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[Intervention Review]

Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation

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ABSTRACT

Background

Nicotine replacement therapy (NRT) aims to replace nicotine from cigarettes to ease the transition from cigarette smoking to abstinence. It works by reducing the intensity of craving and withdrawal symptoms. Although there is clear evidence that NRT used after smoking cessation is effective, it is unclear whether higher doses, longer durations of treatment, or using NRT before cessation add to its effectiveness.

Objectives

To determine the effectiveness and safety of different forms, deliveries, doses, durations and schedules of NRT, for achieving long-term smoking cessation, compared to one another.

Search methods

We searched the Cochrane Tobacco Addiction Group trials register, and trial registries for papers mentioning NRT in the title, abstract or keywords. Date of most recent search: April 2018.

Selection criteria

Randomized trials in people motivated to quit, comparing one type of NRT use with another. We excluded trials that did not assess cessation as an outcome, with follow-up less than six months, and with additional intervention components not matched between arms. Trials comparing NRT to control, and trials comparing NRT to other pharmacotherapies, are covered elsewhere.

Data collection and analysis

We followed standard Cochrane methods. Smoking abstinence was measured after at least six months, using the most rigorous definition available. We extracted data on cardiac adverse events (AEs), serious adverse events (SAEs), and study withdrawals due to treatment. We calculated the risk ratio (RR) and the 95% confidence interval (CI) for each outcome for each study, where possible. We grouped eligible studies according to the type of comparison. We carried out meta-analyses where appropriate, using a Mantel-Haenszel fixed-effect model.

Main results

We identified 63 trials with 41,509 participants. Most recruited adults either from the community or from healthcare clinics. People enrolled in the studies typically smoked at least 15 cigarettes a day. We judged 24 of the 63 studies to be at high risk of bias, but restricting the analysis only to those studies at low or unclear risk of bias did not significantly alter results, apart from in the case of the preloading comparison. There is high-certainty evidence that combination NRT (fast-acting form + patch) results in higher long-term quit rates than single form (RR 1.25, 95% CI 1.15 to 1.36, 14 studies, 11,356 participants; I^2 = 4%). Moderate-certainty evidence, limited by imprecision, indicates that 42/44 mg are as effective as 21/22 mg (24-hour) patches (RR 1.09, 95% CI 0.93 to 1.29, 5 studies, 1655 participants; I^2 = 38%), and that 21 mg are more effective than 14 mg (24-hour) patches (RR 1.48, 95% CI 1.06 to 2.08, 1 study, 537 participants). Moderate-certainty evidence (again limited by imprecision) also suggests a benefit of 25 mg over 15 mg (16-hour) patches, but the lower limit of the CI encompassed no difference (RR 1.19, 95% CI 1.00 to 1.41, 3 studies, 3446 participants; I^2 = 0%). Five studies comparing 4 mg gum to 2 mg gum found a benefit of the higher dose (RR 1.43, 95% CI 1.12 to 1.83, 5 studies, 856 participants; I^2 = 63%); however, results of a subgroup analysis suggest that only smokers who are highly dependent may benefit. Nine studies tested the effect of using NRT prior to quit day (preloading) in comparison to using it from quit day onward; there was moderate-certainty evidence, limited by risk of bias, of a favourable effect of preloading on abstinence (RR 1.25, 95% CI 1.08 to 1.44, 9 studies, 4395 participants; I^2 = 0%). High-certainty evidence from eight studies suggests that using either a form of fast-acting NRT or a nicotine patch results in similar long-term quit rates (RR 0.90, 95% CI 0.77 to 1.05, 8 studies, 3319 participants; I^2 = 0%). We found no evidence of an effect of duration of nicotine patch use (low-certainty evidence); 16-hour versus 24-hour daily patch use; duration of combination NRT use (low- and very low-certainty evidence); tapering of patch dose versus abrupt patch cessation; fast-acting NRT type (very low-certainty evidence); duration of nicotine gum use; ad lib versus fixed dosing of fast-acting NRT; free versus purchased NRT; length of provision of free NRT; ceasing versus continuing patch use on lapse; and participant- versus clinician-selected NRT. However, in most cases these findings are based on very low- or low-certainty evidence, and are the findings from single studies.

