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The development and testing of new nicotine replacement treatments: from 'nicotine replacement' to 'smoking replacement'

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ABSTRACT

Griffith Edwards, unusually in the 1970s, saw tobacco use as falling within the remit of addiction research, and brought Michael Russell to the Addiction Research Unit [ARU] to initiate research into smoking. The work of the tobacco section of ARU paved the way to a better understanding of tobacco dependence and to developing nicotine replacement treatments. Michael Russell pioneered the idea of attractive nicotine replacement products with an acceptable safety profile replacing cigarettes on the open market and ending the tobacco epidemic, envisaging a transition from medicinal and temporary 'nicotine replacement' to recreational and potentially permanent 'smoking replacement'. Mike's prediction that the pharmaceutical industry would develop such devices did not materialize. Instead, two such products were generated by the tobacco industry (snus) and independent developers (electronic cigarettes). Another of Mike's hopes was that regulators would adopt rational policies, and that tobacco control activists would become supportive of smoking replacement once they thought through the implications. Until now, the 'smoking replacement' idea has been met with vigorous opposition from some tobacco control activists. The voices of researchers with historical links to ARU are prominent in arguing in favour of harm reduction and e-cigarettes. The most important debate ever to occur in tobacco control is under way and it carries the signature of Griffith Edwards' ARU.

Keywords Electronic cigarettes, nicotine regulation, nicotine replacement, tobacco dependence.

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INTRODUCTION

Griffith Edwards' impact on the field of tobacco dependence and its treatment was indirect, but profound. Griffith saw tobacco use as falling within the remit of addiction research, which was a view rather unusual at the time. He brought Michael (Mike) Russell to the Addiction Research Unit (ARU) to initiate research into smoking and, as the saying goes, the rest is history.

Mike's enormous contributions are covered elsewhere [1]. This paper focuses on current developments anticipated by Mike Russell, but materializing only after his death: the emergence of nicotine replacement devices which provide smokers with a safer and satisfactory alternatives to smoking rather than promoting cessation of nicotine use altogether, i.e. a transition from medicinal and temporary 'nicotine replacement' to recreational and potentially permanent 'smoking replacement'.

ARU work on smoking, nicotine and harm reduction

Mike Russell's early studies were instrumental in clarifying the importance of nicotine in driving smoking behaviour and in developing nicotine replacement treatments for smokers [2]. The ARU conducted the first studies of nicotine chewing gum, a product that became the first pharmacotherapy for smoking to be used worldwide (e.g. [3]). The Unit also completed pioneering work on the nicotine nasal spray, which provides faster nicotine absorption [4], and examined the efficacy of the nicotine patch [5]. Behind these developments was the realization that nicotine itself is not particularly harmful, and outside pregnancy it may pose little or no risk. As Mike memorably put it: 'people smoke for nicotine but die from tar' [6].

We had already observed previously that there was a small proportion of nicotine replacement therapy (NRT) users who continued to use the products beyond the

recommended 3-month period [7]. Nicotine nasal spray, which provides nicotine faster than nicotine chewing gum, generated about three times as many long-term users [4]. The speed of nicotine delivery seemed to determine not just the probability that the product will be used long term, but also the probability that users will enjoy it. Long-term users of nicotine nasal spray reported that they like their NRT more frequently than did long-term users of nicotine chewing gum.

Throughout this period, we were discussing the implications of a gadget which would provide nicotine in an efficient and enjoyable way without the tobacco toxins. It would very probably improve the efficacy of treatment, but more importantly it could have the potential to simply replace cigarettes.

When a US company developed a nicotine inhaler we conducted the first study of its effects on smoking cessation, with considerable expectations [8]. The results were disappointing, in that the effects of the device were similar to those observed with the gum. The device did not emit any smoke, provided few sensorimotor stimuli and looked conspicuously medicinal, but it also clearly provided only the slow buccal absorption of nicotine. Later studies confirmed this [9]. The product was eventually launched as a new nicotine replacement treatment formulation and it remains a useful option in the NRT range, but it is not particularly popular with smokers.

