Nicotine replacement combined with a novel compound (ProBAN) for smoking cessation: A pilot study

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BACKGROUND: Smoking cessation rates with available pharmacological therapies remain suboptimal. Anecdotal observations with a combination of sublingual pralidoxime and ipratropium (ProBAN) suggested that these agents in combination with nicotine gum improved quit rates.
OBJECTIVE: To determine whether ProBAN together with nicotine replacement improves quit rates compared with nicotine replacement alone.
DESIGN: A 12-week, prospective, double-blind, randomized, placebo controlled pilot study.
SETTING: University-affiliated outpatient clinic.
POPULATION STUDIED: Healthy adult smokers were recruited via advertisements. Of 107 subjects seen at the screening visit, 27 were excluded because of comorbid illness or concomitant medication use.
INTERVENTIONS: Of 80 eligible subjects, 40 were randomly assigned to receive treatment with ProBAN sublingual tablets and nicotine gum (treatment group), and 40 to receive placebo tablets and nicotine gum (control group) for 12 weeks. The primary outcome was complete continuous abstinence of smoking from one through 12 weeks after the quit date.
MAIN RESULTS: There were no adverse effects in the treatment group. At one week after the quit date, 35% of ProBAN-treated subjects had quit compared with 18% of control subjects (odds ratio [OR] 2.5, 95% CI 0.9 to 7.2). Corresponding quit rates at four weeks were 28% and 15% (OR 2.1, 95% CI 0.7 to 6.5), at eight weeks were 25% and 13% (OR 2.3, 95% CI 0.7 to 7.6), and at 12 weeks were 23% and 13% (OR 2.0, 95% CI 0.6 to 6.7), respectively.
CONCLUSIONS: This pilot study indicated that ProBAN combined with nicotine replacement doubled the continuous sustained quit rate compared with nicotine replacement alone, with no adverse effects. Although not statistically significant due to the size of the study, this result suggests that it may be an effective therapy for smoking cessation, and larger studies are warranted.

Key Words: *Drug therapy; Randomized, controlled trial; Smoking cessation*

Étude pilote sur un substitut de la nicotine combiné à une molécule nouvelle (ProBAN) pour l'arrêt du tabagisme

HISTORIQUE : Les taux d'abandon du tabagisme au moyen de traitements pharmacologiques actuellement offerts restent insatisfaisants. Des observations d'ordre anecdotique sur l'association du pralidoxime sublingual et de l'ipratropium (ProBAN) donnent à penser que ces agents associés à la gomme de nicotine peuvent améliorer les taux d'abandon de la cigarette.

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OBJECTIF : Déterminer si ProBAN administré avec un substitut de nicotine améliore les taux d'abandon du tabac comparativement aux substituts de la nicotine seuls.
MODÈLE : Étude pilote prospective à double insu, randomisée, avec témoins sous placebo, d'une durée de 12 semaines.
CONTEXTE : Clinique ambulatoire affiliée à une université.
POPULATION ÉTUDIÉE : Fumeurs adultes en bonne santé, recrutés par le biais des petites annonces. Sur les 107 sujets vus lors d'une visite de sélection, 27 ont été exclus en raison de comorbidités ou de médicaments concomitants.
INTERVENTION : Parmi les 80 sujets admissibles, 40 ont été assignés de façon aléatoire au traitement par ProBAN en comprimés sublinguaux avec gomme de nicotine (groupe traité) et 40 ont été assignés à des comprimés de placebo avec gomme de nicotine (groupe témoin) pendant 12 semaines. Le paramètre principal était l'abstention complète et continue de tout tabac, de la première à la 12^{e} semaines après la date de cessation.
PRINCIPAUX RÉSULTATS : On n'a noté aucune réaction indésirable dans le groupe traité et une semaine après la date fixée pour l'abandon, 35 % des sujets traités par ProBAN avaient cessé, contre 18 % des sujets témoins (rapport des cotes [RC] : 2,5; IC : 95 %, 0,9 à 7,2). Les taux de cessation correspondants après quatre semaines étaient de 28 % et de 15 % (RC : 2,1, IC : 95 %, 0,7 à 6,5); à huit semaines, 25 % et 13 % (RC : 2,3, IC : 95 %, 0,7 à 7,6) et à 12 semaines, 23 % et 13 % (RC : 2,0, IC : 95 %, 0,6 à 6,7), respectivement.
CONCLUSIONS : Cette étude pilote a indiqué qu'associé aux substituts de nicotine, ProBAN double le taux d'abstinence continue et soutenue par rapport au traitement par substituts de nicotine seuls, et ce, sans réactions indésirables. Bien qu'en raison de la taille de l'étude ce résultat ne soit pas statistiquement significatif, il suggère néanmoins que ce traitement puisse s'avérer une mesure antitabac efficace et des études de plus grande envergure s'imposent.

