Pharmacotherapy for Treating Tobacco Dependence
What is the Ideal Duration of Therapy?

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Abstract

Various forms of nicotine replacement therapy and bupropion have been found to be efficacious and well tolerated for treating patients dependent on tobacco. However, the currently recommended duration of treatment with pharmacotherapy may be insufficient for some smokers to achieve sustained abstinence from tobacco. Extending the use of pharmacotherapy beyond the recommended timeframe may be an effective strategy for helping tobacco users achieve abstinence and for preventing relapse to tobacco use, especially among those who are highly dependent and those who are concerned about bodyweight gain following cessation.

Several studies have reported on long-term use of various pharmacotherapies. These studies have demonstrated that such long-term use is not harmful. Moreover, compared with continued smoking, long-term use of pharmacotherapy exposes patients to relatively small amounts of nicotine and none of the cancer-causing chemicals found in cigarettes and other tobacco products. However, more research is needed to further clarify questions regarding the ideal duration of therapy. Two questions have yet to be answered: In what populations of smokers is long-term therapy an effective strategy for achieving abstinence and preventing relapse? Does wider availability of nicotine replacement therapy lead to initiation of nicotine addiction by children and others not using tobacco products? Also, as with all medications, additional documentation of the safety of prolonged use of pharmacotherapy is important.

The aim of this review is to present the current evidence supporting the notion that long-term therapy for treating tobacco dependence may be appropriately considered for some tobacco users.

Pharmacotherapy is an essential cornerstone of treatment for tobacco dependence. Various forms of nicotine replacement therapy (NRT) and bupropion have been found to be efficacious and well tolerated for treating individuals dependent on to-bacco. However, a significant number of former smokers have difficulty maintaining abstinence and thus relapse even after use of pharmacotherapy. Relapse rates up to 80% have been reported in the first year following cessation.[1,2] Therefore, re-

lapse management is an essential component for promoting long-term treatment success following tobacco cessation.

Among the reasons cited for relapse in quitters using pharmacotherapy is that the smoker was not maintained for a sufficient period on the medication.[3-5] The optimum duration of pharmacotherapy to aid smoking cessation is unclear, and a consensus has not been reached. The current recommendations for the duration of therapy to treat smokers trying to quit are based on trials designed to determine effectiveness and safety of the medications: 'Increased efficacy may require deviating from the protocols of clinical trials that were designed primarily to determine whether the medications were of sufficient benefit to merit approval by regulatory agencies, not necessarily to optimize efficacy'.[6] For some former smokers, long-term use of pharmacotherapy may be an effective strategy to prevent relapse to tobacco use.

In determining whether long-term therapy should be recommended for nicotine replacement medications and/or bupropion in tobacco dependence treatment, some general concepts must be taken into consideration. First, given that there is no universally accepted definition of 'long-term' therapy, for the purposes of this review, long-term refers to any use of medication beyond that recommended by product labelling as noted in the *Physicians' Desk Reference*.[7] Second, the concept of increasing efficacy by optimising the duration of therapy must include consideration of the time course of nicotine withdrawal symptoms, abuse liability of the medication, evidence of added benefit and the safety of prolonged use. Third, the concept of harm reduction through nicotine maintenance involves weighing the relative risk of the extended use of these medications with that of continued smoking.

This paper will attempt to weigh the evidence for the prolonged use of pharmacotherapy for optimising smoking cessation and preventing relapse. We will present the various forms of pharmacotherapy currently recommended as adjuncts for treating tobacco use and dependence in the US Public Health Service Clinical Practice Guideline.[8] We will summarise the current forms and availability of the medications, the recommended dosages and duration of treatment, and the current recommendation concerning long-term use. Also, we will review information about the time course of nicotine withdrawal symptoms, the abuse liability of the medications and any evidence of added benefit of prolonged use beyond the recommended timeframe. Information about the safety of prolonged use of the drug relative to the risk of harm resulting from relapse to tobacco use without long-term therapy will be explored. Finally, we will present an argument for, as well as against, extended use of pharmacotherapy to treat tobacco dependence.

