

Combination nicotine replacement therapy (NRT)

© 2021 National Centre for Smoking Cessation and Training (NCSCT)

Review author: Sophia Papadakis

Review editors: Andy McEwen and Tom Coleman-Haynes

Review consultant: Susan Montgomery

Original 2012 briefing: Author: Paul Aveyard. Editor: Andy McEwen. Reviewers: Melanie Chambers, Jennie Kenyon, Andrea Dickens, Hayden McRobbie, John Stapleton and Robert West

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 smokers quit 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 smokers 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 smokers 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 smokers with additional control over 'urges to smoke' and withdrawal symptoms. The NRT patch provides a steady supply of nicotine throughout the day and the fast-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 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 smokers is exceptionally rare. Smokers inhale very large doses of nicotine when smoking. Even with combination NRT, smokers are unlikely to ever receive doses of nicotine that are higher than that they receive from their tobacco use.^{1,5-8} If smokers 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 smokers to pay for such treatment or part of it. 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 fast-acting NRT product (i.e. two fast acting products)?

Answer: You can very safely combine any form of NRT. All of 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 fast-acting NRT products have the same mechanism of action (as described above), the recommendation remains that the fast 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 fast-acting product. The combination of more than one fast-acting product is considered safe practice.

7. Should combination NRT be reserved for very heavy smokers?

Answer: Combination NRT is suitable for all smokers. It may be particularly beneficial for smokers who have used single-form NRT in a previous quit attempt but relapsed while using it, smokers who feel they need something more than a patch or other single-form NRT, and heavier smokers. 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 smokers with lower levels of consumption.^{1-3,6}

8. Can combination NRT be used in pregnant smokers?

Answer: Combination NRT can be used for pregnant smokers and might be particularly helpful to those women who are more-dependent smokers 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 4-week quit rates and did not result in adverse pregnancy outcomes or children at 2-years follow-up.¹⁰ While these studies did not report on combination NRT, routinely collected data from 3,880 pregnant smokers attempting to quit from 44 Stop Smoking Services in England showed the use of combination NRT (patch + fast-acting) 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 very dependent smokers?

Answer: Smokers who are more dependent generally benefit from higher doses of NRT. Combination NRT (patch + fast-acting product) is recommended for all more-dependent ('heavy') smokers. In addition, the use of more than one patch may better manage withdrawal and cravings among more-dependent smokers.^{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 fast-acting products. High dose NRT has been found to be well tolerated and safe among more-dependent smokers.^{6,15,16} This should be no surprise as two patches (21mg or 25mg) would deliver similar nicotine concentrations to what a smoker would otherwise get from smoking 40 – 60 cigarettes per day.^{7,15,16} Such dosing, however, will completely avoid the high levels of nicotine 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 more-dependent smokers.

Evidence: Research has shown that higher dose patch (42/44mg) is more effective in managing withdrawal symptoms in highly-dependent smokers 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 of smokers and the limited available evidence suggests effects may be mediated by level of nicotine dependence.^{1,6,8} The Cochrane review which included five high quality randomised trials that report on abstinence rates at 6-months or longer did not find a benefit of 42/44mg patches vs 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 4-week and 6-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 internationally including Canada, the United States, and Australia for many years.¹⁷⁻²¹ The Cochrane review also found a benefit of the higher dose, 4 mg, gum vs 2mg gum (RR 1.43, 95% CI 1.12 to 1.83, 5 studies). Importantly, results of a subgroup analysis suggest that only smokers who are highly dependent are likely to benefit from the higher dose gum.

10. Should high-dose NRT be used with all heavily dependent smokers?

Answer: The use of two patches plus fast acting NRT can be considered among smokers of 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 more-dependent smokers. The general guidance is that a higher nicotine dose (i.e., two patches) + fast-acting NRT product can be considered for smokers:

- whose cravings and/or withdrawal symptoms are not being well managed with combination NRT (1 patch + fast acting), 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 smokers?

Answer: We know that one 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 more-dependent smokers.^{22,23} There is evidence that high-dose NRT may be superior to single-form NRT in managing urges and withdrawal. While most smokers 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 of smokers and above all is a safe practice.

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

Answer: NRT products can be used with e-cigarettes. Both NRT products and e-cigarettes deliver nicotine to smokers and can be combined. There is limited research examining the efficacy of combining nicotine patches with e-cigarettes. However, the rationale for combining nicotine patches with nicotine containing e-cigarettes is that it offers the same benefits as fast-acting NRT (i.e., relief of 'breakthrough cravings'). The more rapid delivery offered by vapes may appeal to and/or benefit smokers alongside the steady state nicotine delivered 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 (Champix)?

