

Transcript

Let's talk e-cigarettes

Podcast 36, October 2024, Professor Stephen Higgins University of Vermont

Speaker 1: Musical intro & outro

Speaker 2: Nicola Lindson, NL

Speaker 3: Jamie Hartmann-Boyce, JHB

Speaker 4: Stephen Higgins

Musical intro

If asking your mate down the pub about vaping is what they probably say, no one agrees if it's safer or 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 might give you different advice.

Speaker 2

Hi, my name is Nicola and I'm a researcher based at the University of Oxford in the UK.

Speaker 3

And I'm Jamie and I'm a researcher based at the University of Massachusetts Amherst in the United States.

Speaker 2

We are both members of 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 research 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've found that month and then go into more detail about a particular study or topic related to e-cigarettes.

Speaker 3

Hi everyone and welcome to this October episode of Let's Talk E-Cigarettes. We ran our searches on the 1st of October 2024 and we found 5 new papers. Three of them were linked to studies we already had included in our Cochrane Review. And two of them were new trials. I'm going to have Nicola tell you about the first of those right now in a nutshell.

Speaker 2

Som, the first study was a pilot study led by Doctor Tracy Smith at the Medical University of South Carolina and funded by the American Cancer Institute. A total of 30 participants motivated to quit smoking were randomly assigned to receive E cigarettes

or to receive receive nicotine replacement therapy. In the form of both patches and lozenges. In both cases, the participants received 5 weeks worth of the product and were asked to set a quit date one week after the study started. This was a short-term study with less than six months follow up. So, for the purposes of our review, we are only interested in the reports of respiratory symptoms which were measured at 4 weeks. After the set quit date, so respiratory symptoms were found to decrease in both of the study groups. So the e-cigarette and the NRT groups. But there was a greater decrease in the e-cigarette group. However, what we really should be aware that these results are based on a a very small number of participants, 30 participants in total, and so we can't draw any strong conclusions from that.

Speaker 3

Thanks so much, Nicola. Our second study this month is entitled Reduced nicotine cigarettes and E cigarettes in high risk populations and it actually brings together evidence across 3 linked randomized clinical trials. I had the pleasure of talking to Professor Stephen Higgins from the University of Vermont in the US about this important study in this month's deep dive.

So, this study was funded by a tobacco center of Regulatory Science grant, which are funded by the NIH and FDA in the USA, and Professor Higgins is going to tell you all about it.

So if you could start telling us a bit about your background and what got you into e-cigarette research.

Speaker 4

Yeah, sure. Yeah. Well, first, it is a pleasure to be with you here. And I'm trained as a behavioral pharmacologist in the area of addictions. I've had a long-standing interest in cigarette smoking and how it's kind of taken hold in vulnerable populations. People are more disadvantaged economically. People have comorbid substance use disorders or other psychiatric conditions. Those, those are the populations that have the hardest time completely giving up nicotine. At least we can try. And so that had me open and interested in harm reduction. And actually the whole, the whole idea of trying to reduce smoking in this population is to reduce harm. But E cigarettes as a way for those who were unable to quit. Well, maybe they could transition to a product that's not as toxic.

Speaker 3

Awesome. When did you first start doing e-cigarette research?

Speaker 4

Well, very recently as of I guess 2020 and it was through. So I have one of these T cores, grants, Tobacco Centers of Regulatory. Science and we were looking at reduced nicotine content, cigarettes. So they're, just to remind you or remind myself, the the concept behind that is we understand for decades now that nicotine is the constituent in cigarettes that produces chronic use and addiction. And because nicotine is a drug, then that effect must be dose-dependent. And so is there a dose or a level of nicotine in a cigarette that we could reduce to produce less or no addiction, and this is an idea that came up first raised by Neal Benowitz and Jack Henningfield in 1993 or somewhere close to that. And then there was some initial effort to investigate it. But there was some lawsuits filed by tobacco manufacturers. So long story short, it got put on a back burner

