Nicotine-replacement therapy: a proven treatment for smoking cessation

Robson N, MBBS, MMed, PhD
Department of Primary Care Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
Correspondence to: Associate Professor Dr Noorzurani Md Haris Robson, e-mail: noorzurani@hotmail.com
Keywords: smoking; quit; cessation; nicotine; nicotine-replacement therapy; NRT; tobacco; dependence

Abstract

Smoking is a major cause of cardiovascular diseases, respiratory diseases and cancer. Despite the high prevalence of smokers worldwide, smokers are often neglected and not offered effective assistance with quitting their habits. In order to overcome this public health burden, effective treatment is needed to help smokers stop smoking. Among the pharmacological treatments available, nicotine-replacement therapy (NRT), when prescribed in combination with behavioural support, has been proven to be effective in helping a wide range of smokers to quit. NRT helps smokers during the withdrawal process by replacing a proportion of the nicotine formerly obtained from cigarettes. NRT is available in many formulations. The commonly prescribed formulations are nicotine gum, nicotine patches, nicotine inhaler and nicotine nasal spray. The choice of which NRT to prescribe depends on the patient's condition, established guidelines and protocols and availability. This article aims to review the role of NRT in smoking cessation.

Ⓟ **Peer reviewed. (Submitted: 2009-08-31, Accepted: 2009-01-10).** **SA Fam Pract 2010;52(4):298-303**

Introduction

Cigarette smoking, a leading cause of morbidity and mortality, is associated with cardiovascular and respiratory diseases, cancer and stroke. The World Health Organization (WHO) reported that cigarette smoking presently kills up to four million people annually and that, by the year 2030, up to 10 million smokers will die annually worldwide.[1] Cigarette smoking is also a major public health concern in South Africa. The prevalence of smoking is 27.1% among men and 8.9% among women. The Medical Research Council reported that 8% of deaths in South Africa are attributed to cigarette smoking.[2] Therefore, it is important to establish effective treatments to help current smokers to stop smoking.

Nicotine has been recognised as the main substance responsible for tobacco dependence. The inability of or difficulty for many smokers to stop smoking is mainly due to the addictive properties of nicotine.[3] Nicotine in cigarettes acts as a pharmacological agent that reinforces the consumption of cigarettes and produces significant withdrawal symptoms in its absence.[4] In recent years, the literature has reported newer drugs for smoking-cessation treatment.[5] Several pharmacotherapies are available to assist smoking intervention strategies. One of the established pharmacotherapies for smoking cessation is nicotine-replacement therapy (NRT). Many clinical guidelines recommend NRT as a first-line treatment for smokers seeking pharmacological treatment to stop smoking.[5,6] NRT helps smokers to alleviate withdrawal symptoms associated with smoking cessation by replacing a proportion of the nicotine formerly obtained from cigarettes.[5,7] This article aims to briefly review NRT as a pharmacological aid for smoking-cessation treatment.

Source of data

A search of the literature was conducted using the Cochrane Library and OvidMedline up to 8 January 2010 using the keywords "nicotine", "replacement", "primary care", "family" and "medicine". The search produced a total of 104 articles on nicotine replacement and primary care and 20 articles on NRT and family medicine from Ovid Medline and four articles from Cochrane Library. Articles chosen were narrowed down to those published in English and limited to studies done on human subjects. Case reports, meta-analyses, review articles and clinical trials evaluating the safety, efficacy and adverse effects of NRT were included.[5,8–10]

Nicotine-replacement therapy

NRT aims to replace the nicotine obtained from cigarettes, thereby reducing withdrawal symptoms when stopping smoking. Worldwide, NRT is available in a variety of formulations, such as chewing gum, transdermal patches, a

nasal spray, an inhaler, sublingual tablets and lozenges.[5,10,11] The Cochrane Review (2008) of over 132 trials of NRT involving more than 40 000 people found that NRT helped smokers to stop smoking by increasing the chances of cessation by 50 to 70%, with or without additional counselling.[5] NRT was shown to be effective for smoking cessation with or without additional counselling, although heavy smokers may require higher doses of NRT than smokers who smoke fewer cigarettes.[5,10,12–14]

