyone. I hope the New Year is off to a good start. As always, we ran our searches at the beginning of this month, so in January we found one new ongoing study which Nicola, will you tell us about in a nutshell?

NL: So, yes, Jamie, we found one new ongoing study which is based in China. It's unclear who it's funded by, but the study is a randomised controlled trial where people are going to be randomised to either counselling plus an e-cigarette or counselling alone. The study investigators are aiming to recruit around 300 participants and are hoping to finish the study sometime this year.

JHB: FAB Look forward to seeing that. And in this month's deep dive. I had the pleasure of speaking to Professor Jonathan Folds at Penn State University in the US about a randomised controlled trial that his team did. The main results of it for our review came out over the course of the summer, but we hadn't had a chance to talk to him yet. And this is a really big study. It's in 520 current adult smokers. It's a four arm study, a randomised controlled trial and he will tell you more about it. So could you start by telling us a little bit about yourself and what brought you to study in e-cigarettes?

JF: Okay. My name's Jonathan Foulds. I'm a professor of public health sciences at Penn State College of Medicine. I've been here for about 12 years. I used to work at what's now Rutgers School of Public Health in New Jersey on smoking cessation. And before that, I was in the UK. I worked at University of Surrey for three years, and before that in St George's Medical school. And before that I got into smoking at the Institute of Psychiatry in London with Mike Russell and Martin Jarvis and Anne McNeil. So I've been doing tobacco research for maybe 30 years or something. I went to the Institute of Psychiatry in 1989. My PhD was in the role of nicotine in smoking and smoking cessation. And Robert West was also a co-supervisor as well. So it was partly on NRT, partly on the psychological effects of nicotine. And I helped on some of the trials that were done there. And like an assistant, when Gaye Sutherland did our trial of the nicotine nasal spray. And then I did the first trial of

nicotine patches in the UK. So it was all about NRT. And then when I went to St George's, I was part of a trial with Robert West and Peter Hajek comparing the patch, the gum, the nasal spray and the inhaler. And then the thing that got me into the kind of harm reduction side, like replacing cigarettes with less harmful products, was when I got invited to give a talk, a World Health Organisation meeting. It was in Helsinki and I was asked to talk about smokeless tobacco, which I didn't really know that much about. I'd written a little bit about snus, so I prepared the presentation and I basically just said what seemed to be obvious, that obviously smokeless tobacco like snus, is much less harmful than smoking because it doesn't cause respiratory disease. It doesn't go to your lungs, it doesn't cause lung cancer therefore. The meeting was in Scandinavia, and so there's a lot of people from Sweden there, and they became very, very upset while I was sitting. So at that point I realised, wow, I thought this seemed like common sense, but clearly it's not a widely accepted concept. So I better kind of deal about research. And that resulted in me writing a kind of review that was published in Tobacco Control on the role of snus and improving public health in Sweden. That wasn't the exact title, but that was the gist of it. And that was also very controversial. In fact, a bunch of very eminent people insisted on writing a rebuttal to the review at the time and so forth. So again, I was still sort of taken aback by the whole idea that something that seems obvious on its face that inhaling 7000 chemicals and switching to just printing about smokeless tobacco that's been made in a way that it's not carcinogenic, you don't have oral cancer. The idea that this could be a bad thing to get people off of something that's much more harmful into something that's much less harmful people not accepting that. I was a bit taken aback by it. So I was a little bit into the debate about harm reduction, but it was kind of an academic debate really, because Sweden was really the only country that was having an effect on their own public health by this becoming a popular product. Another thing that got me involved in harm reduction was I was asked to be an expert witness in some legal cases about lung cancer. And I remember being deposed by the lawyers. And so there was a lawyer interviewing me and it's all being recorded and there’s a video and a stenographer those six lawyers and five of them were just on their BlackBerrys. That's what people used at the time. And they weren't paying attention. They were just earning their $500 an hour by being there. And then I remember I was asked the question of, well, “there's no such thing as a safe tobacco product is there Dr Foulds?”. And I was supposed to say “no”.