1. Current Recommendations for Therapy

In order to provide perspective on long-term use of pharmacotherapy, it is important to review the current recommendations for the duration of therapy based on labelling as reported in the *Physicians' Desk Reference*.[7] All product labels advise that use beyond the recommended period has not been tested in clinical trials and is not recommended, and that users should consult a doctor before using the medication beyond the recommended time period. We recognise that different medications and prescribing instructions may apply to different countries. Therefore, readers are advised to refer to local prescribing sources and instructions. The recommendations as detailed in the US for use of the various pharmacological aids for treating tobacco dependence are outlined below in sections 1.1 to 1.5.

1.1 Nicotine Gum

Nicotine gum is available over-the-counter (OTC) in the US in two doses (2 or 4mg per piece). The dosage recommendation is to chew one piece every 1 to 2 hours for weeks 1 to 6, one piece every 2 to 4 hours for weeks 7 to 9 and one piece every 4 to 8 hours for weeks 10 to 12. The maximum dosage is 24 pieces per day. The recommended duration of treatment is 12 weeks.[7]

1.2 Nicotine Patch

Nicotine patches are available both OTC and by prescription. The recommended OTC and prescription nicotine patch dosage is 21 mg/day for weeks 1 to 6, tapered to 14 mg/day for weeks 7 and 8 and then tapered to 7 mg/day for weeks 9 and 10. Those smoking ≤10 cigarettes per day are advised to start at 14 mg/day instead of 21 mg/day. The recommended duration of treatment with nicotine patches is 8 to 10 weeks. The Nicotrol®[1] patch is available OTC as a 15mg dose to be worn for 16 hours per day for 6 weeks.[7]

1.3 Nicotine Nasal Spray

Nicotine nasal spray is available by prescription only. Each 10ml spray bottle contains 100mg of nicotine (10 mg/ml). One dose of nicotine nasal spray (two sprays, one in each nostril) is considered to contain 1mg of nicotine. The recommendation is one to two doses per hour, which may be increased to a maximum of 40 doses per day for 3 months followed by tapering down of the daily dose. The recommended minimum dosage is eight doses per day, and the recommended duration of treatment is up to 6 months.[7]

1.4 Nicotine Inhaler

Nicotine inhalers are available by prescription only. The recommended dosage of nicotine inhalers is 6 to 16 cartridges per day (each contains 10mg of nicotine). The recommended duration of treatment is 12 weeks followed by a 6- to 12-week period of weaning. Therefore, 6 months is the maximum recommended length of therapy.[7]

1.5 Bupropion

Bupropion is available by prescription only. The recommended dosage of bupropion is 300 mg/day for 7 to 12 weeks. Maintenance therapy of 300 mg/day for up to 6 months has been proven efficacious.[7] Bupropion usage may be continued

for up to 6 months in the US or up to 1 year in Canada.[9]

2. Time Course of Nicotine Withdrawal Symptoms

Nicotine withdrawal symptoms vary from individual to individual, but usually involve unpleasant effects such as subjective anxiety, irritability, difficulty concentrating, restlessness, impatience, hunger, tremor, racing heart, sweating, dizziness, nicotine craving, insomnia, drowsiness, headaches, digestive disturbances and depression.[10]

It has traditionally been believed that the nicotine withdrawal syndrome, in the aggregate, follows a predictable timeline and is nonvariable among different smokers and only weakly related to relapse. However, new research indicates that this is probably not the case for individuals, and that relapse risk is predictable by looking at the distinct patterns, severity and timing of withdrawal symptomatology.[11,12] Relapse may be predictable by looking at the duration, severity and graph shape (i.e. the configuration of peaks and valleys in withdrawal when severity is plotted against time) of withdrawal. Piasecki et al.[11] found that individuals with 'atypical' patterns of smoking withdrawal were more likely to relapse than those who showed a gradual elimination of withdrawal. Individuals who experience withdrawal symptoms that increase with time or remain elevated over an extended period of time are at higher risk for relapse than those who have withdrawal symptoms that steadily decline.[11,12]

Given the observed heterogeneity of withdrawal patterns over time, it follows that therapy to treat withdrawal must likewise be heterogeneous and individualised, not relying on the 'one size fits all' principle. Some tobacco users may require long-term therapy to achieve and maintain abstinence. For example, since heavy smokers tend to report more difficulty quitting and experience more withdrawal symptoms, which thus puts them at increased risk for relapse, perhaps long-term therapy with nicotine replacement medications and/or bupropion should be considered. On

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1 Use of tradenames is for product identification only and does not imply endorsement.

the other hand, if less-dependent smokers report fewer withdrawal symptoms, they might not necessarily require long-term pharmacotherapy to prevent relapse but may maintain abstinence through behavioural strategies such as skills training and coping strategies.

