International Journal of Innovative Research and Advanced Studies (IJIRAS)
Volume 5 Issue 1, January 2018

ISSN: 2394-4404

Nicotine Replacement Therapy – A Review

Dr. Ankita Gupta

Department of Public Health Dentistry, The Oxford Dental College, Hospital and Research Centre, Bengaluru, India

Dr. Pulkit Vaid

Department of Pediatrics and Preventive Dentistry, Himachal Dental College, Sundernagar, India

Dr. A. G. Shabana

Department of Public Health Dentistry, Sri Venkateshwaraa Dental College Ariyur Puducherry, India

Dr. Astha Joshi

Department of Public Health Dentistry, The Oxford Dental College, Hospital and Research Centre, Bengaluru, India

Abstract: ***More than one billion people worldwide currently smoke tobacco – about one quarter of adults – and tobacco use currently kills more than five million people worldwide each year. Nicotine addiction has been identified as the primary contributor to continued widespread tobacco use worldwide. Although the health benefits of smoking cessation are well publicized, few smokers successfully quit on a long-term basis. A number of pharmacological agents have been shown to approximately double long-term smoking cessation rates and have, therefore, been recommended as first-line therapy for the treatment of nicotine dependence in the clinical practice guidelines. Nicotine replacement therapy continues to be a first line smoking cessation therapy and it has an expanding role in assisting previously considered special patient populations to quit smoking. Nicotine replacement therapy (NRT) is a class of nicotine delivering medicines which help people to stop smoking by acting at brain nicotine receptors, thus reducing withdrawal symptoms. This review summarizes the different types of Nicotine Replacement Therapy, its formulation, uses, dosage, method of use, advantages, side-effects, precautions, indications and contraindications.***

Keywords: Nicotine, Nicotine Replacement Therapy, smoking cessation

I. INTRODUCTION

Tobacco is the single greatest preventable cause of death in the world today, killing up to half the people who use it. According to the ICMR report, India is the 4th largest producer of tobacco. Tobacco kills 90 persons per hour, 2200 per month and 800000 per year.

Tobacco use is a risk factor for six of the eight leading causes of death in the world. Smoking tobacco causes cancer of the lung, larynx, kidney, bladder, stomach, colon, oral cavity and oesophagus as well as leukaemia, chronic bronchitis, chronic obstructive pulmonary disease, ischemic heart disease, stroke, miscarriage and premature birth, birth defects and infertility, among other diseases.

The economic impact of tobacco consumption is not too good either. 9000 crore cigarettes smoked are being consumed in a year costing Rs. 18,000 crore; Rs. 24,400 crore is the sale value of all tobacco products. And what is the result of these whopping statistics? India gets 400,000 cancer cases annually and 1300,000 cases of heart diseases. India is world leaders in oral cancer and spends Rs. 27,761 crores on treating tobacco related diseases.

The International Classification of Diseases (ICD-10) has recognised that "tobacco dependence" is a disease.[4] It is encouraging to note that the WHO and the Government of India (GOI) have taken the initiative for effective tobacco control. In India the Ministry of Health and Family Welfare, Government of India has taken a positive stand and has opened 13 tobacco cessation clinic all over India.

Despite increasing awareness to the harmful effects of tobacco, smoking continues to be significant health risk factors. Studies show that 75-80% of the smokers want to quit smoking, one third make a serious attempt to quit but only 1-2% is abstinent at the end of first year. Tobacco

contains nicotine, which is addictive, makes the process of quitting often very prolonged and difficult. Pharmacotherapies for smoking cessation are an essential element of multicomponent approach to smoking cessation.

Nicotine replacement therapy (NRT) is a class of nicotine delivering medicines which acts at brain nicotine receptors, thus reducing withdrawal symptoms. It is a 'clean' form for delivering nicotine, which is not accompanied by the main carcinogens and other toxic substances found in tobacco products and produced by their combustion. The effectiveness of NRT in aiding cessation is well established and is supported by the highest level of clinical evidence. Thus an attempt is made to review the different types of Nicotine Replacement Therapy, its formulation, uses, dosage, method of use, advantages, side-effects, precautions, indications and contraindications.

II. TOBACCO DEPENDENCE

Cigarette smoking is associated with both pharmacological and behavioural dependence. Nicotine is the primary substance found in tobacco that causes dependence on cigarette smoking. Inhaled nicotine takes about 10-19 seconds to reach the brain and its stimulation releases chemicals which ensure feeling of goodness, alertness and energy.

