

Nicotine – friend or foe? The complex interplay between nicotine dependence, it's role in harm reduction and risk communication.

Our field has a difficult relationship with nicotine. On the one hand, Michael Russell's famous quote: "People smoke for nicotine, but they die from the tar" (<https://doi.org/10.1136/bmj.1.6023.1430>) paved the road for the development of effective smoking cessation treatments based on nicotine in the 1970/80s, such as nicotine replacement therapy (NRT), that helped drive down smoking rates. Over 20 years later, the proliferation of e-cigarettes, delivering nicotine effectively without combustion, meant that harm reduction became a reality. E-cigarettes help those unable or unwilling to stop smoking with medication to switch to a reduced risk product without complete cessation of one or more tobacco constituents, namely nicotine, resulting in ever lower smoking rates (ref). On the other, we know that nicotine is not an innocuous substance. There are well-documented cardiovascular effects (ref), nicotine is dependence-forming and may impact the developing brain (ref). The increasing youth use of e-cigarettes, first seen in the US (ref) and now in Europe (ref), is therefore concerning, particularly if it occurs among adolescents who have never smoked. This issue of *NTR* sheds some light on the equivocal role that nicotine plays in our efforts to curb the tobacco epidemic and the need for nuanced communication regarding its effects.

Huang et al (ref) study shows nicotine's utility for the testing of potential medication to treat tobacco addiction. In a rodent model, dextromethorphan (a cough suppressant used in over-the-counter medication) was shown to reduce nicotine-induced reward and drug-seeking behaviour in nicotine-dependent rats during withdrawal. Of course, such animal models using nicotine rely on this being a useful proxy for studying human addiction. One concern is that these models use noncontingent nicotine administration, with minipumps, rather than self-administration, as is the case for humans. Chellian et al's review (ref) shows that, similar to humans, rodents become gradually dependent on nicotine over time across various self-administration paradigms, especially if access is intermittent and longer, highlighting the usefulness of this approach. Interestingly, as growing evidence suggests that e-cigarettes may result in dependence, this is also seen in rodents with nicotine aerosol self-administration. However, animal models exclusively use adult rodents and, it is argued, using newer self-administration paradigms, the gradual development of dependence needs to be studied over a longer time, starting in adolescence, to increase ecological validity and reflect human experience.

The paper by Walters et al (ref) dives deeper into the drivers of dependence in young adulthood, showcasing the use of nicotine craving as a tool for investigating potential behavioural interventions. In this ecological momentary assessment study, 18-25 year old smokers and vapers were asked to stop product use and, followed over a month, were periodically prompted via an app to respond to questions measuring positive/negative affect, emotion differentiation (the ability to distinguish emotional states) and craving. Both positive and negative affect were associated with greater cravings in the moment, but this relationship was attenuated among those with higher negative emotion differentiation, suggesting that heightened emotional states may be misinterpreted as nicotine cravings for those with low emotion differentiation. While this study did not analyse smokers and vapers separately, it identifies a modifiable treatment target, emotion differentiation, to support young adults, who may be particularly vulnerable to intense affect, to stop product use. At the population-level, Teh's et al (ref), age-period-cohort model assesses changes in smoking intensity across several cross-sectional representative surveys in Malaysia, covering a 20-year period. Although smoking intensity, operationalised as cigarette consumption, is arguably an imperfect measure of nicotine addiction (<https://pubmed.ncbi.nlm.nih.gov/25063772/>), there are two key findings here relevant to the discussion of nicotine dependence and harm reduction. First,

more recent cohorts displayed higher smoking intensity, consistent with the much debated “hardening hypothesis” (<https://pubmed.ncbi.nlm.nih.gov/12745505/>). i.e., the idea that over time, those persisting with smoking will be more resistant, hard-core smokers. Notwithstanding the fact that this recency effect may reflect other sociocultural differences, resulting in Malaysia finding itself in an earlier stage of the tobacco epidemic (Ref), if true, it also highlights the need for harm reduction to help those increasingly more addicted smokers to switch away from combustible cigarettes. Second, smoking intensity increased up to the age of 60, which again would support the “hardening hypothesis”, but which the authors also link to early smoking initiation seen among older smokers. Picking up the discussion in Chellian et al (ref) and reported elsewhere (Ref – Breslau), this underscores that danger of early nicotine exposure being associated with later, more powerful cigarette addiction and thus nicotine dependence.

This leaves us with a conundrum. Nicotine has been helpful for the development of effective cessation treatment and harm reduction methods for addicted smokers. However, many in our community are deeply concerned about the increasing availability of nicotine in appealing e-cigarettes, which, even if these divert youth away from the most harmful of nicotine-delivery products – cigarettes (ref), may lead to a new wave nicotine-dependent adolescents, and thus adults, with all the unknowable effects this entails. So, how should we communicate the risks of nicotine? The ambivalent attitude towards nicotine in our field has unintended consequences elsewhere. O’Brien et al’s (ref) study of adolescents in the PATH study confirms what has been observed in adults, including medical professionals (ref), that nicotine is seen as causing smoking-related harms beyond addiction, such as cancer. While on the positive side, those having higher risk perceptions were less likely to start using nicotine-containing products a year later, on the negative side, even among adolescent smokers nearly half believed that nicotine in NRT was harmful, which may reduce the use of effective medication to help these smokers stop. Similarly, Emery et al (ref), reporting on the development of a questionnaire on NRT for smoking cessation in pregnancy, acknowledge the need to take these misperceptions about nicotine in NRT into account and assess them. This new scale can be used to measure beliefs prior to treatment and, if necessary, address wrong beliefs to increase low adherence rates to NRT in this population. Both studies highlight the very real implications of the, at times, problematic treatment of nicotine in research, driven mainly by concerns about nicotine dependence *per se*. Clearly, no-one wants to see a generation of nicotine-dependent youth, and more effective measures to limit access to nicotine, especially combustible nicotine, are needed. But when it comes to communicating research to the wide public, we must avoid conflating the relatively limited harm of nicotine dependence with its effects on maintaining tobacco addiction, and therefore tobacco-related harm, not least because of the impact this has on risk perceptions of those most in need of nicotine-based treatment: tobacco users.