JHB: Yeah.

JF: And there are legal argument and their defence was that if they can't be made any safer, then the company has no choice but to either go out of business or just keep selling it. And I said, “Well, there are much safer tobacco products, for example, as a product called snus in Sweden that doesn't cause lung cancer”. And so if your company, which is a tobacco company and in actual fact your company started as a smokless tobacco company and it then morphed into cigarette company, if you had decided to not sell a product that causes lung cancer.

JHB: Yeah.

JF: And had gone and sold another tobacco product that doesn't cause lung cancer then the person who's got lung cancer in this case would have used that instead. But at that point, I noticed that the other five lawyers put their BlackBerrys down and started paying attention. So I thought, Oh, that's interesting. Maybe I'm onto something here. But the reality was that snus has never really had much traction in the United States. Of course it's been than most of Europe. Partly because the public health authorities, including the surgeon general in the United States, basically said that it was just as bad as smoking. So once again I got more interested in it because I thought people who are, you know, respected authorities are saying things that are, in my opinion, just wrong and factually inaccurate. In actual fact, possibly harmful to public.

JHB: Yeah.

JF: But I think that's part of the reason that snus never really had much of a chance in the United States. Why would smokers switch to another tobacco product if public health is telling them that tobacco product is just as bad for you as cigarettes? You know, and people say, it's only Sweden where it was. Well, if you tell them it's just as bad, then why with it? There's no logical reason to say, if you like your cigarettes. And of course, then e-cigs came along. And at first, I didn't really take much interest. I remember the first time I saw one was at the World Conference in Tobacco and Health and in Washington, D.C. by 2007, I think and I remember I saw them somebody had a booth there and it looked like a big cigar. And he puffed on it. I didn't kind of buy one and we buy ordered one shortly after, and I puffed on it a little bit myself. And I know that I'm sensitive to nicotine because of in some of our studies at the Institute of Psychiatry, we sampled some of the products and one of my studies involved giving subcutaneous injections and so we practised on the high dose we were planning to use. I got sick and vomited. So we knew that was too high. So I took a few puffs on the e-cig and it didn't really affect me. And I thought, this is just like a theatre prop. It really doesn't deliver nicotine. It looks, you know, you can, you can substitute the behaviour, but it's not really a practical thing that's going to help people quit. But then, as you know, these products have developed.

JHB: Yeah.

JF: And then years later, I was here at Penn State and FDA had the ability to regulate tobacco products. At that particular time, they hadn't deemed it to regulate e-cigarettes. So, we applied for our own FDA funded centre and I collaborated with Tom Eisenberg's group, Virginia Commonwealth University, and part of their centre at that time we proposed to do a two centre trial of e-cigarettes, and the trial that we did was not a smoking cessation trial.

JHB: Yeah.

JF: It was a trial really the way it was worded and the proposal was to develop methods to evaluate tobacco products, particularly novel tobacco products and their harmfulness, particularly when used by smokers who weren't necessarily trying to quit.

JHB: Absolutely.

JF: That seemed to be the way that many people who are trying e-cigs or small snus products or any of these novel products that were coming on the market, they would see them on the store and maybe see them as advertised, and they would kind of try them for a maybe without being seriously trying to quit. And then there was another reason that we couldn't propose to do a cessation trial, which was that the funding for these research centres came from the FDA Center for Tobacco Products. Now, if you if you're proposing to evaluate it as something to help you quit smoking, that's a therapeutic indication. And there's another part of FDA that regulates therapeutic claims. The Center for Drug Evaluation and Research. And so technically the, group that had the money for the tobacco research, the Center for the Tobacco Products couldn't fund anything that had a therapeutic component to it. So although when we proposed the design of our trial we, I at least, had a hope that if we included in our trial an e-cigarette with a good nicotine delivery, something approaching a cigarette, I had a hope that some of the people in the trial who initially didn't want to quit my kind of thing. You know what? I'm using this to reduce and it's actually not that hard and it seems to be less harmful and stinky than my cigarettes. I'm gonna keep going and quit. So I had a hope that that may happen, but the trial was not designed for that purpose. The primary outcome was NNAL. You know the carcinogen biomarker in urine. And the people we recruited had to be people who did not have