3. Using Long-Term Pharmacotherapy to Improve the Efficacy of Tobacco Dependence Treatment

A number of factors must be taken into consideration when determining whether nicotine replacement medications and/or bupropion should be used long term as a way to optimise the duration of therapy and improve the efficacy of tobacco dependence treatment. Factors to consider include the abuse liability of the medication, whether there is evidence of added benefit with long-term therapy and the safety of prolonged use of the medication. All of these factors will be considered for each of the pharmacotherapies currently available.

3.1 Abuse Liability

As defined by West et al.,[13] 'abuse liability refers to the extent to which a product will be used for other than therapeutic purposes. Dependence potential refers to the extent to which users become dependent, subjectively, physically or behaviorally, and may involve the inability to stop or control use'. Factors thought to mediate the abuse liability of NRTs are rapid onset of action, achieving high blood nicotine concentrations, low number of adverse effects, easy availability, high frequency of use and social acceptability.[14]

Bupropion has been shown to have very low abuse potential according to surveillance data involving over 6 million people.[9]

West et al.[13] compared the abuse liability and dependence potential of nicotine patches, nicotine gum, nicotine nasal spray and nicotine inhalers among smokers motivated to quit by looking at the continued use of products at 15 weeks after the quit date despite advice to cease use at 12 weeks. They found that the abuse liability of all four NRT products was low, with 2% of patch users, 7% of gum and inhaler users and 10% of nasal spray users continuing to use the NRT product at week 15. Among those people who were abstinent from smoking at 15 weeks, the incidences were 8% for patch users, 25% for gum and inhaler users and 37% for nasal spray users. They also found little evidence of withdrawal discomfort related to discontinuing use of the NRT products. However, individuals using the inhaler reported increased strength of urges to smoke after discontinuing use.[13]

In another study[15] examining combination therapy for smoking cessation using the nicotine inhaler and nicotine patch, investigators found no evidence of abuse liability with the nicotine inhaler because there was no increase in inhaler use noted during or after the 12-week treatment period. The abuse liability of the patch was not evaluated in this study.

Previous studies[16-19] have found that abrupt discontinuation of nicotine gum resulted in withdrawal symptoms. In one study among smokers who had used nicotine gum to stop smoking,[20] 30 to 40% used the gum beyond the recommended 3 months, and 15 to 20% used it for more than 1 year. Another study found that decreased cost increased nicotine gum usage beyond the recommended period.[21] These results, however, may be less informative for real-world situations where nicotine gum is not provided free for an extended period of time. On the other hand, research indicates that increasing the cost of nicotine gum may decrease appropriate use, thus making the gum less effective than it should be for smoking cessation.[21]

Sutherland et al.[22] found that 43% of participants abstinent from smoking who had used the nicotine nasal spray (11% of all those assigned active spray) continued to use the spray at 12 months compared with none of the individuals who were abstinent from smoking in the placebo group. They also found that the amount of nicotine nasal spray used per day increased over time among those who used it beyond the recommended 3 months, suggesting the development of tolerance to the medication. However, another explanation for the increased amount used per day is that the spray's

adverse effects lessen with time and therefore perhaps the spray becomes less irritating to use. These findings may be viewed as evidence that there is some abuse liability associated with nicotine nasal spray.

Similarly, Hjalmarson et al.[14] found that 10% of all participants (29% of those abstinent from smoking) continued to use the nasal spray at 12 months despite advice to use it for only 3 months. However, unlike in the study by Sutherland et al.,[22] Hjalmarson et al. did not find escalating use of nasal spray over time. They found that the number of doses used per day was stable over time even up to 1 year later.

