Bittoun's 'Combination nicotine replacement therapy algorithm" A case for endorsement by the Statewide Respiratory Network.

ABSTRACT

We are in the era of evidence based best practice in healthcare. Clinicians are ethically and legally obliged to give advice based in the sciences for which we have a high level of evidence. Smoking cessation interventions are among the most cost effective and have a significant impact upon the burden of chronic disease. For "clinical care" to facilitate the practice of evidence based smoking cessation interventions, considerable improvement in the use of Nicotine Replacement Therapy (NRT) is required. NRT is often restricted by the predominantly theoretical and conflicting precautions and warnings contained in the product information. As smoking is the cause of the most preventable chronic diseases and the greatest burden on healthcare in the Western world, clinicians ought to look beyond the usual sources of pharmaceutical information and become familiar with the growing abundance of evidence clearly establishing the safety and effectiveness of NRT in all combinations.

KEY WORDS (smoking cessation, nicotine, nicotine replacement therapy (NRT), chronic disease, combination therapy, best practice, premature mortality)

Introduction

Smoking is widely regarded as the most preventable cause of chronic disease and premature mortality in the western world[1,2]. Tobacco use is the single risk factor associated with the greatest burden of disease in Australia[3]. The World Health Organisation predicts that by 2030 tobacco will be attributable to one in every ten deaths globally (across all ages). This will represent 8.3 million people annually. The available smoking cessation strategies are therefore the most financially beneficial

Brett Windeatt RN. Chair – Smoking Cessation Working Group, Statewide Respiratory Network

interventions available in contemporary health care[1, 4]. Nicotine Replacement Therapy (NRT) doubles the smoker's probability of cessation and is the most commonly used therapy in smoking cessation[5]. To maximise the benefits of NRT, it is imperative that clinicians become familiar with the wealth of post marketing research and understand what strategies work most effectively[5].

Labelling and licencing: barrier

Rather than examining the significant harm attributed to continued tobacco smoking for which no legal liability can be assigned to any regulatory medical body, the safety focus of healthcare is too heavily weighted upon assessing risks associated with and the potential harm of using NRT[6].

Interestingly, innovative uses of NRT contravene labelled instructions and precautions. This may give rise to the implication that adverse consequences of its use are the liability of the advising professional even though the risk of continuing smoking outweighs any potential and unsubstantiated adverse reactions of NRT. In contrast, Bittoun (2007) reports that smoking cessation experts worldwide are of the opinion that with respect to NRT, both "more" and for "longer" is both safe and effective based on the available evidence [7].

In 2006, the Australian smoking cessation campaign experienced an enormous step forward. The TGA approved a new indication for combination therapy as a result of Nicorettes evidence for combination therapy in [8, 9]. Since then, other pharmaceutical companies have developed evidence based indications for combination NRT therapy.

These include QuitX patch/gum Nicabate patch/gum or lozenge (MIMS 2010)[10, 11, 12, 13].

While the safety and success of combination NRT is widely accepted in the literature and the evidence base is continually building[5,6,14] there remains many misconceptions about this practice exist among smokers and clinicians as a direct result of current labelling warning against this practice[14]. Combining a NRT patch with gum provides a steady blood nicotine level with the added ability to increase the level of nicotine in response to more intense cravings or stressful situations, therefore giving the smoker the opportunity for greater control over their withdrawal symptoms[6].

In their study comparing the number and duration of medications used in relation abstinence to rates, Steinberg et al summarised that they observed higher abstinence rates in smokers who used more medications in combination for longer periods [14]. Further, it was also extensively noted that patients reported they would have attempted combination therapy previously if they had not been advised against it by product information or by their health care professional. The authors conclude that their findings support what is known as "off label" use of NRT including the practice of combining NRT with bupropion [14]. Bupropion is an atypical antidepressant which is believed to aid smoking cessation through its inhibition of dopamine and noradrenaline reuptake[15]. In a study that observed the combined use of NRT and bupropion, it was demonstrated that at one year the outcome of smoking cessation was doubled in the group using combination therapy[15]. Summarised concisely, there is no evidence to suggest that any combination of NRT is harmful[6].

