

A Combination Nicotine Replacement Therapy (NRT) Algorithm for Hard-to-Treat Smokers

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Many smokers have not succeeded in quitting using a single nicotine replacement mode. An algorithm was developed for clinicians to enhance success rates when recommending nicotine replacement therapy (NRT) to smoking patients. The algorithm is based on clinical experience with chronic smokers with respiratory illnesses attending one-on-one smokers clinics in the Central Sydney Area Health Service. Based on transdermal nicotine therapy (patch) other forms of NRT are added if required for 'breakout' smoking for 2 weeks. Outcomes have shown 60% confirmed continuous abstinence at 3 months. Smokers can be safely and successfully treated symptomatically for nicotine withdrawal relief using combination NRT aggressively. This enhances treatment efficacy by minimising relapse in the first few weeks and months of quitting.

Nicotine withdrawal symptoms are the major cause of relapse in smokers. Withdrawal symptoms and relapse most frequently occur within the first few days of a quit attempt. Fifty per cent of spontaneous quitters relapse within the first week (Garvey, Bliss, Ryan, & Hitchcock, 1992). It has been shown that there is an inverse relationship between nicotine withdrawal symptoms and baseline nicotine plasma levels (Russell, 1990; Hurt et al., 1993). It has also been shown that smokers are not a homogenous group and that they show intersubject variations in these baseline plasma nicotine levels (Hurt et al., 1993). Nicotine levels derived from smoking vary between individuals due to individual pharmacokinetics and the manner (or topography) of their smoking (Russell, 1990). Smokers' nicotine plasma levels *just* (2 minutes) after smoking a cigarette may range from 10 to 80 ng/ml irrespective of brand, strength, numbers of cigarettes per day or past history of smoking (Russell, 1990; Hurt et al., 1993).

Nicotine replacement therapy (NRT) has been shown to be effective in aiding some smokers to quit smoking; however, single forms of NRT have shown poor (20%–25%) long-term abstinence rates (Silagy, Lancaster, Stead, Mant, & Fowler). It has been shown that a majority of smokers when using any single type of nicotine replacement therapy are not adequately receiving 'replacement' doses (Hurt et al., 1993; Benowitz: 1991). Plasma levels rarely achieve 15 ng/ml with any single fixed dose nicotine replacement therapy (Table 1).

Additionally, irrespective of dose, peak plasma levels using nicotine patch may occur 6 to 8 hours after initial application (Lane et al., 1993; Russell, 1988). There may also be an initial higher level of nicotine on the first day of patch wearing due to remnant nicotine from the previous day's smoking and nicotine derived from nicotine patches only reach a steady state dose after three days of continuous wear, with no accumulation (Hurt et al., 1993).

In a review of NRT use in Australia, Paul, Walsh and Giris (2003) showed one third of Australian smokers had used a form of NRT, that most of these (61%) had used a form of NRT for no more than 2 weeks and that one third of NRT users smoked concomitantly.

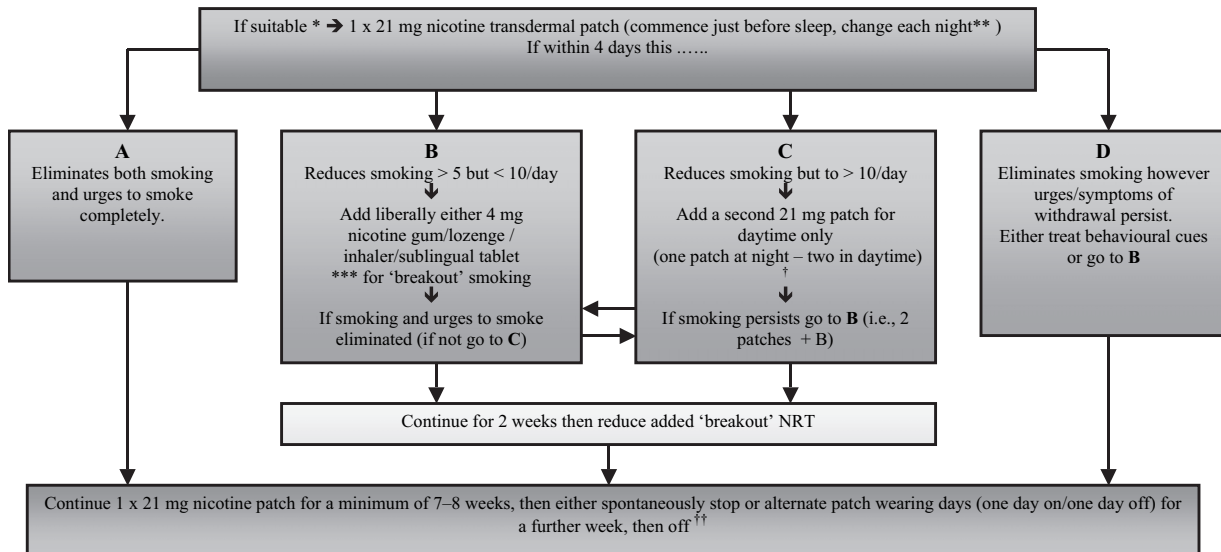
On the basis that a single form of nicotine replacement was inadequate, that concomitant smoking using NRT was safe (Hurt et al., 1993), that it took many hours to achieve an adequate nicotine plasma level and that

