

# **Global State of Tobacco Harm Reduction**



# Nicotine and Medical Research – A Background

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### Introduction

Nicotine has been widely accepted as a smoking cessation aid in the form of Nicotine Replacement Therapies (NRT) since the 1980s, and has been included in the World Health Organization's List of Essential Medicines to treat 'nicotine dependence' since 2009.¹ But the therapeutic use of nicotine in medicine has a history – and potentially a future – that extends beyond its most common application. Research has indicated that nicotine could be a promising drug in managing and treating certain conditions, including Parkinson's disease, Alzheimer's disease, neurodivergences, and psychosis.

However misconceptions about nicotine, due to its association with smoking and concerns over addiction, still need to be addressed in the medical field. In this Briefing Paper, we will examine why researchers are interested in the potential therapeutic properties of this intriguing molecule. In a related Briefing Paper we also look at the therapeutic potential of nicotine with respect to Parkinson's disease, Alzheimer's disease and mental health.

### What is nicotine?

Nicotine is a naturally occurring dinitrogen alkaloid (C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>) found in a number of plant species, most notably those from the Nicotiana genus of the Solanaceae or nightshade family; in plants, it acts as a natural insecticide.<sup>2,3</sup> Members of the Solanaceae family include familiar fruits and tubers, such as peppers, tomatoes, aubergines (eggplant) and potatoes,<sup>4</sup> although the amounts of nicotine in these plants is significantly lower than that found in the tobacco plant.<sup>5</sup> When ingested by humans, nicotine has a stimulant effect. It triggers the release of a variety of neurotransmitters including dopamine, a neurotransmitter associated with pleasure and reward.



### Ethno-medical uses of tobacco

Tobacco, and therefore nicotine, has a long history of use in traditional medicinal and religious practices in the pre-Colombian societies of the Americas. In this part of the world, the uses of tobacco have centred on nicotine's painkilling, gastrointestinal and mood-affecting properties.<sup>6</sup> Fifteenth-century European explorers returned from South America brandishing tobacco as a panacea,<sup>7</sup> or cure-all, due to their observance of indigenous tobacco use.<sup>8</sup> The tobacco plant is still used in traditional medicinal practice in South America.<sup>9</sup>

### A misunderstood molecule?

In the words of Michael Russell, considered one of the foundational figures in tobacco harm reduction, "people smoke for nicotine but die from the tar". When tobacco combusts, a range of products are produced. Tobacco smoke contains more than 4,000 chemical

constituents, of which 70 are known carcinogens.<sup>11</sup> Nicotine is the second most abundant constituent of tobacco smoke,<sup>12</sup> and is a key component in reinforcing combustible tobacco use.

Nicotine's capability to encourage repeated use has been conflated with the many detrimental health impacts associated with smoking. However, nicotine's physiological effects are comparatively few compared to the catastrophic impacts of the carcinogenic components of cigarette smoke. Some researchers judge the risk level of nicotine use in isolation from tobacco smoke to be similar to that of caffeine.13 Nicotine in NRT products has been listed as an Essential Medicine by the WHO since 2009, and as of 2025 the range of NRT products on the Model List of Essential Medicines consists of transdermal patches, lozenges, oral sprays and chewing gum at various strengths.14 Since the advent of safer nicotine products, the UK National Health Service, 15 the New Zealand Ministry of Health<sup>16</sup> and several leading public health institutions including the Royal College of Physicians<sup>17</sup>, have sought to debunk misinformation about nicotine, actively endorsing nicotine vaping, for example, as a smoking cessation aid.

# What are nicotine's potential therapeutic effects? The significance of nicotine in the brain and body

Neurons are specialist cells in the brain and nervous system that convey information throughout the body using electrical or chemical signals; neurotransmitters are the chemical messengers that move information between neurons.<sup>18</sup>

When it is ingested (via inhalation, orally or transdermally), nicotine, a psychoactive substance, affects the processes of the nervous system in various ways. This is because nicotine closely mimics the chemical interactions of a neurotransmitter called acetylcholine, which binds to nicotinic acetylcholine receptors that can be found throughout the central nervous system. <sup>19</sup> Nicotinic acetylcholine receptors help to modulate the release of other neurotransmitters, including dopamine, in the central nervous system. <sup>20</sup> They can be found in cholinergic and dopaminergic neurons, cells which pass electrical signals through the body using acetylcholine and dopamine as neurotransmitters. Nicotinic acetylcholine receptors also respond to a number of other chemical compounds, not exclusively nicotine.

