Improving smoking cessation approaches at the individual level

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WHY ASSIST CESSATION?

Treatment of tobacco addiction

Most smokers show symptoms of addiction to nicotine.[1] The symptoms and signs of addiction are described by diagnostic classification systems, such as the *Diagnostic and Statistical Manual of Mental Disorders*. However, perhaps the most important symptom in this context is the failure of attempts to stop smoking when a person tries to accomplish this. Frequent smoking is thought to set up a subconscious learning process linked to the release of nicotine from cigarettes.[2] When a person decides to stop smoking, s/he is afflicted by urges to smoke, often in places where smoking has previously taken place.[3] Furthermore, such a person usually experiences withdrawal symptoms.[4] These are mostly adverse moods, but with some physical symptoms as well. It is thought that these urges to smoke are primarily responsible for the failure of most attempts to stop smoking. Without support around half of all attempts to stop fail within the first week of attempted abstinence.[5] The typical smoker who seeks treatment for cessation has never managed more than a few weeks without smoking.[6] The period of withdrawal varies by symptom, but typically lasts a few weeks.[4] Therefore most smokers' experience of not smoking is state of withdrawal and perhaps beliefs that smoking is a stress reliever, for example, stem from experiencing withdrawal during abstinence.

The two main approaches to assist cessation are pharmacotherapy and behavioural support. Pharmacotherapy for smoking cessation aims primarily to reduce the intensity of urges to smoke and/or ameliorate the aversive symptoms. Behavioural support aims to boost or support motivation to resist the urge to smoke and develop people's capacity to implement their plans to avoid smoking. These interventions last typically only a few months. It is thought that during these months, the strength of the associative learning between smoking and reward diminishes and most symptoms of withdrawal remit.[7] After these few months, most smokers should have overcome their addiction and should be able to remain off cigarettes.

When doctors and others treat smokers for smoking cessation, they are generally treating the symptoms of tobacco withdrawal, namely the urges to smoke and the withdrawal symptoms. The prime reason why we provide this treatment is that we recognise addiction to tobacco as a medical disorder, that is, amenable to treatment and people ask for this treatment.

Treating tobacco addiction is part of medical treatment

Using tobacco, primarily smoking cigarettes, has been strongly and causally linked with several adverse health consequences. In most countries, the prime causes of excess mortality in smokers are cancers (especially lung cancer), cardiovascular disease and chronic obstructive pulmonary disease.[8] It seems likely that if smoking causes disease, then stopping smoking would ameliorate it and indeed there is growing evidence for the efficacy of smoking cessation in the management of various diseases. For example, there is evidence from a meta-analysis of cohort studies that stopping smoking after a myocardial infarction reduces the risk of recurrence and death by about a third.[9] Similarly, a meta-analysis of cohort studies showed that stopping smoking after a diagnosis of potentially curable lung cancer also greatly reduces the risk of recurrence and death.[10] For chronic obstructive pulmonary disease, cohort studies show that smoking cessation appears to be the only treatment that reduces the rate of decline in lung function[11] and subgroup analysis from randomised controlled trials (RCTs) show the benefits of steroid inhalers on lung function depend on a patient stopping smoking.[12] Many patients diagnosed with serious smoking-related disease stop smoking, but many continue, mostly as a result of the failure of their attempts to stop smoking rather than a desire to continue smoking in the face of disease.[13] Consequently, doctors and healthcare staff should discuss the role that smoking plays and provide appropriate (maximal) assistance with cessation for their patients.

The public health argument

We have proposed that some people who smoke seek help to manage their addiction or find themselves unable to stop despite an immediate clinical need to do so. This is an argument to provide cessation support as part of routine medical care, but many countries have taken the view that cessation services should be widely promoted as an instrument of public health.

This argument for runs as follows. In many countries, smoking presents the largest avoidable risk factor for ill health. A typical lifelong smoker loses 10 years of life,[8] which is more than from moderate hypertension[14] and about the same as from morbid obesity (a small proportion of all obesity).[15] Cessation prior to the age of about 40 years avoids most of the harm, while continued smoking thereafter leads to a loss of 3 months of life for every year smoked.[8] Many people consult their primary care doctor at least annually and s/he

is usually tasked with providing a range of preventive interventions, for example, screening and management of hypertension. In the case of smoking and of hypertension, it is possible to reduce blood pressure significantly and stop smoking by lifestyle reform.[16] In both cases, there is good evidence that medical interventions increase the success rates. Therefore it seems reasonable for the medical system to opportunistically identify hypertension and smoking and to offer medical intervention often. Although there are differences in the conditions, the argument for both as public health interventions is similar.