Table 1

Comparison of Mean Nicotine Peak Plasma Levels From Cigarettes and Some NRTs Available in Australia

Cigarettes	NRTs
Any cigarette (brand and number irrelevant) range: 10–100 ng/ml depending on topography of smoking (deep inhalations can double blood levels)	1 × 2 mg nicotine gum/lozenge/ sublingual tablet = 7 ng/ml
	1 × 4 mg nicotine gum/lozenge = 15 ng/ml
	1 × 21 mg nicotine patch = 10 ng/ml

Bittoun Combination Nicotine Replacement Therapy Algorithm[#]



* KEEP IN MIND CONTRAINDICATIONS: (1) PREGNANCY OR LIKELIHOOD (Use other more pulsatile form of NRT)
 (2) RECENT CARDIOVASCULAR EVENT (within 48 hours)
 ** Applying patch last thing before sleep allows the slow rise of nicotine overnight — the likelihood of first cigarette of the day ‘urge’ is strongly diminished.
 *** Either 4 mg nicotine gum or lozenge depending in patient choice. Inhaler or sublingual tablet recommended over the others if patient needs faster reinforcement.
 † No evidence in the literature or in our experience of toxicity. Consider reducing concentrations if nausea occurs.
 †† There is no evidence in the literature for wearing (or reduction) of patch strengths.

Figure 1
 Bittoun Combination Nicotine Replacement Therapy Algorithm[#]

Note. [#]Based on ‘Combination Therapy in Hard to Treat Smokers’, paper presented at the Second National Conference on Tobacco Control, Melbourne and TSANZ Annual General Meeting, Adelaide, March 2003.

patches were simple to use, a regimen of NRT dosage based on symptoms of withdrawal an easy to follow algorithm (Figure 1) was developed for practical clinical use.

Method

All smokers were started on a 21mg nicotine patch, as there is good compliance with this product. The patch was applied *immediately* before sleep. To ensure adequate dosage of NRT the first follow-up was within 3 days, but not sooner than commencing patch therapy as smoking ‘breakout’ and/or cravings while using NRT is often experienced within this period after commencing treatment. Additional NRT is then recommended if required and a second follow-up again occurs within 3 to 4 days and more if necessary to adjust doses. Included in this algorithm are instructions regarding duration of treatment. A 7-week treatment is recommended on the same high dose patch and, as there is no evidence that weaning off NRT is required (Fiore, 2000), treatment may abruptly stop thereafter.

Contraindications

As there are no contraindications in cardiac disease if the patient is still smoking and non-NRT has failed (Fiore, 2000), we recommend immediate use following

the algorithm, as soon as is the patient is stable in these cases. There are concerns about using chronic nicotine delivery devices such as nicotine patch in pregnancy (Cohen et al., 2005). In pregnancy or likelihood of pregnancy, where nonuse of NRT has failed, we recommend other forms of NRT rather than a patch. Gums, inhalers, lozenges or sublingual tablets containing nicotine deliver low pulsatile doses of nicotine that simulate smoking but allow for short remissions between doses.

Outcomes Using the Algorithm

In an independent review of a cohort of referred smokers diagnosed with respiratory illness attending the smokers’ clinic ($n = 62$) 60% showed 3 months validated (expired carbon monoxide, Bedfont® Smokerlyser) point prevalence abstinence on their combination therapy regimen according to the algorithm (Holt, Frommer, Faundez, & Madronio, 2004). Patients who did not attend for follow-up were treated as smokers. All patients attending our smoking cessation clinic had made multiple quit attempts and all had used at least one single form of NRT in the past. Combinations recommended ranged from the wearing of two 21 mg nicotine patches and/or the addition of 2 or 4 mg nicotine gum, inhaler, sublingual tablets and lozenges when required for ‘break-out’ smoking. The

added NRT was gauged on individual symptoms of withdrawal and urges to smoke. Smokers attended an average of 6.2 occasions over 3 months. Participants purchased their own medications.

