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Potential conflicts of interest

P. Tønnesen has undertaken research and consultancy for, and received travel funds and honorary for scientific presentations, from pharmaceutical companies that develop and manufacture aids to smoking cessation.

WHAT'S NEW IN SMOKING CESSATION?

P. Tønnesen

INTRODUCTION

The aim of this paper is to give an overview and an update of the effect of counselling and pharmacological drugs in smoking cessation with varenicline being the newest agent on the market.

Nicotine vaccination, as a possible tool for smoking cessation and relapse prevention, will also be covered. Assessments familiar within this area are questionnaires for measuring of nicotine dependence, motivation to quit, withdrawal symptoms and carbon monoxide (CO) as the most commonly used biochemical measure of smoking abstinence. In last year's European Respiratory Society Buyers' Guide, a comprehensive article focused on CO assessment and CO-monitors. The present article will present some guidance on how to choose between the various drugs to be used in smoking cessation, for the individual smoker.

Experience seems to show that reimbursement of counselling, as well as drugs in this area, is a way to increase the use of drugs in smoking cessation, in accordance with clinical guidelines.

Long-term cigarette smoking shortens the expected duration of life by ~10 yrs. Smoking cessation has been found to be among some of the most cost-effective medical interventions with a cost of around €400–1,500 per quality adjusted life year (QALY) gained [1, 2, 3].

Smoking has a major aetiological role in diseases, such as lung cancer, chronic obstructive pulmonary disease (COPD), myocardial infarction (MI) and other cardiovascular disorders and worsens the outcome of asthma as well as of surgery [4, 5].

One of the main reasons for daily tobacco smoking is nicotine addiction [6]. Counselling combined with pharmacotherapy is the mainstay in smoking cessation therapy and there are three first-line pharmacological agents to be used in smoking cessation.

Several high-quality meta-analyses have been performed in this area, examining different interventions for smoking cessation, *e.g.* the Cochrane Database, the US Agency for Healthcare Policy and Research (AHCPR) publication and the National Institute for Clinical Excellence (NICE) guidelines from UK [7–12].

COUNSELLING

Regarding the most minimal intervention, *i.e.* self-help materials for smoking cessation, one would expect a small effect and, indeed, that is the case with only a 1% increase in quit rate [13, 14, 15].

Telephone counselling can be used as a supplement to face-to-face interventions, or to substitute for face-to-face contact as an adjunct to self-help interventions. It can also be timed to maximise the level of support around a planned quit date and scheduled in response to the needs of the recipient. In proactive telephone counselling, the counsellor initiates the calls to provide the smoker with support to make an attempt at quitting and proactive telephone counselling increased effectiveness when compared to self-help materials (odds ratio (OR) 1.41; 95% CI 1.27–1.57). In reactive counselling, the support is provided *via* helplines or hotlines that take calls from smokers; meta-analysis shows a small effect from this intervention (OR 1.33; 95% CI 1.21–1.47) [16–19].

Advice, given by the general practitioner or nurses, has shown a small but significant increase ►

in the odds of quitting (OR 1.69, 95% CI 1.45–1.98) [20, 21]. This equates to an absolute difference in the cessation rate of ~2.5% in smokers who received medical advice compared with those who did not.

It is not very surprising that there is a dose-response relationship between the intensity of support for smoking cessation and the level of abstinence rates. Even minimal (<3 min) intervention is effective. However, there is a dose-response effect from person-to-person counselling with regards to time used in each session as well as with the number of sessions, *i.e.* four or more sessions seems especially effective [9]. A scenario, which could have good odds of being used in the daily clinic could be 4–5 sessions of 10 min duration during the first 3 months after quit day (after 1–2 weeks, 3–4 weeks, 6 weeks, 10–12 weeks). There seems to be an effect of cooperation between two different clinician types (physician, nurse, psychologist, *etc.*) and this is often the case in daily clinics, *i.e.* the doctor will advise the smoker to quit and then the nurse will spend more time on counselling [9].

Group therapy is not more effective than individual counselling [22, 23]. Group therapy is better for helping people stop smoking than no intervention (OR 2.17; 95% CI 1.37–3.45) and than self-help therapy (OR 2.04; 95% CI 1.60–2.60). However, there is not enough evidence to evaluate whether group therapy is more effective, or cost-effective, than intensive individual counseling [23].