Smoking is a major health risk in society (1) and, thus, smoking cessation is an important preventive health measure (2). However, cessation rates with available pharmacological therapies are suboptimal. Most smoking cessation programs use nicotine replacement with a variety of delivery systems. While results vary, a meta-analysis of nicotine replacement therapies in smoking cessation has shown a small but increased odds ratio (OR) of abstinence to 1.71 (95% CI 1.56 to 1.87) compared with control interventions (3). Although nicotine replacement therapy is effective in aiding smoking cessation, these relatively low quit rates suggest that nicotine alone does not address all aspects of the complex neuropharmacology involved in smoking addiction. Furthermore, in a recent study comparing bupropion with placebo, the continuous abstinence rates at 12 months were 18% and 8%, respectively (4), further suggesting that a single pharmacological agent is unlikely to address all of the neurological dysfunction associated with smoking addiction and the smoking withdrawal syndrome.

In addition to nicotine, tobacco smoke contains multiple other chemicals, including many pesticides used in the agricultural production of tobacco (5). Among the most common of these are the organophosphates and, to a lesser extent, carbamate pesticides (6,7). Chronic low level exposure to these toxins can result in an accumulation within body fat stores not only of the primary toxins but also of many metabolites (8). These chemicals may have a cumulative 'non-nicotinic' effect at both the synaptic and neuroreceptor levels in the central nervous system as they are continuously released into the circulation. Fatty accumulation of organophosphates has been associated with behavioural changes not unlike those seen in tobacco withdrawal (9-11). Acetylcholinesterase reactivators (oximes), together with anticholinergic agents, are acknowledged therapies for the treatment of organophosphate and carbamate insecticide toxicity (12,13). The oxime pralidoxime is widely available for clinical use to treat organophosphate poisoning. Atropine is used to treat both organophosphate and carbamate poisoning.

We hypothesized that chronic, low level exposure to toxins in addition to nicotine may play a significant role in smoking addiction. Consequently, drugs that have inherent anticholinergic activity and the potential to counter the biochemical effects of pesticides may be useful in promoting smoking cessation by reducing withdrawal symptoms.

Preliminary anecdotal observations suggested that pralidoxime 5 mg and ipratropium 1 μg (an atropine analogue with a more favourable side effect profile) combined in a sublingual tablet (ProBAN, Synapse Pharmaceuticals International Inc, Canada), used together with nicotine gum, were associated with improved quit rates and decreased withdrawal symptoms compared with nicotine replacement alone. This experience served as the impetus for this proof-of-concept pilot study.

The purpose of this study was to determine, in a randomized, placebo controlled study among healthy adult smokers motivated to quit, whether a combination of sublingual pralidoxime 5 mg and ipratropium 1 μg (ProBAN) together with nicotine replacement improves the rate of smoking cessation compared with nicotine replacement alone.

SUBJECTS AND METHODS

Study protocol: Investigational new drug approval for use of ProBAN was received from the Health Protection Branch, Ottawa, Ontario. The study protocol was approved by the ethics research committee of St Joseph's Hospital, Hamilton, Ontario. All subjects who participated in the study provided written consent.

Design: This 12-week, double-blind, parallel group, randomized, placebo controlled pilot study was conducted at the Firestone Regional Chest and Allergy Unit at St Joseph's Hospital.

