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Vaccines Against Nicotine

How Effective are They Likely to be in Preventing Smoking?

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Abstract

Cigarette smoking is the most preventable cause of death in industrialised countries. 30% of all deaths in smokers in the 35 to 69 years age range are attributed to chronic cigarette smoking; smokers dying in this age cohort lose an average of 23 years of life. Public health campaigns have attempted to reduce initiation of smoking in adolescents and to foster quitting in dependent smokers. The prevalence of smoking has declined in the US to 25% of the population, but this figure has held constant for the last decade.

Vaccines against nicotine are a novel concept in the field of smoking cessation research and have not yet reached the stage of clinical testing. Vaccines could reduce smoking behaviour in 3 groups of smokers: (i) current smokers attempting to quit; (ii) former smokers wanting to avoid the possibility of relapse; and (iii) adolescent smokers before they become confirmed smokers. The rationale behind the approach is that nicotine is the pharmacological agent controlling the rate of cigarette smoking, and reducing its rate and extent of uptake into the brain may have therapeutic benefits.

The current definition of addiction to drugs encompasses the notion of a chronic relapsing disorder that persists even in the face of negative consequences.[1] From this definition it can be seen that nicotine addiction may be the quintessential example of an addictive disorder. Nicotine addiction, primarily in the form of cigarette smoking, is the most preventable cause of death in industrialised societies. Mortality estimates suggest that 30% of smokers in the 35 to 69 years of age cohort die from smoking-related diseases.[2] Overall estimates predicted that 21 million people in industrialised nations would die from tobacco-related diseases during the 1990 to 1999 decade. Moreover, there are proven benefits of smoking cessation. For example, former smokers live longer than those individuals who continue to smoke. Smokers quitting before age 50 years have half the risk of dying in the next 15 years compared with those individuals who continue to smoke. Smoking cessation reduces the risk of former smokers contracting lung cancer, other cancers, cardiovascular disorders and stroke, and nonmalignant lung disease.[3]

1. Why a Nicotine Vaccine?

Nicotine is viewed as the primary addictive agent in cigarette smoke.[4] The 1988 US Surgeon General's report concluded that cigarette smoking can be considered a form of drug addiction and that the behavioural and pharmacological processes associated with nicotine addiction are similar to those of heroin (diamorphine) and cocaine addiction. For example, nicotine affects dopamine release in the nucleus accumbens,[5] an effect common to morphine[6] and amphetamine.

Self-administration is a behavioural technique that utilises a contract for an emitted behaviour to obtain a 'reinforcer', in this instance a drug. In the laboratory, animals fitted with intravenous catheters for drug delivery learn to emit behavioural responses, e.g. pressing on a manipulandum, to obtain the drug reinforcer. Humans, usually drug-experienced, will also perform behavioural tasks to obtain drug delivery. Compounds that are self-administered are considered to be positive reinforcers, i.e. increase the probability of future drug administration. The technique can be used to assess behavioural contingencies and biological or pharmacological factors that increase or decrease self-administration behaviour. Nicotine sustains self-administration by the intravenous route in primates[7] and humans[8,9] under experimental conditions. Thus, in the absence of tobacco smoke, taste and other sensory cues, nicotine has been demonstrated to act as a positive reinforcer. The reinforcing effects of nicotine are dependent upon its rate of delivery. Rapid delivery of nicotine results in pleasurable subjective effects,[10] whereas slow infusion[11] or transdermal delivery[12] results in limited subjective and physiological responses.

This pharmacokinetic-pharmacodynamic relationship between delivery rate of a drug of abuse and reinforcement has also been reported for cocaine self-administration.[13] Rhesus monkeys will cease to self-administer intravenous cocaine if the rate of drug delivery falls below a critical level. Neurobiological effects associated with cocaine administration are clearly subject to the rate of cocaine delivery, and presumably the rate and extent of cocaine binding to brain sites that sustain the behavioural response. The 'rate hypothesis' has been articulated as being potentially significant for treatment of cocaine dependence.[14] The basis for a cocaine vaccine is the ability of the vaccine to bind to cocaine in the extracellular space and prevent or reduce its uptake into the brain. Consequently, the neurobiological events maintaining drug intake and dependence may be diminished to the extent that pharmacokinetic variables influence the maintenance and course of the dependence.

