What doctors should consider before prescribing e-liquids for e-cigarettes

An Australian standard for prescribing e-cigarette nicotine has arrived — are you prepared with the facts?

Various nicotine replacement therapies (NRTs) have been approved by the Therapeutic Goods Administration (TGA) as safe and effective smoking cessation aids. However, many smokers are now turning to electronic cigarettes (e-cigarettes) to reduce their tobacco consumption, even though there is a lack of clear, unbiased data on whether, and how effectively, e-cigarettes aid tobacco smoking cessation.[1] There is also growing evidence that they may cause harm.[2] Emerging evidence shows concurrent use of tobacco cigarettes and e-cigarettes may be worse than either just smoking or just vaping, particularly for cardiovascular health.[2]

In early 2021, the TGA announced that a standard for vaporiser nicotine products was in development. The announcement further inflamed debate during public consultation. Therapeutic Goods (Standard for Nicotine Vaping Products) (TGO 110) Order 2021,[3] which came into effect on 1 October 2021, does not refer to e-cigarettes themselves (which remain unapproved by the TGA as smoking cessation devices), but rather the nicotine-containing liquids (e-liquids) used in them. TGO 110 defines key aspects of e-liquids, such as permitted nicotine concentrations that can be supplied and a small list of chemicals currently banned from inclusion in these products. This is especially pertinent for Australian general practitioners and respiratory specialists, as e-cigarette users (vapers) can now legally access e-liquids containing nicotine locally with a prescription. Doctors need to be registered as an authorised nicotine prescriber or provide via a special access scheme through an Australian pharmacist registered to supply nicotine. This is a significant change for vapers who previously sourced nicotine from overseas under the TGA Personal Importation Scheme (https://www.tga.gov.au/personal-importation-scheme)

TGO 110 provides no guidance to GPs as to how to manage e-cigarette prescriptions, but Royal Australian College of General Practitioners guidelines advise that doctors should promote approved NRTs and proven pharmaceutical therapies accompanied by behavioural support before considering e-cigarettes.[4] As always, doctors should use their own judgement of a patient's intent before prescribing any medication. Here, we provide an outline of what doctors should consider when prescribing nicotine for e-cigarettes to patients.

There is growing international concern surrounding the high concentrations of nicotine available for vapers, largely due to nicotine's addictive and toxic properties. The European Union has limited e-liquid nicotine concentrations to 20 mg/mL,[5] a concentration that leads to plasma nicotine levels similar to those achieved by NRTs (dependent on puffing topography and e-cigarette type).[6] TGO 110 permits nicotine content in prescribed e-liquids up to 100 mg/mL in base form (or equivalent when the nicotine is in a salt form). The highest concentration in ready to use nicotine products currently sold overseas is 59 mg/mL. Use of high nicotine concentrations correlates with increased risk of long term use of e-cigarettes or relapse to tobacco cigarettes.[7] On the other hand, there are concerns that using too low a nicotine concentration at the beginning of a cessation attempt may lead users to compensate by increasing consumption and puff topography,[8] resulting in increased exposure to the numerous non-nicotine toxicants in e-cigarette liquids,[2] and that it may also be less effective in reducing cravings.[9]

At present, there is little evidence as to the "ideal" nicotine concentration in e-cigarettes to help tobacco smokers to transition to complete nicotine abstinence. However, e-liquids containing 18 mg/mL have been shown to reduce cravings to a similar extent as traditional tobacco cigarettes,[10] and have been reported as adding small benefits on tobacco smoking cessation above those obtained with NRTs.[11] As such, 18 mg/mL, which is close to the EU maximum concentration of 20 mg/mL,[5] may be a prudent starting concentration.

A clinical trial which compared e-cigarettes with NRT combined with at least 4 weeks' behavioural support in both groups found higher smoking abstinence success rates in the e-cigarette group; however, less than 5% of the NRT group were still using NRT at the 1-year mark, compared with 40% for the e-cigarette group.[11] While median nicotine levels dropped from 18 mg/mL (interquartile range [IQR], 16–18 mg/mL) at the start of the trial to 12 mg/mL (IQR, 6–18 mg/mL) at 6 months, there was only a < 10% decrease in the subsequent 6 months (median, 11 mg/mL; IQR, 5–18 mg/mL),[11] again reinforcing that ongoing structured behavioural support is needed to attain nicotine abstinence. Interestingly, a 2020 case report described a successful