Subjects: Healthy adults 25 to 55 years of age, motivated to stop smoking, who had a five- to 35-year smoking history and who had smoked 10 to 30 cigarettes/day for the previous two years, were recruited through advertising. High commitment to quitting smoking was assessed as a score of 8 or higher on a 10-point, 100 mm visual analogue scale (each point marked at 10 mm intervals) on which a score of 0 indicated absolutely no motivation to stop smoking and a score of 10 indicated maximal motivation to quit smoking (14). Only one smoker from any household was enrolled in the study. Subjects were excluded if they had comorbid illness or

depression (Beck Depression Inventory score of 10 or higher) (15), used concomitant medications, had a history of alcohol or drug abuse, were significantly overweight (body mass index greater than 30 kg/m^2) or had participated in any other smoking cessation program within the previous three months. Pregnant or breastfeeding female subjects were excluded. Female subjects of childbearing age were expected to be using reliable birth control methods for the duration of the study.

Outcomes: The primary outcome was continuous and complete abstinence from one through 12 weeks from the quit date, as assessed by self-reporting and biochemical confirmation of carbon monoxide in expired air of less than 10 parts per million (ppm). Missed visits were regarded as indicating treatment failure and a return to smoking. A secondary outcome of the study was the incidence of possible adverse events relating to the medication, assessed by means of subject-reported symptoms and laboratory data.

Sample size: There were no previous data on this novel smoking cessation compound to assist in the calculation of an appropriate sample size for the present study. It was hoped that this study would generate pilot data for sample size calculations that could be applied to future definitive studies. In estimating the sample size for this pilot study, it was thought that the minimally important difference worth detecting between the two groups would be a doubling in the quit rate in the actively treated group compared with the control group. The power calculations were based on the following assumptions: mean quit rate of 18% at 12 weeks in the control group, mean quit rate of 36% at 12 weeks in the active group, conventional alpha-specification 0.05 and beta-specification 0.2. On the basis of these assumptions, it was calculated that 40 subjects would be required in each treatment group to allow for greater than 80% power to detect the minimally important clinical difference. While greater than 90% power to detect this difference would have been preferable, the study was limited by cost constraints.

Baseline assessments: Subjects were screened by telephone interview for eligibility according to specified inclusion and exclusion criteria. Potentially eligible subjects were scheduled for an appointment (visit 1), and mailed a package providing an overview of the study, demographic and health questionnaires, a Beck Depression Inventory (a 21-item questionnaire completed by the subject that assesses the severity of depressive symptoms) and a patient information booklet. The questionnaires were completed by the subjects before their scheduled visit.

At the first visit, further study information and orientation were provided, and the historical and demographic questionnaires were reviewed. Eligible subjects provided written consent to participate in the study. All subjects completed a Fagerström Tolerance Questionnaire as a measure of nicotine dependence. The eight-item Fagerström Tolerance Questionnaire is a widely used measure of nicotine dependence with a score ranging from 0 to 11; a score of 6 or greater indicates higher levels of dependence (16). A medical history and physical examination were completed. Baseline exhaled carbon monoxide levels (Micro CO Monitor, Micro Medical Limited, United Kingdom) and blood biochemical and hematological parameters were measured. Brief counselling (less than 10 min duration) on smoking cessation was provided. Patients were instructed on maintaining a daily smoking diary, and a target quit date was set for two weeks later. After review of biochemistry and hematology results, eligibility for randomization was confirmed by the investigating physician.

Randomization: Subjects were randomly divided into blocks of four with stratification for sex, level of education (secondary school versus higher than secondary school) and level of nicotine dependence (a score of 0 to 5 versus a score of 6 to 11 on the Fagerström Tolerance Questionnaire) – all factors that are known to influence smoking cessation.

Allocation concealment: Treatment allocation was concealed from the investigators and subjects for the duration of the study. A research secretary (independent of the study) and the hospital pharmacy held a key to the randomization numbers. The active ProBAN tablets contained pralidoxime 5 mg and ipratropium 1 μg, and were identical in appearance and labelling to the placebo medication (Synapse Pharmaceuticals International Inc, Canada). Nicotine gum was standardized using 2 mg Nicorette gum (Hoechst Marion Roussel Canada Inc, Canada). Batches of the study medication were independently packaged and labelled by the hospital pharmacy.