until 2009. Line when the Food and Drug Administration for the first time got regulatory authority over tobacco products, including cigarettes, and that gave them authority to introduce if they thought it would protect the public health and nicotine standard, they have expressed interest in moving that forward. And they needed clinical trials to support. Well, I guess, before the most recent announcement to move forward, they need the clinical trial. And and so we propose to look at this issue in the most vulnerable populations because they're the populations that we have exclusively focused on and our group here at the University of Vermont and other groups, were looking at the general smoking population and we wrote a proposal and 1st we were just going to look at how these populations responded to reduced nicotine content cigarettes in well controlled clinical trials and then a program of studies along, the same lines that I just mentioned. The idea is if you reduce the nicotine content, they'd be the cigarettes be less reinforcing and if they're less reinforcing people may be more open to quitting.

Speaker

Hmm.

Speaker 4

But then we think that there is going to be a subgroup and we have some evidence that there are subgroups who just can't quit nicotine per se are going to have a difficult time. So we wanted to do a study to see if availability of E cigarettes would enhance potentially the effect of reducing nicotine content in terms of moving people off of combusted cigarettes and so these ideas were looked at in controlled trials and including the most recent one with e-cigarettes. Simultaneously with moving forward on this idea of setting a nicotine standard, the FDA is faced with a lot of political pressure to do something about the marketing of E cigarettes, especially flavored E cigarettes, which are more appealing to children, to youth. So we were watching them constrain availability of E cigarettes in preferred flavors that adults and youth like. But the concern is about the youth liking them.

Speaker 3

Yeah.

Speaker 4

And so we were worried, I guess a little bit or curious. Well, those two policies may be working against each other and but there's not really any evidence from controlled studies one way or the other. And so we wanted to do a controlled study on that.

Speaker 3

Well, I love this study. I think it's such an elegant design and so incredibly policy relevant. So could you tell us a little bit about the new study or studies what exactly they set out to look at. Did you get any challenges getting these studies off the ground?

Speaker 4

So I can answer that first one. The biggest challenge was covid.

Speaker 3

Oh, just that.

Speaker 4

The study was supposed to start January 2020, and no sooner we're talking about getting, going and COVID hit, so we had to reconfigure everything to be done remotely and that took until, or almost exclusively remotely, and that took until October of 2020 and we got it going. But in the way of background, so we the three populations we work with are women who we're thinking about our economically disadvantaged, but we operationalize that by lower educational attainment and they're a group that if you look in the smoking literature, smoke as far as the decreases over years, they're pretty resistant to that, smoking at high rates and if they're reproductive age, then there is the possibility of adverse effects on multi, multiple generations. And so that's one of the populations we have long standing interest in. So they're included in the we look at with nicotine reduction. The second group is people who have opioid use disorder, and that's a comorbidity that's notoriously associated with smoking. Yeah, prevalence rates of 85% or whatever. And then the third group we were interested in are people that have other psychiatric conditions. And there we look at people with affective disorders simply because it's the most prevalent form of a psychiatric condition.

Speaker 2

Obscure science term definition, affective disorders. Mood disorders with marked disruptions in emotions, for example, depression and bipolar disorder.

Speaker 4

And so we run randomized clinical trials in each population, but we analyze the data together to see are there any interactions population differences, if there are, then we parse those out. If there aren't, then we report it as one big study. And so that's the approach we took with this most recent study with E cigarettes. So the basic design was we use in in these studies. And this is not just us, but in this literature on reduced nicotine content. The cigarettes that general approaches you get research cigarettes from the National Institute on Drug Abuse. And so they and they come in different doses and but they all look the same. So you could do a double-blind study. And one of the dose levels or one of the cigarettes is equivalent in nicotine content to what's typically available commercially so 15.8mg of nicotine per gram of tobacco and then the dose that, they have varying reduced nicotine content doses, and the one that we're using in this study is the lowest dose that's available and it's 0.4mg per gram of tobacco milligrams and nicotine per gram of tobacco. That's a big difference, 40 fold difference, huge difference.

