SMOKING CESSATION

SUMMARY

- **Smoking is the greatest single preventable cause of death in Ireland**
- **All six Nicotine Replacement Therapy (NRT) products and bupropion are available on GMS. Choice should be made on the smokers personal preference, tolerance for side effects for each product and dependence on nicotine**
- **Combination NRT may be more effective than using single products. NRT is not contraindicated in patients with cardiovascular disease**
- **Bupropion (Zyban®), the first non-nicotine smoking cessation aid was licensed last year**
- **All forms of NRT and bupropion have been proven to be significantly more effective than placebo in helping smokers quit**

Smoking is a global epidemic and poses huge challenges for the healthcare profession. Every year, 7,000 people die in Ireland from smoking related diseases, this is ten times more than the number killed each year on our roads.
Approximately 31% of the Irish population smoke, with a slightly higher prevalence in males (32%) than females (31%). When these figures are further categorised by age, the youngest age group (18-35 years) exhibit a significantly higher rate of 40%.[1] **Another cross-sectional study focused specifically on school-going children aged 9-17 years and found that by the age of 15-17 years a third of both boys and girls are current smokers and 40% of girls in social class 5 to 6 are smokers.**[2] **Smokers were asked of their intentions to stop smoking. 74% of smokers said they had tried unsuccessfully to quit, the majority on their own even though unaided quitting has very high failure rates compared to any other strategies. A quarter of all smokers die in middle age from tobacco related diseases and half of all smokers will die from smoking related diseases.**
The good news is that stopping smoking, even after many years has substantial health benefits. Smokers who quit well into middle age avoid most of the subsequent risk of lung cancer, and stopping before middle age avoids more than 90% of the risk attributable to tobacco.[3] **Smokers should therefore be encouraged to use nicotine or non-nicotine therapy as a cessation aid as it is effective and safe if used correctly. The Irish College of General Practitioners have published guidelines on the management of smoking cessation in general practice.**[4] **Updated guidelines were published last year.**[5] **Prochaska and DiClemente devised a five stage model of addictive behaviour. The five stages are Precontemplation, Contemplation, Action, Maintenance and, sometimes, Relapse. The aim is to allow smokers to move through the wheel of change by applying appropriate interventions in each stage. Relapse is common and most smokers will move back and forward between stages before permanently quitting. Success rates increase with each attempt.**[6]
Smoking is one of the most important risk factors for coronary heart disease. The UK antismoking pressure group has estimated that smoking cessation is 17 times more cost effective than the use of statins to lower cholesterol. In addition, unlike other preventative strategies, smoking cessation is unlikely to result in long term health risks. Looking at counselling alone, for example, even if it only increases quit rates by 1-3% it is still considered to be highly cost effective.[7]

The Department of Health and Children has approved the reimbursement of NRT for eligible GMS patients with effect from the 1st of April 2001. Bupropion is already available since its launch.
This bulletin will look at the different forms of nicotine replacement products available, their effectiveness and safety. Their use in specific patient groups will also be discussed. Bupropion, will also be reviewed.

NICOTINE GUM

The first type of NRT to become widely available was nicotine chewing gum. There are two strengths of gum, 2mg and 4mg. The nicotine gum cessation programme is based on a 12-week programme. Patients should chew one piece of gum whenever they have the urge to smoke. A common error is incorrect technique. The gum should be chewed very slowly until the nicotine is tasted or a slight tingling sensation is felt in the mouth. Chewing is then stopped and the piece of gum is "parked" between the gum and the cheek while absorption takes place by the buccal mucosa. When the taste fades, the gum is chewed again and the procedure repeated. Each piece only lasts 20-30 minutes and enough pieces should be chewed to keep cravings away. The maximum dose depends on which product is being used. In addition, patients should be advised to avoid acidic beverages 15 minutes before and during nicotine gum use as they have been found to reduce buccal absorption of nicotine. There have been numerous trials showing nicotine gum to be significantly more efficacious than placebo gum or no treatment.[8]
Among the most highly dependant smokers using the Fagerstom test for nicotine dependance (table one) the 4mg gum is more effective. This is because steady state nicotine concentrations are higher with the 4mg gum than the 2mg dose. Although highly variable, the blood level of nicotine in smokers approaches 44ng/ml whereas with the serum nicotine levels with gum average 30-60% of those found in cigarette smokers. Nicotine gum produces large variations in peak levels when chewed which mimics the fluctuations seen in smoking itself.
The main side effects of the gum include throat irritation, indigestion, nausea, headache, and faintness. Most of these are minor and transient.[9,10]
In summary, the nicotine gum can substantially aid smoking cessation, particularly among highly dependant smokers.