In a manner analogous to the relationship between the delivery rate for cocaine and its reinforcing effects, the 'rate hypothesis' would also pertain to nicotine. In other words, the ability of nicotine to sustain self-administration is subject to the rate of delivery of the drug. Interruption of nicotine delivery may enhance smoking cessation efforts. This concept also has significance in the treatment of current but not yet dependent smokers, as a nicotine vaccine could theoretically reduce the rate and extent of nicotine entry into the brain. If the reduction of nicotine uptake were large enough, it is plausible that dependence formation could be blocked or reduced.

The rationale for a nicotine vaccine in currently dependent or formerly dependent smokers at risk of relapse is 2-fold: (i) to reduce the rate and extent of nicotine uptake into the brain; and (ii) as a consequence of (i), to attenuate or block the reinforcing effect of nicotine. The blocking of the reinforcing effect could lead to diminished drug-seeking behaviour and facilitate smoking cessation in dependent smokers. We also speculate that the reinforcing effect may be responsible for 'priming'. Priming is defined as a propensity of a drug to initiate an increase in drug craving and intake following a single drug administration in a formerly dependent user. The priming effect is robust and can lead to relapse; it was initially based on clinical observations in alcohol-dependent patients and cigarette smokers but has since been validated in laboratory animals.[15] The priming effect is illustrated by a study[16] of a group of regular smokers who had remained abstinent for 4 days. Half the group were instructed to smoke 4 cigarettes, while the other half continued to remain abstinent. In the group who received the priming doses of nicotine, a greater proportion resumed smoking.

However, nicotine is not the only active pharmacological agent in cigarette smoke and this fact should be kept in mind in smoking cessation programmes. More recently, it has been demonstrated that a constituent of tobacco smoke can also inhibit monoamine oxidase A and B in the brain.[17,18] These enzyme isoforms catabolise brain amines and

their inhibition may contribute to the mood elevating effects of cigarette smoke. It has also been suggested that the high rates of depression in smokers may be linked to this observation, and that smoking cessation strategies may need to take this observation into account. One antidepressant, amfebutamone (bupropion), has been shown to be effective in smoking cessation efforts[19-21] and could be used in combination with a nicotine vaccine.

2. Experimental Evidence for a Nicotine Vaccine

Traditionally, vaccines are used for protection against a variety of infectious diseases. The technologies used for the production of these vaccines can and have been applied to more unconventional targets such as immunisations to prevent pregnancy, peptic ulcer, atherosclerosis and drug addiction.[22]

The general concept of vaccination for drug addiction was first described by Bonese et al.[23] for treating heroin addiction. Recently, the feasibility of active immunisation as a treatment strategy for cocaine[24-29] and nicotine[30-32] addiction has been investigated. Data to date are very encouraging and efforts in the development of nicotine and cocaine vaccines are continuing. We will also report on some results with a cocaine vaccine, as many issues in development are similar.

3. Issues Related to a Nicotine Vaccine

A clinically useful nicotine vaccine must be able to produce adequate amounts of high affinity, nicotine-specific antibodies to bind a sufficient amount of nicotine delivered during the first several puffs after cigarette smoking to reduce the rate or extent of nicotine entering the brain and block its reinforcing effect. The rapid binding of nicotine to reduce the amount of nicotine entering the brain to a subpharmacological level is critical to the success of the vaccine in blocking the reinforcing effect of nicotine. In sections 3.1 to 3.3, issues related to the development of a nicotine vaccine for treating nicotine addiction are discussed.

3.1 Immunogenicity

Nicotine is a small non-immunogenic molecule and must be conjugated to a carrier protein to make it immunogenic. Immunisation of animals with nicotine conjugates has been used for decades for the production of nicotine-specific antibodies for immunoassays. Recently, active immunisation with 2 different nicotine conjugates in rats showed that the pharmacokinetics and pharmacological effects of nicotine were modified.[30,32] The antibodies raised were of high affinity (affinity constant 10^7 to 10^8 L/mol) and high specificity with limited or no cross-reactivity to other ingredients presented in tobacco cigarettes, the major metabolite of nicotine (cotinine) or the nicotine receptor ligand acetylcholine. The development of a nicotine conjugate that can elicit nicotine-specific antibodies and is itself stable with a reasonable shelf-life and suitable for clinical use is technically achievable.