It is important to note that, in most studies, the applied counselling has been delivered by nurses with some training in smoking cessation. It is not necessary to use psychotherapy delivered by psychologists; and “in-office supportive care” might be a better terminology than counselling, so as not to distract doctors.

Table 1. Efficacy of first line drugs: efficacy from the Cochrane register.

Comparison	Sustained quit rates for 1 yr
NRT <i>versus</i> placebo (103 studies) [7]	1.77 (1.66–1.88)
BupropionSR <i>versus</i> placebo (16 studies) [8]	1.97 (1.67–2.34)
Varenicline <i>versus</i> placebo (5 studies) [9]	3.22 (2.43–4.27)

Data are presented as odds ratio (95% confidence interval). NRT: nicotine replacement therapy.

PHARMACOTHERAPY FOR SMOKING CESSATION

The three first-line agents for smoking cessation are nicotine replacement therapies (NRT), bupropionSR and the recently marketed drug, varenicline. All are recommended to be used for around 3 months. A Cochrane meta-analysis reported an OR for NRT *versus* placebo of 1.73 (95% CI 1.62–1.85; 108 studies) for 6–12 months abstinence, for bupropionSR *versus* placebo of 1.97 (95% CI 1.67–2.34; 16 studies) and for varenicline *versus* placebo of 3.22 (95% CI, 2.43–4.27; 5 studies) [7, 8, 9] (table 1).

Nicotine replacement therapy

Nicotine replacement therapy (NRT) has been on the market for several decades and is the agent with the most extensive documentation (>100 randomised controlled trials) and the longest post-marketing experience [7]. The plasma nicotine concentrations attained with NRT are a half to one-third of the levels during smoking [24]. NRT almost doubles the 1-yr quit rate when used for 2–3 months with no statistical difference in efficacy between the five different formulations: skin patch, chewing gum, “inhaler”, sublingual tablets (or lozenges), and nasal spray and with a small increase in quit rate when two different formulations of NRT are combined [7, 10]. NRT has been shown to be effective in different settings, ranging from

smoking cessation specialist clinics to over-the-counter treatments without any counselling or support, in “healthy” smokers and in patients with COPD [25–28]. The adverse events are mostly mild and transient, and the most common are local irritation from nicotine on skin or mouth and throat but seldom nicotine “overdose” symptoms. NRT has been found safe in patients with cardiovascular disorders [29, 30]. There are differences between the formulations of NRT with the patch often used to deliver a basal degree of nicotine substitution combined with one of the others to be used as needed to suppress intermittent withdrawal symptoms. 5–10% of nicotine chewing gum users will use the gum after 1 yr due to nicotine dependence but long-term use does not seem to have significant adverse health effects. Combination of nicotine patches and one of the fast action formulations (gum, nasal spray, inhaler, sublingual tablet) seems to be especially effective and is highly recommended [10]. A nicotine mouth spray has recently been marketed in Scandinavia.

Varenicline (Champix, Chantix)

Varenicline is a partial agonist of the important nicotine receptors, $\alpha_4\beta_2$, in the CNS but exerts also an antagonist effect, *i.e.* it acts like nicotine and also decreases the pleasure by smoking. It has been found effective relative to placebo in two large trials with relative heavy counselling in “healthy” ►

smokers and with a higher quit rate when compared with bupropionSR although only statistical significant after 1-year in one of the two trials [31, 32]. Adverse events have been nausea in approximately one-third, vomiting in up to 5% and vivid dreams in 10% [8]. Varenicline has been on the market for ~2 yrs. In post-marketing, there have been reports of depression, suicidal behaviour and also suicides in patients still smoking on varenicline and this have been added to the labelling. It has to be remembered that smokers often have several somatic and psychiatric comorbidities; so, whether these represent potential side-effects from varenicline or are, instead, to be suspected by chance in this population of smokers is not possible to conclude. However, when a smokers starts to quit smoking, questions about previous

depression or suicidal thoughts should be noted and repeated at the recommended follow-up visits, independent of the agents used for smoking cessation.