Speaker 3

You.

Speaker 4

And the reason is we found out that in prior studies in these same populations, that nicotine exerts an amazing degree of control over their preference for smoking, which they prefer to smoke. So it looks like to protect the public health, you'd have to go as low as you can go and in the legislation, the FDA cannot go to 0 and that's written into the legislation. So the 0.4 dose is one that's been researching as about as low as you could go without.

Speaker

OK.

Speaker 3

Interesting.

Speaker 4

Going to 0 because you don't even want to go say functionally zero, because then that they can contest that in court. But this is a dose that has some, you know, behavioral effects, psychoactive effects, but is a minimal dose.

Speaker 2

Psychoactive effects are caused by stimulation or depression of the central nervous system and affect mental processes such as perception or mood.

Speaker 4

And here we in this study, we assign people to one of four conditions, the standard high dose nicotine content cigarette. That's our control condition. The very low nicotine content cigarette that I just mentioned, then two other groups. The third group gets the very low nicotine content cigarette. Plus we provide an e-cigarette and we're using the Juul e-cigarette. But in that third condition, the only flavor pod is classic tobacco that time. That's what they were allowed to have on the market in the US. And then the 4th condition is the same, VLNC. Cigarette and the same jewel E cigarettes, 5% nicotine level in the in the pods, but they could choose from among eight different flavors that Juul makes, including sweet and fruity flavors, which are the ones most liked by kids, and that the FDA is most interested in keeping out of the hands of kids and maybe off the US market, so. It's a 16 week trial and people come in once a week to get supplied with cigarettes. We supplied them with the research, they get randomly assigned to one of these conditions. We have the three vulnerable populations I describe. They're going to get cigarettes from us and then in two of the groups in the two e-cigarette conditions, they also get E cigarettes and pods that are equivalent and number of pods that are equivalent to the number of cigarettes they are smoking at baseline. So if they want to do a total substitution, they have enough product to do that.

Speaker

OK.

Speaker 4

They wanted to do a mix. They could do that as well. And so we just asked them to use only the products we're providing and tell us if they use other products, we won't. We won't hold that against them, but try your best to use just products we're providing.

Speaker

Mm-hmm.

Speaker 3

Yeah.

Speaker 4

And then come in once a week. Let us assess you. Twice during a study at weeks 8 and 16, we're going to have you bring in a first void urine specimen so we can look at biomarkers to really confirm how much you're smoking and or how much nicotine you're exposed to, including from the E cigarettes. And then. The primary outcome was how much smoking are you doing in total in the final week. So it kind of we've given you these products we've given you time to get used to them, how much has it changed your behavior come week 16 and what we find is each of the VLNC cigarettes reduce smoking compared to that control condition. But the availability of the flavored E cigarettes enhances that effect. So you get a significantly larger reduction.

Speaker

Enter.

Speaker 4

So the reductions let me try and I don't have them exactly memorized, but it's about I think maybe 8 cigarettes per day reduction with the VLNC alone from the baseline level with the, with the control condition and then when you have the the tobacco flavor, it's not significantly different from that. So it's not really enhancing the effect of the VLNC, but if you if you give them access to the flavored, you get about a 14 or 15 cigarette reduction. So it you know, very significant different from the tobacco flavored VLNC condition, the tobacco flavored e-cigarette and VLNC condition or VLNC alone or of course the the control. So in this area of research, it's whomping effect.

Speaker 3
Absolutely.

Speaker 4
And then number of days that you went without any combusted cigarettes, significantly greater when you had those flavored E cigarettes available. So I think however you're less dependent severity at least on the brief wisdom test. So I think I think it has a big effect. Big in terms of enhancing.