Treatment intervention: Randomly assigned subjects were reviewed, together with their smoking diary, one week before the set quit date (visit 2), and exhaled carbon monoxide levels were measured. All subjects had the intervention and randomization to active or placebo ProBAN explained to them. Both groups were given an orientation to smoking cessation, withdrawal expectations and the proper use of the study medications. They could use one or two pieces of 2 mg nicotine gum after each study tablet (placebo or active). The subjects were instructed that when they felt an urge to smoke, they should suck on or place a study tablet sublingually until it had dissolved, then chew the nicotine gum. Instructions for using nicotine gum were that subjects should bite down twice, and then 'park' it in their cheek for a minute, repeating this slowly for as many times as required to achieve a feeling of satisfaction or until the taste of the gum became unpleasant, at which point they were to remove the gum from their mouth. Subjects were allowed to take two pieces of gum if they thought that one piece was insufficient. They were instructed always to take a study tablet before chewing nicotine gum, and always to chew nicotine gum after taking a study tablet.

Subjects were allowed to use active or placebo sublingual ProBAN tablets and 2 mg of nicotine gum up to three times/day during the week immediately preceding the agreed quit date. This dosing regimen was substantially lower than that given in the weeks immediately following the quit date and was done to allow subjects to gain experience in the proper use of the trial medications. Subjects were also urged to reduce the number of cigarettes smoked in the week before the quit date, and the low dose regimen of study medications

TABLE 1
Characteristics of pralidoxime and ipratropium (ProBAN)*-treated and control subjects at baseline

	ProBAN (n=40)	Control (n=40)
Men (n)	19	19
Education: postsecondary (n)	27	23
Fagerström score	5.3 (2.2)	5.7 (2.0)
Age (years)	39.9 (8.2)	39.4 (7.6)
Weight (kg)	71.5 (14.3)	74.8 (11.2)
Age started smoking (years)	16.4 (3.5)	15.5 (4.4)
Cigarettes/day	21.5 (6.7)	21.4 (6.2)
Years smoked	22.9 (7.3)	23.0 (7.3)
Exhaled carbon monoxide (ppm)	30.6 (13.7)	26.1 (9.4)
Beck Depression Inventory score	4.7 (3.6)	4.5 (3.1)

*Data expressed as mean (SD) unless otherwise stated. There were no significant differences between the groups. ppm Parts per million. *Synapse Pharmaceuticals International Inc, Canada*

was thought to help diminish the craving for cigarettes during that week. Subjects were called by telephone two to four days after the randomization visit to reinforce proper use of the study medication in preparation for their quit date.

The quit date visit (visit 3) occurred one week after visit 2, after which subjects were encouraged to use the sublingual tablets and gum as often as they felt the urge to smoke, up to a maximum of 12 times/day, for six weeks. The frequency of use was determined by the subjects as dictated by their urges within the recommended dosing schedule. At the first visit, subjects were also given a 'contingency pack' containing 30 study tablets and 30 pieces of nicotine gum, together with appropriate instructions, to use in the event that dispensed medication ran out before their next scheduled appointment. Subjects were assessed one week (visit 4) and four weeks (visit 5) after quit day.

At each visit, the smoking diaries were reviewed and exhaled carbon monoxide levels measured. On each visit, the subjects returned their study medication and nicotine gum packages, which were reviewed for medication use, and new study medication was supplied. ProBAN and nicotine doses were tapered from week 6 over the following six weeks (down to six doses of study tablets and gum per day for weeks 7 to 8, four doses/day for weeks 9 to 10 and two doses/day for weeks 11 to 12) and discontinued at 12 weeks. Subjects were instructed to use a minimum of four doses of study tablets and gum each day for the first eight weeks (on waking and at lunch, supper and bedtime), then at least two doses each day for weeks 9 and 10 (on waking and at supper). There was no minimum dosage for weeks 11 and 12. Subjects were also told not to use more than 20 pieces of nicotine gum in any 24 h period. Subjects were seen at eight weeks (visit 6) and at the conclusion of the study at 12 weeks (visit 7). Hematology and biochemistry variables were checked at baseline, visit 5 (week 4 after quit date) and visit 7 (week 12 after quit date). Subjects were asked to report any concerns about adverse effects to the investigators within one working day.

