

Episode 40: Nicotine - From Potential Benefits to Hidden Dangers

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Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week, we're going to be taking a look at nicotine and some of the more surprising sides, I think, of nicotine. Rebecca, childhood time, what's your earliest memory of knowledge of nicotine or nicotine products?

That look was priceless. What do you mean that look was priceless? I don't even know. No, it's funny.

I guess it's very different for me because my dad was always a smoker, so I was always brought up in a house where my dad smoked and it was something he did and I wasn't allowed. You must've been exposed at school, right? There must've been friends that would smoke behind the bike shed. Oh, I was never cool enough to be part of the smoking crowd.

Oh, but you were at least aware that there was one. There you go. Nicotine is one of those substances that's become somewhat endemic in society in so many cultures. Virtually always, up until recently, in association with tobacco and tobacco products.

And we're not actually going to dwell too hard on tobacco this week, but actually we're going to be looking at nicotine itself and pharmaceutical use of nicotine and exposure to pure nicotine. Fun fact, did you know not only is nicotine found in tobacco but it's also found in other nightshade family plants, including tomatoes and aubergine. That is a fun fact, I didn't know that. In very, very low concentrations.

Yeah. Before we jump into today's episode, if you want to stay up to date with our content, you can find us on Instagram at @the_tox_lab. We also have a LinkedIn page, which we're quite active on. And for those of you who don't use social media but want to get in contact with episode suggestions, you can email us at thetoxlab@gmail.com.

So the first thing we wanted to look at this week is actually potential therapeutic roles of nicotine. Before we dive into that, let's talk a little bit about what nicotine is. So what is nicotine? Well, nicotine is an alkaloid.

It's found mostly in the tobacco plant. Although as I said, it can be found in trace amounts in other nightshade family plants. And it's evolved as a natural pesticide effectively. It stops insects wanting to eat that tobacco plant because it's poisonous to the insects.

And it works by binding to receptors called nicotinic acetylcholine receptors. And they're named because they are nicotine responsive. So acetylcholine receptors are proteins found in the nervous system. They're essentially ligand gated ion channels.

And when acetylcholine binds to the receptor, it causes an electrical signal to fire. And so nicotine can also fire these receptors. And they're found in a few parts of the body actually. They're present in the brain and the central nervous system and they're involved in reward pathways, attention, stimulation and crucially memory.

We'll come back to that function in a moment. They're also found in the peripheral nervous system and control muscles. In terms of its pharmacological effects, there's really two sides to nicotine. At low doses, you get a stimulant effect increase in alertness, increase in heart rate.

At higher doses, it can actually cause a very toxic effect. And we'll talk about some of the toxic effects of nicotine a bit later on. So we wanna have a look today, first of all, at some potential emerging therapeutic benefits of nicotine. So Rebecca, why don't you introduce us to our first paper today?

So this first paper is a review article talking about the impact of nicotine on cognition in patients with schizophrenia. So it has been noted that patients with schizophrenia do have an extremely high prevalence of smoking compared to the general population. And it's speculated this might be possibly a form of self-treatment. So in schizophrenia, there are lots of effects that are noted.

So you get a reduction in acetylcholine, a reduction in nicotinic acetylcholine receptors, an increase in GABA. And in smoking, these are adverse. You get an increase in acetylcholine because nicotine is binding to the nicotinic acetylcholine receptors and you get a decrease in GABA. So it's thought that smoking in these patients might be self-treatment, but it is also noted that patients with schizophrenia often smoke way before their disease presents and increased smoking rates have been linked to an earlier disease onset, a poorer quality of life, poorer prognosis, and increased disease severity.

And there's just, I think, so many factors that might be at play. Yeah, I'm certainly aware of anecdotal evidence that does say that patients with schizophrenia do often report smoking more frequently than maybe background risk would suggest. It can be really tricky to unpick some of that, can't it? Because there can be a lot of social factors as well.