Nicotinic acetylcholine receptors and their behaviour are important for understanding how certain neurological conditions progress and impact everyday life for people living with them. They play important roles in cognition – attention, learning and memory – and the reward pathways that affect motivation and pleasure. They also affect motor control processes, which coordinate and regulate the body's movements. Loss of nicotinic acetylcholine receptors in both dopaminergic and cholinergic neurons has been associated with the progression of neurodegenerative conditions such as Alzheimer's Disease

and Parkinson's Disease. <sup>21,22,23,24</sup> Broader abnormalities with the function of nicotinic acetylcholine receptors and the neurons that use them have been linked to a number of other neurodevelopmental and psychiatric conditions including schizophrenia, ADHD, epilepsy, Tourette's syndrome, depression and anxiety. <sup>25,26,27,28,29</sup>

Due to its ability to selectively bind to nicotinic acetylcholine receptors, nicotine has remained a compound of interest for researchers exploring disorders affecting memory and cognitive function. Nicotine has been shown to improve cognitive function in some individuals, including those with Alzheimer's disease, as well as people with existing cognitive deficits, but healthy non-smokers experience minimal cognitive benefits from using nicotine. A number of studies have also highlighted improvements in cognitive function in people with schizophrenia when nicotine is administered, 4,34,35,36 and similarly cognitive improvements have been observed in people with HIV who use nicotine, counteracting the impact of HIV-associated neurocognitive disorders.

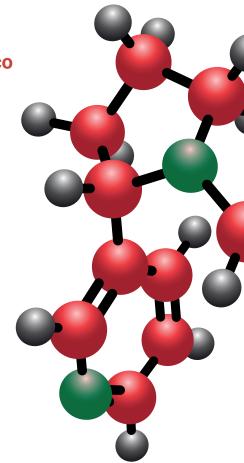
However, nicotine's performance-altering abilities appear to be restricted to people with underlying cognitive difficulties. For healthy nonsmokers with no underlying cognitive difficulties, nicotine offers minimal improvement, or worse performance, in cognitive function tests.<sup>38,39</sup>

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# Separating the epidemiology of nicotine from tobacco

Epidemiological data that emerged in the 20<sup>th</sup> century established a striking relationship between smoking and Parkinson's disease: that people who smoke appear to have a significantly lower risk of developing Parkinson's disease. The discovery of this inverse relationship between smoking and Parkinson's was surprising, as there are few other conditions with a similar relationship with smoking,<sup>40</sup> and this has prompted further investigation into the potential neuroprotective properties of particular constituents of tobacco smoke. A 2018 study with over 220,000 participants puts this startling relationship into numbers, finding that current smokers are 50% less likely to eventually develop Parkinson's disease, while former smokers were 20% less likely to eventually develop Parkinson's disease.<sup>41</sup>

Epidemiological research looking at nicotine use and the prevalence of particular neurological/mental health conditions has primarily used tobacco smoking data to analyse these health trends, as these data are significant in number and are spread over a long period of time. This leads to difficulties determining whether it is nicotine that could be responsible, as opposed to other chemical components of tobacco smoke, for the cognitive improvements seen in some people who smoke.



Some researchers have theorised that other compounds found in tobacco smoke, including carbon monoxide, a common byproduct of tobacco combustion, may contribute to the lower levels of Parkinsonism seen in people who smoke.<sup>42</sup> Research using rodent models has indicated that low doses of carbon monoxide help modulate oxygen levels within animal cells, and partially protect against the neurodegeneration associated with Parkinson's.<sup>43</sup> Importantly however, the neuroprotection offered by these components of tobacco smoke does not outweigh the overall detrimental impact of smoking.