All commencing smokers (intention to treat) were included in the follow-up data, dropouts assessed as relapsed to smoking. We have seen no evidence of compensatory smoking while on combination. As in other experiences (Hughes et al., 1999) serial measurements of expired carbon monoxide levels show a drop when smoking while using NRT, implying smokers are not inhaling deeper to effect a higher plasma nicotine level. There have been no reports of adverse reactions using combination therapies nor smoking concurrently in our or other experiences (Shiffman, Hughes, Di Marino, & Sweeney, 2003; Hughes, Goldstein, Hurt, & Shiffman, 1999; Benowitz, Zevin, & Jacob, 1998).

Discussion and Conclusion

The use of combination therapy is not novel and has been recommended in the past in harder-to-treat smokers by this and other authors (Bittoun & Petrie, 1994; Sweeney et al., 2001). There have been no reported adverse side effects of toxicity from either combination therapies or smoking while using NRT. There is a debate in the literature as to whether higher doses of nicotine in patches alone may be helpful (Hughes, 1995; Paoletti et al., 1996; Killen et al., 1999), though Fagerström suggests that the addition of an alternate form of self-administered NRT to 'top-up' a baseline of nicotine derived from transdermal patches may add to the efficacy of combination therapy (Fagerstrom, Schneider, & Lunell, 1993).

Limitations

Although this algorithm has not been studied in a randomised control trial our high success rates may be in part due to the intensity of the individualised treatment, the diagnosis of a smoking-related illness and higher motivated patients referred to our clinic who pay for their own medication.

Failure rates of over the counter NRT may be growing both in Australia (Paul, Walsh, & Girgis, 2003) and overseas (Russell, 1990; Paul, Walsh, & Girgis, 2003). Many smokers experience the need to smoke while using NRT but are fearful of smoking simultaneously and may subsequently abandon the quit attempt. As these products are readily available to purchasers without a prescription, clinicians and pharmacists need a better understanding of why some smokers fail in quit attempts. Ours is the first self-explanatory algorithm designed to be used in clinical practice.

With the ever-increasing economic and social burden of smoking-related diseases there is clear evidence that intensive smoking cessation interventions is cost-effective (Parrott & Godfrey, 2004). The algorithm was developed in order to encourage medical and nonmedical clinicians

to use combination nicotine replacement therapy more intensively and to understand that it is safe and that it may enhance success rates. Using this algorithm, nicotine replacement therapy is less likely to be nicotine 'relapsement' therapy.

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References

- Benowitz, N.L. (1991). Pharmacodynamics of nicotine: Implications of rational treatment of nicotine addiction. *British Journal of Addiction*, 86, 495–499.
- Benowitz, N.L., Zevin, S., & Jacob, P., III. (December, 1998). Suppression of nicotine intake during ad libitum cigarette smoking by high-dose transdermal nicotine. *Journal of Pharmacology & Experimental Therapeutics* 287(3), 958–962.
- Bittoun, R., & Petrie, J. (1994, March). *Clinical use of combining nicotine patch and nicotine gum*. Paper presented at The International Congress on Smoking Cessation, Glasgow.
- Bohadana, A., Nilsson, F., Rasmussen, T., & Martinet, Y. (November, 2000). Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: A randomized, double-blind, placebo-controlled trial. *Archives of Internal Medicine*, 160(20), 3128–3134.
- Cohen, G., Roux, J.C., Grailhe, R., Malcolm, G., Changeux, J.P. & Lagercrantz, H. (March, 2005). Perinatal exposure to nicotine causes deficits associated with a loss of nicotinic receptor function. *Proceedings of the National Academy of Sciences of the United States of America*, 102(10), 3817–3821.
- Dale L.C., Hurt, R.D., Offord, K.P., Lawson, G.M., Croghan, I.T., Schroeder, D.R., et al. (November, 1995). High-dose nicotine patch therapy: Percentage of replacement and smoking cessation. *Journal of the American Medical Association*, 274(17), 1353–1358.
- Fagerstrom, K.O., Schneider, N.G., & Lunell, E. (1993). Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. *Psychopharmacology* 111(3), 271–277.
- Fiore, M., (June, 2000). US Department of Health and Human Services, Public Health Service, Treating Tobacco Use and Dependence: Clinical Practice Guideline.
- Garvey, A.J., Bliss, R.E., Hitchcock, J.L., et al. (1992). Predictors of smoking relapse among self-quitters: A report of the normative aging study. *Addictive Behaviors*, 17, 367–377.
- Holt, P., Frommer, M., Faundez, T., & Madronio, C. (November, 2004). *Chronic and complex priority health care programs: Evaluation of the COPD Program*. University of Sydney, Australia: Sydney Health Projects Group.
- Hughes, J.R. (November, 1995). Treatment of nicotine dependence — Is more better? *Journal of the American Medical Association*, 274(17), 1390–1391.