Reports of escalating use were not found with the nicotine patch, nicotine inhaler or nicotine gum, which all have different pharmacodynamic profiles to the nicotine nasal spray.[16]

3.2 Added Benefit of Prolonged Use

In the Lung Health Study,[23] it was observed that participants who used nicotine gum liberally and for a longer period of time were more successful at quitting than those who used the gum in cautious amounts and for a shorter period of time. In a study to examine the predictors of smoking cessation at the end of treatment and relapse over the first 2 years in the Lung Health Study, Nides et al.[24] found that extended use of nicotine gum probably prolonged the abstinence of more dependent smokers, thereby increasing their post-treatment quit rates. However, they also found that extended nicotine gum use (at 4 months) predicted relapse for men at 12 months, and extended use to 12 months predicted relapse for both men and women at 24 months. A possible explanation for these apparently conflicting findings is that those who used the gum long term were more dependent smokers and would have relapsed sooner if not for long-term gum use. The authors also speculate that individuals who were late relapsers had less confidence in their ability to quit smoking and in their ability to quit gum use without relapsing. The authors concluded that the extended use of nicotine

gum without the development of additional coping skills might lead to late relapse to smoking.[24]

In another study, Murray et al.[25] found that gum use at 1 year was inversely associated with sustained abstinence from smoking over 5 years for all age and gender subgroups of participants. They concluded that long-term gum use did not predict long-term abstinence from smoking. They also speculated that those individuals still using the gum at 1 year were possibly more nicotine addicted, more insecure about becoming and remaining smoke free and at risk for relapse.

Hajek et al.[26] studied the occurrence, determinants and effect on bodyweight gain of long-term nicotine gum use, defined as any use of nicotine gum at 1 year. They found that long-term use of the gum was an essential ingredient of treatment success for some smokers and that long-term gum users gained less bodyweight. They also found that long-term gum users tended to be heavier smokers and tended to use more gum per day during the treatment period than those who failed treatment and those who successfully quit without using the gum long term.

A meta-analysis by Fiore et al.[27] found no apparent treatment benefit in extending the use of the nicotine patch beyond 8 weeks. Also, Tønnesen et al.[28] completed a study to determine whether a higher dosage and longer duration of nicotine patch therapy would increase success rates as part of a European multicentre, randomised, double-blind, placebo-controlled smoking cessation trial. They found that continuation of treatment beyond 8 to 12 weeks did not increase success rates at 1 year.

Stapleton et al.[29] found no difference in risk of relapse to smoking after 1 year in participants who were abstinent from smoking and who used nicotine nasal spray for 1 year compared with those who stopped use at the recommended 3 months or at some other point prior to 1 year. Another study of nicotine nasal spray found that prolonged use for 12 months resulted in less bodyweight gain.[22]

Hays et al.[30] conducted a study to determine if long-term therapy with bupropion would decrease

the rate of relapse among smokers who had recently quit. They noted that 12 months after beginning medication, 55.1% of bupropion recipients remained abstinent from smoking compared with 42.3% of those taking placebo. In addition, 6 months after the end of treatment, the point prevalence abstinence rate remained significantly higher in those taking bupropion compared with those taking placebo. An additional benefit observed with long-term use of bupropion was significantly less bodyweight gain than in individuals taking placebo.[30]

3.3 Safety of Prolonged Use

Data on the safety of prolonged use of bupropion and NRT products other than gum are extremely sparse. Several studies have reported the long-term use of nicotine gum and have not found such use to be harmful.[20,24-26,31] West and colleagues[13] speculate that long-term use of NRT is considered safer than continued smoking, so if the choice is between continued smoking and prolonged use of NRT, the latter is preferred from a health standpoint. Likewise, Hughes et al.[20] argue that nicotine gum may be safer than cigarettes because of the lower levels of nicotine and the absence of carbon monoxide and carcinogens. In the Lung Health Study,[31] there was no evidence of significant adverse outcomes for people who used nicotine gum for up to 1 year. In addition, there was no evidence of significant adverse outcomes for those who used nicotine gum and concomitantly smoked cigarettes. The Lung Health Study also found that follow-up with intensive instruction and monitoring of individuals using nicotine gum resulted in fewer adverse effects.

