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Nicotine replacement: an update

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The rationale for Nicotine Replacement (NR) is that when a smoker stops smoking cigarettes, the administration of nicotine from a different modality such as a gum, will decrease the withdrawal symptoms during the initial phase of smoking abstinence. The pharmacological dependence on cigarettes is more or less transferred to the nicotine replacement product, enabling the subject to focus his or her recourses on the behavioural aspects of coping with the strongly ingrained habit. Usually, the pharmacological dependence is not fully maintained because of a lower nicotine dose than during smoking. After a variable period of 2-6 months the nicotine supplementation can be tapered off gradually. In essence the nicotine dependence is *transferred, tapered* and *eliminated.*

The most recent Cochrane meta-analyses has identified 111 trials with over 40,000 participants validated to a primary comparison between any type of NR and a placebo or non-NR control group. The relative risk (RR) of abstinence for any form of NR relative to control was 1.58.

The vast use of NR products is for abrupt smoking cessation treatment. However there are also other indications approved for all or some of the products. These are; reduction to quit, temporary abstinence and smoking reduction (without intent to stop completely). An example of temporary abstinence can be to stop smoking 4-6 weeks before elective surgery which has been shown to improve the outcome and reduced complications of the surgery.

NR comes in many forms, gum, patch, lozenge, sublingual tablet, oral inhaler, nasal and mouth spray and pouch. All forms are generally equally effective. Choice of product is therefore largely a matter of preference.

Combining products have been found to be more effective than using a single product. Under-dosing is very common with NR treatment. Many smokers, particularly more dependent smokers with a higher intake of nicotine are having great difficulties to fully substitute with current NR products. A solution to this has been to combine products, usually a patch with a faster acting product like a gum. The nicotine patch delivers nicotine in a passive form and produces relatively steady levels of nicotine in the body. Apart from a higher dose with combining products it also allows the users to respond to „breakthrough" cravings with acute nicotine doses. These cravings, while usually brief, can be quite intense and are likely significant contributors to relapse.

A meta-analysis has evaluated the incremental efficacy of starting nicotine patch treatment prior to quitting compared to the current regimen of starting patch treatment on the target quit day. It was found that pre-cessation patch treatment to produced a significant increase in quit rates at six months (OR = 2.17) compared to current regimens starting patch at quit day. The most common length of the pre-quitting use has varied between 1-3 weeks. The mechanisms are thought to be a reduction in smoking and nicotine dependence and a blunting of the reward from the cigarettes smoked on top of the nicotine patch. It may also be reassuring and increase self-confidence for the patient to know that the treatment works which is not always the case when treatment is started at the day of abstinence.

Duration of use should be determined by the subject's need, i.e. risk to relapse to cigarettes. Lifelong use of NR would be preferable if smoking is the alternative.

In terms of pharmacokinetics the NR products of today are much slower to reach Tmax than cigarettes which also reduce their efficacy. Recently there have been some product developments, a mouth spray and a small pouch to stick under the upper lip that might give faster uptake of nicotine and better acceptance among users than the traditional forms.

The dominating practice have been to inform patients that smoking just one cigarette is very likely to damage the attempt and lead to full relapse. Therefore therapy is often interrupted and stopped when a lapse occurs. Although it may be important and productive to strongly warn against just one cigarette there is a rising concern among clinicians and researchers if treatment should be stopped. It has also been suggested that the effect of the treatment is not enough and that the dose and frequency of use should be adjusted upwards. However at the time being there is no good trial proving this assumption.

The safety of NR medications when used alone or concurrently with smoking has been well demonstrated in numerous clinical trials. In general, nicotine-delivering medications provide lower doses than those obtained by cigarette smoking, and the rate of nicotine infusion to arterial blood is substantially slower for nicotine medications. Despite the fact that nicotine can produce adverse effects, severe adverse effects rarely occurs when people are smoking, or using NR products, because tobacco users quickly learn to not exceed certain nicotine concentrations. When smoking is the alternative there are no contraindications for NR.

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