The dose of nicotine replacement required by the individual smoker depends on the usual nicotine consumption (amount of tobacco or number of cigarettes), and the 'form' and strength of nicotine content.[5,10] It is recommended that the initial dose be sufficiently high to allow complete suppression of nicotine withdrawal symptoms and gradually reduced as tobacco abstinence is established.[10,11]

In South Africa, a special formulation of NRT is available as a nicotine mouth spray.[15] Among the NRT formulations available, nicotine patches are considered a 'passive' dosing form, as they are applied once a day and nicotine is slowly absorbed though the skin.[5,16] Nicotine gum, lozenges, sublingual tablets and inhalers are 'acute' dosing forms, as they allow the smoker to self-administer a dose of nicotine on an as-needed basis.[5,17,18] Acute-dosing products are more beneficial for some smokers as they can titrate the amount and timing of doses. Thus, smokers with greater withdrawal symptoms can titrate a higher dose of nicotine, and those with acute adverse effects can reduce their nicotine intake.[5,10,19]

NRT relieves withdrawal symptoms by substituting some of the nicotine normally obtained from cigarettes.[4] The degree of relief obtained is related to the dose. Studies have reported that many smokers did not take optimum doses of NRT for a variety of reasons. Some stopped using it due to adverse effects, some were afraid of becoming dependent on NRT, some falsely believed that nicotine caused tobacco-related disease and others denied being addicted to nicotine and failed to understand medical treatment.[10,18,20]

In smoking-cessation therapy, an adequate dosage of NRT is important to control craving and withdrawal symptoms in order to prevent relapse.[18] It is reported that combination NRT treatment was superior to single NRT treatment in achieving one-year abstinence rates,[5,21] and that treatment duration had to be long enough to control symptoms that persisted several weeks after cessation.[22]

Recently, it has been suggested that if a smoker was not able to stop smoking completely, sustained smoking reduction would be beneficial as it reduces exposure to tobacco smoke. It was also suggested that smoking reduction might motivate smokers to stop by gradually allowing them to take control of their smoking.[23] NRT has been reported to help sustain and achieve smoking reduction, where 10% of subjects on NRT who had earlier stated that they were unwilling or unable to stop smoking at baseline were abstinent at two years.[24] Furthermore, beside treatment for smoking cessation, the new indication for NRT was also for temporary abstinence (use of NRT to control nicotine craving and withdrawal symptoms during situations in which smokers were unable to smoke, as in the workplace, in hospitals or on long-haul flights). This could help smokers to familiarise themselves with NRT products, and may help them to stop smoking when they are ready to.[11]

Withdrawal symptoms

Stopping smoking is difficult, as smokers experience withdrawal symptoms that begin within hours of smoking the last cigarette. The maximal intensity is felt within the first week and most of the affective symptoms reduce by four weeks.[25] However, symptoms such as hunger and cravings may persist longer but these symptoms lessen over time.[26] Studies have observed heterogeneity in nicotine withdrawal symptoms among smokers trying to stop smoking.[4,21] This variability in the pattern, severity and timing of withdrawal symptoms is important, as it could predict relapse after treatment.[27] This observed variability means that therapy to treat nicotine withdrawal symptoms should be individualised. It was found that combined NRTs provide better relief of withdrawal symptoms. For example, the combination of a nicotine patch and another acute dosing formulation provides steady nicotine (through the patches) and immediate self-titrated relief (through the acute NRT such as a nicotine nasal spray, nicotine lozenge or nicotine gum) of the withdrawal symptoms.[10,28]

Cessation rates and efficacy

Earlier meta-analyses of 81 studies (49 on nicotine gum) that compared smoking-cessation rates with NRT or placebo reported that 18% of subjects receiving nicotine chewing gum were abstinent at 12 months, compared to 11% in the placebo group. The odds ratio for being abstinent with nicotine gum was 1.63 compared to placebo. The 4 mg of nicotine gum was better suited for the highly dependent smoker than the 2 mg.[10,11,29] Recent evidence of the effectiveness of NRT for smoking cessation from the Cochrane Review (2008) of 111 trials of the five types of NRT formulations and over 43 000 subjects found that the risk ratio (RR) for nicotine gum was 1.43, 1.66 for nicotine patches, 1.90 for the nicotine inhaler, 2.00 for oral tablets/lozenges and 2.02 for the nicotine nasal spray.[5] A more recent study further confirmed that NRT was effective in maintaining smoking abstinence at six months, where smokers receiving NRT had double success rates of abstinence compared to placebo.[10] Thus, NRT has been shown to be effective for smoking cessation at six months and at one year.

