Which drug to be used in smoking cessation?

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Abstract: There are 3 first-line medications for smoking cessation i.e. nicotine replacement therapy (NRT), varenicline (a partial nicotine receptor agonist) and slow-release (SR) bupropion. All 3 agents approximately double 1-year quit rates when used for 3 months, although varenicline seems to be a little more efficacious than bupropion SR. An un-blinded study comparing varenicline with nicotine patches are analysed in details and it is concluded that the validity of that study is low regarding the relative efficacy of varenicline versus NRT. Depression and suicidal attempts have been reported with varenicline use but it is probably not induced by varenicline but by the quitting process *per se*. It is recommended that the first agent to be used in smoking cessation should be NRT as it is the best documented product with mild side effects. It might be optimal to combine the patch with either gum, inhaler, sublingual tablets or nasal spray. In subjects that have failed with NRT, varinicline should be the choice. Bupropion SR is preferred to subjects with depression or smokers who have failed with the previous two agents, due to the many contra-indications and side effects of bupropion SR. With one of the 3 agents combined with follow-up visits with counselling, one can expect a 1-year quit rate around 20–25%.

Key words: bupropion SR, meta-analysis, nicotine replacement therapy, side effects, smoking cessation, varenicline

One of the most meaningful therapies in medicine is to get tobacco smokers to quit. Long-term cigarette smoking shortens the expected duration of life with approximately 10 years. Smoking cessation has been found to be among some of the most cost-effective medical interventions with a cost of around 400–1500 Euros per quality adjusted life year (QALY) gained. Smoking has a major etiological role in diseases such as lung cancer, chronic obstructive pulmonary disease (COPD), myocardial infarction (MI) and other cardio-vascular disorders and worsens the course of several diseases such as arterial hypertension, asthma as well as the outcome of pregnancy.

One of the main reasons for daily tobacco smoking is nicotine addiction. Counselling combined with pharmacotherapy is the mainstay in smoking cessation therapy and today there are 3 first-line pharmacological agents to be used in smoking cessation. The 3 first-line agents for smoking cessation are nicotine replacement therapies (NRT), slow-release (SR) bupropion and the recently marketed drug – varenicline, all to be used for around 3 months. Cochrane meta-analyses reported an odds ratio for NRT vs. placebo (108 studies) of 1.73 (95% CI 1.62–1.85) for 6–12 months abstinence, for bupropin SR vs. placebo (16 studies) of 1.97 (95% CI 1.67–2.34) and for varenicline vs. placebo (5 studies) of 3.22 (95% CI 2.43–4.27) [1-3].

But how to select between these products in general and for the individual smoker?

Nicotine replacement therapies has been on the market for several decades and is the agent with the most extensive documentation (more than 100 randomised controlled trials) and the longest post-marketing experience. The plasma nicotine concentrations attained with NRT are approximately 1/2 to 2/3 of the levels during smoking. Nicotine replacement therapies almost doubles one year quit rate when used for 2–3 months with no statistical difference in efficacy between the 5 different formulations i.e. 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. Nicotine replacement therapies has been shown to be effective in different settings such as smoking cessation specialist clinics, in general practice combined with minimal counselling, in "healthy" smokers and in patients with COPD. The adverse events are mostly mild and transient, and the most common are local irritation from nicotine on skin or mouth and throat and seldom nicotine "overdose" symptoms. Nicotine replacement therapies has been found safe in patients with cardio-vascular disorders. Nicotine replacement therapies are available over-the-counter without the possible barrier of getting a prescription from the physician. 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

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used as needed to suppress intermittent withdrawal symptoms. From five to ten percent of nicotine chewing gum users will use the gum after 1 year due to nicotine dependence but the long-term use does not seem to have significant adverse health effects.

Bupropion SR is an anti-depressant agent but the effect in smoking cessation is probably through dopamine release in the central nervous system (CNS). One major adverse effect is generalised seizures which are correlated with high peak plasma concentration of bupropion and of that reason it is administered as slow release. Seizures are to be expected in 1(–2) per 2000. Also allergic reactions such as urticaria have been reported (1–2%) with more serious allergic reactions occurring in 0.1%. Other drugs also metabolized in CYP2B6 have to be used with care. Bupropion SR have been found safe and effective in patients with cardio-vascular diseases and COPD and also effective in general practice with minimal counselling. Combination with NRT seems safe but does not increase long-term quit rate.

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. both act like nicotine and also decrease the pleasure by smoking. It has been found effective relative to placebo in 2 large trials with relative heavy counselling in "healthy" smokers and with a higher quit rate when compared with bupropion SR although only statistical significant after 1-year in one of the two trials [4]. Adverse events have been nausea in approximately 1/3, vomiting in up to 5% and vivid dreams in 10% [5]. Varenicline has been on the market for almost 1 year. Post-marketing there has been reports about depression, suicidal behaviour and suicides also 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 co-morbidities, so if the above represent a potential side effect from varenicline or is 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.

There are on-going trials with varenicline in patients with cardio-vascular diseases and COPD. However, there are no trials with varenicline in general practice or with minimal support with few visits. It does not seem rational to combine varenicline with neither NRT nor bupropion SR.

A head-to-head comparison with varenicline and nicotine transdermal patch has recently been published in Thorax with the conclusion that varenicline demonstrated a greater abstinence rate than nicotine patch at end of treatment [6].

In this multi-national 24 centre study, 376 and 370 smokers were randomly allocated to varenicline for 12 weeks and nicotine patch (21 mh/24 h) for 10 weeks in an open-label trial. There were weekly visits during the first 12 weeks followed by 7 clinic visits and 5 telephone calls in the follow-up period from months 3 to 12.