AEs, SAEs and withdrawals due to treatment were all measured variably and infrequently across studies, resulting in low- or very low-certainty evidence for all comparisons. Most comparisons found no evidence of an effect on cardiac AEs, SAEs or withdrawals. Rates of these were low overall. Significantly more withdrawals due to treatment were reported in participants using nasal spray in comparison to patch in one trial (RR 3.47, 95% CI 1.15 to 10.46, 922 participants; very low certainty) and in participants using 42/44 mg patches in comparison to 21/22 mg patches across two trials (RR 4.99, 95% CI 1.60 to 15.50, 2 studies, 544 participants; I^2 = 0%; low certainty).

Authors' conclusions

There is high-certainty evidence that using combination NRT versus single-form NRT, and 4 mg versus 2 mg nicotine gum, can increase the chances of successfully stopping smoking. For patch dose comparisons, evidence was of moderate certainty, due to imprecision. Twenty-one mg patches resulted in higher quit rates than 14 mg (24-hour) patches, and using 25 mg patches resulted in higher quit rates than using 15 mg (16-hour) patches, although in the latter case the CI included one. There was no clear evidence of superiority for 42/44 mg over 21/22 mg (24-hour) patches. Using a fast-acting form of NRT, such as gum or lozenge, resulted in similar quit rates to nicotine patches. There is moderate-certainty evidence that using NRT prior to quitting may improve quit rates versus using it from quit date only; however, further research is needed to ensure the robustness of this finding. Evidence for the comparative safety and tolerability of different types of NRT use is of low and very low certainty. New studies should ensure that AEs, SAEs and withdrawals due to treatment are both measured and reported.

PLAIN LANGUAGE SUMMARY

What is the best way to use nicotine replacement therapy to quit smoking?

Background

Nicotine replacement therapy (NRT) is a medicine that is available as skin patches, chewing gum, nasal and oral sprays, inhalers, lozenges and tablets that deliver nicotine to the brain. The aim of NRT is to replace the nicotine that people who smoke usually get from cigarettes, so the urge to smoke is reduced and they can stop smoking altogether. We know that NRT improves a person's chances of stopping smoking, and that people use it to quit. This review looks at the different ways to use NRT to quit smoking, and which of these work best to quit smoking for six months or longer.

Study characteristics

This review includes 63 trials covering 41,509 participants. All studies were conducted in people who wanted to quit smoking, and most were conducted in adults. People who enrolled in the studies typically smoked at least 15 cigarettes a day at the start of the studies. Studies lasted for at least six months.The evidence is up to date to April 2018.

Key results

Using nicotine patch and another type of NRT (such as gum or lozenge) together made it 15% to 36% more likely that a person would successfully stop smoking than if they used one type of NRT alone. People were also more likely to quit successfully if they used higher-dose nicotine patches (containing 25 mg (worn over 16 hours) or 21 mg (worn over 24 hours) of nicotine compared to 15 mg (worn over 16 hours) or 14 mg of nicotine (worn over 24 hours)) or higher-dose nicotine gum (containing 4 mg of nicotine compared to 2 mg of nicotine). Using NRT before a quit day as well as after may help more people to quit than only using it after, but more evidence is needed to strengthen this conclusion. However, people who smoke have the same chances of quitting successfully whether they use a nicotine patch to quit or another type of NRT, such as gum, lozenge or nasal spray.

We also looked at how long NRT should be used for, whether NRT should be used on a schedule or as wanted, and whether more people stop smoking when NRT is provided for free versus if they have to pay for it. However, more research is needed to answer these questions.

Most studies did not look at safety. Where studies did look at safety, very few people experienced negative effects of NRT. Evidence from another review shows that NRT is a safe medication.

Quality of the evidence

There is high-certainty evidence that combination NRT works better than a single form of NRT, that higher-dose nicotine gum works better than lower-dose gum, and that there is no difference in effect between different types of NRT (such as gum or lozenge). This means that future research is very unlikely to change our conclusions. This is because the evidence is based on a large number of participants, and the studies were well-conducted. However, the quality of the evidence was moderate, low or very low for all of the other questions we looked at. This means that our findings may change when more new research is carried out. In most cases this is because there were not enough studies, there were problems with the design of studies that do exist, and these studies were too small. We rated all of the evidence looking at the safety of using NRT in different ways to be low or very low quality, because many studies did not report on safety.