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12-week e-cigarette cessation attempt following pharmacist-supported staggered nicotine reduction combined with additive small behavioural goals such as not vaping during certain hours of the day or at certain locations, or limited number of puffs per day in someone with high nicotine dependence.[12] This case study combined with the clinical trial data described above[11] highlights that structured behavioural support combined with a nicotine tapering plan can lead to nicotine abstinence. GPs should therefore consider prescribing nicotine-containing e-liquids for short periods as part of an agreed abstinence plan (Royal Australian College of General Practitioners guidelines recommend ≤ 20mg/mL free-base nicotine and a 3-month prescription maximum),[4] allowing monitoring of progress and any negative health effects at regular intervals. This is important, as long term use of e-cigarettes may itself increase the risk of adverse health effects.[2]

While it is well understood that tobacco cigarettes are carcinogenic and that nicotine is a scheduled poison, e-cigarettes come with an added complication — flavours. There is increasing evidence that some flavouring chemicals (flavourants), including those found in Australian e-liquids, may pose a greater risk to health than others.[2] A small number of flavourants known to be dangerous are prohibited under TGO 110. However, flavourants are not currently required to be proven safe for vaporisation and inhalation before being allowed to be included in Australian e-liquids, and it is likely that there are toxic flavourants not banned under TGO 110. Moreover, the addition of flavourants may be counter-productive to the goal of smoking cessation. Nicotine has an adverse taste that may lower the desire to vape. Flavourants can mask this, which may result in prolonged use of higher nicotine concentrations compared with unflavoured e-liquids, and thus longer user of e-cigarettes overall and greater exposure to inhaled toxicants.[13] Given that the long term health effects of e-cigarettes remain largely unknown, unflavoured e-liquids should be preferentially prescribed. We acknowledge that some individuals may require or prefer flavoured e-liquids to achieve nicotine abstinence, so it is critical that they be educated that no flavouring chemicals are approved for inhalation and that there is evidence that many pose a risk to health.[2] This should be part of the discussion as to why complete abstinence should be the goal rather than long term e-cigarette use.

GPs should be aware that emerging data implicate effects of flavourants on nicotine absorption and the nicotinic dopamine pleasure effect by reducing the number of available receptors. This could affect a patient's smoking cessation attempt by increasing nicotine addiction. Studies have shown that flavoured e-liquids can significantly increase plasma nicotine levels up to 1.66 fold,[14] likely associated with the effect of flavourants on acidity and nicotine absorption. For example, menthol flavourants act as negative allosteric modulators (which indirectly reduce the time of nicotine receptors in the open/signal transduction state) of nicotinic acetylcholine receptors, resulting in slower nicotine metabolism and pathway activation, thus enhancing the addictive properties of nicotine.[15,16] This is one reason why menthol has been banned in tobacco cigarette products in many jurisdictions,[17] although it is not yet banned in tobacco cigarettes in Australia. It is reasonable to assume that menthol will have the same effect when used in e-cigarettes, but it is not a banned ingredient in TGO 110. Further, a 2020 study shows that farnesene (which creates a green apple flavour) increased nicotine reward-related behaviour in mice even in the absence of nicotine, and that it stimulated nicotinic acetylcholine receptor function and enhanced nicotine's potency for activating nicotinic acetylcholine receptors on dopamine neurons.[18] A study using functional magnetic resonance imaging found that strawberry vanilla e-cigarette use engaged the taste-related brain regions while suppressing activation of the neural circuits characteristically engaged during smoking and nicotine exposure.[19] This suppression could lead to vapers using e-cigarettes more frequently, or using e-liquids with higher nicotine concentrations, to elicit the same nicotine reward. Taken together, these findings warrant caution in prescribing flavoured e-cigarettes, to ensure that they do not lead to increased and/or prolonged use of e-cigarettes.

In our opinion, the current evidence suggests it is critical that physicians be aware of the effects of nicotine concentration and flavourants when prescribing e-liquids to Australian vapers. Prescribing physicians should combine e-cigarettes with structured behavioural support to promote tobacco cessation and, ideally, complete nicotine abstinence, rather than seeking to reduce patients' nicotine intake through dual use of e-cigarettes and tobacco cigarettes. A starting level of nicotine should be chosen that is no higher than that in tobacco cigarettes, but which is sufficient to suppress nicotine cravings. The (perceived) benefits of inclusion of flavourants on smoking cessation must be balanced with their potential for toxicity and promotion of nicotine addiction. The prescribing physician should strongly suggest using unflavoured e-liquids and educate the patient on the health risks of e-liquid flavourants. This should continue until such a time as the TGA provides further evidence to support which (if any) flavours do not have detrimental effects on smoking cessation attempts or users' health.

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