TABLE 2
Number (%) of smokers in each group (n=40) who stopped smoking (complete and continuous abstinence) at one, four, eight and 12 weeks after quit date

Quit at	ProBAN*	Control	Odds ratio	95% CI
One week	14 (35%)	7 (18%)	2.5	0.9 to 7.2
Four weeks	11 (28%)	6 (15%)	2.1	0.7 to 6.5
Eight weeks	10 (25%)	5 (13%)	2.3	0.7 to 7.6
12 weeks	9 (23%)	5 (13%)	2.0	0.6 to 6.7

**Pralidoxime and ipratropium; Synapse Pharmaceuticals International Inc, Canada*

Statistical analysis: Data were analyzed using SPSS for Windows, Release 8.0 (SPSS Inc, USA). Descriptive statistics were used to summarize the baseline clinical and demographic characteristics of the study subjects, with qualitative variables expressed as percentages and quantitative variables reported as the arithmetic mean ± SD. All randomly assigned subjects were analyzed on an intention-to-treat basis. Nonparametric tests (χ^2, Fisher's exact test) were used for between-group comparisons of quit rates, with results expressed as ORs with 95% CIs.

RESULTS

Of 107 subjects seen at the screening visit, 27 were excluded because of comorbid illness (including depression) or concomitant medication use. Of the 80 eligible subjects, 40 received ProBAN sublingual tablets together with Nicorette gum (treatment group), and 40 received placebo tablets and Nicorette gum (control group). Randomization according to the stratification variables resulted in balanced groups. There were no significant differences between the treatment and control groups at baseline (Table 1).

An intention-to-treat analysis showed that 35% of ProBAN-treated subjects had quit one week after quit day compared with 18% of the control subjects (OR 2.5, 95% CI 0.9 to 7.2). Corresponding figures at four weeks were 28% and 15% (OR 2.1, 95% CI 0.7 to 6.5), at eight weeks were 25% and 13% (OR 2.3, 95% CI 0.7 to 7.6), and at 12 weeks were 23% and 13% (OR 2.0, 95% CI 0.6 to 6.7), respectively (Table 2).

The mean carbon monoxide measurement at the end of follow-up for those who had stopped smoking was 8.8 ppm compared with 21.4 ppm in those who had not quit smoking. There were no significant differences in the number of sublingual ProBAN tablets or pieces of nicotine gum used by active treatment subjects who were not smoking at four, eight and 12 weeks and those who had not stopped. Similarly, there were no significant differences between the number of sublingual tablets or pieces of gum used between the ProBAN-treated and control groups at four, eight and 12 weeks.

Smokers using ProBAN who were less nicotine dependent (Fagerström Tolerance Questionnaire score of 5 or lower) were more likely to quit smoking by one week after quit date than those with high nicotine dependence (OR 2.8,

95% CI 0.6 to 12.6), as were smokers who had at least postsecondary education (OR 3.6, 95% CI 0.8 to 16.1). These differences did not achieve statistical significance.

No adverse effects were reported in the ProBAN-treated group. In the placebo group, one subject developed oral aphthous ulcers, thought to be related to the nicotine gum; one subject developed a transient, symmetrical, inflammatory polyarthritis, which resolved over four weeks; one subject developed self-limiting abdominal cramps and diarrhea; and one subject experienced a single episode of hyperventilation that she attributed to the study medication. ProBAN-treated subjects who were not smoking at the end of the study period had no significant change in their body weight (mean change –0.28 kg), while those who received placebo treatment who quit gained a mean 0.83 kg during the 12-week study period. None of these differences were statistically significant.

DISCUSSION

With increasing societal pressure and personal health care concerns, motivation to stop smoking is increasing. Many smokers have tried repeatedly to quit, but smoking cessation rates remain low (17). An effective pharmacological approach to smoking cessation would have great societal benefits. This randomized, placebo controlled pilot study suggests that the novel drug ProBAN in combination with nicotine replacement provides a doubling of the sustained quit rates over a period of 12 weeks compared with nicotine replacement alone. At one, four, eight and 12 weeks after the quit date, twice as many subjects in the ProBAN-treated group maintained their abstinence as in the placebo-treated group. Although these differences did not quite achieve statistical significance due to the small sample size of the pilot study, the doubling of the quit rate at each time point suggests that the compound ProBAN enhanced the effect of nicotine replacement in helping people to stop smoking.