So a subtype of nicotinic acetylcholine receptors, alpha-7, are involved in modulating synaptic plasticity. These have a decreased affinity to nicotine compared to certain other receptors. So they do not desensitize receptors at lower doses and they remain active longer. And these are abundant in the prefrontal cortex and the hippocampus in the brain.

A reduction in alpha-7 nicotinic acetylcholine receptors is linked with sensory gating failure, which is seen in patients with schizophrenia. And this is basically the ability to distinguish between irrelevant and significant stimuli and might be involved in the pathways linked with sensory overload and cognitive deficiencies in these patients. And it has been noted that when patients are given nicotine or an alpha-7 nicotinic acetylcholine receptor agonist, you do correct these sensory gating defects.

So there's a plausible biological mechanism for why nicotine and nicotine analogs, actually, particularly these subunit-specific ones, may have some benefit. I think this paper we looked at, didn't we? It was a review paper looking at a number of studies that have been attempted to try and answer some of this question. And really the evidence is quite mixed, isn't it?

And some of the studies showed potential benefits of nicotine for usually short-term improvements in symptoms. And yet some studies showed no real benefit. And I think there's a lot of co-factors going on, isn't there, whether they were smokers before the study or not versus current smokers at diagnosis and antipsychotic treatment can be a big factor and antipsychotic metabolism, depending on the antipsychotic can be affected by smoking status. So there really was a lot going on in this data set.

Although there is this mechanism and there certainly is some studies that seem to be encouraging, I'm curious as to see where it goes, to see whether there'll be more studies in the future, potentially some benefit. If nothing else might help reveal some of the underlying mechanistic causes to illnesses like schizophrenia. So let's delve into another population then where there's some suggestion that nicotine may have a beneficial effect. And that is in patients with dementia and how that can have a role potentially in improving working memory and so on.

Now the paper we're gonna look at this week was another review study that was carried out 2024, so relatively recent. And again, the logic behind this is similar to the logic in studying nicotine in patients with schizophrenia, in Alzheimer's disease and other forms of dementia actually, there is a generalized loss of nicotinic acetylcholine receptors and actually established treatment in dementia and Alzheimer's disease is the use of certain cholinesterase inhibitors. Drugs like galantamine and donepezil work to stop the breakdown of acetylcholine.

And so the logic is, instead of using a drug that stops the enzyme breaking down the natural ligand, could we use nicotine or nicotine analog to stimulate the same receptor? So again, this paper really served as a review to summarize the evidence and it was quite big actually, they looked at 39 clinical trials, not just looking at nicotine, crucially they were looking at nicotine and other nicotine analogs. A total of 16 different drugs were investigated, so there's been quite a lot of research looking at nicotine analogs as therapeutics.

And there was some improvement in symptoms actually, there was improvements in attention and mental processing speed, particularly with nicotine patches, that seemed to be one of the more effective treatments. And again, similar to what you were saying in the schizophrenia studies, alpha-7 agonists in particular did seem to show some promise. Now actually one thing the schizophrenia paper didn't seem to do very well is it didn't talk about safety. There was very much this series of studies looking at nicotine use versus non-nicotine use, but there wasn't so much in terms of pharmacological intervention and studies.

And interestingly in this Alzheimer's and dementia studies, there were some safety measures reported and generally the drugs were well tolerated. Adverse effects were nausea, dizziness, headaches. Also I think really the conclusions were that nicotine and its analogs are promising, but again, like the schizophrenia paper, the outcomes were really variable. There wasn't conclusive evidence.

Some studies didn't show positive effects. And so again, the evidence is really quite mixed. There's a mechanistic link as to why these drugs might be beneficial, but at the same time, it wasn't conclusive. There were studies that didn't support this hypothesis.

I think as is often the case, this is very messy data, isn't it? Dementia isn't one thing. Yeah, it's really tricky to unpick and people who do have dementia can have like multiple different forms, like Alzheimer's and vascular dementia, for example. So it's always gonna be a really messy data set.