Potential adverse effects of NRTs

Among the side effects reported were slight throat irritation, sore mouth, increased salivation and hiccups due to excessive swallowing of dissolved nicotine. Other adverse effects were gastrointestinal disturbances, including flatulence and borborygmi, headache, dizziness, nausea and vomiting. Less frequent adverse reactions include palpitations, erythema and urticaria. As for the potential for being addictive, it was reported that only about 5 to 20% of smokers may become addicted to nicotine gum.[11] NRT should be cautiously prescribed to patients with cardiovascular diseases. However, when compared to cigarettes, it was shown that NRT caused fewer cardiovascular effects than nicotine delivered by tobacco smoke, and that it is generally safe for the vast majority of smokers.[30]

Health risk of nicotine

One of the common reported misconceptions regarding NRT is the effect of nicotine on health.[29] Nicotine addiction sustains smoking; however, it is the other components in cigarette smoke that cause lung cancer, chronic bronchitis and emphysema.[31] It has been described that smokers smoke for nicotine, but die from tar, carbon monoxide and other harmful gases taken with the nicotine.[32] Cigarette smoking causes acute cardiac events by producing a hypercoagualability state that promotes thrombosis. This is attributed to the bolus doses of nicotine in cigarette smoke and does not occur with the gradual delivery of nicotine via NRT.[29] There is no evidence that NRT increases the risk of heart attacks.[5]

Dependence and abuse potential of NRT

The abuse potential of nicotine had been closely linked to the route of administration and resulting pharmacokinetic profile.[29] The likelihood that a substance would be abused depends on the time between administration and central reinforcement.[33] The addictiveness depends on the dose and speedy delivery to the brain. Cigarette smoking is addictive because nicotine is absorbed via the pulmonary circulation (rather than the systemic venous circulation), which means that nicotine reaches the brain in about 10 seconds (more rapidly than via the intravenous route). Cigarettes also contain ammonia, which increases the pH of smoke and speeds up the delivery of free nicotine and theobromide, which dilates the airways and facilitates inhalation.[29] In contrast, NRT has low potential of abuse as it does not produce the rapid, high arterial nicotine concentration that cigarettes do.[33,34]

Nicotine gum

Nicotine gum has a tobacco-like, peppery taste. It is available in original, mint or citrus flavours. It is also available in 2-mg and 4-mg doses.[5] The 2-mg gum is recommended to be prescribed to occasional smokers and those who smoke < 20 cigarettes per day. The 4-mg gum is recommended for smokers who smoke ≥ 20 cigarettes per day, for highly dependent smokers and for those who have withdrawal symptoms when taking the 2-mg gum.[5,11,12]