Even more disappointingly, all later NRT products produced by the pharmaceutical industry remained in the same category of low nicotine doses delivered at a slow rate. This was due in part to substantial regulatory hurdles facing any deviation from the parameters established during the long and difficult process of medicinal licensing of nicotine chewing gum.

The US drug licensing authority, the Food and Drug Administration (FDA), took a particularly cautious approach to NRT. Although NRT was clearly one of the safest products on the pharmacy shelves and was eventually available over the counter, the FDA insisted on dramatic warnings implying that using NRT combinations or even using NRT while smoking is dangerous. Given that these warnings were addressed to smokers who were obtaining much higher doses of nicotine plus a range of toxins in clinically dangerous quantities from cigarettes, this was seriously misguided. The same attitude of exaggerated caution and the refusal to match hypothetical product risks to real risks of smoked tobacco characterizes current attitudes of medicinal regulators to snus and e-cigarettes.

The attitude to NRT by the UK Medicine Licensing Authority (MHRA) was much more rational and liberal. The influence of the ARU is the most likely reason. Mike's pupils and collaborators, including Jonathan Foulds, Martin Jarvis, Ann McNeill, Lesley Owen, Martin Raw and Robert West, all contributed to calls for relaxing the overcautious labelling of NRT products (e.g. [10]).

Mike Russell and 'smoking replacement'

Mike Russell made an early suggestion that a safe and satisfactory nicotine delivery device could end the tobacco epidemic. One of his last papers, published in 1991, was entitled: 'The future of nicotine replacement' [11]. It is only a few pages long and should be made compulsory reading for tobacco control activists and policy makers.

Rather than rephrasing its contents, below are a few illustrative quotations from this paper.

'Some time in the 21st Century we would see the rapid demise of tobacco smoking. How soon this can be achieved will depend on how soon we adopt rational policies. It is essential for policy makers to understand and accept that people would not use tobacco unless it contained nicotine, and that they are more likely to give it up if a reasonably pleasant and less harmful alternative source of nicotine is available'.

'It will be assumed throughout that our main concern is to reduce tobacco-related disease and that moral objections to the recreational and even addictive use of a drug can be discounted provided it is not physically, psychologically or socially harmful to the users or to others'.

'It is not so much the efficacy of new nicotine delivery systems as temporary aids to cessation, but their potential as long-term alternatives to tobacco that makes virtual elimination of tobacco a realistic future target'.

'Such products should be actively promoted on the open market to enable them to compete with tobacco products'.

'Until they have thought it through, those in the anti-smoking movement may fear that their clear simple message will be complicated and undermined. It need not be changed. There is only one fight and that is against tobacco and tobacco-related disease… Availability of a substitute for tobacco will help the anti-smoking message to be heeded '.

The key and still highly controversial suggestion is that we should not worry if a clean nicotine product provides what smokers want, i.e. a 'smoking replacement' for recreational use rather than just a temporary medicinal 'nicotine replacement'.

Current controversies

One aspect of Mike's prediction did not materialize: he expected the smoking replacement to be invented by the pharmaceutical industry as a natural successor to the early NRT products he helped to develop. He underestimated the stifling burden of medicinal regulation and the lack of enthusiasm by the pharmaceutical industry to innovate commercially successful goods. NRT products still cling to

somewhat lame parameters established by nicotine chewing gum in the 1970s. Any substantial improvements would require new licensing applications at prohibitive costs. This hurdle, combined with the cautious attitude of regulators and the pharmaceutical industry, meant that incremental evolution of pharmaceutical NRT did not happen.

Instead, two products with the promise Mike was predicting were generated by the tobacco industry (snus) and independent developers (electronic cigarettes). They both stumbled on another of Mike's unfulfilled hopes. Regulators did not adopt rational policies, and until now most tobacco control activists do not support harm reduction and smoking replacement.

The case of snus

Snus is a Swedish ground tobacco product held behind the lip. The manufacturing process differs from US oral tobacco. Its use may entail a degree of risk, but it is at least an order of magnitude safer than smoking [12].

Snus delivers levels of nicotine comparable to cigarettes higher and faster than those provided by NRTs, and although there is no arterial 'bolus' this seems sufficient for many smokers, particularly men, to use snus instead of cigarettes.