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## **Developments in current research**

The inverse relationship between smoking and Parkinson's, as well as other neurodegenerative conditions such as Alzheimer's, indicates a potential role of nicotine in the prevention of these diseases, especially

as there are now many ways of delivering nicotine without smoking tobacco. It also raises a question of whether nicotine can be used in the treatment of these diseases by delaying onset or disease progression. That nicotine might be associated with a lower likelihood of having certain diseases does not necessarily mean that it will have therapeutic effects. Likewise, the possibility that nicotine might have a preventive effect does not necessarily mean that it will have therapeutic effects, and vice versa. For example statins protect against cardiovascular disease, but do not treat cardiovascular events such as stroke or heart attacks.

A number of researchers are currently involved in the investigation of nicotine's impacts on cognitive function, particularly among people with Alzheimer's and Parkinson's. We explore this in more detail in our second Briefing Paper on this topic. For example, the MIND project is examining whether controlled doses of nicotine, using nicotine patches, can impact memory loss and attention in people with mild cognitive impairment (MCI),<sup>44</sup> which is consequential as people with MCI have an above-average risk of subsequently developing dementia.<sup>45</sup>

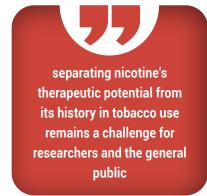
A number of studies have investigated the links between nicotine use and an apparent protective effect against Parkinson's disease, 46,47,48,49,50,51 finding that nicotine helped delay the disease's onset and could help prevent damage associated with neurodegeneration. 52 Neuroprotection refers to a treatment's ability to slow or prevent the loss of neurons due to neurodegeneration. Potential neuroprotective properties of nicotine have also been observed in relation to Alzheimer's. 53,54

Nicotine might potentially have a role as a therapeutic component in counteracting the side effects of the Parkinson's medication Levodopa. <sup>55,56</sup> One researcher in this field has noted that nicotine "may be the only drug that is useful for reducing [medication induced side effects in Parkinson's] without making Parkinson's disease worse". <sup>57</sup>



one researcher in this field has noted that nicotine "may be the only drug that is useful for reducing [medication induced side effects in Parkinson's] without making Parkinson's disease worse" Researchers have also highlighted the unexpected difficulties and failures in translating the epidemiological evidence supporting nicotine's therapeutic potential into the further stages (Phase II and Phase III) of clinical studies.<sup>58</sup> Problems with effective trial design, including issues with appropriate nicotine dose, are issues that have been proposed to be hampering the success and continuation of studies involving nicotine's alleged therapeutic effects.

Nicotine patches have frequently been the administration route of choice in studies researching the cognitive and attention improving qualities of nicotine, with their wide availability and low cost proving attractive



for future treatment options should further research show the clinical effectiveness of nicotine patch interventions. <sup>59,60</sup> However, separating nicotine's therapeutic potential from its history in tobacco use remains a challenge for researchers and the general public. Researchers must still overcome systemic barriers to carry out nicotine research. It has been noted that there is a distinct challenge of separating the investigation of nicotinic receptors from the negative perceptions of nicotine (as tied in with tobacco) in the medical community. <sup>61</sup> Recruitment for studies involving nicotine also remains problematic, with negative perceptions about the risks of nicotine reducing the pool of volunteers for large-scale studies involving nicotine. <sup>62</sup>

### **Conclusion**

Separating nicotine's therapeutic potential from its history in tobacco use remains a challenge for researchers and the general public due to nicotine's long association in reinforcing combustible tobacco use. But an ever-growing scientific literature is expanding our understanding of nicotine's role in the research of, and potential treatment of, a number of common and life-limiting conditions. Stemming from longstanding epidemiological evidence and nicotine's proven mechanisms of interaction with the central nervous system, and in conjunction with its low cost and wide availability, there exist a number of current and future research opportunities to explore the impact of nicotine and related molecules in addressing some of the world's most serious and ongoing public health concerns. This will be explored in further detail in our second Briefing Paper exploring the potential impact of nicotine in a number of neurodegenerative and mental health conditions.



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