Nicabate NRT patch product information reads that a smoker achieves an average blood nicotine level of 44 nanograms/m[11].This level varies and can be as high as 100nanograms/ml in many smokers[16]. In comparison, the 21mg NRT patch, currently the strongest available in Australia, provides a nicotine blood level range of between 9-17 nanograms/ml and does not reach therapeutic levels for between six and ten hours[11] Post-marketing comparisons demonstrate that the mean nicotine plasma level from a 21mg patch is approximately 10nanograms/ml When using 4mg oral NRT, the average nicotine serum level is approximately 15nanograms/ml[16].

When a 4mg oral NRT product is combined with a 21mg NRT patch, the blood nicotine levels achieved are only then **about half** that attained by the average smoker, therefore having limited therapeutic benefit and unsatisfactorily meeting the smokers cravings for nicotine. Further, when we consider the manufacturers reported maximum nicotine plasma level of 17nanograms/ml from a 21mg NRT patch, even two patches used in combination don't achieve the plasma level of 44nanograms/ml required by the average smoker.

Firstly, when deliberating NRT safety we must consider that we are dealing with both a low dose and slowly absorbed dose of nicotine compared with that received from tobacco smoke. Secondly, nicotine is the least harmful component of tobacco but is the drug of dependence that keeps people smoking. The myriad of other toxins in tobacco smoke are responsible for tobacco related disease. Therefore, using NRT will always be safer than continuing to smoke[17].

NRT use while still smoking

A recent positive change in the indication for NRT is the TGA's approval for Nicorette gum and inhaler to be used to assist a smoker to cut down then quit[18]. This new indication is likely to introduce more smokers to NRT assisting them to reduce cigarette consumption prior to having to quit completely. Studies suggest in addition to reducing the number of cigarettes smoked by at least 50%, the use of NRT has been shown to lead to complete cessation in 4% of smokers who had no intention of stopping[18]. In Australia, Nicabate use the term "reduce to quit" with gum and lozenge products approved for harm reduction use[12,13].

NRT has been shown to be extremely effective in preventing a lapse during a smoking cessation attempt from evolving into a relapse to smoking. This is demonstrated in a randomized controlled trial of 324 smokers making a cessation attempt[2]. Participants receiving active nicotine replacement patches were at least three times less likely to progress from a lapse to relapse during a cessation attempt than the placebo group. A relapse is described as a return to baseline smoking during a period of abstinence following the use of one cigarette.

Unfortunately, with the exception of the Nicabate pre-quit indication approved in 2008, much of the current labelling on NRT patch products largely prevent these potential benefits because the instructions clearly state that the user must have stopped smoking prior to use. This circumstance once again demonstrates that inconsistent product labelling has the potential to cause misunderstanding regarding the use of this general sale item, both by consumers' and health care professionals.

Additionally, the users of QUITX patches, for example, are warned they may suffer an overdose of nicotine if they continue to smoke while using a NRT patch[10]. This warning of potential overdose is inconsistent with other NRT labelling such as the Nicorette gum product. Nicorette gum product labelling correctly states that **smokers are known to self-titrate their blood nicotine levels and that concomitant use of NRT gum or inhaler while smoking is unlikely to cause either nicotine overdose or achieve plasma nicotine levels higher than smoking alone**[9]. A statement to this effect should therefore be applied to NRT in all its forms and across all the commercial products. If the labelling remains inconsistent across commercially available products, it is imperative that clinical judgement based upon the best available evidence be employed by clinicians. That is, NRT needs to be used liberally in a regime based on the symptoms of withdrawal (including continued smoking) and not single forms of the product that do not achieve adequate blood nicotine levels for highly nicotine dependent smokers[16]. NRT should also be treated as a generic product. For example, if Nicabate 21mg patches are safe to use while still smoking as per TGA approval, it is reasonable to deduce that the smoker is very unlikely to suffer any adverse effects simply because they purchase another brand.