Smokers who are prescribed nicotine gum should be advised that chewing nicotine gum is not the same as chewing regular chewing gum. Nicotine gum should be chewed slowly until a slight tingling is felt in the mouth. The smoker should then stop chewing and place (park) the chewing gum between the cheek and gum. When the tingling sensation is diminished (after approximately one minute), the smoker is then advised to start chewing again. It is also important to inform the smoker not to chew nicotine gum too fast, not to chew more than one piece of nicotine gum at a time, and not to chew one piece too soon after another. Nicotine gum should be chewed for around 30 minutes, and the administration could be repeated one to two hourly to prevent nicotine withdrawal symptoms, up to a maximum dose of 60 mg daily. After 20 minutes of intermittent chewing, almost 90% of the available nicotine is released from the gum. The availability is also dependent on the rate and intensity of chewing, the amount of saliva produced during chewing and whether saliva is swallowed or expectorated. The nicotine level rises faster than with a nicotine patch.[11,12] Each piece of nicotine gum contains 2 mg or 4 mg of nicotine bound to an ion-exchange resin, which permits the slow release of nicotine. When administered, up to 50% of the nicotine content of the nicotine chewing gum is absorbed through the buccal mucosa. This absorption provides relief of nicotine withdrawal symptoms. Nicotine ingested through the gastrointestinal tract is extensively metabolised on first pass through the liver. Plasma nicotine concentration rises considerably slower than after smoking, with peak concentration occurring 30 minutes after initiation of chewing.[35] Because of this slower rise, peak to trough nicotine concentrations vary less in a subject chewing one piece of gum compared to smoking one cigarette.[36] It has been reported that after chewing a piece of nicotine gum, 0.8 mg nicotine is absorbed by buccal and 0.06 mg nicotine is absorbed in the gut [37] The venous nicotine levels from the 2-mg and 4-mg gum were reported to be about one-third and two-thirds, respectively, of the steady-state (i.e. between-cigarettes) levels of nicotine achieved with cigarette smoking (peak of 35 ng/ml and trough of 25 ng/ml).[35] Nicotine via cigarettes is absorbed directly into the arterial circulation; thus, arterial levels from smoking are reported to be five to ten times higher (peak nicotine concentration of 100 ng/ml) than those from the 2-mg and 4-mg gums.

The nicotine in the chewing gum is released at variable rates depending on the intensity and duration of chewing. In those who chew slowly and intermittently every few minutes,

nicotine is released continuously over 30 minutes.[38,40] Thus, special instructions need to be given to patients on how to chew the nicotine gum, as chewing the gum rapidly may lead to excessive nicotine release, resulting in effect in 'over-smoking', with side effects such as light-headedness, nausea, vomiting, hiccups, indigestion and throat irritation. The gum or the nicotine-rich saliva should not be swallowed as this may cause abdominal discomfort, heartburn and nausea.[33,39] Other side effects of nicotine gum are difficulty in chewing, sore jaw, burning in the mouth and throat irritation.[12,13]

Nicotine gum reduced the incidence and severity of tobacco withdrawal symptoms, such as irritability, anger and impatience, more effectively than placebo when a nicotine-dependent person was prohibited from smoking.[41] It was also shown to markedly reduce the incidence and severity of hunger, which may persist for several weeks or months after stopping smoking.[40,41] However, the results with regard to cravings were inconsistent. In an earlier study, Cohen et al[41] showed that subjects had reduced craving symptoms when they chewed nicotine gum during temporary nicotine deprivation. However, later on, Cohen et al[40] reported that the subjects did not report any reduction in craving.

Studies by Silagy et al reported cessation rates after one year of treatment of 11% with placebo, 18% with 2-mg nicotine gum and 17% with 4-mg nicotine gum in those with mild nicotine dependence, and 8% with placebo, 20% with 2-mg nicotine gum and 26% with 4-mg nicotine gum in those with severe nicotine dependence.[11,12] When compared to placebo, the odds ratio for smoking cessation with nicotine gum was 1.63 (95% CI, 1.49–1.79).[42]

Nicotine patch

This transdermal formulation takes advantage of the ready absorption of nicotine across the skin. Patches are available as 24-hour and 16-hour patches. The patches are applied daily each morning, beginning upon cessation of smoking. Nicotine via patches is slowly absorbed. At the onset of use, venous nicotine levels peak six to ten hours after administration. Nicotine levels remain fairly steady with a decline from peak to trough of 25 to 40% with the 24-hour patches. Nicotine levels obtained with the use of patches are typically half of those obtained by smoking. The maximum plasma concentration of nicotine after application of a 15 mg patch is between 9 and 15 ng/ml.[14,43] The recommended dosage prescription for the nicotine patch is 21 mg/day for up to six weeks. After four to six weeks, patients are usually tapered to a middle dose (e.g. 14 mg/24 hours or 10 mg/16 hours) and then again in two to four weeks to the lowest dose (7 mg/24 hours or 5 mg/16 hours). However, smokers who smoked < 10 cigarettes/day are recommended to start at a 14-mg/day dose instead of the 21-mg/day dose. The recommended total duration of treatment is usually six to twelve weeks. The common side effects of nicotine patches are skin reactions, insomnia, increased or vivid dreams and nausea.[12,13]