Hughes et al.[20] found that even individuals who used nicotine gum for up to 10 months had no withdrawal symptoms with gradual reduction of use. In addition, the probability of relapse to smoking following cessation of nicotine gum was not increased after prolonged use. They attributed the dependence on the long-term use to the psychoactive properties of nicotine in the gum, because study participants continued using the gum beyond the recommended 4 months. However, participants were also told to use the gum until they felt confident that they had conquered the withdrawal from tobacco, and free gum was made available beyond the recommended stopping point. The authors concluded that long-term use is prevalent but rarely persists, so physicians can defer intervening for patients exhibiting long-term use unless it extends more than 1 year beyond the quit date.[20] The authors also stated that there were not enough scientific data at that time to suggest that physicians should routinely encourage long-term use of nicotine gum.

Hurt et al.[32] conducted a randomised trial to compare three different methods of cessation from long-term nicotine gum use by individuals who had used the gum for 14 to 56 months (median duration of 36 months). They found no significant differences in the three methods examined (abrupt cessation, taper with placebo gum and taper with nicotine gum) in terms of helping participants become abstinent from gum use while maintaining abstinence from smoking. They concluded that motivated individuals could stop long-term nicotine gum use without relapse to gum use or smoking by either brief tapering or abrupt cessation. The authors also noted that long-term use of nicotine gum still exposes these people to a relatively small amount of nicotine compared with continued smoking given the usual pattern of gum use noted among study participants.[32]

Some studies have found evidence of dependence on nicotine gum such as increased withdrawal symptoms during abstinence of gum use, cravings for nicotine gum and other symptoms consistent with nicotine withdrawal.[16,18,19,33] Studies have shown that abrupt cessation of nicotine gum use can produce withdrawal symptoms that are similar to those occurring after smoking cessation but that are less intense.[16] West and Russell[19] examined withdrawal from long-term nicotine gum (2mg) use among former heavy smokers (average cigarette consumption was 34 per day) where the average duration of gum use was 20 months. In this study they found that abrupt withdrawal from long-

term nicotine gum use could lead to subjective withdrawal effects similar to those of cigarette withdrawal. Thus, it can be argued that the withdrawal symptoms experienced by participants in these studies were the result of previous dependence on tobacco that had been present long before nicotine gum use. Moreover, there are no known reports of nicotine gum abuse by nonsmokers.[17]

In conclusion, a number of studies point to the use of nicotine beyond the recommended timeframe as evidence of abuse liability. However, in most studies, the gum was made available at no cost even beyond the advised stopping point. This may be an indication that people were receiving mixed or contradictory messages and as a result simply chose to extend the therapeutic use of the products. Also, in most studies, participants who used the gum for longer periods tended to have been the more dependent smokers.

4. Harm Reduction Through Nicotine Maintenance Therapy

Harm reduction through nicotine maintenance therapy may be considered a mechanism for decreasing the risks associated with continued smoking and involves weighing the relative risk of extended use of NRT against the numerous health risks associated with continued smoking or tobacco use. Nicotine itself is relatively safe compared with tobacco products that deliver a number of other toxic substances in addition to nicotine. These other toxic substances are felt to be responsible for tobacco-attributable morbidity and mortality. In addition, NRT products deliver lower doses of nicotine at slower rates compared with smoking. There is no evidence that NRT confers more risk than cigarettes and tobacco in terms of cardiovascular events, respiratory disease and carcinogenic risk. Several studies have documented a lack of an association between nicotine patches and gum and acute cardiovascular events, even in those who continued to smoke while using the nicotine replacement product.[8] Most tobacco control experts would agree that prolonged use of

pharmacotherapy is preferable to continued tobacco use from a health standpoint.[8,13,20,34,35]

For a comparison of the risks and benefits associated with prolonged use of NRTs, see table I.