To facilitate a strong and appropriate immune response, immunogens are often coadministered with immunostimulating adjuvants. Although alum is the only adjuvant approved for human use by the US Food and Drug Administration, other adjuvants currently under clinical evaluation have been shown to enhance immune responses.[33,34] However, immune responses in individuals are quite variable and the amount of elicited antibodies in humans could be modest. To maintain an adequate immune response, we speculate that patients will probably need regular boosters.

3.2 Binding Capacity

Nicotine is absorbed rapidly from cigarette smoking and reaches the brain in 10 to 20 seconds.[35] Nicotine concentrations in the arterial plasma immediately after a puff are much higher than those in the venous plasma and vary considerably among smokers, from 7 μg/L[36] to greater than 100 μg/L.[37] Peak arterial nicotine concentrations range from 15 to 120 μg/L, occurring at 1 to 10 minutes after smoking.[36-39] If nicotine vaccination is to be successful, the nicotine-specific antibodies produced after immunisation must have adequate binding

capacity, a function of affinity and quantity, to block a sufficient amount of nicotine in the arterial blood from delivery to the brain.

The amount of specific immunoglobulin G (IgG) that can be produced by active immunisation in humans is limited, with usual immunisations, to no more than 0.1 to 0.2 g/L[32,40,41] (approximately 4 to 8 μmol of binding sites in total plasma) or 1 to 2% of total IgG. When the antibodies are of adequate affinity, an equivalent molar dose of antibody to the total body burden of drug (hapten) is not required to significantly reduce the drug-induced behavioural effects of phencyclidine,[42] cocaine,[27,29] heroin[23] and nicotine[32]. Nicotine intake for smokers averages 37mg (range from 1 to 79mg) of nicotine per day,[11,43,44] but the average nicotine intake from a cigarette averages 1mg or 6 μmol.[11,43] It is reasonable to expect that the antibody produced by immunisation would be able to alter the pharmacokinetics of nicotine and the reinforcing effect after cigarette smoking.

As demonstrated in an animal model by Pentel et al.,[32] modification of the pharmacokinetics, behavioural and cardiovascular effects of nicotine was achieved in immunised rats when the antibody level was about 0.1 to 0.2 g/L, a level potentially achievable in humans. Figure 1 shows a 64% reduction of brain nicotine concentration in the active immunised rats compared with the controls at 3 minutes after an intravenous dose of nicotine 0.03 mg/kg.[32] That dose level was equivalent on a mg/kg basis to the nicotine intake of 2 cigarettes by a smoker, and the serum nicotine concentrations in the control rats were comparable to those seen in regular smokers (10 to 40 μg/L).

In passively immunised rats, the nicotine-specific antibodies also attenuated the increase in systolic blood pressure produced by a subcutaneous nicotine dose of 0.035 mg/kg in a dose-related manner (fig. 2).[32] The stimulation of locomotor activity (measured over the first 5 minutes immediately after injection) induced by a subcutaneous nicotine dose of 0.28 mg/kg was also completely blocked in passively immunised rats, with antibody levels similar to those observed with active immunisation

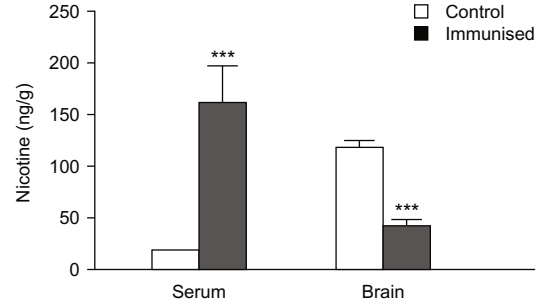

Fig. 1. Serum and brain nicotine concentrations in actively immunised rats. At 3 minutes after a single nicotine dose of 0.03 mg/kg, the serum nicotine concentration was higher in immunised rats compared with controls, and the brain nicotine concentration was decreased by 64%. Values are means ± SE; *** indicates $p < 0.001$ (reproduced from Pentel et al.,[32] with permission).