In a clinical trial comparing the 24-hour and 16-hour patches, it was found that the 21-mg/24-hour patch yielded consistently better control of cravings in the early morning and throughout the day, with greater reductions in anxiety, irritability and restlessness. Smokers using the 24-hour patches also had longer abstinence than those using the 16-hour patches.[44] The main advantage of nicotine patches over other nicotine formulations is that they are simple to use, and hence produce better compliance than the other nicotine formulations. On the other hand, nicotine patches do not adequately protect against acute cravings that may be provoked by smoking-related stimuli, as nicotine is delivered slowly.[19]

Nicotine nasal spray

Nicotine nasal spray is a nicotine solution in a nasal spray bottle. Each 10 ml of nasal spray bottle contains 100 mg of nicotine (10 mg/ml). Each nasal spray dose (two sprays, one in each nostril) averages about 1 mg of nicotine per administration. This formulation produces a more rapid rise in nicotine levels than nicotine gum; the rise in nicotine levels produced by nicotine spray falls between those produced by nicotine gum and cigarettes. Peak nicotine levels occur within 10 minutes, and venous nicotine levels are about two-thirds those of between-cigarettes levels. Reported venous concentrations of nicotine after a single 1-mg dose of nasal spray ranged between 5 and 12 ng/ml, and time to peak plasma concentration (T max) with nasal spray was 11 to 13 minutes for a 1-mg dose. This time rise is slower than for delivery by cigarettes, but faster than other nicotine treatment products.[45] Hurt et al suggested that a dose of 1-mg nicotine nasal spray relieved spontaneous nicotine withdrawal symptoms, including cravings, more rapidly than a single dose of 4-mg nicotine gum.[46] Smokers are advised to use the product for up to six months, including a tapering period. The common side effects reported are nasal and throat irritation, rhinitis, sneezing, coughing and watering eyes.[12,13]

Nicotine mouth spray

Nicotine mouth spray is a formulation of NRT specially available in South Africa. It is available in a treatment package of three strengths (initial at 1 mg per actuation of the vial and the last at 0.33 mg per actuation). This formulation has been tested in a randomised controlled trial in healthy smokers who wanted to stop smoking and its efficacy was found to be comparable to nicotine gum and nicotine inhaler.[15] Smokers were also reported to prefer nicotine mouth spray over other formulations (nicotine gum, nicotine sublingual tablets and a nicotine nasal spray).[47] The reported adverse effects were burning of the tongue/throat, nausea and hiccups.[15]

Nicotine inhaler

The nicotine inhaler is formed of plugs of nicotine placed inside hollow cigarette-like rods. The plugs produce a nicotine vapour when warm air is passed through them.[48] The product is not a true inhaler, as absorption is primarily by oral mucosa rather than through the bronchi or lungs.[49] Nicotine delivered via this method is 36% absorbed into the oral cavity, 36% in the oesophagus and stomach, and only 4% by the lung.[50] A dose consists of a puff or inhalation. Each cartridge contains 10 mg of nicotine, of which 4 mg of nicotine can be delivered, and 2 mg is absorbed. However, nicotine delivered primarily depends on the number of inhalations, where 80 puffs deliver 4 mg of nicotine. The recommended dosage is six to sixteen cartridges/day.[51] Nicotine inhalers produce venous nicotine levels that rise faster than with nicotine gum but slower than with the nicotine nasal spray, with nicotine blood levels of about one-third those of between-cigarettes levels.[52] The inhaler was designed to satisfy the hand-to-mouth behavioural aspects of smoking and is recommended to be used for 12 weeks, with a maximum of six months. The reported side effects are throat irritation and coughing.[14,43]

