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Nicotine Fact Sheets

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Fact Sheet 1: Nicotine – The Basics

Debunking Myths and Misconceptions

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This series of Nicotine Fact Sheets, beginning with the basics, has been devised to aid colleagues and health workers to navigate the complexities arising from often conflicting and dated information or from popular misunderstandings about Nicotine. Evidence for each point is provided with references. Other Fact Sheet topics to follow will be Nicotine and the Heart, Nicotine and the Lungs, Nicotine, the Brain and Mental Health, Nicotine and Pregnancy and Nicotine and Carcinogenesis.

NICOTINE AND TOBACCO

1. Nicotine is extracted from the tobacco plant and ***is not made synthetically*** (Roselius et al., 1979). The tobacco farmers and industry must grow, produce, and extract nicotine for both combustible and non-combustible usage of all nicotine-containing products. It is illegal to grow tobacco in Australia.
2. Nicotine is a naturally occurring alkaloid only found in the tobacco plant and some other plants (Hukkanen et al., 2005).
3. Larger lower tobacco plant leaves are more dilute, smaller top leaves are more concentrated in nicotine content (Tassew & Chandravanshi, 2015).
4. ***Many thousands of chemicals in cigarettes are naturally occurring*** in the tobacco plant itself (as they are in many other leafy plants) and are not "added" (Centers for Disease Control and Prevention et al., 2010).
5. ***Nicotine is colourless and odourless.*** Yellow stains are from burning leaf (called tar).
6. Ingredients are added to enhance flavouring, increase alkalinity for palatability, or improve burning in combustible tobacco (Centers for Disease Control and Prevention et al., 2010).

NICOTINE INTAKE

7. ***There are significant genetic predispositions to becoming nicotine dependent***. The nicotine Acetyl Choline Receptor, predominately the $\alpha 4\beta 2$ subunit, response to nicotine may be heightened in individuals and is a familial trait (National Cancer Institute, 2009; Tuesta et al., 2011).

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8. Nicotine is extremely well absorbed through the respiratory tract, including the nose, mouth, airways and ears (Hukkanen et al., 2005).
9. Nicotine is poorly (and slowly) absorbed through the skin and even less so through the gut (Hukkanen et al., 2005).
10. ***Most of the nicotine inhaled either by smoking or vaping is exhaled as a normal function of the lungs*** (Lutfi, 2017).
11. ***Very small (measured in nanograms)*** but effective amounts of nicotine diffuse through the lung airways and alveoli into the arterial blood that is perfusing the lungs at any one time (Benowitz et al., 2009).
12. People who smoke and/or vape accurately titrate nicotine dosage according to personal needs. To increase the nicotine diffusion, they may engage in breath-holding, taking more puffs or using more product—allowing for more transit time of nicotine into the blood perfusing the lungs. Conversely, to reduce nicotine diffusion they may reduce the number of puffs or puff lightly. The manipulation of nicotine intake is known as the "topography" of smoking (American Thoracic Society, 1996) or vaping (Dawkins et al., 2016).
13. The "flux" of nicotine, mgs/puff/sec coming out of vapes depends on the apparatus. Current technology allows for a finer, quicker, higher delivery of nicotine. This technology has been intentionally developed to make vapes more rewarding and improve the transition from combustible tobacco (Gold & Lerman, 2012; Shihadeh & Eissenberg, 2015).
14. Speed of delivery into the arterial blood via the lungs is essential to the neuropharmacological brain "reward" and dependence. This inter-arterial delivery has quicker access to the brain as it bypasses the venous system entirely. Hence lung delivery of nicotine is the ideal manner to get nicotine into the brain (Henningfield & Keenan, 1993).

NICOTINE METABOLISM

15. ***Arterial plasma levels of nicotine are in nanograms*** per litre (ng/L), not milligrams per litre (mg/L), despite nicotine levels in the intake being in milligrams (Benowitz et al., 2009; Hukkanen et al., 2005).

16. Nicotine is quickly excreted and metabolised. It has a half-life ranging between 40 minutes to 2 hours (Benowitz et al., 2009; Hukkanen et al., 2005)
17. The liver enzyme P450 CYP 2A6 metabolises nicotine, and there are substantial and significant genetic variations in this enzyme. ***Individuals may be fast or slow metabolisers of nicotine which influences the frequency of nicotine use and responses to Nicotine Replacement Therapy (NRT).*** Fast metabolisers need more NRT for efficacy, slow metabolisers need less (Gold & Lerman, 2012).
18. Various ingested substances can inhibit the enzyme P450 CYP 2A6, directly affecting nicotine plasma levels (Hakkola et al., 2020). Inhibitors include grapefruit (Hukkanen & Benowitz, 2005) and some medications.
19. Other significant nicotine metabolising enzymes are CYP 2B1 and CYP 2E1. They are known to be induced by alcohol (Bittoun, 2011).
20. Age, gender, hormones, pregnancy and ethnicity influence nicotine metabolism. Metabolism slows down with age and females generally metabolise nicotine faster than men. During the pre-menstrual phase and throughout pregnancy nicotine metabolism is faster still (Benowitz et al., 2006; Bowker et al., 2015; Murphy et al., 2018). Metabolism of nicotine is generally faster amongst Europeans (e.g. Turkish) and slower amongst Asian population groups (Delijewski et al., 2019; Gold & Lerman, 2012).

GENERAL NICOTINE TOXICITY

21. Symptoms of nicotine toxicity and physical overdose are rare in adults (Benowitz, 1998; Mayer, 2014).
22. Symptoms of physical toxicity and overdose hierarchy include nausea, vomiting, tachycardia, ventricular fibrillation, and cardiac arrest (Benowitz, 1998; Mayer, 2014).
23. There is a hierarchy of nicotine effects dependent on the speed of delivery (Henningfield & Keenan, 1993) (see Figure 1).

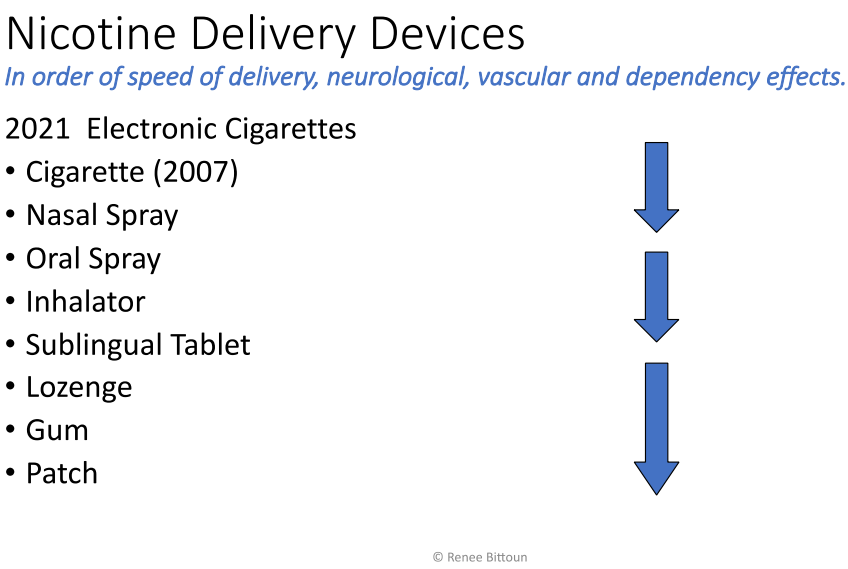

Figure 1. Nicotine Delivery Devices and Speed of Delivery

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