Further dismissing theses 'potential for overdose warnings', is the Fagerstrom and Hughes meta analysis that show blood nicotine levels were unchanged when NRT gum and inhaler were used while still smoking[19]. Perhaps the most significant finding in this study is that while both NRT gum and inhaler or patch were used while continuing to smoke, there was a 30% reduction in the measured carbon monoxide level and a 50% reduction in total cigarettes smoked. In addition, where smokers had the intention to quit or received instruction to reduce the number smoked, there was a

greater reduction in both cigarettes smoked and carbon monoxide levels[19] . This is consistent with the findings in the studies cited earlier.

Also supporting the safety profile of using NRT while smoking during cessation programs are the Fagerstrom and Benowitz studies described by McNeill et al., that show total nicotine intake remained broadly stable in smokers attempting to reduce their smoking while measured carbon monoxide levels decreased[6]. There is no evidence to suggest that using NRT products while continuing to smoke is harmful and as a discussed above there is considerable evidence to suggest that the practice can reduce the number of cigarettes smoked, measured carbon monoxide levels and exposure to the other toxins contained in tobacco smoke[6,18,19].

A further example of the successful use of NRT while still smoking is the randomised controlled study by Schuurmans et al. examining the effect of a two week pre-treatment with transdermal NRT on nicotine withdrawal symptoms and subsequent cessation rates[20]. There was no significant difference in the withdrawal symptoms reported by either the active or control group. However, at six months continued abstinence rates more than doubled in the group pre-treated with NRT prior to a cessation date compared to placebo. Both groups received eight weeks of NRT following cessation. Abstinence rates verified by carbon monoxide testing (CO) were 22% and 9% respectively. The successful participants in the pre-treatment group were those smoking greater than 16 cigarettes per day and who had higher initial scores for the Fagerstrom Test for Nicotine Dependence and expired CO readings[20]. Not only is the safety profile of NRT further established by this study, this is a clear example of increased efficacy with more liberal use of this product.

There is no evidence in the literature of instances of nicotine toxicity from using NRT either in combination or while continuing to smoke[16]. The case for NRT safety while using it more dynamically than current labelling dictates is thus well established and the body of evidence supporting its efficacy in reducing tobacco use is solid.

NRT and harm reduction

The described safety of concomitant NRT use while still smoking and in particular the reduced carbon monoxide levels measured illustrates why conversely, cutting down the number of cigarettes smoked without NRT can be more harmful[19]. It is common for smokers to be advised to cut down their cigarette consumption as a means to cessation despite overwhelming evidence against this strategy[6]. This practice is believed to be associated with compensatory smoking which involves the smoker attempting to extract more nicotine from each cigarette and thereby inhaling greater amounts of carbon monoxide and other toxins associated with tobacco smoke[6], [19, 21]. As argued by Bittoun, it is therefore safer to smoke while using NRT than smoking without[22].

NRT and cardiovascular disease

In 2005 the United Kingdom's medication regulatory authority changed the licence for NRT to allow its use for combination therapies of multiple products and additionally the use of NRT while still smoking [5]. The research in the UK and USA in addition to clinical experience has clearly established the safety profile of NRT [6]. Mc Neill et al. suggest that the method by which NRT is regulated by the pharmaceutical

licencing authority of many countries does not effectively consider the risk benefit ratio of NRT use compared with the harm of continued smoking (2001). In contrast, the current evidence for the safety of NRT is such that the pharmaceutical regulatory body in France was among the first to remove all of the contraindications to NRT including the widely documented contraindication of cardiovascular disease and pregnancy [23]. The unsubstantiated doubts about the safety of NRT continue to be a barrier to effectively assisting smokers with cardiovascular disease today.

All NRT products available in Australia now only contain precautions regarding the use of NRT in the presence of cardiovascular disease if the patient is hospitalised and currently haemodynamically unstable (Mims, 2010). The evidence overwhelmingly establishes the safety profile of NRT in haemodynamically stable cardiac patients and asserts that if there were any possibility of health risks, these are far outweighed by the very real risks of continued smoking [6,17].In all patients who want to cease smoking, including those with cardiovascular disease, tobacco would always be identified the greater threat to health if the clinician employed the common medical risk/benefit assessment that is used in other areas of clinical care.