NICOTINE PATCH

The nicotine patch was designed to decrease the withdrawal symptoms resulting from smoking cessation without the compliance difficulties reported with nicotine gum.[11] **There are a number of different brands of patch available that deliver a controlled amount of nicotine over 16 or 24 hours. They are useful for patients with moderate dependency who need baseline nicotine in their system.**
In a comprehensive meta-analysis there was no difference in clinical effectiveness with the 16 hour compared to the 24 hour patch.[8] **The 24-hour patch may be more suitable for someone who smokes within 20 minutes of waking however there is no correlation between reduction in morning cravings and total smoking abstinence.**[12] **The 24-hour dosing resulted in superior relief of craving and withdrawal during the first 2 weeks of abstinence (when symptoms are at their peek), although the 16-hour regimen may have lower relapse rates.** [13,14] **In**

addition, use of the patch for up to 8 weeks was as effective as longer courses of treatment. This may be helpful in reducing the cost of NRT. One large trial which compared a 28 to a 12 week course of treatment found no evidence of benefit from longer treatments.[15] **Despite recommendations that the patch strength be decreased over a time period, the Cochrane meta-analysis found no difference in effect in trials where the dose was tapered or weaned compared to those where withdrawal was abrupt.**[8]

The efficacy of nicotine patch was less strongly related to nicotine dependence, unlike nicotine gum, perhaps because the patch cannot deliver a bolus of nicotine to satisfy craving.[16]

In summary, the transdermal patch is suitable for all but the most heavily dependent smoker. It has the advantage of being discreet, convenient to use, requires minimal instruction and is well tolerated both topically and systemically. The main unwanted effects with the patch are application skin reactions, for example erythema and itching.

NICOTINE INHALER

The nicotine inhaler consists of a mouthpiece and a replaceable nicotine cartridge. Through sucking on the inhaler, nicotine vapour is drawn into the mouth where it is absorbed through the buccal mucosa. Little or no nicotine reaches the lungs. It provides about 30% of the nicotine delivered from cigarette smoking (approximately the same as the 2mg gum and slightly less than that provided by patches). This device provides just enough nicotine to reduce smoking withdrawal symptoms, but also gives smokers something to do with their hands and mouth to tackle the behavioural aspects of smoking. Three trials have shown the nicotine inhaler to be effective and safe.[17,18,19] **The inhaler should be used whenever the urge to smoke is felt, up to a maximum of 12 cartridges daily. A common usage error with the nicotine inhaler is not to change the cartridge often enough as the taste lingers on the tip of the inhaler and may result in under-dosing. The most frequently reported adverse events are local; cough and irritation of the mouth and throat.**

NICOTINE NASAL SPRAY

One of the main objectives of developing a nasal nicotine spray was to produce a smoking cessation aid that more closely mimicked the rapid delivery of nicotine produced by smoking cigarettes.[20] **The nicotine nasal spray is particularly suited to smokers who require rapid relief of tobacco withdrawal symptoms. Approximately 56% of one dose of nicotine nasal spray enters the systemic circulation with peak plasma concentrations achieved after only 10 minutes.**[21] **To date, 4 trials have shown nicotine nasal spray to be effective.**[22,23,24,25] **The patient use the spray when required with a recommended level of 1 or 2 sprays into each nostril per hour. Dosage should not exceed 2 sprays to each nostril per hour during waking hours (ie maximum daily total 64 sprays). The nasal spray device is similar to gum or inhaler systems by offering a more flexible delivery system that will enable the user to adapt nicotine use according to need. The most commonly reported side effects are irritation in the nose, watery eyes, sneezing, irritation in the throat and coughing. Most of these are mild or moderate and of short duration.**

NICOTINE LOZENGE

The 1 mg sugar-free lozenge has equivalent efficacy to nicotine 2mg gum. Each lozenge is sucked until the taste becomes strong and is then lodged between the gum and cheek. When the taste fades, the lozenge is sucked again and the process repeated until it dissolves completely (about 30 minutes). The dosage should be individualised according to the patient's nicotine dependence. Initially 1 lozenge should be taken every 1-2 hours. The usual dose is 8-12 lozenges daily with a maximum of 25. The main side effects are irritation of the throat, excess salivation, hiccups and mild dyspepsia. Slower sucking will usually overcome these problems.[26]