a plan to quit in the next six months, they but they had to be people who are interested in using a product to help them reduce their smoking. That was the inclusion criteria. So we did that study it was 520 people. On the design of it was that they were randomised with 130 each group to either use a high nicotine delivery he cigarette, 36 milligrams per mil or a low to medium which is 8 milligrams per mil or a placebo or a cigarette substitute, which is like a a plastic tube that had a bit of a cigarette feel to it and you could adjust the draw resistance.

And so we gave all of these groups the same instructions to use the product instead of a cigarette trying to replace, and they were encouraged to reduce their smoking by half in the first couple of weeks, and then the next couple of weeks to reduce it by another 25%. So from 20, down to five, after a month, and then they were instructed to try and maintain that level, keep going, we never told them to quit, you know, so reduce as much as you can. And then they were followed up at periodically over over six months. So, that was the design of the trial and the main outcome was, I mean we measured CO at every appointment and we had them recording all the cigarettes they smoke throughout the trial. And so we knew in our mind that when you have CO2, and you have cigarette recording, you've got a definition of did anybody quit. In the protocol that was listed with that kind of as an exploratory variable, you know, we had the ability, but it was more explicitly the number of cigarettes per day that we were going to measure. And that was one of the outcomes in the primary paper. But once the primary paper which was published on the primary outcomes, and most of the secondary outcomes, then we set about writing up the paper about well did it have any effect on quitting? Absolutely.

JHB: And tell us what what did you find? I kind of know, but for the listeners, what did you find on quitting?

JF: You know? Yes. So what we found was, I've got it right in front of me. So I might try and remember, so one of the things that was different in this trial was that with a smoking cessation trial, you get people to have a quit day at the beginning. And then you know, a lot quitting the quit day, and then it's downhill from there. Well, in this trial didn't quit the beginning, partly because they were told not to they were told to cut down by half. But over time, the quit rate and the high nicotine group increased. It wasn't a very high quit rate. It's not like, you know, half the participants just went, woohoo, I'm gonna use these e-cigs just instead now. But by the end of the trial, it was 11% in the high nicotine group, it's about 4% in the low nicotine group. I think there's 3% and the cigarettes substitute. And it was like 1% or less 0.8% and the placebo, so there was a bit of a dose response effect a little bit surprising that the lower nicotine e cig didn't have a bigger effect to me, because you know, as you know, people can titrate how much nicotine they get. And you know, one of the best aspects of this trial, I think, compared to

JHB:exactly

JF: lots of the randomized trials of e-cigarettes was that Tom Eisenberg's group had done good studies of the PK of each of these doses with the device that we were using in the trial. So we knew that the high nicotine, and he's done these studies, not just then he done them in both experienced users and novice users. Of course, we now know and a number of studies that when people first are given an e-cigarette, and they've never used one, then you put them into a lab to do a PK study, they get less nicotine, even though you might say we want you to take 10 puffs and five minutes, you know, standardized puffing, they get less. Whereas if you go back and more experienced e-cigarette use only you get them to come in and do that they get about double. So we got a dose response effect. And the kind of planned analysis where we compared the quit rate six months at the end of the randomized phase of the trial between the different doses, then the high dose was significantly

higher than the placebo or the cigarette substitute. And we put a figure in the paper, that it kind of showed that the high dose, they were all increasing because people are encouraged to reduce their smoking, you know, people think, Oh, I think they'll quit and things happen in their life. So there was not much improvement on placebo group. But the 8 milligrams per ml group was gradually going up, but very slowly and not significantly better. And the high dose group, the line was going up. And you know, if you think about it, if that had continued, you know, for another couple of years, maybe more people would have quit. Maybe like you, I don't want to put words in your mouth. Yeah, I am a big fan of randomized control trials as a way to discover if something works, right.