An observational study of 33 247 first time NRT users examined the use of NRT and the risk of acute myocardial infarction, stroke and death. It found NRT use is clearly not associated with any increased risk of these adverse events and the conclusion did not differ according to race, sex, pre-existing angina, hypertension, or the type of NRT used[1]. The study further suggests that the use of NRT should be amongst first line therapies for this patient group who represent one of the largest groups most likely to benefit from smoking cessation [1].

Haustein et al concluded that while smoking cessation improved cardiovascular parameters, the use of NRT did not negate or diminish these improvements [24]. Smoking cessation in subjects using NRT was shown to decrease plasma fibrinogen, haematocrit, and haemoglobin leading to reduced plasma viscosity, all factors associated with reducing risk of ischaemic heart disease and stroke. The authors further conclude that in addition to NRT having no significant effects on the myocardial blood supply, the risk factors for coronary artery disease can be reduced after only a few days of NRT therapy even if cigarette consumption is not immediately completely ceased.

A Combination algorithm to support practice

It is logical to conclude that because there is evidence nicotine is accepted as having very few harmful properties on its own, the use of NRT as a means of ceasing or reducing the smoking of tobacco, which contains a myriad of lethal chemicals, is safe and its use should be widely encouraged. Unfortunately, current labelling of NRT products restrains the use of evidence based and effective applications particularly for clinicians including nurses. The clinician's concerns stem from fears of medico-legal implications and conflict with evidence based recommendations that are inconsistent with the manufacturer's labelling. This clash continues to be a barrier to increasing smoking cessation rates in Australia. Actively addressing and settling the inconsistencies between the growing evidence base and common practice with respect to NRT could optimise reductions in morbidity and mortality rates and the associated costs to the health care system now and into the future.

In the paper titled *"A combination NRT algorithm for hard to treat smokers"*, Bittoun reports that there have been no serious recorded events associated with NRT. If nausea is encountered, dosages are reduced. The algorithm treats smokers by using up to two 21mg NRT patches simultaneously in addition to as much oral NRT needed to effectively treat cravings and urges. In a formal trial using aggressive combination NRT according to the algorithm, there was a 60% carbon monoxide verified thirty day abstinence rate demonstrated[16]. Efficacy aside, it is the safety profile of NRT that needs to be appreciated if this treatment is going to be used as effectively as possible.

The endorsement and use of the internationally acknowledged "Bittoun - *Combination Nicotine Replacement Therapy algorithm*", by the Statewide Respiratory Network, will help transcend the existing inconsistencies arising from NRT product labelling and give clinicians an authoritative guide to an effective safe use of this generic product. Endorsement by the network will provide a simple practice framework to non-prescribing clinicians who otherwise would not routinely discuss medication use that are based on contemporary literature rather than solely on product labelling.

Where supported by the literature, "off label" prescribing is arguably an accepted part of medical practice. Therefore, "off label" use would not be so much a practice concern if intensive smoking cessation interventions were going to be largely delivered by medical officers. However, it is non-medical health care professionals who currently conduct the more intensive smoking interventions and are the group most likely to do so into the future. Therefore, these clinicians require endorsed guidelines such as the combination NRT algorithm to both ensure better patient outcomes while maintaining scope of practice considerations. Further, the

endorsement of such an algorithm will also act as a much needed authoritative **medical statement**, thereby educating the healthcare community that **NRT is always safer than continuing to smoke, is safe in all its combinations and safe to use while continuing to smoke.**

Summary

It was beyond the scope of this discussion to provide an exhaustive description of the practical applications of NRT. However, it has clearly established that credible literature provides extensive evidence that NRT is safe in all forms and combinations. Therefore, in order to achieve better patient outcomes, clinicians need support through guidelines and endorsed decision support tools that transcend the restrictive and inconsistent instructions contained in NRT product information. There are after all, no such restrictions on the manner in which people use deadly tobacco on a daily basis.

References

1.Hubbard R, Lewis S, Smith C, Godfrey C, Smeeth L, Farrington P and Britton J (2005) Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke and death, *Tobacco Control* 14: 416-421.