If these arguments are accepted, it would seem odd for a doctor not to recommend smoking cessation and provide assistance in the form of medical intervention, much as they would, for example, in managing hypertension or hypercholesterolaemia. Treatments for smoking cessation are 'among the most cost effective of all healthcare interventions'.[17] Consequently, governments that promote cessation treatment as an instrument of public health have produced strategies to ensure that treatments for cessation are widely available and that doctors recommend these to their patients as often as possible, together with strategies to ensure that the public are aware of opportunities to use support to stop smoking (see companion review by Shu *et al*[18] on promoting cessation at the population level).

ASSISTING CESSATION

Brief interventions by doctors

The simplest intervention that we can make to increase smoking cessation is for a doctor to advise their patient to stop smoking. This is relatively easy to accomplish, takes only a few seconds and a systematic review of RCTs shows it is effective.[19] Most people who hear such advice will not act on it, and most people who act on it will not succeed.[19] However, in view of the wide reach of primary care doctors, this intervention is of paramount importance to public health and it is important to maximise the effectiveness of these few seconds. The most common intervention doctors make is to advise cessation (because it will prevent ill health), but a systematic review of RCTs show that offering support for smoking cessation (such as medication or behavioural support) enhances the rate at which people attempt to stop smoking.[20]

Pharmacotherapy

Pharmacotherapy aims to reduce the intensity of withdrawal phenomena and probably works by reducing the frequency and or intensity of urges to smoke. All effective smoking cessation medication accomplishes this,[21 22] and the most effective medication suppresses urges to smoke to a greater degree.[22] Smoking cessation will succeed if, at every given moment where smoking is possible, the motivation to smoke is lower than the motivation to abstain.

There are three pharmacotherapies currently licensed widely throughout the world for smoking cessation: nicotine replacement therapy (NRT), bupropion and varenicline. In addition, there are several other medications shown to be effective and used in some countries, most notably nortriptyline and cytisine.

NRT comes in various formats but the most notable difference is between the nicotine patch and all other forms. The nicotine patch requires once daily application but all other forms provide NRT in formats that require repeated use, usually into the oral cavity. All NRT formats produce irritant local effects at the site of administration, but otherwise appear safe, even for people with serious medical disorders, and are certainly safer than smoking.[23] In theory, if people smoke for nicotine, NRT should replace cigarettes and make quitting easy. However, tobacco addiction is maintained by more than just nicotine,[24] and the nicotine delivery from cigarettes is very different from that achieved by all forms of NRT.[25] Cigarettes deliver a relatively high bolus of nicotine effectively into the pulmonary venous circulation and hence relatively high concentration into the arteries to the brain. NRT is effectively absorbed into the systemic venous circulation and much more slowly than through the alveolae, thus delivering a much lower concentration to the brain. There are no proven effective nicotine inhalation devices available currently for technical reasons, but companies are working to produce such and these may prove to be more effective than currently available forms of NRT.

For many smokers, the current best treatment with NRT will be combination NRT. Arguably, the most sensible combination will be a nicotine patch with a short-acting form. Exposure to smoking cues can provoke craving, and short-acting NRT ameliorates this,[26] whereas this may not be the case with nicotine patches. In any case, a systematic review of RCTs and a subsequent trial show that combination NRT is more effective than single form.[27] Subgroup analysis from RCTs show that more dependent smokers have a lower chance of abstinence than do less dependent smokers. However intranasal NRT, the most rapidly absorbed product, abolishes this difference in outcome.[28 29] Together these data should encourage the search for more rapidly acting forms of NRT that might prove effective in the face of episodic craving.