In a recent study in patients with cardiovascular diseases, varenicline was shown to be effective and safe with even a little higher difference in quit rates compared with placebos [33].

There are on-going trials with varenicline in patients with COPD and depression. However, there are no trials with varenicline in general practice or with minimal support and few visits. Although it does not seem rational to combine varenicline with either NRT or bupropionSR, studies have been planned to evaluate this.

In a multi-national, 24-centre study, 376 and 370 smokers were

randomly allocated varenicline for 12 weeks and nicotine patch (21 mg·24 h⁻¹), respectively, for 10 weeks in an open-label trial [34].

Continuous quit rates at week 8 (9) -24 was higher for varenicline *versus* NRT but not statistically significant. The continuous quit rate at week 8 (9) -52 for varenicline *versus* NRT was 26.1 *versus* 20.3% (p=0.056) and, when all randomised subjects were included, the difference did reach significance. There was no significant difference in the 7-day point prevalence after 24 and 52 weeks.

Due to potentially serious limitations and bias in that study, it is not possible to conclude that varenicline is superior to NRT. However, the positive message from the trial is that we can expect a 1-yr continuous quit rate of 20–26% and a 1-yr point prevalence of 31–35%, *i.e.* 1 in 3 were quitters after 1 yr.

Indirect comparison by NICE reported that varenicline was more effective than bupropionSR (OR 1.58 95% CI 1.22–2.05) and NRT (OR 1.66 95% CI 1.17–2.36) [12].

However, we still need an adequately designed and conducted double-blind, placebo-controlled trial to assess the relative efficacy of varenicline *versus* NRT.

BupropionSR (Zyban®)

BupropionSR (Zyban®) is an older antidepressant drug, an amineketone agent, with an inhibitory effect on noradrenaline and dopamine reuptake but it might also have a direct effect on neuronal nicotinic receptors. Analysis of pooled data from two randomised controlled trials (n=722) with bupropion reported smokers with the genotype for dopamine receptors A2/A2 (DRD2 Taq1A) were three-times more likely, relative to placebo, to be abstinent which mean that genotype A1/A1 or A1/A2 did not

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benefit from bupropion [35]. However, the cost-effectiveness of targeting therapy by genotyping is doubtful.

BupropionSR 300 mg was compared with nicotine patch 21 mg·24 h⁻¹, placebo and the combination of bupropion and nicotine patch. Bupropion was used for 9 weeks and nicotine patches for 8 weeks [36]. The sustained quit rates after 1 yr were 5.6% (for placebo), 9.8% (nicotine patch), 18.4% (bupropion) and 22.5% (bupropion and nicotine patch). The two bupropion groups achieved a higher success rate compared with placebo and nicotine patch.

A sustained success rate of 18–23% is in accordance with the success rates found in many studies of NRT with support in the same range as in the aforementioned studies.

Another study randomised smokers to bupropionSR (n=121) or placebo (n=123) for 7 weeks, in which both groups had a nicotine patch for 2 months supplemented with counselling. No significant difference was found between the two groups, with a 1-yr quit rate of 22% (for Bupropion) and 28% (placebo), respectively. Validated quit rate was 19% *versus* 24%, respectively [37].

In that study, 404 COPD patients (smokers with 15+ cigarettes·day⁻¹) in 11 centres in the USA were allocated to bupropionSR for 3 months or placebo, in a design with moderate intensive support (*i.e.* 10 visits) with weekly individual sessions during the first 7 weeks [38]. Most patients were mild COPD in Stage I (forced expiratory volume in 1 s (FEV1) >50%) and 15% in stage II (FEV1 35–49%) with a cigarette consumption of 28 cigarettes·day⁻¹ and 52 pack-yrs, and a Fagerström score of 7 (maximum score is 11). Abstinence rate was significantly higher up to 6 months in the bupropion group

versus placebo (16 *versus* 9%, respectively). After 1 yr, the significance was lost with a success rate of 10 *versus* 8%, respectively, which is much lower compared with similar studies of bupropion in healthy subjects.

In a well-conducted study in 71 general practices in Italy, consisting of 593 smokers with five visits and three telephone calls, the 4–52-weeks sustained quit rate was 25% for the bupropion group and 14% for the placebo group [39].