2.Shiffman S, Scharf D, Shadel W, Gwaltney C, Dang Q, Paton S and Clark D (2006) Analyzing milestones in smoking cessation: Illustration in a nicotine patch trial in adult smokers, *Journal of Consulting and Clinical Psychology* 74: 276-285.

3. New South Wales Health (2002) Guide for the management of nicotine dependent inpatients, Summary of Evidence, accessed at http://www.health.nsw.gov.au on 28 February 2007.

4.McEwen A, West R and Owen L (2004) GP prescribing of nicotine replacement and bupropion to aid smoking cessation in England and Whales, *Addiction* 99(11): 1470-1474

5. West R (2006) New approaches to smoking cessation, Timely Topics in Medicine: *Respiratory Medicine* September.

6. McNeill A, Foulds J and Bates C (2001) Regulation of nicotine replacement therapies (NRT): a critique of current practice, *Addiction* 96: 1757-1768.

7. Bittoun R (2007) The treatment resistant smoker, *Medicine Today* (8) 8:16-24.

8. Nicorette combination therapy consumer information web page, accessed at http://www.nicorette.com.au/product_combined.cfm on 28 February 2007.

9. Mims online (n.d.) Nicorette patch, gum, microtab, and inhaler prescribing information, accessed at http://www.mims.com.au on 18 December 2010.

10. Mims online (n.d.) QuitX patch prescribing information, accessed at http://www.mims.com.au on 18 December 2010.

11. Mims online (n.d.) NicabateCQ and NicobateCQ Clear prescribing information, accessed at http://www.mims.com.au on 18 December 2010.

12. Mims online (n.d.) Nicabate gum prescribing information, accessed at http://www.mims.com.au on 18 December 2010.

13. Mims online (n.d.) Nicabate Lozenge prescribing information, accessed at http://www.mims.com.au on 18 December 2010.

14. Steinberg M, Foulds J, Richardson D, Burke M and Shah P (2006) Pharmacotherapy and smoking cessation at a tobacco dependence clinic, *Preventive Medicine* 42: 114-119.

15. McRobbie H, Lee M and Juniper Z (2005) Non-nicotine pharmacotherapies for smoking cessation, *Respiratory Medicine* 99(10): 1203-1212.

16. Bittoun, R. (2006) A combination nicotine replacement therapy (NRT) algorithm for hard to treat smokers, *Journal of Smoking Cessation* (1)1:3-6.

17. Zwar N, Bell J, Peters M, Macdonald C and Mendelsohn. (2006). Nicotine and nicotine replacement therapy – the facts, *Pharmacist* (25)12: 969-973.

18. Action on Smoking and Health ASH (2007) Nicotine replacement therapy, Guidelines for healthcare professionals on using nicotine replacement therapy for smokers not yet ready to quit, accessed at http://www.ashaust.org.au/pdfs/NRTguide0702.pdf on 20 March 2007.

19.Henningfield J, Fant R, Buchhalter A and Stitzer M (2005) Pharmacotherapy for nicotine dependence, *A Cancer Journal for Clinicians* 55: 281-299.

20.Schuurmans M, Diacon A, van Biljon X and Bolliger C (2004) Effect of pre-treatment with nicotine patch on withdrawal symptoms and abstinence rates in smokers subsequently quitting with the nicotine patch: a radomized controlled trial, *Addiction* (99)5: 634-640.