5. Discussion

5.1 Argument for Long-Term Use of Pharmacotherapy

Pharmacotherapy has proven very effective for treating tobacco use and dependence. The benefits of prolonged use of pharmacotherapy are evident and seem to outweigh the potential harms. The abuse potential of bupropion and NRT products is low, as demonstrated in a number of studies, and these products are less harmful than cigarettes and tobacco as they do not contain all of the cancer-causing chemicals found in tobacco. Moreover, long-term use of some of the pharmacotherapies available may help prevent relapse in a number of former tobacco users. However, since some studies show that those individuals who did not continue to use NRT after 1 year were more likely to sustain smoking cessation over 5 years, long-term use of NRT might be beneficial only to a certain point beyond which it is associated with relapse. On the other hand, this may be attributable to the characteristics of those who continue to use NRT beyond a year (i.e. more dependent smokers, those with less confidence in their quitting ability). There is clearly a need for more research in the area of the long-term use of pharmacotherapy for treating tobacco dependence and preventing relapse.

Russell[37] argued that in order to make real strides towards eliminating tobacco use, we must not focus on the efficacy of new nicotine delivery systems as temporary aids to cessation but consider their potential as long-term alternatives to tobacco. If our main concern is to reduce tobacco-related diseases and not necessarily eliminate addiction to nicotine, we should promote mechanisms of nicotine delivery that are free of the many cancer-causing compounds found in tobacco. He proposes that certain nicotine replacement products be made readily available and palatable and

Table I. Comparison of the risks and benefits of the prolonged use of pharmacotherapies for treating tobacco dependence

	Nicotine patch	Nicotine gum	Nicotine nasal spray	Nicotine oral inhaler	Bupropion
Recommended duration of treatment	Up to 6-10 weeks, including tapering period	Up to 12 weeks	Up to 6 months, including tapering period	Up to 6 months, including tapering period	Up to 6 months
Abuse potential	Minimal	Low	Moderate	Low[a]	Minimal
Benefits of prolonged use					
improved abstinence	No	Yes	Unclear	Yes	Yes
decreased relapse risk	No	No[b]	No	No evidence	Yes
less bodyweight gain	No evidence	Yes	Yes	No evidence	Yes
Relative risk of cardiovascular events, respiratory disease or cancer compared with smoking	Markedly less	Markedly less	Markedly less	Markedly less	Markedly less

a   Few studies are available.[36]

b   There is evidence that prolonged use of nicotine gum is associated with relapse.

that they be deliberately promoted on the open market for long-term use in order to compete with tobacco products. He argues that active promotion of nicotine replacement will help many countries achieve sustained declines in smoking prevalence, with the added bonus of decreasing environmental tobacco smoke exposure.[37] Warner et al.[38] question whether the healthcare community should continue to regard abstinence as the only therapeutic goal, or if perhaps we should consider a 'harm-reduction' strategy using long-term nicotine maintenance products that deliver nicotine without the other toxic substances found in tobacco products. McNeill et al.[39] argue that NRTs should be made as widely available as cigarettes and that they should be designated and used for smoking reduction, to support temporary abstinence and for long-term maintenance use.

5.2 Argument Against Long-Term Use of Pharmacotherapy

Readily available nicotine-containing products might induce children and others who are not using tobacco to initiate nicotine use resulting in subsequent addiction. For example, there is concern that a 'nicotine mint lozenge', to be marketed by a tobacco company, will be attractive to children and possibly lure them into a lifetime of nicotine addiction.[40] Another concern is that readily available nicotine-containing products will help people

without the intention of quitting to maintain their cigarette smoking by providing nicotine in situations where they are not allowed to smoke.[38] In addition, a number of studies have shown that a course of long-term NRT (particularly gum) appears to be negatively associated with maintenance of long-term cessation of smoking.[24,25] Finally, although NRTs are well tolerated when used for the short term, more data are necessary on the safety of their long-term use.

6. Conclusions

Arbitrary limitations on the duration of use of medications to treat tobacco dependence may serve to prevent a number of people from achieving and maintaining lifelong abstinence from tobacco products.[41] Since tobacco dependence is and should be treated like a chronic disease, we should not limit the duration of treatment or the number of treatment courses when our desired goal is to reduce harm, promote health and ultimately assist the patient in achieving long-term cessation of tobacco use. Currently, there is not a sufficient evidence base to recommend long-term or maintenance pharmacotherapy for all smokers trying to quit, because neither the safety nor efficacy of such use has been unequivocally established. However, given the varied temporal course of nicotine withdrawal and considering prior patient experience with quitting, long-term maintenance therapy should

be considered an appropriate therapeutic plan for selected individuals.

Acknowledgements

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