During the past 25 years, Sweden recorded the largest reduction in male smoking prevalence of any developed nation, and it has now the lowest male smoking prevalence in Europe. This was accompanied by dramatic reductions in lung and oral cancer and improvements in cardiovascular health in men. There has been no sign of snus acting as a gateway to smoking [13]. Similar developments have been recorded in Norway, where snus is also available [14].

Anyone unaware of the purging zeal of tobacco control activists would naturally assume that these real-world experiments must have persuaded any previously hesitant regulators and public health bodies to promote snus in all countries with high smoking prevalence. Alas, in a remarkable debacle of public health decision-making, snus has been banned by the European Union (EU) and the ban remains in place, impervious to evidence and common sense. European regulators seem to be determined to protect the market monopoly of deadly cigarettes, and proclaim absurdly that the ban on snus is in the interest of public health.

The case of e-cigarettes

The snus fiasco is currently being re-enacted with a new 'smoking replacement' device, e-cigarettes. The potential repercussions are even worse this time, because the product being banned or crippled has a realistic chance to evolve into a genuine and complete replacement of cigarettes.

During the past few years, smokers in economically developed countries have been showing growing interest in electronic cigarettes (EC) that are designed to deliver nicotine, with the chemicals which make cigarettes dangerous either absent or present only at trace levels. EC in their current form do not yet match cigarettes, although in the hands of experienced users some models are already capable of delivering cigarette-like levels of nicotine [15]. The crucial point is that EC are undergoing rapid development, with dozens of small companies competing to improve the product. Their popularity among smokers is increasing, and they are already threatening cigarette markets [16].

The European ruling, which is to become law in 2016, threatens to stop product evolution and to skew the competition between EC and cigarettes heavily in favour of cigarettes. It is likely to block developments making EC competitive against cigarettes; limit nicotine content to below that needed by dependent smokers; raise EC costs to uncompetitive levels; and put obstacles to EC availability. EC will fall predominantly into the hands of the tobacco industry, who are likely to be the main player with resources to tackle the licensing processes, and who will have little interest in abolishing the cigarette market. Small agile innovators will go out of business.

From the public health viewpoint, this makes little sense. There are two consumer products competing for smokers' custom. One of them is much more dangerous than then other. Regulators are limiting the safer product and the dangerous one is left to rule unopposed. The reasons such moves are desired by the tobacco and pharmaceutical industries are obvious. If EC are allowed to develop to match cigarettes, they would first undermine the market for smoking cessation medications and later kill cigarettes. If they are kept in their current 'not yet very good' form, it may offer additional commercial opportunities for the tobacco industry that is acquiring leading EC brands, without jeopardizing cigarette markets. Protecting tobacco and pharmaceutical interests, however, should not feature highly on the public health policy agenda.

An increasing number of academic commentators are joining smokers in protesting against these developments. The voices of researchers with historical links to the ARU are prominent in arguing in favour of harm reduction and e-cigarettes [17]. The weight of opinion may yet swing as more data are emerging and people are thinking through the relevant issues. There is also a saving grace, in that the linked UK and EU regulations will ban 'unlicensed' EC only from 2017. EC now need to race against time to become a match for cigarettes as quickly

as possible. Cigarettes had more than a century to evolve into what they are now. EC will have under 2 years. Good luck to them.

CONCLUSIONS

The work of the Addiction Research Unit paved the way to understanding tobacco dependence and developing nicotine replacement treatments. Mike Russell pioneered the idea of attractive nicotine replacement products replacing cigarettes on the open market and ending the tobacco epidemic. Two products, Swedish snus and e-cigarettes, have appeared, matching Mike's predictions, but until now the 'smoking replacement' idea has been meeting vigorous opposition from tobacco control activists and regulators. An important fraction of academic voices trying to prevent regulations intended to cripple these developments can be traced back to the influence of Mike Russell and the work of the ARU. The most important debate that has ever occurred in tobacco control is under way, and it carries the signature of Griffith Edward's ARU.

Declaration of interests

Peter Hajek has received research funding and provided consultancy for manufacturers of stop-smoking medications. He has no links to any e-cigarette manufacturers.

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