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The prescribing of varenicline and vaping (electronic cigarettes) to patients with severe mental illness

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POSITION STATEMENT

Purpose of document

This position statement provides advice and recommendations to psychiatrists on the prescribing of varenicline, and the use of electronic cigarettes (EC), as strategies to support people with severe mental illness (SMI) to stop smoking.

Summary of key messages and advice

Smoking rates among people with SMI are much higher than in the general population, contributing to increased morbidity and premature mortality among this group. Psychiatrists are well placed to help them stop smoking.

The decline in prescriptions of stop smoking treatments needs addressing: greater investment is required in stop smoking services – tailored to meeting the needs of people with SMI – which provide access to a range of effective treatments.

Psychiatrists should give more consideration to prescribing varenicline, which is a generally safe and well-tolerated medication shown to increase rates of smoking cessation in psychiatric and non-psychiatric populations. We will work with other organisations to raise awareness and ensure psychiatrists understand the efficacy and safety of this medication.

While we do not fully understand the long-term risks, psychiatrists should advise their patients that ECs are an effective option for some people to give up smoking and are substantially safer than continued tobacco use. All mental health providers should have policies in place that facilitate the safe and effective use of ECs.

Background

People with SMI (such as schizophrenia and bipolar disorder) die, on average, 17 years prematurely. These are *stolen years*, lost because of lung, heart, stroke and vascular diseases. Smoking causes all four of these and, additionally, 27% of all cancer deaths (Peto *et al*., (2012).

Despite coordinated efforts within health and other services, particularly since 2008, the differences in life expectancy between people with SMI and the rest of the population has increased. The largest preventable component of premature death for this group is smoking (Peto *et al*., (2012).

This is against a backdrop of a long-term decline in smoking rates, to the extent that the vast majority of adults (~85%) in the UK are non-smokers (Office for National Statistics, 2018). Much of this decline can be attributed to the range of national tobacco control measures[1] that have countered years of advertising, sponsorship, product placement and misinformation from Big Tobacco. However, smoking rates among people with an SMI remain stubbornly high – for example, in England, 40.5% of people with an SMI are smokers (PHE Local Tobacco Control Profiles, 2016).

This is associated with several factors. Health inequalities, principally poverty, make smoking and its harmful effects more likely. People with mental health problems, especially anxiety, appear to be more addicted to nicotine, and many will begin or lapse into heavy smoking during a crisis psychiatric hospital admission.

Most people with SMI are therefore more likely to need help to quit smoking. Psychiatrists are well placed to support these individuals given their understanding of the processes of addiction and the clinical contact they have with them as patients. This paper aims to provide advice and recommendations to help with this role, with a focus on varenicline and EC use. We hope it will allow College members to support patients with SMI to become tobacco free – working with them, their carers, health and other professionals to achieve the same low smoking rates as the rest of the population. Parity of esteem means people with mental health problems deserve the same physical health as others, and the same opportunities to prevent diseases.

Interventions to support patients with SMI stop smoking

Stop smoking services

Comprehensive support for smokers wishing to quit is provided across the UK through smoking cessation services – in England, these are now commissioned by local authorities, while they are provided as a part of NHS services in Northern Ireland, Wales and Scotland. They provide practical support and pharmaceutical treatments on prescription – including nicotine replacement therapy (NRT)[2] and

1 Including taxation increases, progressive advertising and marketing restrictions, educational campaigns, age of sale restrictions and health warning on packaging.

2 Many individuals access NRT products over-the-counter or via a stop smoking service as a way of quitting. NRT is a medication that provides a low level of nicotine, without the tar, carbon monoxide and other poisonous chemicals present in tobacco smoke. It can help reduce unpleasant withdrawal effects, anxieties and cravings which may occur when stopping smoking. This treatment has long been the mainstay of smoking cessation, and is available as skin patches, chewing gum, inhalators, tablets, oral strips and lozenges, and nasal and mouth spray.

other medications such as varenicline and bupropion – which can help smokers to quit.