So there is currently a very, very large randomized clinical trial going on now. Like all big clinical trials, it's got a snappy acronym name. It's called the MIND trial, Memory Improvement Through Nicotine Dosing, obviously. And this really is a large multi-center interventional study to see whether nicotine delivered in patch form can improve memory and functioning.

So I think this will be the study, hopefully, that will tell us really the outcome. It's certainly the biggest study and the longest running study that has ever been done. And actually, one thing we haven't touched on here, but we should probably mention, science involving nicotine can sometimes be influenced by the funding sources. There have been a lot of studies done in the past on nicotine and tobacco, whereby tobacco companies have put some money into it, or indeed anti-smoking lobbies have put some money into it.

So it can be really tricky to find unbiased evidence. And interestingly, the MIND study claims no tobacco companies have been involved in the study design. And I think we await the results, and we really do. So let's switch gears then, and let's stop talking about potential therapeutic benefits of nicotine, and actually look more at acute toxicity with nicotine.

As I said at the start, nicotine at low doses acts like a stimulant and potentially has effects on working memory, as we've discussed. At high doses, nicotine can be incredibly toxic. And acetylcholine receptors are present in lots of parts of the body, including the muscles that control breathing. And a fair few drugs actually can cause toxicity via interfering with this mechanism.

The most infamous being cholinesterase inhibitors. So nerve agents and certain pesticides, hemlock actually interestingly, not a cholinesterase inhibitor, but that also binds to acetylcholine receptors and activates it and then stops it deactivating, which leads to muscle paralysis. And nicotine can do the same thing in very high doses. And when I say very high doses, it's not that high really.

So let's turn our attention to some acute toxicity data. So this paper is looking at nicotine ingestion among young children between 2010 and 2023. So they used national poison data system data on nicotine exposures in children under six years of age between January the 1st, 2010 and the 31st of December, 2023. So this includes data from all 50 US states and Washington DC.

They limited ingestions to be exposures to single substance and exposures categorized as unintentional slash general. And they further split this data into different product categories, including chewing tobacco, cigarettes, nicotine pharmaceuticals, e-cigarette devices, e-cigarette liquids, other and unknown. And they also look at different product formulations, including gums and lozenges, liquids, pouches, powder slash granules, and then tablets, capsules or caplets. And like with a lot of the poison data system data we've discussed previously on this podcast, they categorized it in two different healthcare outcomes and different effects.

So they had no treatment received at a healthcare facility, treated, evaluated and released, admitted to critical care, admitted to non-critical care unit, refused referral or did not attend an unknown. And then effects range from like no effect to minor effect up to major effect death or unknown. So 134,663 exposures met the criteria. 56% of these affected males, 99% of these occurred at a residential address and 76% were children younger than the age of two.

How many cases were there and over what period of time? 134,663 and that's over 13 years. That's still a lot per year, isn't it? That's a huge number.

And these are completely like unintentional ingestions as well. So 37% of these cases had no effect, 20% minor effect, 42% weren't followed up and it was deemed there was minimal clinical effect or that was a non-toxic exposure, but there were some quite serious outcomes. So 1.2% of these cases involved moderate effect, 39 ingestions were a major effect and there were two fatalities and the proportion of moderate effects increased with increasing age with children aged five, one and a half times more likely to experience a serious medical outcome.

In terms of product categories that caused these major effects, chewing tobacco had the highest proportion of serious medical outcomes at 1.8% followed by e-cigarette liquids and e-cigarette devices. And then in terms of product formulations, pouches were associated with the highest proportion of serious medical outcomes followed by liquids and gums or lozenges. So the rate of nicotine ingestion over this time period per 100,000 people did increase by 59.4% from 2010 to 2015. And then there was a significant decrease of 34.1% between 2018 and 2023.

In terms of the sorts of types of nicotine that were seen over this period, there was a significant increase in liquid ingestion exposures up until 2015 and then there was a significant decrease up to 2023. And I think this kind of coincides with the Child Nicotine Poisoning Prevention Act of 2015 where they introduced charge resistant liquid nicotine packaging, which kind of stopped these exposures from happening as often. Ingestion of pouches increased by 760% between 2020 and 2023. They do comment that there's no data in the pouch category before this time because the category hadn't

been created in the database.