Varenicline is a nicotinic partial agonist, meaning it stimulates and blocks nicotinic receptors in the brain. A systematic review of randomised trials (and other evidence) show it is more effective than single-form NRT and bupropion.[30] It is typically advised for use for up to 2 weeks prior to stopping smoking. It might be important that varenicline blocks nicotinic receptors while smoking. Tobacco addiction is thought to be maintained by an acquired drive to smoke, that is, learnt from repeated reward following inhalation of cigarette smoke. If varenicline blocks the ability of nicotine to bind to the ventral tegmental area of the brain and stimulate the reward from cigarettes, this might begin to undermine the learnt drive to smoke. If so, taking varenicline for longer while smoking might further undermine smoking and make abstinence easier. Indeed, one randomised trial with a short-term outcome showed good evidence that longer use of varenicline while smoking undermined reward and led to improved cessation.[31] The same effect might be achieved by nicotine itself (eg, delivered by patches), which tends to depolarise the nicotinic receptor and render them insensitive to further nicotine (from cigarettes). This so-called nicotine preloading has been associated with improved cessation outcomes compared with post-cessation use only, but a systematic review of RCTs showed the data are inconsistent and insufficient to recommend for routine use.[32] Nevertheless, this use of combined agonist/antagonist approach is worth further investigation.

Cytisine is also a partial nicotinic agonist. A systematic review of RCTs showed evidence that it was more effective than placebo, but deficiencies in these trials means the conclusion appears uncertain.[33] A recent trial run to modern standards has shown that cytisine is clearly effective.[34] This is important because the current retail cost for cytisine is only a few US dollars, and this puts cessation treatments within financial reach of many of the world's smokers, most of whom cannot afford currently licensed products.

Antidepressants have been used to support cessation, principally on the belief that depression is a withdrawal symptom and a history of or occurrence of depression during cessation is associated with a worse outcome.[35] Bupropion and nortriptyline were both first used as antidepressants and ameliorate mood related withdrawal symptoms but their effect on cessation is not mediated through this effect.[36] However, selective serotonin reuptake inhibitors also ameliorate mood related withdrawal symptoms[37] and are effective as antidepressants,[38] but a systematic review of RCTs shows no evidence that they are effective in smoking cessation.[39] The mode of action is probably not a class effect of antidepressants, but probably relates to particular aspects of their complex pharmacology.

A systematic review of randomised trials shows that bupropion increases the rate of cessation by about 70%.[39] The mechanisms of action of nortriptyline and bupropion may differ from that of NRT and so several trials have tested whether combining one of these antidepressants with NRT is more effective than either the antidepressant or NRT alone. The data are insufficient to exclude a small benefit of combination, but it is clear that the effects are not additive.[39]

Behavioural support

Behavioural support works to enhance cessation rates by boosting motivation to stop smoking and supporting people's capacity to avoid smoking in the face of urge to smoke. Most typically it consists of regular weekly clinic appointments with a therapist, sometimes with other smokers trying to stop smoking. By its nature, behavioural support is a multicomponent intervention, working in several ways to increase abstinence. This makes it difficult to establish which components are effective. Furthermore, adding actions incrementally to behavioural support is only likely to have modest effects on apparent benefit, even if efficacious, making it difficult to detect improvements on behavioural support in randomised trials. Direct trials of broad, often theoretically based interventions versus interventions with a different theoretical approach show little evidence to favour one form of treatment programme over another.[40] This may suggest that a key common component is non-specific. Smokers experience discomfort when trying to stop and can always remove the discomfort and still meet their goal by 'quitting tomorrow'. By creating loyalty to a programme, therapist, or group, programmes can overcome this tendency to procrastinate because clients or patients are held to account. However, the difficulty of detecting differences in modest effects means we cannot be sure of this conclusion, which is speculative.

There is some evidence that the effects of behavioural support and medication are independent and therefore that they are additive (or multiplicative).[40] It is likely also that behavioural programmes support the efficacy of medication by enhancing adherence. However, surprisingly few trials have examined specific interventions to enhance adherence to smoking cessation medication, given it is an oft-reported problem by therapists. This is an area where further work is needed.