Although likely to be caused in part by the reductions in the proportion of people smoking, it is concerning to see declines in NHS prescriptions of stop smoking treatments (NRT, varenicline and bupropion). The British Lung Foundation (2018) found a decline in England by 75% between 2005–06 and 2016–17, in Scotland by 40% between 2012–13 and 2014–15 and in Wales by two thirds between 2005–04 and 2016–17). It should, however, be noted that there has been a large increase in access to non-prescription stop smoking treatments in Wales which is not reflected in the data.

The College supports more investment in stop smoking services as a default (opt-out) service. We also know that if people are recruited into these treatments in secondary care services, they are around 30% more likely to have a positive outcome compared to those in community-based settings (Stead *et al.*, 2016).

There is growing evidence to support the effectiveness of in-house smoking cessation advisors within mental health organisations (Action on Smoking and Health (2016), and we call for specific resources to support peer support workers. There are also resource implications for the investment of clinicians' time into smoking cessation, and buying additional equipment – for example, carbon monoxide monitors to verify ex-smoking status. We urge members to advocate for these essential supports locally.

In supporting patients with SMI who are smokers, the College believes psychiatrists need to give greater consideration to prescribing varenicline, as well as the role of ECs. The following section explores these two areas in greater detail.

We commend Smoking Cessation Training to our members and trainees, available locally and free online at http://www.ncsct.co.uk/.

Varenicline

The Royal College of Physicians' 2018 report, *Hiding in Plain Sight,* concluded that the NHS and public health are failing in their duties of care to patients who smoke. Across the UK, one in four people who successfully quit smoking used varenicline prescribed by their GP or a stop smoking service. Psychiatrists work mostly in secondary care, and meet the highest proportion of tobacco dependent patients of any specialty. We know psychiatrists have not been prescribing this medication in significant amounts for patients with SMI.

Evidence to support prescribing of varenicline to those with SMI

Short-term varenicline use is effective and safe over its 12-week course. It needs to be prescribed 2 weeks before a planned quit date. In addition to the multiple health benefits of quitting smoking, patients will save money and may be able to achieve dose reductions in some common psychiatric medications.

The only negative side-effect is the potential for weight gain, and psychiatrists should work with patients, families and multiple agencies to provide support in this area. While concern has been expressed about adverse neuropsychiatric events, it has been concluded by well-designed cohort studies, meta-analyses and a large prospective double-blind randomised controlled trial that there is no significant increase in risk in patients prescribed varenicline.

- In 2009, a cohort study published in the BMJ – which utilised 80,660 men and women aged 18–95 years from the General Practice database – there was no clear evidence found for varenicline being associated with self-harm, increased depression or suicidal ideation.

- In 2016 the EAGLES study – a double-blind, randomised, placebo-controlled clinical trial which, in part, studied the neuropsychiatric safety and efficacy of varenicline – concluded that there was no significant increase in neuropsychiatric adverse events in those prescribed varenicline.

Overall, varenicline is a generally safe and well-tolerated medication which has been proven to increase rates of smoking cessation in psychiatric and non-psychiatric populations, including at reduced dosage, and as a medication is more effective than NRT or bupropion.

More detailed advice and evidence in relation to the prescribing of varenicline can be found at Appendix 1.

The high cost of varenicline (trade name is Champix) is possibly having an impact on levels of prescribing. Therefore, it is important that clinicians and commissioners recognise that even before cheaper, generic forms are made available across the EU in 2021, it remains cost effective given the reduction in multimorbidity and early mortality in people who smoke.

College Position

The Royal College of Psychiatrists believes:

- psychiatrists should consider the prescription of varenicline when clinically indicated as one of the options to support patients with SMI to stop smoking

- in light of the underuse of varenicline in circumstances that it will provide clinical benefit, we will work with other organisations to raise awareness among psychiatrists (and other prescribers) of its efficacy and safety.

There is an alternative medicine to varenicline in the form of bupropion (brand name Zyban). This is a medication originally used to treat depression but has since been found to help people quit smoking. It is not clear exactly how it works, but it is thought to have an effect on the parts of the brain involved in addictive behaviour. It is only available on prescription, so a patient will usually need to see a GP or contact an NHS stop smoking service to use it.