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 smokers, there is some evidence that combining varenicline with NRT may benefit more-dependent smokers.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 more-dependent smokers, 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 6 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 smokers 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 more-dependent smokers 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 believed to be the principal receptor involved in maintaining nicotine addiction.^{20, 25,28} There are several other nicotine receptors, and in more-dependent smokers 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

References

- Lindson N, Chepkin SC, Ye W, et al. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2019, Issue 4. Art. No.: CD013308.
- Hartmann-Boyce J, Chepkin SC, Ye W, et al. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev*. 2018, Issue 5. Art. No.: CD000146.
- Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*. 2013, Issue 5. Art. No.: CD009329.
- National Institute for Health and Care Excellence (NICE). Stop smoking interventions and services: NICE guideline NG92. NICE; 2018. www.nice.org.uk/guidance/ng92
- Fagerstrom KO, Schneider NG, Lunell E. Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. *Psychopharmacology (Berl)*. 1993;111(3):271–7.
- Mills EJ, Wu P, Lockhart I, et al. Comparison of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis. *Ann Med*. 2012;44(6):588–97.
- Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease and therapeutics. *Ann Rev Pharmacol Toxicol*. 2009;49:57–71.
- Carpenter MJ, Jardin BF, Burriss JL, et al. Clinical strategies to enhance the efficacy of nicotine replacement therapy for smoking cessation: a review of the literature. *Drugs*. 2013;73(5):407–26.
- Claire R, Chamberlain C, Davey MA, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev*. 2020 Mar 4;3(3):CD010078.
- Cooper S, Taggar J, Lewis S, et al; Smoking, nicotine and pregnancy (SNAP) trial team. Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial. *Lancet Respir Med*. 2014;(9):728–37.
- Brose, L.S., McEwen, A. & West, R. Association between nicotine replacement therapy use in pregnancy and smoking cessation. *Drug Alcohol Depend*. 2013;132(3):660–4.
- Shiffman S, Ferguson SG, Gwaltney CJ, et al. Reduction of abstinence-induced withdrawal and craving using high-dose nicotine replacement therapy. *Psychopharmacology*. 2006;184(3–4):637–44.
- Hatsukami DK, Mooney M, Murphy S, et al. Effects of high dose transdermal nicotine replacement in cigarette smokers. *Pharmacol Biochem Behav*. 2007;86:132–9.
- Ferguson SG, Shiffman S, Gwaltney CJ. Does reducing withdrawal severity mediate nicotine patch efficacy? A randomized clinical trial. *J Consult Clin Psychol*. 2006;74(6):1153–61.
- Fredrickson PA, Hurt RD, Lee GM, et al. High dose transdermal nicotine therapy for heavy smokers: safety, tolerability and measurement of nicotine and cotinine levels. *Psychopharmacology (Berl)*. 1995;122(3):215–22.
- Dale LC, Hurt RD, Offord KP, et al. High-dose nicotine patch therapy. Percentage of replacement and smoking cessation. *JAMA*. 1995;274(17):1353–8.
- Mendelsohn C. Optimising nicotine replacement therapy in clinical practice. *Aust Fam Physician*. 2013;42(5):305–9.
- The Royal Australian College of General Practitioners (RACGP). Supporting smoking cessation: a guide for health care professionals. RACGP; 2020. <https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/supporting-smoking-cessation>
- Tulloch H, Pipe A, Els C, et al. Flexible, dual-form nicotine replacement therapy or varenicline in comparison with nicotine patch for smoking cessation: a randomized controlled trial. *BMC Med*. 2016;14(80).
- Hurt RD, Ebbert JO, Hays JT, et al. Treating tobacco dependence in a medical setting. *CA Cancer J Clin*. 2009;59(5):314–26.
- Ottawa Model for Smoking Cessation. Frequently asked questions: pharmacotherapy. <https://ottawamodel.ottawaheart.ca/education/frequently-asked-questions>
- Yong HH, Borland R, Balmford J, et al. Heaviness of smoking predicts smoking relapse only in the first weeks of a quit attempt: findings from the international tobacco control four-country survey. *Nicotine Tob Res*. 2014;16(4):423–9.
- Robinson JD, Li L, Chen M, et al. Evaluating the temporal relationships between withdrawal symptoms and smoking relapse. *Psychol Addict Behav*. 2019;33(2):105–16.
- McNeill A, Brose LS, Calder R, et al. Vaping in England: an evidence update including vaping for smoking cessation, February 2021: a report commissioned by Public Health England. London: Public Health England; 2021.
- Ramon JM, Morchon S, Baena A, et al. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. *BMC Med*. 2014;12:172.
- Koegelenberg CF, Noor F, Bateman ED, et al. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. *JAMA*. 2014 Jul;312(2):155–61.
- Hajek P, Smith KM, Dhanj A, et al. Is a combination of varenicline and nicotine patch more effective in helping smokers quit than varenicline alone? A randomised controlled trial. *BMC Med*. 2013;11(140).
- Ebbert JO, Hays JT, Hurt RD. Combination pharmacotherapy for stopping smoking. *Drugs* 2010;70(6):643–50.
- Chang PH, Chiang CH, Ho WC, et al. Combination therapy of varenicline with nicotine replacement therapy is better than varenicline alone: a systematic review and meta-analysis of randomized controlled trials. *BMC Public Health*. 2015;15:689.
- Leone FT, Zhang Y, Evers-Casey S, et al. Initiating pharmacologic treatment in tobacco-dependent adults. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2020;202(2):e5–e31.
- Rigotti N. Pharmacotherapy for Smoking Cessation. UpToDate; 2021. <https://www.uptodate.com/contents/pharmacotherapy-for-smoking-cessation-in-adults/abstract/19>
- Howes S, Hartmann-Boyce J, Livingstone-Banks J, et al. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2020, Issue 4. Art. No.: CD000031.