Given the difficulties of incremental randomised trials to assess the components of behavioural support, some have taken another approach to identifying effective intervention components. This approach uses a taxonomy of behavioural change techniques, which goes beyond broad descriptions (such as cognitive behavioural therapy) to identify the single component elements of a behavioural intervention (such as providing feedback on performance or prompt specific goal setting).[41] It is possible to deconstruct evidence from randomised trials of effective interventions to describe the components in terms of the taxonomy and to differentiate effective from ineffective interventions by the behavioural change techniques used.[42 43] It is also possible to code either behavioural support treatment manuals or therapy sessions for the use or non-use of particular behavioural change techniques. The UK has a network of otherwise similar clinics but which vary greatly in the behavioural change techniques used and that see hundreds of thousands of smokers annually. This variation provides a natural experiment with which to examine whether techniques are associated with better outcomes.[44] Planned experiments, where techniques are taught to some but not all practitioners, would strengthen the evidence further and may overcome the difficulties of the RCT in this context.

Alternative approaches to delivering behavioural support

Even with vigorous promotion of formal cessation treatment only a minority of smokers who try to quit smoking do so using that support. One approach to improve reach is to provide behavioural support programmes by media other than face-to-face clinical encounters. The most established format is by telephone. Telephone support can provide an 'emergency' contact service for the user and leads to economies of scale for the health services that provide or commission this. The format that has best evidence of effectiveness is 'proactive' cessation support, meaning regular telephone calls by appointment, much as occurs in face-to-face support. There is strong evidence of efficacy from a systematic review of RCTs.[45]

A less established format is internet-based support. Users log on to a website and are typically encouraged to return regularly, much as in the typical clinic pattern. Many of the activities that take place in clinics can be delivered over the internet. Although such sites will obviously attempt to be engaging, they inevitably lack the relationship-forming element that might be important in telephone or clinic-based support. Adherence to the programme is usually lower in internet-based interventions. Nevertheless, systematic reviews of RCTs show that such interventions are effective, but there are insufficient data to know whether they are equally or more effective than telephone or clinic-based support.[46] Recently, mobile telephones have become available that have good access to the internet and can display complex information graphically. So-called smartphones have capacity to provide interventions when needed, for example, in the face of temptation to smoke. Text (SMS) messages provide the same kind of intervention without human contact. A systematic review of RCTs showed there was insufficient evidence that these enhance long-term cessation.[47] However, a recent very large trial showed strong evidence that this form of support was effective.[48] Text message support is likely to be particularly affordable and accessible for many people in developing countries.

IMPROVING CESSATION SUPPORT

There is clear evidence that cessation support enhances the prospects of a quit attempt succeeding, so it is disappointing that relatively few attempts use optimum support. Further interventions are required to ensure that effective interventions are available and are used more often.[18] However, the focus of this review is on interventions that assist cessation for the individual. With optimal treatment, about half of all smokers can end treatment abstinent, but most will resume smoking in the future. It is not altogether clear why, because such people are usually adamant that they will not do so. We might take the

view that withdrawal finishes after a few weeks,[4] and that learnt associations between reward and smoking have been extinguished. However, observational data show that many people do not show the typical of rise in withdrawal and then fall over weeks.[49] Rather urges to smoke rise and fall and are often associated with adverse moods. We need more work to understand the immediate causes of return to smoking if we are to prevent this. That said, there have been a number of trials that have examined the efficacy of interventions for relapse prevention.

The most commonly studied approach used to prevent relapse is that of Marlatt and Gordon in which smokers are taught to recognise high-risk situations and create plans to prevent themselves smoking. A systematic review of RCTs showed no evidence of efficacy.[50] The systematic review also showed no evidence that other behavioural interventions are effective. Progress in this field has been hampered however, because such RCTs have typically enrolled smokers at the point of cessation, not after the initial period of cessation is over. This will tend to dilute the size of effect that such interventions might be expected to have. One study that enrolled only abstinent smokers tested a further 3 months of varenicline in people who had completed the initial 3 months. This study showed that abstinence was higher at the end of treatment and 3 months later.[51] A subgroup analysis showed that this effect appeared to be confined to those people who had lapsed after quit day.[52] There is insufficient though suggestive evidence that longer than standard use of NRT may also prevent relapse.[50] It is unlikely that long-term medication, as used, for example, in hypertension, will be a commonly used intervention to prevent relapse, but episodic use may be and further work in this area is needed.

