Combination nicotine replacement therapy (NRT)

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Introduction

The need for the original NCSCT briefing on combination NRT in 2012 was established when commissioners and managers of Local Stop Smoking Services identified that, despite the evidence regarding its safety and efficacy, obtaining support and funding for combination NRT was in some cases difficult. Since that time, clinical experience and evidence regarding the role of combination NRT in increasing success with quitting has expanded greatly and it has now been established as **standard treatment.**

This updated briefing is intended as a resource for commissioners, managers and staff of stop smoking services and summarises the latest evidence and practice guidance related to combination NRT. The briefing is designed to provide answers to a series of commonly posed questions. Included among these are questions the NCSCT has received from Local Stop Smoking Services.

For more information on the National Centre for Smoking Cessation and Training (NCSCT) and on the NCSCT ethical policy please visit our website: **www.ncsct.co.uk**

Combination NRT

1. How strong is the evidence that combination NRT is effective?

Answer: There is strong evidence that combination NRT (combining a patch with a faster-acting product) is more effective in helping people stop smoking than using just one form of NRT.[1–3] Combination NRT has been found to result in long-term quit rates that are comparable to those achieved with varenicline. Combination NRT and varenicline are the two most effective stop smoking medications.[3] NICE recommend combination NRT for all people who smoke more than 10 cigarettes per day.[4]

Evidence: The highest quality evidence comes from a Cochrane Review of NRT.[1] This systematic review included fourteen trials, involving more than 11,000 participants with long-term smoking cessation outcomes comparing combination NRT to single-form NRT. Combining the results of these studies shows a clear advantage of combination versus single-form NRT use (risk ratio [RR] 1.25; 95% CI: 1.15 – 1.36).[1] This means that combination NRT is likely to give a 25% increase in long-term cessation rates, but the likely true effect lies within a range of 15% to 36%. Additionally, a Cochrane Review and network meta-analysis of smoking cessation pharmacotherapies found long-term quit rates for combination NRT were similar to those achieved with varenicline (odds ratio [OR] 1.06; 95% CI 0.75 to 1.48).[3]

2. Why is combination NRT more effective than a single NRT product?

Combination NRT provides people with additional control over 'urges to smoke' and withdrawal symptoms. The NRT patch provides a steady supply of nicotine throughout the day and the faster-acting NRT product can be used by clients to meet their specific needs for additional nicotine ('top up'), either in response to 'breakthrough' urges and/or withdrawal symptoms by using at times or in settings or situations where these might be predicted to occur.

3. What products should be used and how?

Answer: The option that has been most commonly evaluated involves the use of a patch plus a faster-acting form such as gum, inhalator, lozenge, microtab, mouth or nasal spray.

4. Is combination NRT safe?

Answer: Yes, combination NRT is safe. Nicotine 'overdose' associated with NRT use in people who smoke is exceptionally rare. People who smoke inhale very large doses of nicotine when smoking. Even with combination NRT, people are unlikely to ever receive doses of nicotine that are higher than those they receive from their tobacco use.[1,5–8] If people experience adverse symptoms, such as nausea, they can simply reduce the dose or frequency of administration of the additional product (e.g. lozenge, spray, etc).

5. Shouldn't the client pay for one product?

Answer: Combination NRT is more effective than single forms of NRT and is a highly cost-effective approach to treating nicotine dependence. It would be against the ethos of public health bodies to require people to pay for such treatment. Smoking cessation treatments are highly cost-effective judged against other medical interventions. The incremental benefit of combination NRT over single-form NRT approximates the incremental cost, it is therefore understandable that combination NRT would be cost-effective as judged by NICE criteria.

6. Can you combine more than one faster-acting NRT product (i.e. two faster-acting products)?

Answer: You can very safely combine any form of NRT. All the products are simply different delivery systems for nicotine. Although not a common occurrence, if you have a client who might prefer and/or benefit from the use, for example, of three NRT products (e.g. patch, inhalator and spray), this is safe practice. Allowing clients to experiment with which products suit them best can be helpful. Given, that all faster-acting NRT products have the same mechanism of action (as described above), the recommendation remains that the faster-acting NRT products selected be combined with the patch.

Evidence: All evidence on combination therapy, at the time of this publication, has specifically tested patch plus a faster-acting product. The combination of more than one faster-acting product is considered safe practice.