NRT in non-Caucasian populations

Most of the studies on NRT have been done and reported among the Caucasian population.[17,53] Given the cultural and ethnic diversity of smokers in the world and in South Africa, there is a need to identify special characteristics of non-Caucasian smokers and what works in these populations. Recent data support the use and efficacy of NRT in non-Caucasian populations.[54] It was found that African-American smokers displayed a preference for mentholated cigarettes and have higher salivary cotinine levels despite smoking fewer cigarettes. Similarly, South African black people smoke fewer cigarettes per day (< 10 cig/day) and many smoked mentholated brands. Smokers who smoked mentholated cigarettes were shown to be less successful at stopping smoking than those who smoked non-mentholated cigarettes. It has been suggested that black people who are light smokers and who smoke mentholated cigarettes may require higher doses of NRT to maintain abstinence.[54–56]

Comparison of NRT and other non-nicotine medication for smoking cessation

A recent report found that NRT had similar efficacy to bupropion (NRT vs bupropion, OR, 1.09, 95% CI, 0.93–1.31, p = 0.28) but however less efficacious than varenicline (varenicline vs NRT, OR 1.56, 95% CI, 1.23–1.96, p = 0.0002) in maintaining short-term smoking abstinence at four weeks.[57]

Conclusion

Cigarette smoking is associated with significant morbidity and mortality. Therefore, aggressive efforts are needed to promote smoking cessation and to treat smokers. Effective treatments combined with behavioural support and the 5 As framework of smoking cessation of Ask, Advise, Assess, Assist and Arrange should be offered to every smoker who is motivated to stop smoking. NRT has been available for more than two decades and has been shown to be safe and effective for stopping smoking.

References

1. World Health Organization: The Surveillance and Monitoring of Tobacco Control in South Africa, 2003 Available from http://repositories.cdlib.org/tc/whotcp/ATLAS2003 (Accessed 03/03/2010)
2. Burki T. Smoking in South Africa. Lancet Oncol 2008;9(12):1127.
3. Benowitz NL. Nicotine addiction. Primary Care: Clinics in Office Practice 1999;26(3):611–31.
4. Schuurmans MM, Diacon AH, Van Biljon X, Bolliger CT. Effect of pre-treatment with nicotine patch on withdrawal symptoms and abstinence rates in smokers subsequently quitting with the nicotine patch: A randomized controlled trial. Addiction 2004;99(5):634–40.
5. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database of Systematic Reviews 2008;(1):CD000146. DOI: 10.1002/14651858.CD000146.pub3.
6. Le Foll B, George TP. Treatment of tobacco dependence: Integrating recent progress into practice. Canadian Medical Association Journal 2007;177(11):1373–80.
7. Silagy C, Stead LF. Physician advice for smoking cessation [Update of Cochrane Database Systematic Reviews 2000;(2):CD000165; PMID: 10796499]. Cochrane Database of Systematic Reviews 2001;(2):CD000165.
8. Zwar N. Smoking cessation: What works? Australian Family Physician 2008;37(1–2):10–4.
9. Moore TJ, Furberg CD. Varenicline and suicide: Risk of psychiatric side effects with varenicline. BMJ 2009;339:b4964. doi: 10.1136/bmj.b4964.
10. Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: Systematic review and meta-analysis. BMJ 2009;338: (b1024) 867-880.
11. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation [Ipdate of Cochrane Database Systematic Reviews 2000;(3):CD000146; PMID: 10908462]. Cochrane Database of Systematic Reviews 2001;(3):CD000146.
12. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation [Update of Cochrane Database Systematic Reviews 2001;(3):CD000146; PMID: 11686953]. Cochrane Database of Systematic Reviews 2002;(4):CD000146.
13. Sims TH, Fiore MC. Pharmacotherapy for treating tobacco dependence: What is the ideal duration of therapy? CNS Drugs 2002;16(10):653–62.
14. Sutherland G. Current approaches to the management of smoking cessation. Drugs 2002;62(Suppl 2):53–61.
15. Bolliger CT, Van Biljon X, Axelsson A. A nicotine mouth spray for smoking cessation: A pilot study of preference, safety and efficacy. Respiration 2007;74(2):196–201.
16. Shiffman S, Sweeney CT, Dresler CM. Nicotine patch and