But between 2019 and 2022, eight milligram pouches showed a large increase in sales more so than the traditional two and four milligram pouches. And then super products that are made outside the US can have a nicotine content ranging from between 30 to 130 milligrams, which is insane. 30 to 130 milligrams. There were some 19th century self experiments that was reported in textbooks and safety labels and became repeated throughout history saying that 30 to 60 milligrams could be fatal.

So this is a huge amount. Although I do think that has since been proven wrong and I think it's more likely to be between 500 to 1000 milligrams. But still, this is still huge, isn't it? Bearing in mind a cigarette probably only contains 10 to 15 milligrams, but probably actually only a bit of that is actually absorbed one to two migs.

These pouches really are quite strong, aren't they? And I think the really worrying thing about pouches is they're so brightly colored in their packaging and basically marketed at children that with these higher dose pouches being available, that does provide a real risk. Yeah, I was gonna come on to that, but I just wanna go back to the trends over time. Interestingly, you talked about chewing tobacco having quite a high proportion of poisonings.

I guess in some respects that makes sense because chewing tobacco goes in the mouth. This is a slightly foreign concept to me. Chewing tobacco isn't really a thing I've ever come across in the UK. And the trends in general really seem to reflect what we have observed in terms of reductions in smoking, but an increase in vaping.

And now, as you say, a move towards nicotine pouches. I wasn't aware of nicotine pouches until six months, a year or so ago, where they seem to be everywhere. And for those who are listening that aren't aware, these are not tobacco products. These are pouches that are impregnated with nicotine and release nicotine over a period of time.

You stick it between your lip and your gum and it's absorbed through the gum membrane. They seem to become very popular recently. And as you say, they are sometimes like flavored. I guess nicotine tastes bitter.

I haven't actually looked into it. My assumption is that it's a bitter tasting alkaloid and therefore flavorings can kind of mask that bitterness. It does seem to be a bit of a worrying concern that that many, was it 1,000% increase? 760%, not far off.

Across three years, huge increase in pouch exposures leading to toxicity. Yeah, in this data set, pouches only accounted for 1.4% of ingestions, but at least 1% of cases involving pouches involved a medical admission. So quite serious outcomes. So not only did the frequency increase, but actually these were much more significant exposures, more likely to lead to serious harms.

Again, because that dose is relatively high. So in the UK, they're not even currently broadly regulated. They're not tobacco products. So they don't fall under any tobacco law.

They do fall under general consumer safety requirements, but they're not medicinal. And therefore there's no age restrictions. Anybody can buy them in theory. Whether shops are maybe taking a safe approach and perhaps they are, but in theory at least, they're not currently regulated.

Although I think there are plans to change that. So 81% of exposures did not receive medical treatment at healthcare facility. 16% were treated, evaluated, and then released. And 0.5% of exposures involved a medical admission.

And the proportion of children admitted also increased with increasing age. It does appear that e-cigarette liquids and devices and nicotine pharmacy tools had a high proportion of medical admissions. And as I touched on a bit earlier, there were two fatalities reported within this time period. The first involved a 12 month old boy who was found unresponsive in an asystolic at home after ingesting liquid nicotine of an unknown concentration.

And a 17 month old boy was also found unresponsive with e-cigarette liquid on his mouth, hands, and on the ground. And this was found to be a concentration of 18 milligrams per millilitre. It was a 16.5 milliliter container, which was only a third full with the child safety dropper removed. Post-mortem blood samples were taken, which showed a nicotine level of 300 nanograms per millilitre and caffeine present at 222 nanograms per millilitre.

Yeah, I remember both of these cases. I'm sure they made headlines. They're both really sad cases, aren't they? But it just shows actually how dangerous vape liquid can be.