7. Should combination NRT be reserved for people who are very dependent on tobacco

Answer: Combination NRT is suitable for all people who smoke. It may be particularly beneficial for people who have used single-form NRT in a previous quit attempt but relapsed while using it, people who feel they need something more than a patch or other single-form NRT, and people who are more dependent on tobacco. The majority of research conducted on combination NRT has involved individuals who smoke at least 10 – 15 cigarettes per day; we have less information about the value of combination NRT among people with lower levels of consumption.[1–3,6]

8. Can combination NRT be used in pregnancy?

Answer: Combination NRT can be used in pregnancy and might be particularly helpful to those who are more dependent on tobacco or who are struggling with withdrawal symptoms and/or urges to smoke.

Evidence: The Smoking, Nicotine And Pregnancy (SNAP) study, as well as the Cochrane review on the pharmacological interventions for smoking cessation in pregnancy, have reported on the safety and efficacy of NRT in supporting quitting in pregnant women.[9,10] The SNAP study found the NRT patch doubled four-week quit rates and did not result in adverse pregnancy outcomes or children at two-year follow-up.[10] While these studies did not report on combination NRT, routinely collected data from 3,880 pregnant women attempting to quit from 44 Stop Smoking Services in England showed the use of combination NRT (patch plus faster-acting product) resulted in significantly higher four-week quit rates (37%) than single-dose NRT (25%) or no medication (16%).[11] It is important to note that the rate of nicotine metabolism is increased during pregnancy; enhanced levels of NRT will therefore be helpful in inducing and sustaining cessation.

9. What options are available for people who are highly dependent on tobacco?

Answer: People who are more dependent on tobacco generally benefit from higher doses of NRT. Combination NRT (patch plus faster-acting product) is recommended for all people who are more dependent on tobacco. In addition, the use of more than one patch may better manage withdrawal and cravings among those who are more dependent.[8,12–14] The use of a second patch may serve as a more feasible method for achieving higher nicotine dose, given it does not require frequent administration, as is the case with the faster-acting products. High-dose NRT has been found to be well tolerated and safe among people who are more dependent on tobacco.[6,15,16] This should be no surprise as two patches (21mg or 25mg) would deliver similar nicotine concentrations to what a person would otherwise get from smoking 40 – 60 cigarettes per day.[7,15,16] Such dosing, however, will completely avoid the high levels of carbon monoxide, tar, and other harmful chemicals that accompany the inhalation of cigarette smoke. As such, the use of a second patch is a strategy that can be safely considered when treating people who are more dependent on tobacco.

Evidence: Research has shown that higher dose patch (42/44mg) is more effective in managing withdrawal symptoms in people who are more dependent on tobacco compared to a single NRT patch (21/25mg).[6,12–14] While a high-dose approach is safe, there is mixed evidence of superiority of dual patch compared to single patch in the general population and the limited available evidence suggests effects may be mediated by level of nicotine dependence.[1,6,8] The Cochrane review which includes five high-quality randomised trials that report on abstinence rates at six months or longer did not find a benefit of 42/44mg patches versus 21/22mg patch on rates of long-term quitting, although a benefit of 25/21mg patches was found over 15/14mg patches.[1] A review by Mills using the same five studies reported high-dose NRT (>22mg) patch significantly increased four-week and six-month quit rates compared to standard NRT dose (<22mg).[6] The differences in these findings relate to the methods used to analyse data and more research is needed to guide practice. While using two patches is not a well-established practice in English Local Stop Smoking Services at present, it has been a standard practice in many specialised stop smoking centres in countries such as Canada, the United States and Australia for many years.[17–21] The Cochrane review also found a benefit of the higher dose 4mg gum versus 2mg gum (RR 1.43, 95% CI 1.12 to 1.83, 5 studies). Importantly, results of a subgroup analysis suggest that only people who are highly dependent on tobacco are likely to benefit from the higher dose gum.

10. Should high-dose NRT be used with all people who are highly dependent on tobacco?

Answer: The use of two patches plus faster-acting NRT can be considered among people who smoke 40 or more cigarettes per day, or those close to that consumption who are more dependent based on the Heaviness of Smoking Index (HSI). The use of a second patch can be assessed on a case-by-case basis and with the reassurance that there is almost no likelihood of overdose or adverse effects in those who are more dependent on tobacco. The general guidance is that a higher dose (i.e. two patches) plus faster-acting NRT product can be considered for people:

- whose cravings and/or withdrawal symptoms are not being well managed with combination NRT (one patch plus faster-acting product), or
- who did not get adequate relief of withdrawal symptoms from a single nicotine patch dose during a prior attempt.