lozenge are effective for women. Nicotine & Tobacco Research 2005;7(1):119–27.
17. Shiffman S. Nicotine lozenge efficacy in light smokers. Drug & Alcohol Dependence 2005;77(3):311–4.
18. Hajek P, West R, Foulds J, Nilsson F, Burrows S, Meadow A. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. Archives of Internal Medicine 1999;159(17):2033–8.
19. Shiffman S, Fant RV, Buchhalter AR, Gitchell JG, Henningfield JE. Nicotine delivery systems. Expert Opinion on Drug Delivery 2005;2(3):563–77.
20. Lerman C, Patterson F, Berrettini W. Treating tobacco dependence: State of the science and new directions. Journal of Clinical Oncology 2005;23(2):311–23.
21. Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: A randomized, double-blind, placebo-controlled trial. Archives of Internal Medicine 2000 Nov 13;160(20):3128–34.
22. Benowitz NL. Nicotine replacement therapy: What has been accomplished – can we do better? [Erratum appears in Drugs 1993 May;45(5):736]. Drugs 1993;45(2):157–70.
23. Abdullah AS. How far should we promote smoking reduction in order to promote smoking cessation? APJCP 2005;6(2):231–4.
24. Bolliger CT. Practical experiences in smoking reduction and cessation. Addiction 2000;95 Suppl 1:S19–24.
25. Gritz ER, Carr CR, Marcus AC. The tobacco withdrawal syndrome in unaided quitters. Br J Addict 1991;86(1):57–69.
26. Hughes JR. Tobacco withdrawal in self-quitters. J Consult Clin Psychol 1992;60(5):689–97.
27. Piasecki TM, Jorenby DE, Smith SS, Fiore MC, Baker TB. Smoking withdrawal dynamics: III – Correlates of withdrawal heterogeneity. Experimental & Clinical Psychopharmacology 2003;11(4):276–85.
28. Schneider NG, Cortner C, Gould JL, Koury MA, Olmstead RE. Comparison of craving and withdrawal among four combination nicotine treatments. Hum Psychopharmacol 2008;23(6):513–7.
29. Le Houezec J. Role of nicotine pharmacokinetics in nicotine addiction and nicotine replacement therapy: A review. International Journal of Tuberculosis & Lung Disease 2003 Sep;7(9):811–9.
30. Okuyemi KS, Ahluwalia JS, Harris KJ. Pharmacotherapy of smoking cessation. Archives of Family Medicine 2000 Mar;9(3):270–81.
31. Van der Strate BW, Postma DS, Brandsma CA, et al. Cigarette smoke-induced emphysema: A role for the B cell? Am. J. Respir. Crit. Care Med. 2006; 173: 751-758,
32. Smith CJ, Perfetti TA, King JA. Perspectives on pulmonary inflammation and lung cancer risk in cigarette smokers. Inhal Toxicol 2006 Aug;18(9):667-77
33. Henningfield JE, Keenan RM. Nicotine delivery kinetics and abuse liability. Journal of Consulting & Clinical Psychology 1993;61(5):743–50.
34. Hughes J. Dependence on and abuse of nicotine replacement medications: An update. Oxford: Oxford University Press; 1998.
35. Benowitz NL. Pharmacology of nicotine: Addiction and therapeutics. Annual Review of Pharmacology & Toxicology 1996;36:597–613.
36. Lunell E, Lunell M. Steady-state nicotine plasma levels following use of four different types of Swedish snus compared with 2-mg Nicorette chewing gum: A crossover study. Nicotine & Tobacco Research 2005;7(3):397–403.
37. Benowitz NL, Jacob P, 3rd, Savanapridi C. Determinants of nicotine intake while chewing nicotine polacrilex gum. Clinical Pharmacology & Therapeutics 1987 Apr;41(4):467–73.
38. Nemeth-Coslett R, Benowitz NL, Robinson N, Henningfield JE. Nicotine gum: Chew rate, subjective effects and plasma nicotine. Pharmacology, Biochemistry & Behavior 1988;29(4):747–51.