The quit rates were higher for varenicline vs. NRT at end of therapy week 9–12 and week 8–11 i.e. 55.9% vs. 43.2% (odds ratio [OR] 1.70, CI 95% 1.26–2.28). Continuous quit rates week 8 (9)–24 was higher for varinicline vs. NRT but not statistical significant. The continuous quit rates week 8 (9)–52 for varenicline vs. NRT was 26.1% vs. 20.3% ($p = 0.056$) but when including all randomised subjects the difference reach significance. There was no significant difference in the 7-day point prevalence of abstinence after 24 and 52 weeks. Varenicline had a greater effect on withdrawal symptoms and on reduction of smoking satisfaction than NRT. Adverse events were higher for varenicline vs. NRT (nausea 37 vs. 10%, insomnia 21 vs. 19%, headache 19 vs. 10%, abnormal dreams 12 vs. 8%, vomiting 6 vs. 1%) and 8% stopped treatment due to adverse events on varenicline vs. 4% on NRT.

There are several limitations of this study. First this was an open-label study.

The reason stated for not performing a placebo controlled trial was technical problems to create a placebo patch. It could have been easily solved by adding a minimal dose of nicotine to the placebo patch. Positive unrealistic expectations getting a new drug might have favoured varenicline and previous negative experiences with NRT might have discouraged those randomised to the less attractive NRT option. As 46% of the participants had tried nicotine patch previous one would suspect a much lower quit rate this time below 10%. It is not stated how many had used other NRT formulations previous so this might be a reason for a major bias in favour of varenicline.

We found a very low quit rate when we re-treated failures from a nicotine patch trial after 1 year with nicotine patch i.e. 0% after 1 year [7].

The duration of therapy was 12 weeks for varenicline but only 10 weeks for NRT again favouring varenicline. Pre-treatment ("pre-loading") with NRT 1–2 weeks before target quit day might increase quit rate. Also, nicotine patch probably is the least effective NRT formulations, so an adequate comparison today would have been nicotine patch combined with gum, inhaler or sublingual tablet. I would suspect that subjects previous treated with varenicline would also attain a much lower quit rate if re-treated with varenicline.

Taking all this potential serious limitations and bias into account and also that the 1-year abstinence rate did not reach statistical significance this trial is not adequate to conclude that varenicline is superior to NRT. The positive message from this trial is that we can expect a 1-year continuous quit rate between 20–26% and a 1-year point prevalence of 31–35% i.e. 1 in 3 were quitters after 1 year.

Indirect comparison by NICE reported that varenicline was more effective than bupropion SR (OR 1.58, CI 95% 1.22–2.05) and NRT (OR 1.66, CI 95% 1.17–2.36) [8].

However, we still need an adequate designed and conducted double-blind, placebo controlled trial to assess the relative efficacy of varenicline vs. NRT. This is a basic principle to be

used in evidence based medicine and pharmaceutical companies should also adhere to these rules.

Another study from a smoking cessation clinic in London compared quit rates with varenciline versus NRT in routine treatment with historical controls before introduction of varenicline [9]. They found 4-weeks quit rate of 61% with NRT and 72% with varenicline but no data on longer follow-up was reported. Among subjects treated with NRT 73% had previously used NRT probably producing lower quit rates than in native smokers not having used NRT before again favouring varenicline.

So, what can be concluded? Nicotine replacement therapies, bupropion SR and varenicline are all 1-line agents [10-13].

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 contra-indications and available without prescription.

So, of that reason I will recommend NRT 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. Optimization of NRT can be done by pre-loading and combination of two formulations of NRT and proper instruction in adequate use.

In subjects having used NRT previously, I would prefer varenicline as it seems as least equally effective as NRT and more effective than bupropion SR and have fewer side effects. Also, many smokers prefer tablets to be taken twice daily 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 even after a few weeks due to the cost of varenicline.

In subjects suffering from depression and having experienced suicidal thoughts previous I would use bupropion SR.

I would use bupropion SR when NRT and varenciline has failed.

Subjects smoking less than 10 cigarettes per day should use one of the NRT formulations.

In the clinical situation when the physician faces the individual smoker the following factors influence how to select between the 3 agents above: Clinicians familiarities with drugs, patients preferences/previous experience, patients characteristics, cost and possibility for re-imbursement.

Although NRT, varenicline and bupropion all should be regarded as first-line preparations in smoking cessation, I regard NRT as "first-choice" followed by varenicline while bupropion is my third choice. Whatever choice one can expect a 1 year continuous abstinence rate around 20–25%.

It is a very positive thing that another drug has been marketed for smoking cessation. There is a need for all 3 agents in smoking cessation just like the situation in arterial hypertension. As almost 75% of smokers who try to quit fail there is a need for re-treatment.

In fact, we need more drugs in this area. Nicotine vaccination is one promising new therapy under development that may have an effect on relapse. The principle is to induce nicotine antibodies in the blood, so inhaled nicotine from cigarette is prevented to reach the CNS, and in that way decrease the pleasure from smoking [14].

One of the major tasks is to increase the implementation of smoking cessation therapy in the health care system. In USA re-imbursement has been reported to increase the use of adequate smoking cessation therapies according to clinical guidelines. Other tools to increase implementation of smoking cessation is education of health professionals and allocation of specific budgets for this service at clinic level, and incentives to involve physicians in this area. The physicians' role is to ensure who is currently smoking and to engage with them on a long-term project of keeping them smoke free.

In the future every smoker should be meet with a professional smoking cessation service. Thus we can prevent several deaths from smoking during the next 25 years [15].

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