11. Why should Local Stop Smoking Services fund multiple patches for some people who smoke?

Answer: We know that two of the most common reasons for not being able to stop smoking completely and/or relapse in the first four weeks of a quit attempt are urges to smoke and the presence of withdrawal symptoms; this is particularly true among people who are more dependent on tobacco.[22,23] There is evidence that high-dose NRT may be superior to single-form NRT in managing urges and withdrawal. While most people who smoke will not require a second patch, having flexibility within protocols to offer high-dose combination NRT to clients who are more dependent may serve to increase four-week quit rates in this population and above all is a safe practice.

12. Can NRT be combined with vapes (e-cigarettes)?

Answer: Both NRT products and vapes deliver nicotine and can be combined. There is limited research examining the efficacy of combining nicotine patches with vapes. However, the rationale for combining nicotine patches with nicotine vapes is that they offer the same benefits as faster-acting NRT (i.e. relief of 'breakthrough cravings'). The more rapid delivery offered by vapes may appeal to and/or benefit people who smoke alongside the slower delivery of nicotine provided by the NRT patch.

Evidence: Available data collected from English Stop Smoking Services in 2019 – 2020 found a vaping product was used in 5.2% of quit attempts either alone, concurrently, or consecutively in combination with licensed medication.[24] Quit rates with a vaping product and licensed medication concurrently (60.0%), a vaping product alone (59.7%) and varenicline alone (59.4%) were similar. The highest quit rates were found when a licensed medicine and a vaping product were used consecutively (74.1%).[24]

13. Can NRT be combined with varenicline?

Answer: There have been a small number of studies examining the safety and efficacy of combining varenicline and NRT. While these studies have found evidence that combining NRT with varenicline improves success with quitting, the evidence has been mixed. While the use of varenicline with NRT has not been shown to benefit all people making a quit attempt, there is some evidence that combining varenicline with NRT may benefit people who are more dependent on tobacco.[25] Combining these medications has been found to be well tolerated. The combination may result in a slight increase in adverse reactions including nausea, sleep disturbance and headache compared to using either medication alone.[26] More research is needed to make recommendations on the use of combination treatment with varenicline and NRT. Internationally, the combination of varenicline and NRT has been used among people more dependent on tobacco, particularly those using varenicline who continue to experience urges to smoke and/or withdrawal symptoms or those who have reduced their cigarette consumption but not quit completely.[20]

Evidence: Three randomised controlled trials and one observational study have found that the combination of varenicline and nicotine patch may improve smoking abstinence when compared to varenicline alone.[25–28] Several meta-analyses have looked at this data, the most of recent of which was published in 2020.[29–31] Varenicline plus a nicotine patch was associated with an increase in abstinence compared with varenicline alone, measured as seven day point-prevalence abstinence at six months or later (RR 1.36, 95% CI 1.07–1.72).[30] One study analysed data according to cigarette consumption; the abstinence rates among people who smoked more than 29 cigarettes per day were significantly higher in the combination varenicline and NRT group at both 12 weeks (OR 1.39; 95% CI 1.2 to 2.5) and 24 weeks (OR 1.46; 95% CI 1.2 to 2.8) compared to varenicline alone.[25]

14. If a client is already using varenicline why would we expect NRT to add additional benefits?

Answer: It is believed that the partial agonist effect of varenicline on the alpha-4-beta-2 nicotine receptors may not be sufficient to ease cravings and prevent withdrawal symptoms in some people who are more dependent on tobacco, as other nicotine receptors are not affected by varenicline.[20,26,28,29] The addition of NRT may assist with addressing this as its effects occur via a different mechanism and involve nicotine receptors other than the alpha-4-beta-2 receptor, which is believed to be the principal receptor involved in maintaining nicotine addiction.[20, 25,28] There are several other nicotine receptors, and in people who are more dependent on tobacco these nicotine receptors and/or other reward pathways may be playing a role in withdrawal and cravings.[26,27,29]

15. Can NRT be combined with bupropion (Zyban)?

Answer: There is no strong evidence to suggest that combining NRT and bupropion results in superior quit rates than either medication alone; as such this is not a recommended practice.

Evidence: A recent Cochrane review identified 12 randomised controlled trials which examined the combination of bupropion and NRT compared to NRT alone.[32] The review found a non-significant trend toward higher rates of quitting; the confidence intervals suggest that there may also be no benefit of combining the two medications (RR 1.19, 95% CI 0.94 to 1.51; 12 studies, 3487 participants).[32]

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