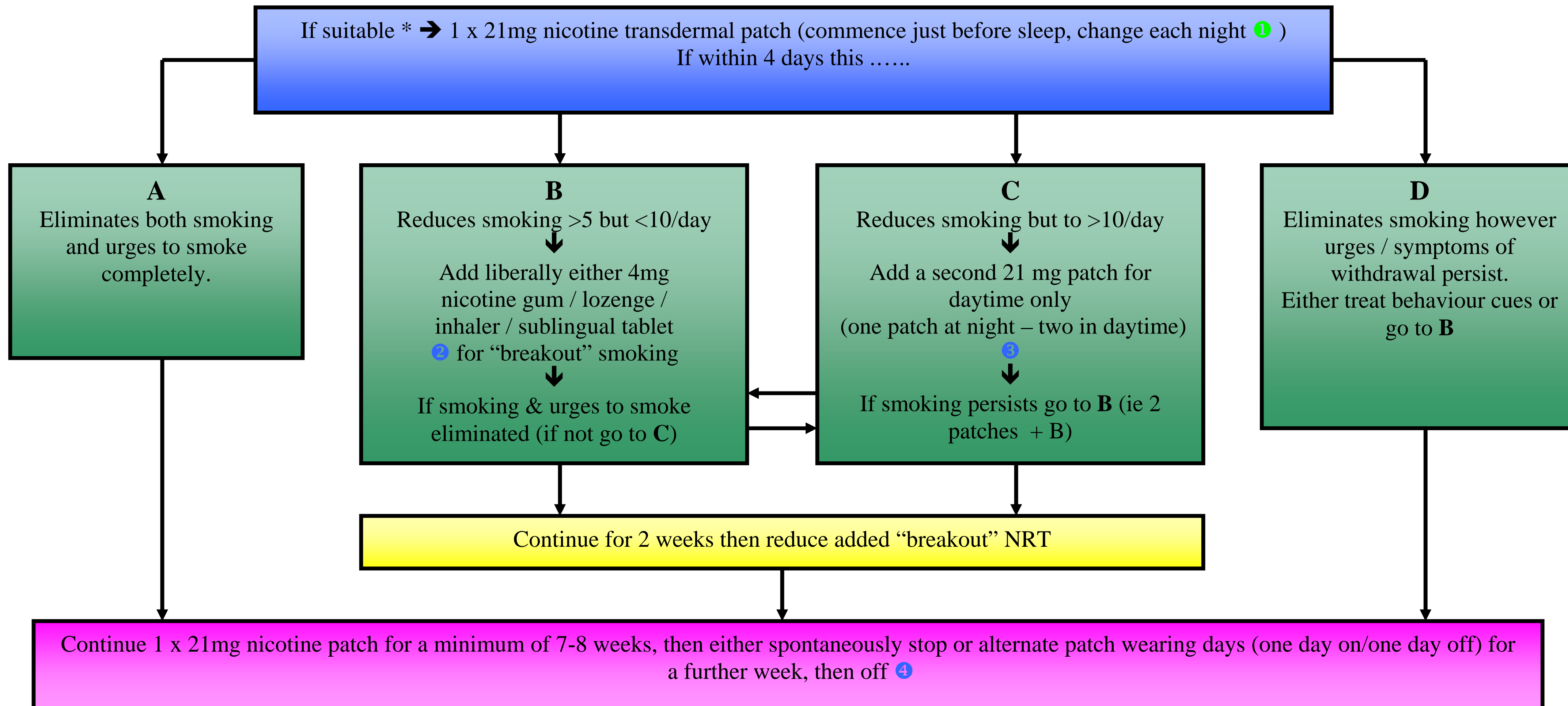
21. Lamberg L (2004) Patients need more help to quit smoking: Counseling (sic) and pharmacotherapy double success rate, *The Journal of the American Medical Association* 292(11): 1286-1290.

22. Bittoun, R. (2007) A decade of over the counter therapeutic nicotine in Australia: Its contribution to improving quit rates and saving lives, *Brain & Mind Research Institute. University of Sydney*

23. Le Houezec J (2005) Why a nicotine vaccine? *Clinical Pharmacology & Therapeutics* 78(5): 453-455.

24. Haustein K, Krause J, Haustein H, Rasmussen T and Cort N (2002) Effects of cigarette smoking or nicotine replacement on cardiovascular risk factors and parameters of haemorheology, *Journal of Internal Medicine* 252: 130-139.

Bittoun Combination Nicotine Replacement Therapy Algorithm#



* KEEP IN MIND CONTRAINDICATIONS: 1) PREGNANCY OR LIKELIHOOD
2) RECENT CARDIOVASCULAR EVENT

Brett Wi

❶ Applying patch last thing before sleep allows the slow rise of nicotine overnight - the likelihood of 1st cigarette of the day "urge" is strongly diminished.

❷ Either 4mg nicotine gum or lozenge depending in patient choice. Inhaler or sublingual tablet recommended over the others if patient