The most common adverse events from bupropion are insomnia (42%) and dry mouth (11%). Aggravation of hypertension is also reported, as well as allergic rash. In ~10–12% of subjects, the treatment was stopped due to adverse events. The most serious adverse event was seizures, which have been reported in 0.1% of depressed patients treated with bupropion. Post-marketing reports have been published with several cases of seizures, even in subjects with no known dispositions to seizures, as well as intentional overdose.

In two studies (n=1025, n=1027) with similar design, varenicline 1 mg *b.i.d.* was compared head-to-head with bupropionSR 150 mg *b.i.d.* and placebo for 3 months. [31, 32]. The quit rate after 1 yr was 22% (and 23%) for varenicline, 16.4% (and 15%) for bupropion, and 8.4% (and 10.3%) for placebo *i.e.* significantly higher quit rates for varenicline *versus* placebo and bupropion. The quit rate was significantly higher for varenicline *versus* burpopion after 3 months but after 12 months only significant in one of the studies. Although the odds ratio is in favour of varnicline over bupropion, it is striking that the 1-yr sustained quit rate is ~20–25% for both drugs in several studies.

Overall, a meta-analysis (n=16 studies) found an OR of 2.06 (1.7–2.4) for bupropionSR for long-term abstinence *versus* placebo [9]. ▶

PRODUCT LISTINGS

In summary, bupropionSR is as efficacious as NRT and probably a little less effective than varenicline. BupropionSR has been found to be effective in specialist settings and in general practice, in healthy subjects and in patients; there is a solid scientific documentation and bupropionSR has been on the market for many years. BupropionSR is generally well tolerated in smoking cessation and is regarded as a first-line medication [9]. Bupropion has a more severe side effect profile than NRT, more contraindications and is only available on prescription.

Nortriptyline: a second-line drug

Nortriptyline, a classic tri-cyclic antidepressant, has been shown to be effective in smoking cessation. It is not clear if the effect in smoking cessation of this agent is drug specific or a class effect. As the potential side effects of nortriptyline are more troublesome and serious compared with bupropion, nortriptyline is relatively seldom used for smoking cessation [40, 41]. An OR of 2.8 (1.7–4.6) was calculated in a meta-analysis with four studies for long-term abstinence in favour of

nortriptyline *versus* placebo [9].

Nortriptyline is regarded as a secondary agent in smoking cessation.

Several other antidepressants have not been found to be effective in smoking cessation, *e.g.* doxepin, fluoxetine, sertraline, moclobemide and venlafaxine [42, 43]. It also means that the selective serotonin reuptake inhibitor has no proven role in smoking cessation.

SELECTION OF DRUG FOR THE INDIVIDUAL SMOKER

NRT, bupropionSR and varenicline are all first-line agents. Of these, NRT seem to have the following advantages: most extensive scientific documentation, effective in healthy and sick smokers, effective with low and high support and in general practice, safe with almost no contraindications and available without prescription.

So, of that reason NRT is recommended as the first choice in naïve smokers not having received NRT before or not having used NRT properly previously. When only

minimal support is administered, NRT is the drug of choice as varenicline has not been tested in such a condition.

One of the problems with NRT is underdosing. Optimisation of NRT therapy can be achieved by pre-loading and with a combination of two formulations of NRT and adequate instruction (table 2).

In subjects having used NRT previously, varenicline is preferable, as it seems at least as effective as NRT and more effective than bupropionSR, with fewer side effects. Also, many smokers prefer tablets to be taken twice daily as opposed to several daily doses of NRT. So, compliance might be higher with tablets; although, in daily practice, it is my personal impression that some patients stop varenicline therapy before 12 weeks and even after a few weeks, due to the cost of varenicline.

BupropionSR is preferable for subjects suffering from depression and having experienced suicidal thoughts previously, as well as when NRT and varenicline has failed.

Subjects smoking fewer than 10 cigarettes-day⁻¹ should use one of the NRT formulations.