Electronic cigarettes

An EC is an electronic device that delivers nicotine in a vapour. This allows you to inhale nicotine without most of the harmful effects of smoking, as the vapour contains no tar or carbon monoxide.

Their use has increased markedly with a rise in the number of adults in Great Britain vaping from 700,000 in 2012 to 3.2 million in 2018 (Action on Smoking and Health, 2018). It is estimated that in 2017, 5.5% of individuals adults aged 16 years and above reported that they currently used an EC (vaped), compared to 3.7% in 2014 (Office for National Statistics, 2018). They have also become the most popular device used in self-directed attempts to stop smoking (West *et al*., 2018). Consequently, it is likely that many patients with an SMI who are smokers are using, have used or have considered using, ECs as a way to quit smoking.

It is therefore important that psychiatrists are able to provide reliable advice on the benefits and risks of their use.

- Using an EC is always better than smoking a cigarette. Public Health England have comprehensively examined the evidence and declared ECs 95% safer than cigarettes (McNeill *et al*., (2018).

Evidence is continuing to emerge on the effectiveness of ECs for smoking cessation, and they have been used with NRT, and in conjunction with varenicline, to help people quit (Action on Smoking and Health, 2016).

As the impact of long-term EC use is unknown, best advice is to use ECs to quit smoking and then gradually reduce and cease EC use. For those who are unable, or unwilling, to stop using them, it is a better option than continuing to smoke.

Research does not show that exposure to the constituents of EC vapour poses specific health risks to bystanders; however, users should consider other people's comfort, and should use their devices in the open air when possible (Action on Smoking and Health, 2016).

There are several considerations for EC use by psychiatric in-patients to ensure that they can be used safely and effectively. This is best supported by mental health provider organisations having policies that facilitate the use of ECs by patients for whom it is the most suitable way to address their smoking. This should ensure that ECs are used in a way that promotes cessation, and minimises other risks such as any potential hazards associated with refillable tanks and fire safety risks associated with unsupervised recharging. The National Fire Chiefs' Council has provided guidance on the latter, E-cigarette use in smoke free NHS settings.

From a broader policy perspective, the wide availability of ECs has led to concerns about children and young people using them and acting as a gateway to tobacco use. While awareness of, and experimentation with, ECs has increased in the UK, regular use among children is rare, and is highest among current smokers. In 2015/16, regular use (at least weekly) of ECs by 11–16 year old never smokers was between 0.1% and 0.5%; among current smokers it was between 7% and 38% (Bauld *et al*., 2017). It is also worth noting that trends in smoking among children and young people do not support concerns that EC use is promoting tobacco use in this age group – for example, the number of regular smokers aged 11–15 decreased from 5% in 2010 to 3% in 2016 (NHS Digital (2017). This suggests that the substantial restrictions on the sale (prohibited to under 18s), advertising and promotion of ECs are effective policies. These should be kept under review to ensure they continue to provide appropriate protection for children and young people.

WE, the College, share the concerns of our physician colleagues: "Tobacco companies, who are likely to enter the harm-reduction (EC) market, have a despicable record for honesty and product safety, and are therefore likely to abuse any freedom to promote alternative nicotine products." (McNeill in RCP's *Nicotine without Smoke*, 2012).

College Position

We believe that although there is limited evidence in relation to the impact of their long-term use, there is growing scientific consensus that ECs are an effective option for some people to give up smoking and are substantially safer than continued tobacco use.

- Psychiatrists should advise patients who smoke that ECs may help them to quit, particularly when used in conjunction with stop smoking treatments, and are a safer than continuing to smoke. They should be encouraged to avoid EC in the long term where possible, provided this does not lead to a return to smoking.

- We support the recommendation of the Parliamentary Science and Technology Committee (2018) that all mental health provider organisations should ensure they have policies in place that facilitate the use of ECs safely and effectively.

- There should be continued efforts to collect national and regional data about quitting, smoking and EC use in populations (general, by age and gender, and groups with mental disorders), varenicline prescriptions, and ongoing research into the best evidence for stopping smoking and nicotine use.