There is a growing recognition that addiction to smoking may involve neurophysiological factors, accounting for the lack of success with nicotine replacement alone. This is highlighted by the use of bupropion (4,18) and nortriptyline (19) as a non-nicotine intervention for smoking cessation. Although bupropion is relatively successful as a smoking cessation aid, 12-month sustained quit rates with bupropion are 18% and are only slightly higher (22%) when bupropion is used in combination with nicotine replacement therapy (4). Bupropion is also associated with adverse effects, including dry mouth and insomnia (4,18), and is contraindicated in subjects who have seizure disorders (20). Thus, there remains a real need for an effective and safe smoking cessation therapy.

ProBAN is a prototype smoking cessation product that combines pralidoxime and ipratropium, and was designed to be used in conjunction with nicotine replacement therapy. The mechanism by which ProBAN enhances the ability of subjects to abstain from smoking is uncertain. However, biological mechanisms for therapeutic approaches to assist in smoking cessation have been described almost exclusively at the level of the nicotinic and non-nicotinic cholinergic receptors, and smoking withdrawal symptoms may have origins in synaptic dysfunction. We presume that the effect of ProBAN is to influence cholinergic transmission, either at the level of the synapse or by other neurochemical pathways. This effect may be mediated by the anticholinergic ipratropium or through the effects of pralidoxime as an antidote to pesticides in tobacco products.

The use of both organophosphate and carbamate pesticides is increasing (21). Pesticide residues in cigarettes are six to seven times higher than permitted by the Food and Drug Administration for other leafy products (22). Tobacco is the only consumable agricultural crop that does not have a tolerance level specifying when the pesticide residue is hazardous (22). Chronic exposure to these contaminants may result in diminished efficiency of neurotransmission at the level of nicotinic and non-nicotinic cholinergic synapses in the brain (23). Countering these toxins in smokers may be one of the mechanisms by which ProBAN exerts its clinical effect. We suggest that the use of ProBAN together with nicotine replacement therapy acts synergistically on other aspects of the cholinergic synapse in conjunction with nicotine, resulting in improved cholinergic synaptic function, fewer withdrawal symptoms and improved quit rates, as seen in the present study. However, ProBAN's mechanism of action requires further study.

The combination of pralidoxime and ipratropium has been shown to be safe, with no reported adverse events in the 40 treated subjects in our study. Pralidoxime is used clinically as an antidote in the treatment of organophosphate poisoning (24). Ipratropium is an anticholinergic drug widely used as a bronchodilator in the treatment of airflow limitation (25). They are known to be safe at significantly higher doses than those contained in this novel product.

The mean weight was unchanged over the 12-week study period in subjects who successfully quit and who received ProBAN compared with a mean gain of 1 kg (nonsignificant) in subjects who quit on placebo treatment. The typical weight gain associated with successful smoking cessation is 3 kg to 4 kg over a six-month period (26). Concern over weight gain inhibits many smokers (especially women) from attempting to quit.

This pilot study was not sufficiently powered to detect a significant difference in the primary outcome measure of continuous sustained smoking cessation. Nonetheless, the data do show trends with a doubling of the sustained quit rate at 12 weeks. It can be reasonably assumed that a larger study would show a significant difference between ProBAN and placebo in combination with nicotine replacement in smoking cessation rates.

Another limitation of the study was its relatively short duration of 12 weeks, and hence, the results are not comparable with smoking cessation studies of 12 months' duration. However, the purpose of this pilot study was to determine whether there was any efficacy of the active medication to justify a further long term study rather than to achieve comparable 12-month results.

CONCLUSIONS

This pilot study suggests that ProBAN combined with nicotine replacement provides greater sustained quit rates than nicotine replacement alone. Although these differences were not statistically significant due to the size of the pilot study, the fact that twice as many treated as control subjects maintained their abstinence from smoking at each time point suggests that ProBAN is effective in combination with nicotine replacement as a smoking cessation aid. The results of this pilot study are encouraging, and larger studies of ProBAN are warranted.

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