SUBLINGUAL NICOTINE TABLETS

The latest nicotine smoking cessation aid is the nicotine microtablet which adds to the range of products available. Each sublingual tablet (2mg) has similar pharmacokinetic properties to nicotine 2mg chewing gum. The recommended dose is one tablet per hour, or for heavy smokers (≥7 on the Fagerstrom Tolerance Questionnaire, see table 1), two tablets per hour. Most smokers will require in the range 8-24 tablets daily with a maximum of 40.[27] **A recent study has shown that smokers using the sublingual tablet as a smoking cessation aid doubled their chances of successfully quitting.**[28] **This result is comparable with those from clinical studies that evaluated other nicotine replacement products. Success rates for complete abstinence for active (sublingual tablet) vs. placebo were 50% vs. 29% at 6 weeks, 42% vs. 23% at 3 months, 33% vs. 18% at 6 months and 23% vs. 15% at 12 months. Cravings were significantly reduced among highly dependent smokers. Adverse events were mild and tolerable, the most common being irritation and soreness in the mouth and throat.**
In conclusion, the nicotine sublingual tablet offers a discrete product that increases the smokers cessation rate compared to placebo, reduces cravings in highly dependent smokers and is well tolerated.

ARE THE DIFFERENT FORMS OF NRT PRODUCTS EFFECTIVE?

Few studies have directly compared the available treatments so it is difficult to recommend one approach over another.[29] **Overall there are no notable differences in terms of their general efficacy or effects on withdrawal symptoms.**[30,31] **A recent meta-analysis by the Cochrane review group identified 88 trials involving nearly 35,000 smokers.**[8] **The main outcome measure was abstinence from smoking after at least 6 months follow-up. All forms of NRT were found to be effective and increased quit rates from 1.5 to 2 fold regardless of the level of additional support and encouragement. The pooled odds ratio of abstinence for any form of NRT relative to control was 1.71. For the different forms of NRT the odds ratio ranged from 1.63 with nicotine gum to 2.27 with nicotine nasal spray. For transdermal patch, nicotine inhaler, and nicotine sublingual tablet, the odds ratios were 1.73, 2.08 and 1.73 respectively. Although the odds ratios were higher for nasal spray and inhaler, this is based on a small number of trials. In addition to the use of NRT, there is a strong positive correlation between counselling intensity and cessation rates.**[32]

COMBINATION NRT

Various combinations of smoking cessation products offer some promise. Combining nicotine gum and patch provide superior quit rates than each product alone.[33,34] The combined use of gum and patch is a convenient therapeutic option as it gives the user a steady intake of nicotine (with the patch) that can be supplemented with nicotine gum to respond to momentary nicotine cravings. Other studies using a combination of the patch and nasal spray[35] and patch with inhaler[36] showed that the combination cessation rates were higher than monotherapy rates. Although NRT products are not licensed for use in combination, studies have proved their effectiveness and suggest that combination therapy may be particularly appropriate for highly dependent smokers who relapse on monotherapy because of persistent cravings or withdrawal symptoms.

BUPROPION

Bupropion (Amfebutamone), Zyban®, the first non-nicotine prescription tablet licensed for smoking cessation was launched in Ireland in September 2000. In vitro studies have demonstrated that this atypical antidepressant is a weak inhibitor of neuronal reuptake of nor-adrenaline and dopamine however the precise mechanism by which it aids smoking cessation is not firmly established.

The efficacy of bupropion has been investigated in two published trials; a placebo-controlled dose-response study and a comparison of bupropion with nicotine patches or a combination of the two.[37,38] Abstinence rates after one year of treatment were 23-30% with bupropion. Expressing these figures as odds ratios, ie success rates in relation to placebo, bupropion increased quit rates by 2.1 to 2.4 fold. This compared to 16% with nicotine patches. In this study, the rate of abstinence with nicotine patches was no different to placebo, a result that is not consistent with other studies. Interestingly, the rate of abstinence was 35.5% with the combination of bupropion plus nicotine patch. Further studies are needed to confirm this. Preliminary data (published only as an abstract) suggest that weight gain may be curtailed with long-term bupropion.

The most common side effects reported are dry mouth and insomnia.[39] Seizures have been reported in 1 in 1000 patients taking 300mg daily and use is contraindicated in patients with a current or past history of seizures. The drug should also be used with extreme caution in patients who have conditions predisposing to a lowered seizure threshold, and concomitant use with drugs known to lower the seizure threshold. Drug interactions need to be considered with bupropion, in particular with monoamine oxidase inhibitors. Bupropion inhibits metabolism by cytochrome p450 2D6 and therefore caution is advised when medicinal products metabolised by this enzyme are administered concomitantly (including certain antidepressants, many antipsychotics, bete-blockers and antiarrythmics).[40]

There were concerns raised recently in the press that a number of fatalities in the UK were associated with bupropion. The Medicines Control Agency (MCA), UK, have indicated that the contribution of bupropion in these fatalities is unproven. To date, 23,000 patients have been treated with bupropion in Ireland. The Irish Medicines Board have received 65 reports of suspected adverse effects

however the majority were felt to be in keeping with those expected of the product and most patients recovered completely. There has been 1 fatality reported during treatment with bupropion however the cause of death was unrelated to its use.