- Hughes, J.R., Goldstein, M.G., Hurt, R.D., & Shiffman, S. (1999). Recent advances in the pharmacotherapy of smoking. *Journal of the American Medical Association*, 281, 72–76.
- Hughes, J.R., Lesmes, G.R., Hatsukami, D.K., Richmond, R.L., Lichtenstein, E., Jorenby, D.E., et al. (1999). Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine & Tobacco Research* 1(2), 169–174.
- Hurt, R.D., Dale, L.C., Offord, K.P., Lauger, G.G., et al. (1993). Serum nicotine and cotinine levels during nicotine-patch therapy. *Clinical Pharmacology Therapy*, 54, 98–106.
- Killen, J.D., Fortmann, S.P., Davis, L., Strausberg, L., Varady, A., et al. (August, 1999). Do heavy smokers benefit from higher dose nicotine patch therapy? *Experimental & Clinical Psychopharmacology*, 7(3), 226–233.
- Kornitzer, M., Boutsen, M., Dramaix, M., Thijs, J., & Gustavsson, G. (1995). Combined use of nicotine patch and gum in smoking cessation: A placebo-controlled clinical trial. *Preventative Medicine*, 24, 41–47.
- Lane, J.D., Westman, E.C., Ripka, G.V., et al. (1993). Pharmacokinetics of a transdermal nicotine patch compared to nicotine gum. *Drug Development and Industrial Pharmacy*, 19(16), 1990–2010.
- Paoletti, P., Fornai, E., Maggiorini, F., Puntoni, R., Viegi, G., Carrozzini, L., et al. (1996). Importance of baseline cotinine plasma values in smoking cessation: Results from a double-blind study with nicotine patch. *European Respiratory Journal*, 9(4), 643–651.
- Parrott, S., & Godfrey, C. (2004). Economics of smoking cessation. *British Medical Journal*, 328, 947–949.
- Paul, C.L., Walsh, R.A., & Girgis, A. (2003). Nicotine replacement therapy products over the counter: Real-life use in the Australian community. *Australian and New Zealand Journal of Public Health*, 27(5), 491–495.
- Pierce, J., & Gilpin, E. (2002). Impact of over-the-counter sales on effectiveness of pharmaceutical aids for smoking cessation. *Journal of the American Medical Association*, 288(10), 1260–1264.
- Puska, P., Korhonen, H.J., Vartiainen, E., Urjanheimo, E.L., Gustavsson, G., & Westin, A. (1995). Combined use of nicotine patch and gum compared with gum alone in smoking cessation. *Tobacco Control*, 4, 231–235.
- Russell, M.A.H. (1988). Nicotine replacement: The role of blood nicotine levels, their rate of change, and nicotine tolerance. In O.F. Pomerleau & C.S. Pomerleau (Eds.), *Progress in clinical and biological research: Vol 261. Nicotine replacement: A critical evaluation* (pp. 63–94). New York: Alan R. Liss.
- Russell, M.A.H. (1990). Nicotine intake and its control over smoking. In S. Wonnacott, M.A.H. Russell, & I.P. Stolerman (Eds.), *Nicotine psychopharmacology: Molecular, cellular, and behavioural aspects* (pp. 375–418). Oxford University Press.
- Shiffman, S., Hughes, J.R., Di Marino, M., & Sweeney, C.T. (2003). Patterns of over-the-counter nicotine gum use: Persistent use and concurrent smoking. *Addiction*, 98(12), 1747–1753.
- Silagy, C., Lancaster, T., Stead, L., Mant, D., & Fowler, G. Nicotine replacement therapy for smoking cessation. [Computer software]. Research. Systematic Review. The Cochrane Library (Oxford).
- Stapleton, J. (January, 1999). Nicotine nasal spray with nicotine patch for smoking cessation: Randomised trial with six year follow up. Commentary: Progress on nicotine replacement therapy for smokers. *British Medical Journal*, 318(7179), 289.
- Sweeney, C.T., Fant, R.V., Fagerstrom, K.O., McGovern, J.F., & Henningfield, J.E. (2001). Combination nicotine replacement therapy for smoking cessation: Rationale, efficacy and tolerability. *CNS Drugs*, 15(6), 453–467.
- Tonnesen, P., Paoletti, P., Gustavsson, G., Russell, M.A., Saracci, R., Gulsvik, A., et al. (February, 1999). Higher dosage nicotine patches increase one-year smoking cessation rates: Results from the European CEASE trial. Collaborative European Anti-Smoking Evaluation. *European Respiratory Society. European Respiratory Journal*, 13(2), 238–246.