(fig. 3).[32] The mean serum nicotine concentration at 5 minutes after the subcutaneous dose was 168 μg/L, a level equivalent to 5 to 10 times that typically observed with regular cigarette smoking (10 to 40 μg/L).[38,39] These data suggest that nicotine-specific antibodies at levels that could be achieved from active immunisation would be capable of modifying the pharmacokinetics and blocking/attenuating pharmacological effects of nicotine at doses or serum concentrations equal to or greater than those typically observed with cigarette smokers.

Data from cocaine vaccine development are also encouraging. Studies by Kantak et al.[29] indicated that a minimal antibody concentration of 0.05 g/L was adequate to block the self-administration of 1 mg/kg cocaine in rats. Since the psychoactive dose of nicotine (1mg)[11,43] is much smaller than that of cocaine (40mg)[45] and the nicotine concentrations (10 to 40 μg/L)[38,39] immediately after smoking are also much lower than those after cocaine injection (550 μg/L),[45] it is anticipated that much less antibody binding capacity is required for blocking the reinforcing effect of nicotine. The potential for the development of a vaccine for treating nicotine dependence would be expected to be greater.

Vaccination may take months to raise adequate antibody levels. Studies in rats indicated that concurrent nicotine administration, at doses producing

serum nicotine concentrations close to those of moderate smokers, during immunisation did not significantly affect the immunogenicity of the vaccine and the ability of vaccination to reduce nicotine distribution to the brain.[46] More studies are needed to define the relationships between the nicotine dose administered during vaccination and its effect on the efficacy and safety of vaccination. However, the data suggest that vaccination as an adjunct to smoking cessation could potentially be initiated before a smoker completely quits smoking.

3.3 Potential for Saturation

One of the major concerns is that the binding capacity of the antibodies from active immunisation is limited and could be saturated. Studies of heroin self-administration by rhesus monkeys indicated that the blocking of self-administration by immunisation was overcome by higher doses of heroin.[47] Pentel et al.[32] also showed that the efficacy of immunisation in reducing brain nicotine concentration was decreased with repeated administration of nicotine.

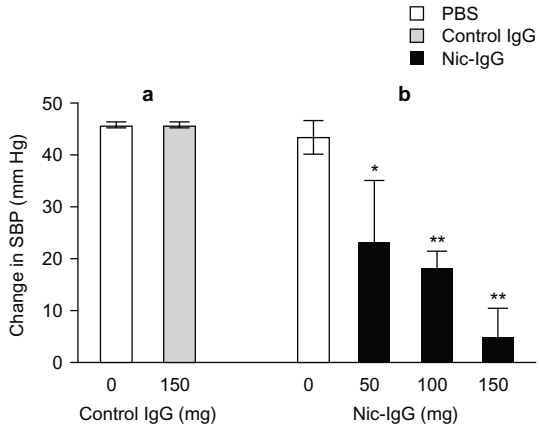

Fig. 2. Changes in systolic blood pressure (SBP) following a single subcutaneous nicotine dose of 0.035 mg/kg. (**a**) SBP increased equally in rats pretreated with either phosphate-buffered saline (PBS) or control immunoglobulin G (IgG). (**b**) The nicotine-induced increase in SBP was attenuated in a dose-related manner by passive immunisation with nicotine-specific IgG (Nic-IgG), and was nearly completely suppressed at the highest dose. Values are means ± SE; * indicates $p < 0.05$; ** indicates $p < 0.01$ (reproduced from Pentel et al.,[32] with permission).