Appendix 1: Varenicline – an overview of the evidence and prescribing guide

Introduction

Nicotine acts in many areas of the brain and starts to exert its effects shortly after inhalation of tobacco smoke. The main area of the brain under consideration for the purposes of smoking addiction is at the level of the mesolimbic system and the nucleus accumbens. Here, nicotine binds to acetylcholine receptors on dopaminergic neurons resulting in the release of excess dopamine in the reward centres of the brain. Nicotine is not degraded quickly and thus acts for longer than acetylcholine. This results in prolonged stimulation, subsequent de-sensitisation and up-regulation of receptors which are thought to drive the dependence on nicotine.

Varenicline is similar in structure to nicotine but acts as a partial agonist at the α4β2 nicotinic acetylcholine receptor with high affinity and selectivity. It is therefore able to modulate the action of nicotine at this receptor sub-type alleviating some of the symptoms of dependence while inhibiting repeated over-stimulation by nicotine (Potts *et al*, 2007) (Stahl, 2013).

Safety

Concerns were raised with regards to the safety of varenicline after post marketing surveillance reported a range of neuropsychiatric symptoms such as suicidal behaviour, violence and agitation (Cahill *et al*, 2009) (Evins, 2013) (Anthenelli *et al*., 2016). However, the initial trials excluded smokers with a psychiatric illness which meant that what was reported was a possibility rather than causation (Evins, 2013) (Jorenby *et al*., 2006).

In 2009, a cohort study published in the BMJ which utilised 80 660 men and women aged 18-95 years from the General Practice database found that while unable to rule out a two-fold increase in risk of self-harm, there was no clear evidence for varenicline being associated with self-harm, increased depression or suicidal ideation (Gunnell, 2009).

In 2013 as part of a review of pharmacological interventions in smoking cessation published by the Cochrane Library, a meta-analysis of 14 trials found no difference between varenicline and placebo in with regards to significant adverse effects including neuropsychiatric events, (Cahill *et al*., 2013).

In 2013 a meta-analysis of 17 placebo-controlled trials including 8 027 patients found no evidence that varenicline is associated with adverse neuropsychiatric effects, and that current or past psychiatric disorder elevated risk equally in both treatment and placebo groups. In addition, the authors of the study also reviewed the USA Department of Defense data set (N=35 800) to ascertain rates of acute neuropsychiatric effects, finding that the overall rate of neuropsychiatric adverse effects was significantly lower for those prescribed varenicline than for those using nicotine replacement therapy (Gibbons & Mann, 2013)

In 2016 the EAGLES study – a double-blind, randomised, placebo-controlled clinical trial which in part studied the neuropsychiatric safety and efficacy of varenicline – concluded that there was no significant increase in neuropsychiatric adverse events in those prescribed varenicline (Anthenelli *et al*., 2016).

Thus, well designed cohort studies, meta-analyses and a large prospective double-blind randomised controlled trial have all concluded that there is no significant increase in neuropsychiatric adverse events in patients prescribed varenicline.

In 2011, the Food and Drug Administration (FDA) in America issued a warning that varenicline may be associated with a small increase in risk of cardiovascular events (FDA, 2011). In 2012, a systematic review and meta-analysis of all the 22 published trials at this point found no clinically or statistically significant increase in cardiovascular adverse events. The FDA also requested a meta-analysis of Pfizer sponsored trials looking at major cardiovascular adverse effects (Ware *et al*., 2013) (Mills *et al*., 2013). This meta-analysis of 7 002 patients in 15 studies concluded that although there was a trend towards a greater number of events with varenicline, this increase is not statistically significant (Ware *et al*., 2013). A further study published in 2013 used a network meta-analysis which included 18 randomised controlled trials of varenicline and found no increase in risk with regards to cardiovascular adverse effects (Mills *et al*., 2013). A retrospective cohort study published in 2015 which utilised the data from 753 GP practices across the UK concluded that while varenicline was not associated with an increased risk when compared to nicotine replacement therapy (NRT) (Kotz *et al*., 2015). A nationwide cohort study in Denmark including 17 926 users of varenicline over 3 years concluded that there was no association between varenicline and increased risk of major cardiovascular events and there was no significant difference between patients with or without cardiovascular disease (Svanström *et al*., 2012).