39. West RJ, Russell MA. Effects of withdrawal from long-term nicotine gum use. Psychological Medicine 1985;15(4):891–3.
40. Cohen LM, Britt DM, Collins FL, Al'Absi M, McChargue DE. Multimodal assessment of the effect of chewing gum on nicotine withdrawal. Addictive Behaviors 2001 Mar–Apr;26(2):289–95.
41. Cohen LM, Collins FL, Jr, Britt DM. The effect of chewing gum on tobacco withdrawal. Addictive Behaviors 1997 Nov–Dec;22(6):769–73.
42. Stead LF, Lancaster T, Silagy CA. Updating a systematic review: What difference did it make? Case study of nicotine replacement therapy. BMC Medical Research Methodology 2001;1(1):1-10.
43. Peters MJ, Morgan LC. The pharmacotherapy of smoking cessation. Medical Journal of Australia 2002;176(10):486–90.
44. Shiffman S, Elash CA, Paton SM, et al. Comparative efficacy of 24-hour and 16-hour transdermal nicotine patches for relief of morning craving. Addiction 2000;95(8):1185–95.
45. Schneider NG, Lunell E, Olmstead RE, Fagerstrom KO. Clinical pharmacokinetics of nasal nicotine delivery: A review and comparison to other nicotine systems. Clinical Pharmacokinetics 1996;31(1):65–80.
46. Hurt RD, Dale LC, Croghan GA, Croghan IT, Gomez-Dahl LC, Offord KP. Nicotine nasal spray for smoking cessation: Pattern of use, side effects, relief of withdrawal symptoms, and cotinine levels. Mayo Clinic Proceedings 1998;73(2):118–25.
47. Schneider NG, Olmstead RE, Nides M, et al. Comparative testing of 5 nicotine systems: Initial use and preferences. Am J Health Behav 2004;28(1):72–86.
48. Hjalmarson A, Nilsson F, Sjostrom L, Wiklund O. The nicotine inhaler in smoking cessation. Archives of Internal Medicine 1997;157(15):1721–8.
49. Lunell E, Molander L, Ekberg K, Wahren J. Site of nicotine absorption from a vapour inhaler: Comparison with cigarette smoking. European Journal of Clinical Pharmacology 2000;55(10):737–41.
50. Molander L, Lunell E, Andersson SB, Kuylenstierna F. Dose released and absolute bioavailability of nicotine from a nicotine vapor inhaler. Clinical Pharmacology & Therapeutics 1996;59(4):394–400.
51. Lunell E, Molander L, Andersson SB. Temperature dependency of the release and bioavailability of nicotine from a nicotine vapour inhaler: In vitro/in vivo correlation. European Journal of Clinical Pharmacology 1997;52(6):495–500.
52. Lunell E, Bergstrom M, Antoni G, Langstrom B, Nordberg A. Nicotine deposition and body distribution from a nicotine inhaler and a cigarette studied with positron emission tomography. Clinical Pharmacology & Therapeutics 1996;59(5):593–4.
53. Shiffman S, Di Marino ME, Pillitteri JL. The effectiveness of nicotine patch and nicotine lozenge in very heavy smokers. Journal of Substance Abuse Treatment 2005;28(1):49–55.
54. Robles GI, Singh-Franco D, Ghin HL. A review of the efficacy of smoking-cessation pharmacotherapies in nonwhite populations. Clin Ther 2008;30(5):800–12.
55. Ahluwalia JS, Okuyemi K, Nollen N, et al. The effects of nicotine gum and counseling among African American light smokers: A 2 x 2 factorial design. Addiction 2006;101(6):883–91.
56. Nollen NL, Mayo MS, Sanderson Cox L, et al. Predictors of quitting among African American light smokers enrolled in a randomized, placebo-controlled trial. J Gen Intern Med 2006;21(6):590–5.
57. Mills EJ, Wu P, Spurden D, Ebbert JO, Wilson K. Efficacy of pharmacotherapies for short-term smoking abstinance: A systematic review and meta-analysis. Harm Reduct J 2009;6:25-30.