One 'medication' strategy that might prevent some long-term relapse is a nicotine vaccine. By conjugating nicotine to an immunogenic protein, it is possible to raise antibodies against nicotine. During smoking, nicotine released into the circulatory system will be bound by circulating antibodies and, if antibodies are present in sufficient quantities, very little nicotine will cross the blood brain barrier. This should mean that smoking becomes gradually less rewarding. If a lapse (smoking episode) occurs, it is possible that full return to smoking will be less likely, as the reward from the lapse will be less than otherwise would have been the case. No phase III trial has been published in the academic literature, but early data show no sign of efficacy of this technology at present.[53]

BROADENING THE REACH OF CESSATION TREATMENT

Treatment programmes for smokers are typically aimed at smokers who can make a firm commitment to quit on a 'quit day'. While, in many countries, a large proportion of smokers report making a quit attempt, most do not.[54] Nevertheless, most smokers report unhappiness with smoking[55] and many smokers in countries with strong tobacco control climates report actively trying to reduce their smoking,[56] most as a prelude to quitting.[57] Unaided, few succeed.[58 59] One strategy to broaden the reach then is to provide smoking cessation treatment to people who do not want to stop smoking immediately.

A systematic review of RCTs showed that quitting by reduction was roughly equally effective as quitting abruptly if people are prepared to set a quit date, but the data were insufficient to exclude important differences in efficacy.[60] In people who cannot set a quit date, a systematic review of RCTs showed that a reduction programme incorporating behavioural support with NRT was more effective than support alone.[61] Likewise, for the same population, a non-systematic review of RCTs showed that behavioural support plus NRT led to more than double the abstinence rate than did brief advice to quit or no intervention, the usual options provided by health services for people with no immediate plans to quit.[62] Several RCTs show that reduction programmes that provide specific behavioural instructions on how to reduce are more successful than general reduction advice.[63] Taken together, this evidence strongly suggests that for many smokers who cannot stop immediately but want to cut down, their best chances of cutting down and then stopping come from following a behavioural support and medication programme that has typically only been provided for people seeking to stop smoking completely. However, current guidelines are cautious about recommending reduction programmes because of several concerns.[64 65] The chief concern is that a message that supports reduction as an alternative to cessation might deter cessation. Many people might decline reduction programmes and therefore the relatively certain benefit for those that join those programmes might be offset by deterring quitting in those that hear the message that 'reduction is good' but do not join a programme. No data on this exist, but it is important to assess this. This approach to smoking cessation might herald a change in paradigm, from supporting specific quit attempts, to supporting (nearly) all smokers most of the time. In essence, it means treating smoking and nicotine addiction like a chronic disease.[66] This is analogous to the polypill, which is envisaged as a prevention for cardiovascular risk for all people at higher risk of harm through age without specific risk factors such as hypertension.[67]

BROADENING THE SCOPE OF CESSATION INTERVENTIONS

The prime aim of interventions to promote cessation at the individual level is to improve health and reduce the ill-health consequences of smoking. Although smoking cessation is remarkably effective at undoing the harm of many years of smoking, it is accompanied by adverse consequences for a minority. For example, there is consistent evidence from several epidemiological studies that the incidence of type II diabetes is raised by 50% compared to continuing smokers,[68 69] which is surprising given that smoking is diabetogenic.[70] The cause is not fully understood, but it may be partly explained by weight gain that four in five smokers experience after cessation. Mean weight gain is about 4–5 kg in the first year (Aubin HJ *et al*. Unpublished data, 2012), but the mean weight gain is more like 7 kg overall.[71] However, the variation in weight gain is great, meaning many people are very different from the mean and that a significant minority gain much more than this. A systematic review of RCTs has shown that most proposed interventions can prevent only a small proportion of this weight gain.[72] Furthermore, available data give insufficient basis for detecting which individuals will gain significantly and targeting interventions at them. Addressing weight gain may therefore become incorporated into individual cessation programmes.

CONCLUSIONS

Individual cessation programmes employing behavioural support and nicotine gum were developed from the 1960s onwards, with the discovery of the central role of nicotine in sustaining addiction, which undermines sincere attempts to stop smoking.[73] Since then, improvements in efficacy have been incremental rather than revolutionary, and the story has been one of broadening access to treatments with new formats. Further progress in improving the rates of cessation within

populations are likely to come from more widespread use of effective aids to cessation and preventing late return to smoking in initial treatment successes.

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