Table 2. Efficacy of first line drugs from US clinical guidelines [10]

	OR (95%CI)	Abstinence rate
Placebo	1.0	13.8
Monotherapies		
Varenicline	3.1 (2.5–3.8)	33.2
High dose nicotine patch	2.3 (1.7–3.0)	26.5
Nicotine gum (>14 weeks)	2.2 (1.5–3.2)	26.1
BupropionSR	2.0 (1.8–2.2)	24.2
Combination therapies		
Patch + <i>ad lib</i> NRT	3.6 (2.5–5.2)	36.5
Patch + bupropionSR	2.5 (1.9–3.4)	28.9
Patch + inhaler	2.2 (1.3–3.6)	25.8

OR: odds ratio; CI: confidence interval; NRT: nicotine replacement therapy.

In the clinical situation when the physician faces the individual smoker, the following factors influence how to select between the three named agents: the clinician's familiarity with the drugs, the patient's preferences or previous experience, the patient's characteristics and the cost and possibility for re-imburement.

Although NRT, varenicline and bupropion should all be regarded as first-line preparations in smoking cessation, I regard NRT as "first-choice", followed by varenicline, with bupropion as third choice. Whichever drug is chosen, one can expect a 1-yr continuous abstinence rate of ~20–25%.

It is a very positive thing that another drug has been marketed for smoking cessation. There is a need for all three agents in smoking cessation, just like in other medical conditions; because almost 75% of smokers who try to quit fail, there is a need for re-treatment.

NICOTINE VACCINATION

Smokers have no antibodies to nicotine, as it is a small molecule. The rationale for nicotine vaccination is that the vaccine (nicotine bound to an hapten) will induce antibodies against nicotine and, as the nicotine from tobacco is bound in the blood by these antibodies, less nicotine will reach the brain. Phase I and II studies have evaluated three different vaccines (NicVAX, NICQb and TA-NIC) [44, 45, 46]. The dosing was been 2–6 injections with 2–4 weeks interval and a later booster dose. Marked inter-individual variability was observed in antibody levels, which decreased by 50% over 6–8 weeks. The vaccines have been well tolerated. Only mild, local

reactions and systemic (flu-like) reactions have been reported.

In the NicQb study, with 133 smokers, 57% of subjects with the ►

highest antibody levels and 31% of controls, quit smoking. In the TANNIC study, 38% of smokers who got the highest dose and 8% of controls quit smoking. In the NicVAX study with 68 smokers, 40% of subjects who got the highest dose and 8% of controls, quit smoking, although ► no additional support was given to encourage participants to quit smoking.

The results from these phase II studies look promising but the sample size was small in all three studies. Thus, larger on-going studies are needed before the efficacy from nicotine vaccination can be evaluated.

OTHER THERAPIES

Other interventions often used are acupuncture, hypnosis, negative affects and cue exposure (*i.e.*, exposing smokers to smoking cues without the opportunity to smoke). However, the evidence is inadequate to support an effect from hypnosis or other alternative

therapies [47]. A meta-analysis comparing active *versus* control acupuncture found that acupuncture was no more effective than placebo [48]. One study has been published about laser therapy in 320 adolescents and did not report any effect of laser therapy (*i.e.* a 3-month quit rate of 25% for laser *versus* 26% for placebo) [49].

One of the major tasks, is to increase the implementation of smoking cessation therapy in the healthcare system. An important question is if re-imburement for smoking cessation therapies, such as counselling and drugs, will affect its appropriate use. Research from the USA has shown that insurance coverage of treatment for smoking cessation results in higher rates of use of evidence-based counselling and drugs and a higher overall cessation rate among the populations covered by this insurance [50].

In the USA, the coverage of medications for smoking cessation was ~25% in 1997 and increased to

90% in 2003. From 2000, the NHS in the UK has offered free counselling and smoking cessation drugs and re-imburement is not an issue in most European countries.

Other tools to increase implementation of smoking cessation include education of health professionals and allocation of specific budgets for this service at clinic level, as well as incentives to involve physicians in this area. The physician's role is to ensure who is currently smoking and to engage with them on a long-term project of keeping them smoke free.

An up-to-date smoking cessation service should be available to all smokers who come into contact with the health care system. The ERS clinical guidelines regarding smoking cessation is a suitable framework for achieving these goals [51]. ■

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