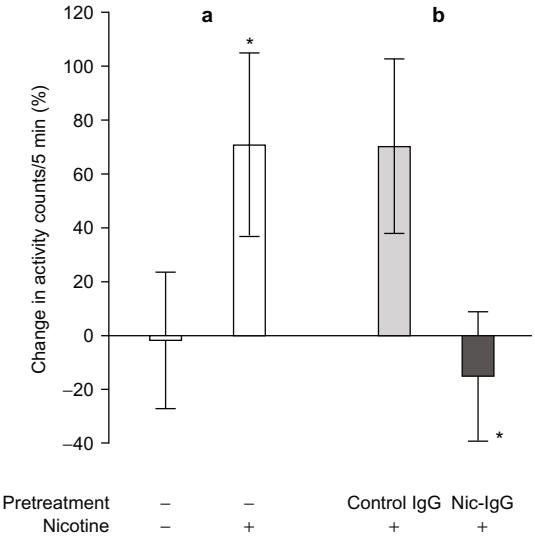

Fig. 3. Changes in activity count in rats after treatment with subcutaneous nicotine 0.28 mg. (**a**) In rats receiving no pretreatment, nicotine significantly increased locomotor activity scores. (**b**) Passive immunisation with nicotine-specific immunoglobulin G (Nic-IgG) completely prevented the nicotine-induced increase in locomotor activity observed in rats receiving control immunoglobulin G (IgG). Values are means ± SE; * indicates $p < 0.05$ (reproduced from Pentel et al.,[32] with permission).

Smokers have been shown to manipulate nicotine intake to achieve their desired effect.[48] Smokers could increase their nicotine dose by smoking more cigarettes to overcome the effect of immunisation. Nicotine metabolism/elimination may also be decreased after immunisation since in general the clearance of a drug is decreased in the presence of drug-specific antibodies.[49-51] Nicotine could persist in the circulation as nicotine-antibody complex for a period of time after an episode of cigarette smoking. During that time, the antibodies available for binding nicotine from subsequent cigarette smoking could be reduced, and consequently the efficacy of blocking the effects of nicotine could also be reduced. The number of cigarettes that a smoker has to smoke to overcome the immunisation effect would be quite variable, depending

upon the immunogenicity of the vaccine as well as the individual's smoking behaviour.

In the study by Pentel et al.,[32] passively immunised rats (serum nicotine-specific antibody concentration of 0.1 g/L) were administered with repeated intravenous doses of nicotine 0.03 mg/kg every 20 minutes for a total of 5 doses. The brain nicotine concentration measured at 1 minute after the last dose was still significantly reduced (by 13%) in immunised rats compared with the controls. The reduction of nicotine distribution to the brain for the last dose (the fifth dose) alone was to a greater extent (reduction by 29%) than for the cumulative dose, although to a lesser extent than for a single dose. The greater effect of the most recent dose suggests that the antibody was not completely saturated by the repeated doses. There were no data on whether the effect of the last dose of nicotine was still attenuated or blocked. The cumulative dose totalled 0.15 mg/kg, equivalent on a mg/kg basis to nicotine intake from 10 cigarettes by a human smoker. The mean serum nicotine concentration (55 μg/L) in the control rats was comparable to steady-state plasma concentrations (18 to 55 μg/L)[52] reported for regular smokers who repeatedly smoked a cigarette every 30 minutes for 4 to 6 hours and consumed a total of 8 to 12 cigarettes. Whether nicotine-specific antibodies produced by vaccination in humans could still retain their ability to modify the pharmacokinetics of nicotine, and consequently the reinforcing effects, after a smoker has continually smoked a number of cigarettes remains to be investigated in clinical trials.

4. Assessment of Clinical Utility

4.1 Safety

Nicotine is a very small molecule that could not itself cross-link antibody molecules. It is also unlikely to form spontaneous protein conjugates that can cross-link anti-nicotine antibodies. It is not anticipated that immune complex disease or hypersensitivity will occur with a nicotine vaccine. The antibodies in general are highly specific and should not cross-react with acetylcholine or other endogenous ligands for nicotine receptors. It is expected that a nicotine vaccine with minimal adverse effects could be developed.

Cocaine is also a small molecule, and the process for the development of a cocaine vaccine is similar to that for a nicotine vaccine. The fact that preliminary results of clinical evaluation of a cocaine vaccine showed very minimal adverse events[53] is also very reassuring.