OTHER NON-NICOTINE MEDICATIONS

Clonidine, an α_2-noradrenergic agonist used to treat hypertension has been shown to reduce cravings and withdrawal symptoms in heavy cigarette smokers. Adverse effects including drowsiness, fatigue and dry mouth limit its use. Of interest, the clonidine studies identified a link between depression and smoking and suggested the value of antidepressant medication for smoking cessation therapy. In one of these trials, 60% of smokers had a history of depression. The efficacy of bupropion, an atypical antidepressant has already been discussed. Results using other antidepressants including nortriptyline, moclobemide, doxepin and fluoxetine need to be further clarified. Efforts to show the potential efficacy of anxiolytics (especially buspiron) have produced conficting results. Buspiron is beneficial for smokers who are anxious prior to smoking cessation however the benefits are only maintained during the treatment period. Speculation that endogenous opioides may be involved in the reinforcing properties of nicotine prompted the investigation of opioid antagonists naltrexone and naloxone as smoking cessation aids. Results to date have been mixed.[41,42]

USE IN SPECIAL POPULATIONS?

A widespread misconception exists that smoking while using the nicotine replacement poses additional dangers to the smokers cardiovascular system. This myth originated from five highly publicised case reports in the media in 1992 shortly after the introduction of the nicotine patch. The Food and Drug Administration (FDA) in the United States subsequently concluded that there was no evidence that the patches contributed to the risk of myocardial infarction in these patients. The Lung Health Study, the largest study on the safety of NRT, and the only one to date to investigate long-term effects (up to five years) found no statistical increase in cardiovascular risk among those who used tobacco and NRT together. Several other studies have also confirmed the cardiovascular safety of NRT.[43,44,45] **If NRT can assist smokers to stop, or reduce cigarette consumption in those who cannot stop, the health benefits far outweigh any risks. While Bupropion is not contraindicated in patients with heart disease there are no clinical trials studying its use in patients with a recent myocardial infarction or unstable heart disease.**

The risks of cigarette smoking during pregnancy are well known to be associated with prematurity, low birth weight and spontaneous abortion .[46] **Despite this, women continue to smoke during pregnancy. Pregnant women who smoke are often highly motivated to quit and may do so without NRT. Behavioural therapy and counselling may be sufficient to ease the withdrawal symptoms. In pregnant women who are unable to quit in these situations, there may be a place for NRT which is safer than continued cigarette smoking. Such use is currently not licensed.**

Nicotine replacement products do not require dose adjustments for elderly patients. The transdermal patch maybe the preferred treatment choice in this group as the simplicity of once-daily application increases compliance. Products requiring dosing may be too difficult to use. Bupropion should be used with caution in these patients with administration at the lower dose.

TABLE 1:FAGERSTROM TEST FOR NICOTINE DEPENDENCE

MAXIMUM SCORE=10
SCORE OF ≥8:MOST HIGHLY DEPENDENT SMOKERS
SCORE OF4-7:LESS DEPENDENT SMOKERS

QUESTIONS	ANSWERS	POINTS
How soon after you wake up do you smoke your first cigarette?	Within 5 minutes 6 to 30 minutes 31 to 60 minutes after 60 minutes	3 2 1 0
Do you find it difficult to refrain from smoking in places where it is forbidden (i.e. church, cinema, library)?	Yes No	1 0
Which cigarette would you hate most to give up?	The first one in the morning Any other	1 0
How many cigarettes a day do you smoke?	31 or more 21 to 30 11 to 20 10 or less	3 2 1 0
Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes No	1 0
Do you smoke if you are so ill that you are in bed most of the day?	Yes No	1 0

COST OF NRT PRODUCTS AND BUPROPION

Cost of Marlboro Lights (20) : £3.88

Product and Manufacturer	Unit Cost £
Nicorette (Pharmacia and Upjohn)	
Gum 4mg *	0.13
Patch 15mg/16hrs	1.42
Inhaler *	0.36
Nasal spray *	0.06
Microtab 2mg *	0.13
Nicotinell (Novartis Consumer)	
Gum 4mg *	0.12
Patch 21mg/24hrs	1.13
Lozenge 1mg *	0.13
NiquitinCQ (SmithKlineBeecham)	
21mg/24hrs	1.41
Zyban (GlaxoWellcome)	
150mg	0.92

- *** Exact daily usage varies depending on the patient**
- **Unit costs, for example one puff of inhaler, one piece of gum, are based on lowest cost according to pack size**
- **Costs are expected to fall with time as the daily usage and/or strength of the product declines**

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