Speaker 3
Yeah.

Speaker 4
The goal of the VLNC policy, if they were to move forward. But I realize, you know, that would have to be balanced by the likelihood, then they would get in the hands of youth. And those are all the things the FDA wants to consider and making policy. And we were just trying to get the data available to them when considering policy of what it means to have these different types of E cigarettes available in the marketplace or no E cigarettes.

Speaker 3
Absolutely. And did you find differences in terms of your different participant groups or were the effects similar across them?

Speaker 4
Yeah. They actually were very, very similar across them, but one of the things that led us, so I I forgot to mention this. So we did it. So this was 2024 publication. In 2020 we published a set of three randomized controlled trials, same populations, a larger range of VLNC cigarettes so the same control and then two or three reduced nicotine content cigarettes. But what we notice especially was pronounced in the population with opioid use disorder, who are heavier smokers and whatnot as they were substituting with smokeless tobacco and other products we could tell by breath CO that we had reduced smoking. So smoke exposure was lower in all three populations. But especially in the opioid use disorder population, they were supplementing with other tobacco products, non combustive which you know has its has its merits, but that's really was just added support to our hypothesis that if you want to give them, yeah, you wanna get them off their combusted tobacco. You wanna get them off of nicotine in tobacco products you might need to have an appealing non combusted alternative. That's so then we hypothesize that the flavored E cigarettes in the the most recent trial would produce the largest effect and that's what we saw. We got no significant interactions in that effect. It applied across populations, but I was very impressed with the reductions we got in that opiate disorder population so. If you go into the supplement that goes with the main report, we have a little forest plot.

Speaker 2

A forest plot is a type of graph which can display intervention effects across different studies or groups, so a comparison can be made.

Speaker 4

That shows even though there was no interaction, the editors and reviewers anticipated questions. But how did each of the populations respond? Could you give us more information? So, so forest plot in there and the affective disorder of population shows the clearest, cleanest differences across conditions, but the opioid use disorder population responded very well as well, yeah.

Speaker 3

That's that's. Great.

Speaker 4

You can get them. You're you. You've got something.

Speaker 3

You're doing well. That's wonderful. So following this study, what would you most like to see be done next, either in research or policy or both?

Speaker 4

Well, I would like to see the FDA do something on this policy, and I realize you know what the political pressures in every different direction I I just glad it's not me, it's Brian he has to make those decisions.

Speaker 3

What a job.

Speaker 4

yeah what a job. But in terms of the science what I would like to see in these areas researchers you know you get like a a direction and then many of us are following that we want to keep the protocol similar. So we've been using people who had no plans to quit smoking or reduce their smoking in the present because we didn't want to confound what they had going on. Whatever factors family factor. Never with what we're manipulating experimentally, but it makes it less likely you're going to get people who do that 16 week trial and say that's it. You know, I am quitting smoking because they had no thoughts of quitting, they they are more likely to go without cigarettes. Like I said during the trial.

Speaker

Hmm.

Speaker 4

When the trial is finished, we have no evidence that. They're quitting smoking.

Speaker

Hmm.

Speaker 4

And so I would like to see a trial like the one I just described, but in people, either a sample that's representative of the US sample in terms of a mix of people who are planning to quit in the near future. Or only that population. Yeah, that's where I think we can learn some new things. So you probably know better than me exactly what proportion of population of people who smoke regularly daily are thinking equipment in their future business is fairly good size.

Speaker

So.

Speaker 3

So pretty high proportion I hear sometimes I hear over half thrown around though depending on what survey you're looking at, it can vary a little.

Speaker 4

They're not in any of these trials, so we need some trials in that population either exclusively or they're represented. And I think it would give the FDA some additional information they don't have now about the likelihood that people would quit in response to the policy.

Speaker 3

Ohh well this has been so interesting. Thank you so much and I think you're the first person we've had on the podcast talking about reduced nicotine content cigarettes, which I know are of great interest as well. So I really appreciate you coming on.