However, the safety of potential nicotine vaccines must be evaluated clinically in both smokers and nonsmokers/ex-smokers. Since vaccines are typically administered by injection, any local reactions at the injection site need to be monitored. In addition, any systemic clinical effects (e.g. fever, headache, mental confusion, joint or muscle ache, nausea and vomiting, etc.), and any abnormality in haematology and blood chemistries associated with vaccination, also needs to be determined.

4.2 Efficacy

A nicotine vaccine could be useful as an aid for smoking cessation, an aid for relapse prevention or for prophylactic use depending upon its immunogenicity. The relapse to smoking for ex-smokers typically occurs with low nicotine exposure, a few cigarettes per day. Dependence forming also occurs first with low nicotine exposure and then gradually progresses to dependence. We speculate that a vaccine of moderate immunogenicity could generate sufficient antibodies capable of blocking/attenuating the reinforcing effect of nicotine from a few cigarettes. This blockade may still be adequate for reducing relapse in ex-smokers or preventing dependence forming in nondependent smokers. For smoking cessation, it is expected that the vaccine must be of adequate immunogenicity so that the nicotine-specific antibodies generated are of sufficient binding capacity to block or attenuate the effect of relatively large amounts of nicotine intake by dependent smokers.

The initial clinical trials should assess the safety, immunogenicity (including nicotine-specific antibody titres and affinities, and plasma antibody concentrations) and efficacy of the nicotine vaccine in

both ex-smokers and smokers. The dose of the vaccine, the number of booster doses and the immunisation schedule required to achieve optimal immune response will need to be determined. The effect of vaccination on smoking behaviour should also be explored in these trials to get a preliminary assessment of the clinical utility of the vaccine. If there seems to be an indication of significant reduction in smoking, as judged from self-reported tobacco use and biochemical measures such as end-expired carbon monoxide or blood cotinine concentrations, then the vaccine would have potential for use as a smoking cessation aid. If there seems to be no clear indication of a decrease in the number of cigarettes smoked by smokers, the vaccine could be tested as an aid to prevent relapse.

Additional clinical pharmacology studies to delineate the relationship between the binding capacity of the antibody (affinity and plasma concentration) and its effect on the pharmacokinetics (distribution and metabolism) and pharmacodynamics (including self-reported subjective effects and cardiovascular effects) of various doses of nicotine would also provide useful data to address the issue of 'saturation' and to define the clinical utility of the vaccine.

The safety, efficacy and clinical effectiveness of the vaccine must be assessed in large clinical trials involving the target populations. For smoking cessation, the duration of continuous abstinence would be one of the outcome measures. For relapse prevention, episodes of relapse to smoking would be the outcome measure.

5. Discussion

The results from animal models suggest that nicotine-specific antibodies at a molar dose lower than the equivalent nicotine dose administered can modify the distribution of nicotine sufficiently to alter its pharmacokinetics and pharmacological effects in rats. These effects were observed at serum nicotine concentrations equal to or greater than those found in typical cigarette smoking in humans.[32] Currently, a cocaine vaccine is being developed and evaluated in clinical trials. Since the nicotine dose self-administered by patients is lower than cocaine, the quantity of antibodies required to bind nicotine is expected to be small. If the cocaine vaccine proves to be successful, it is expected that there would be a greater chance for the success of a nicotine vaccine.

These data suggest the feasibility of developing nicotine vaccines for treating nicotine addiction. The safety and clinical effectiveness of the potential vaccines have yet to be proved in clinical trials in target populations. The vaccine may be effective for smoking cessation, for relapse prevention or for prophylactic use, depending upon its immunogenicity. Frequent immunisation is typically required to achieve optimal immune response. Failure to comply with the immunisation schedule may compromise the efficacy of a vaccine. In addition, the withdrawal syndrome experienced in dependent smokers may also contribute to the failure of smoking cessation treatment for some smokers. Both compliance and the withdrawal syndrome are problems commonly associated with drug addiction treatment. To improve compliance and clinical effectiveness, addiction treatment is usually carried out in a comprehensive treatment programme. Vaccination for treating nicotine addiction should also be used in conjunction with a comprehensive treatment programme, in which behavioural strategies may be offered to assist patients abstaining from cigarette use and medications may be provided to relieve the withdrawal syndrome.