Effectiveness

The aim of prescribing varenicline is to assist people in their smoking cessation. A Cochrane review of nicotine receptor partial agonists found that varenicline as a smoking cessation aid increased the chance

of stopping smoking between two- and three-fold in comparison to non-medicated attempts at quitting (Cahill *et al*., 2016). In addition it seems that those using varenicline are more likely to successfully quit than those using nicotine replacement therapy or bupropion (Cahill *et al*., 2016).

With regards to people suffering from psychiatric disorders, the EAGLES study concluded that varenicline is more effective than bupropion, NRT and placebo for smoking cessation in both non-psychiatric and psychiatric cohorts (Anthenelli *et al*., 2015).

Prescribing (Adults)

Varenicline is an initial 12-week course be the end of which the patient should be abstinent. In addition, at the end of this course a further 12 weeks can be prescribed in those who have achieved abstinence to reduce the risk of relapse.

The course should be started 1–2 weeks prior to a target stop date – 500 micrograms once daily for 3 days, increasing to 500 micrograms twice daily for 4 days, then 1mg twice daily for 11 weeks.

If not tolerated at the higher dose of 1mg twice daily, this can be reduced to 500 micrograms twice daily instead. It is important to note that even at reduced dose of 500 micrograms daily, varenicline is associated with significant quit rates above that of a placebo.

The most common side effect is nausea (Anthenelli *et al*., 2015) (Jorenby *et al*., 2006). Dose titration appears to reduce nausea, and there is a dose-response relationship with the higher dose regime of 1mg twice daily causing greater nausea and 500 micrograms twice daily being comparable to that of placebo groups (Oncken *et al*., 2006). Other frequent adverse effects include dyspepsia, dry mouth, constipation, flatulence, vomiting, insomnia, headaches, dizziness, abnormal dreams, and somnolence (Evins, 2013) (Oncken *et al*., 2006). For a full list of adverse effects, we recommend referring to the summary of product characteristics.

There are no trials of varenicline in pregnancy and is not recommended in women who are pregnant or breast feeding (Cahill *et al*., 2016) (Coleman., 2015) (British National Formulary, 2017).

As per the Medicines and Healthcare Regulatory Agency (MHRA) “Patients should be advised to discontinue treatment and seek prompt medical advice if they develop agitation, depressed mood, or suicidal thoughts. Patients with a history of psychiatric illness should be monitored closely while taking varenicline” (British National Formulary, 2017).

Thomas *et al* (2015) studied 39 randomised controlled trials (total participants were 10,761 people) and their meta-analysis there was "no evidence of an increased risk of suicide or attempted suicide, suicidal ideation, depression, or death with varenicline".

As per the FDA Drug Safety Communication, patients should be warned that varenicline can change their reaction to alcohol with reported decrease tolerance, increased drunkenness, unusual and aggressive behaviour and no memory of events. In addition, there have been the rare occurrences of seizures with the use of varenicline (FDA, 2015).

We have the evidence, so why are prescription rates falling?

The number of prescriptions for varenicline peaked in 2010 at 987 000 and continues to fall every year: https://www.statista.com/statistics/370285/prescription-items-of-varenicline-to-quit-smoking-in-england/

Cuts to public health in general, disproportionately more in local authorities' addictions services, are part of the reason for this decline. Professionals working in NHS secondary care services, specifically the majority of psychiatrists, have not taken up its prescription to redress this. The Royal College of Physicians' 2018 report *Hiding in Plain Sight* described a 2016 audit of stop smoking activities across secondary care as "woefully inadequate". The case for changing our current practices is compelling.

Summary

Varenicline is a generally safe and well-tolerated medication which has been proven to increase rates of smoking cessation in both psychiatric and non-psychiatric populations, including at reduced dosage, and is more effective than NRT or bupropion. Given the significant risks of smoking on physical health and premature death, clinicians should weigh the high risks of smoking against assisting patients to quit with the use of pharmacological intervention which should include varenicline.

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