Speaker 4

Well, thanks. I appreciate you give me a chance to talk about them. I just think it's so science based and so thoughtful of the Bennewitz and Henningfield back in the 1990s. Just think that through, you know it's dose related or is it it's a drug. All drugs do their things in a dose dependent way or dose related way why don't we consider you know what happens if we got rid of the nicotine or at least got it really low. And it I could tell you, I went into these studies understanding we're all trained, nicotine is a good stage. We know that, right? But when you see. It's pretty striking.

Speaker 3

Yeah.

Speaker 4

And under double-blind conditions, the first study we did is the lab study and we give them different opportunities to choose this cigarette cigarette, the nicotine and it's across all levels of their dependent severity, nicotine, males and females tracking nicotine and it is.

Speaker 1

Interesting.

Speaker 4

So so I I just we knew it at some level, but when you see it, it's pretty important, it's pretty impactful and I hope in some ways. How can the FDA not do something on it, knowing that they're charged with protecting the public health and having those that nicotine at where it is now and cigarettes is driving people to keep smoking?

Speaker 3

Yeah. Yeah. Ohh. Much to be seen in the future in this space, I think and hope amazing.

Speaker 4

I hope.

Speaker 2

So that was really interesting, Jamie. It was good to hear about a study that's incorporating the use of these very low nicotine cigarettes and interesting how that was combined with the the e-cigarette and therefore will be eligible for our review. However, as with the other new study we found this month. It's not a long term study, so as Professor Higgins mention. And it's 16 weeks, so we won't be able to look at quitting as part of our review, but there are actually a couple of outcomes that Professor Higgins

didn't mention that will be that we will look at. So one of those was looking at toxicant exposure through looking at something called NNAL, which is a carcinogen which is associated with tobacco use. And another was look, they looked at adverse events. So we'll be able to look at those and compare. E cigarette use with versus no e-cigarette use by looking at the just very low nicotine cigarette arm and we'll also be able to compare those two things between the the two different flavour arms. So in line with the reductions that Professor Higgins mentioned in flavour choice and there be LNC arm very low nicotine. Cigarette on that group also saw greater reductions in NNAL than the other arms, which is kind of in line with the fact that they reduced their tobacco smoking more. So that's what we would kind of expect. And there was also no clear evidence of differences in adverse events or serious adverse events between the arms and that was in a reasonably sized sample. So there were 326 people involved in that study, so that'll be interesting to see alongside the results of the other studies in our review.

Speaker 3

Absolutely. And I, you know, I get very excited when we see new trials that take into account different context. So in this case, what are the effects of E cigarettes if you're in an environment with very low nicotine content, cigarettes as well. One of my hopes for E cigarettes in the long run is that they might be used to help us implement other tobacco control policies to drive down smoking. If we are reducing people's options in terms of combustibles, the most harmful form of tobacco then having something else that they can switch to that is less harmful for people who can't quite entirely really might help these policies achieve their intended effects. I think so. It was great to. See. That

I think that is it from us this month. We hope you're all having a wonderful October wherever you are. Thank you so much for listening. Thank you so much to Professor Higgins for agreeing to come on and talk to us about his studies this month and we look forward to speaking to all of you in November's edition of let's talk E cigarettes.

Please subscribe on iTunes or Spotify and stay tuned for our next episode.

Musical outro

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 about switching to vaping do it. That's what the experts agree. Smoking so bad for you they all concur that vaping beats burning there's much to learn of effect long term yet to be seen.

Speaker 3

Thank you to Jonathan Livingstone-Banks for running searches to Ailsa Butler for producing this podcast and to all of you for tuning. In music is written with Jonny Berliner and I and performed by Johnny. Our living systematic review is supported by funding from Cancer Research UK. The views expressed in this podcast are those of Nicola and I and do not represent those of the funders.