One major concern is that the binding capacity of antibodies produced from vaccination is limited and can be saturable. Smokers could overcome the vaccination effect by repeated smoking. The number of cigarettes that an individual needs to smoke to overcome the effect will depend upon the immunogenicity of the vaccine and the smoking behaviour of the individual. Smokers entering treatment programmes are usually motivated to quit. It is anticipated that the patient's motivation to quit, combined with behavioural treatment, should help discourage patients from attempting to overcome the immunisation effects by smoking more cigarettes.

Cigarette smoking and its consequences represent a major global public health problem and new efforts are needed to reduce its prevalence. Smoking prevalence is a dynamic measure relating smoking initiation rates and cessation rates. New initiatives are warranted to assist current smokers to quit and avoid relapse, as well as initiatives to prevent dependence in adolescents who smoke. Data from the US will be used as illustrative examples of how prevalence could be modified by a vaccine intervention.

Current prevalence estimates of cigarette smoking in the US are that 24.7% of adults are cigarette smokers.[54] This estimate is similar to that noted in 1995[55] and suggests that smoking prevalence may not be declining further. However, other models predict that smoking prevalence will continue to decline, albeit at a slower rate.[56] Given the current rate of 25% prevalence among US 18-year-olds, smoking prevalence rates will decline to a steady-state level of 15 to 16% by the year 2025. Further declines could be accomplished by reducing the prevalence of young current smokers. If a vaccine were effective in reducing the prevalence from 25% to 20%, a new steady-state level of 12% prevalence would be approached by 2020.[56] Thus, a modest reduction in the prevalence of 18-year-old current smokers would assist in halving the smoking prevalence rate from its current level in the next 20 years.

A vaccine for nicotine would probably have the greatest efficacy in adolescents, as many smokers in this cohort (aged 13 to 18 years) are not yet considered to be current smokers. Smoking initiation usually begins at age 13 to 14 years[57] and it takes 2 to 3 years for an individual to progress to daily smoking.[58] In fact, 71% of adult smokers in the US began before age 19 years.[57] Smoking prevalence in adolescents, here defined as any smoking within the last 30 days, is estimated at 39.6% of US high school seniors. An interruption in the dependence-forming process during the period between smoking initiation and daily smoking would have major implications for overall smoking prevalence. Quit rates in the adolescent population are abysmally low.[59] In one study, 83% of current smokers (n = 496) had made at least one unsuccessful attempt to quit smoking. Moreover, it is unclear whether the standard nicotine replacement therapies will be efficacious.[60] There is a great need for evidence-based therapies for smoking cessation in the adolescent population. To this end, the US National Institute on Drug Abuse has started an adolescent smoking cessation clinic to determine what currently available treatments are effective in adolescents. One potential problem in successfully treating adolescent smoking relates to compliance. The utility of the vaccine may be compromised if vaccination compliance is not achieved.

Two other groups that could possibly benefit from a nicotine vaccine are current adult smokers attempting to quit and former smokers wishing to avoid relapse. Given that a vaccine would take time to develop effectiveness, it would have the effect of reducing the unit dose of nicotine gradually, assuming that smoking behaviour was constant. It would have to be empirically determined whether the vaccine would enhance quit rates in smokers in behavioural therapy programmes and in combination with non–nicotine-based pharmacotherapies. Similarly, prevention of relapse would need to be empirically determined. Blockade of priming would be the proposed primary mechanism for the putative efficacy for this indication. 1-year overall abstinence rates in smokers have been reported to be about 3%.[61] An increase in 1-year abstinence rates in the current smoking population would also have a public health benefit and would further reduce smoking prevalence.

6. Conclusion

The potential efficacy and benefits of a nicotine vaccine for smoking cessation will need to be determined in the coming years. The anticipated efficacy is likely be greater in adolescents who are not yet nicotine dependent, although clinical studies will initially commence in adult smokers. Assuming that the vaccine has substantial efficacy and minimal safety problems, a further indication would be

to employ the vaccine for prophylactic purposes in adolescents who have not yet initiated smoking.

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