JHB: Yeah, me too

JF for the obvious reason that we're all familiar with. So you take a large group of people who are kind of similar, and you randomized them to different treatments. And you know, the you're comparing like with like then. So I think this kind of trial was able to show definitively that an e-cigarette that can deliver nicotine almost as well as a cigarette clearly helps people to quit, even if they weren't planning to quit. That was the main conclusion, not a magic bullet, because 11% isn't a high proportion, and certainly not a quick magic bullet. So in the first couple of months, very few people quit in any of the groups. I don't see that as a big problem, because these were people who weren't even planning to quit. And the they were told to reduce. So I don't think there's any big shock, they didn't have a magic effect.

JHB: Absolutely

JF: But you know, one of the ways that our results change my views were that you know, before this trial and looking at these results, if I was to talk to doctors or their training, and they had somebody who had started using an e-cigarette but was still smoking, I would have said. Well, I think you should say to the person that they need to choose a quit day and need to transfer completely. And if they can't do that, then then it's a waste of time, they need to try something else, like an evidence based medicine, like varenicline or something like that. But now I'm not so sure that that's the right advice. Because what we see with e-cigarettes, it's a little bit different with most of the medications where you do pick a quit day, and you switch and either works or it doesn't over the next month or so with e-cigarettes for quite a lot of smokers. And we hear this from other kinds of studies, they gradually learn that the e-cig can deliver and they learn how to use it. And overtime, they reduce smoking, and then at a certain point in time, they just switched completely. And that's quite a common pattern. And I think we should be encouraging smokers to do that, rather than to give up the e-cig and keep smoking.

JHB: Absolutely. And what research do you think should follow on from your study?

JF: So we are actually doing a trial just know, this a short-term trial, it's not as long as this one because the money wouldn't support kind of a long term trial. But it is a trial that randomized the smokers to switch completely. And it's a placebo controlled study with just two groups is kind of design liked a cessation trial, but the funding's from the same source. And so it's actually the main outcome is NNAL again, it's a placebo controlled switching study. And these are people who want to switch who want to quit. So I think it's important that we do more of these trials to clinch the fact that e-cigs, when evaluated a bit like a med work, at least as well as a med.

JHB:Yeah,

JF: And so I think that's important. I personally, you know, much of my research is now is actually on reducing nicotine cigarettes, because FDA has proposed that they're going to ban high nicotine

cigarettes and make it a requirement for all the cigarettes United States that they have 95% less nicotine in them a bit like as now been put into law in New Zealand. So I see part of the role for e-cigarettes in the future that will be a key role is in providing a place for people who are in a country that has implemented that legislation to switch to a safer nicotine product. And in fact, probably even more importantly, I think it is the case that such a law that will basically make it illegal to sell high nicotine cigarettes promises to have the biggest effect on public health of almost any policy in our field that's ever been enacted. And so to me, it's really important that it works. Now one of the ways that it may not work is if there's suddenly a big demand and a big supply of illegal, you know, smuggled cigarettes, they're one of the ways to reduce the demand for those and people who are addicted to cigarettes, and suddenly they can't get any nicotine is to make sure they have an acceptable supply of non smoked nicotine. An e-cigarettes are obviously their first choice. We knew that from the market and the e-cigarettes have been sold. So I think it's really important that in the United States, we have good quality e-cigarettes that have been, you know, authorized by FDA. But more than one we just know, we've got like a couple. And that's not going to be enough. And I think it's really important that we have the evidence to enable FDA to authorize more e-cigarettes. And as you know, that's a really controversial topic, and people have different perspectives on it.

Absolutely.