And therefore how dangerous pouches can be as well. Clearly enough nicotine in a particularly vape liquid bottles because they're so concentrated, aren't they? Designed to get however many puffs over however long a period of time. To consume all of that in one short sitting is a huge nicotine dose.

I do think we're seeing some interesting trends, aren't we, in terms of where we've moved from and where we're moving to. Going back to my memories of my dad smoking, as I say, nicotine was tobacco. There was no separation. And then there was the pharmaceutical, medicine, smoking aids, patches, and later lozenges and all sorts of things like that.

It's only really been in the last 10, 15 years, possibly longer actually, I'm possibly getting really old, that we've seen the vaping trend. And now we're moving towards the pouch trend. We're moving away from tobacco because tobacco is generally considered objectively bad and moving more towards pure nicotine. So going back to the potential pharmaceutical benefits, we looked in a couple of cases whereby there might be medical use, but actually if you could take a nicotine patch and it improved your memory, would you do that?

Possibly, depends on how old I needed to revise for an exam. I'm certainly aware of people using nicotine to improve their memory for exams and things like that. Usually tobacco form, but that's probably because of the circles I keep. I don't really know how effective it is.

Given the evidence was mixed in populations where there might be a medical benefit, I'm not sure it's necessarily gonna be a clear, yes, no answer. There was some recent controversy as well, wasn't there, about nicotine in e-sports. Was there? Yeah, I certainly was aware recently of, maybe it was a survey that was done of e-sports players.

And for those who don't know, e-sports is professional video gaming, professional competitive video gaming. I can't believe we're talking about this. And there has been an increase in the use of nicotine, particularly pouches actually, to try and get an edge in games. It's being used as a performance enhancing drug.

So there is this side to nicotine that goes beyond trying to look cool behind the bike sheds. That obviously carries with it addiction risks. We've not mentioned this at all, but actually nicotine is one of the more addictive substances that has ever been discovered. And as somebody who's gone through it, quitting is hard.

So there clearly are risks to using nicotine as a performance enhancing drug to help you study and potentially in some of those medical cases as well. So what do we think is gonna happen next? I'm intrigued by the studies that have looked at nicotine analogs. Will we see a trend towards other

non-nicotine analogs?

Are other drugs that look like nicotine or act like nicotine, but aren't nicotine? I want to see whether there's gonna be any sort of legislation or restriction on the sale of like nicotine pouches at high doses. Cause there doesn't seem to be anything at the moment whether that will come into effect. I think it's quite an interesting area.

Yeah, I think you're right. I think that there needs to be some regulation clearly, particularly if there are super strength products which are being sold, particularly if they're sold on the open market with no consequence. What was interesting, I think in the poisoning data was that the dose strength of the pouches seemed to go up over time. Yes.

Which does suggest people are moving up the dose, which is what you'd expect in somebody who uses pouches to perhaps escalate their dose. But obviously the higher the dose goes, the harder it is to come off them. Yeah, I think there probably does need to be some regulation. And I'm absolutely shocked actually that these pouches fall through the cracks in the UK legislation that literally anyone could walk into a shop and buy them.

We increased the smoking age from 16 to 18 overnight. And now we've got that staggered, no tobacco sale under a certain age. And yet you can go and buy a pouch and I'm not saying that pouches are as bad as tobacco at all. That's probably not the case, but it does still feel somewhat unusual, doesn't it?

Yeah, and there are definitely harms associated with it. So I think the takeaway from this week is that nicotine may not be all bad. It may have potential medical benefit. And there does seem to be a trend moving away from traditional tobacco products, which clearly carried with them quite a lot of risk towards vaping and pouches, which potentially carry less risk, but clearly no risk.

And it will be interesting to see what happens over the next few years. And particularly if you have got small children around, do keep your vape liquid and your nicotine pouches in a safe place, because there really is enough nicotine in there to cause some very serious harm as we've seen. So I hope you've enjoyed listening this week. Do give us a like and a follow.

That would be really appreciated. Hope you all have an amazing week and we'll see you next time. Bye.