JF: I have another trial ongoing, which is kind of crossing people who are randomized to normal nicotine cigarettes or very low nicotine cigarettes with those same people being given either high nicotine e-cigs, or placebo effects to kind of see the effects. Well, I think it's a great study, unfortunately, both of these trials I'm talking about got funded before COVID.

JHB Of course.

JF: And there were difficulties with the products, because you know that there's all this kind of fuss about authorization of products in America. And then when you combine those two factors, the trials got massively delayed. And then in the meantime, you know, in 2019, we had this EVALI scare in the United States. So the public became quite frightened of e-cigarettes as being dangerous. And so now, we're coming out of the peaks of COVID. And we're able to actually get on with our trial, we're finding it much harder to recruit.

JHB: Sorry to hear that.

JF: Whereas this trial, I was talking about went gangbusters. We recruited, you know, 300 people here at Penn State. It's much harder. And I've heard, you know, lots of colleagues doing other kind of, technically, this is kind of non therapeutic research, because you're telling participants that, yeah, we want to find out what happens, but we can't guarantee that this will improve your health. You know, we can't tell you. And so what it says in the consent form, people in America smokers have become very wary of e-cigarettes,

JHB: Understandably,

JF: They're concerned they're harmful, and they'll kill them and they're just as bad as cigarettes. Yeah, so we're continuing. We're trying to recruit as many as we can, but it's tough going.

JHB: Oh, well, good luck with that. And thank you so much. This has been awesome. And it's gonna give us lots to talk about in the podcast. So thank you so much.

JF: Thank you.

NL: So it was really interesting to hear the stuff that Jonathan had to say about snus and his work in that area, because, probably since he wrote that report, a lot more work has been done showing the beneficial effects that snus have had in Scandinavian countries. But obviously, what we're seeing now here, because snus itself isn't legal and readily available, what has been coming on the market are these nicotine pouches that don't contain any tobacco and just the nicotine. And obviously, there's very little evidence about that now, but I'd be really interested in looking more carefully at those in the future.

JHB: That's right Nicola, I think, you know, they're not massively taken off just yet. But we definitely I think, are seeing use increase of those in the UK in the US as well. I think there are a lot of question marks over it.

NL: And another thing I thought was great about what Jonathan talked about was this point about how e cigarettes is potentially worth looking at them in a different way to how we do usually with pharmacotherapies for smoking cessation, and it's really nice to hear how somebody, you know, maybe starts out with one belief about something, you know, he was saying, previously, he would have just encouraged people to switch immediately, you know, from all their smoking to an e cigarette, but he was saying his opinions kind of changed through looking at the e cigarette research and being involved in it. And seeing that with e-cigarettes, maybe it doesn't need to be that bit more of a gradual process, because people are learning how to use their e cigarette and maybe how to get the best out of them, how to use them in a way that they get the amount of nicotine they need. And I think I've mentioned on the podcast before some of my work has been in looking at helping people to gradually quit smoking. So for me, that was kind of a really interesting point that maybe I should look at a little bit further.

JHB: Absolutely. I think we've talked about this a bit before on the podcast. But it's interesting to watch the research field evolve, right from originally kind of testing whether or not these work to help people quit smoking. Now we're at the point where we have evidence that shows their work, and it's about how do we provide them and provide guidance on them in a way that makes them the most useful? And I think we can't just assume that it's the same as pharmacotherapies. It might be different and I hope we'll see more work coming out on that in the coming years.

So, that is it from us this month. Thank you all so much for listening and to Professor Foulds for the interview. We are going taking a little break for the next couple of months but hope to be back with you later this spring.

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> **Musical extract:** Vaping is safer than smoking may help you quit in the end. But remember to mention the findings we have can’t tell us what will happen long term, even though we know vaping is safer than smoking we may still find cause for concern. If you’re thinking of switching to vaping do it, that’s what the experts agree, smoking’s so bad for you they all concur that vaping beats burning there’s much to learn of effects long term yet to be seen.

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