As the person stops tobacco use, nicotine deprivation occurs, cravings occur causing the smoker to want another cigarette to maintain the pleasurable effects and to prevent withdrawal symptoms such as: dizziness, depression, feelings of frustration, impatience, anger, anxiety, irritability, and trouble sleeping and concentrating. The addictive nature of nicotine follows a classical cycle that has been likened to that of heroin or cocaine. (Figure 1)

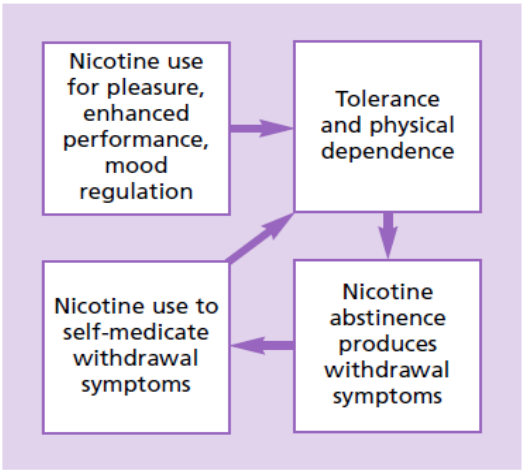

Figure 1: Classical model of addiction as applied to nicotine

III. STRATEGIES FOR TOBACCO CESSATION

The difficulties experienced by smokers who are trying to give up smoking are well documented. Over the last 30 years, many methods have been employed in attempts to help smokers succeed, with varying degrees of success. Interventions can be divided into behavioural or pharmacological treatment.

BEHAVIOUR INTERVENTIONS

These include: Brief advice, behavioural support, behavioural strategies.

IV. PHARMACOLOGICAL TREATMENT

Pharmacological interventions are most effective when combined with behavioural interventions. Current and future pharmacological treatments aim to reduce tobacco use by targeting the mechanisms that reinforce tobacco use.

Pharmacological therapies include anxiolytics, antidepressants, nicotine antagonists etc. However, results to date with other non-nicotine medications have either failed to prove any lasting efficacy, or their use is limited by adverse events or their clinical utility in smoking cessation remains unclear. In contrast, nicotine replacement therapy has consistently demonstrated efficacy in the treatment of tobacco dependence.

V. NICOTINE REPLACEMENT THERAPY

DEFINITION

Nicotine Replacement Therapy, often identified as NRT, is a method of substituting the nicotine in tobacco products by an approved nicotine delivery product so that the tobacco user does not have uncomfortable withdrawal symptoms upon stopping the tobacco product.

The Food and Drug Administration (FDA) has approved these NRT products as effective aids for helping people to quit smoking:

- ✓ Nicotine gum
- ✓ Nicotine patch
- ✓ Nicotine lozenges
- ✓ Nicotine inhaler
- ✓ Nicotine nasal spray

Once you've bought the nicotine replacement product, set a quit date. Start using it as the first thing in the morning of your quit date or soon after your last cigarette – don't wait for cravings to hit first.

VI. NICOTINE GUM

The first NRT that was made available to consumers was trans-mucosally-delivered nicotine polacrilex ("nicotine gum"). A chewing gum delivery system has nicotine, gum base and a buffer system with an improved release rate for the nicotine. Pharmacologically, the regular smoker is dependent upon nicotine, the chemical reinforce of smoking. Nicotine Gum releases nicotine into your saliva. The nicotine is absorbed through the lining of your mouth and enters your bloodstream. This nicotine is sufficient to relieve unpleasant withdrawal symptoms and to decrease the cravings for

smoking. Nicotine Gum helps you give up smoking by relieving nicotine cravings. It will not give you the "buzz" or "hit" you get from a cigarette.[8] The user adjusts to the loss of common smoking sensory reinforcers and learns to eliminate ritual reinforcers. After adjusting to non-smoking lifestyle changes, a gradual reduction in nicotine intake is indicated.[10]

DOSAGE

- ✓ 2mg for those who smoke <25 cigarettes per day.
- ✓ 4mg for those who smoke >25 cigarettes per day.

If you smoke less than 25 cigarettes a day; use according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 piece every 1 to 2 hours	1 piece every 2 to 4 hours	1 piece every 4 to 8 hours

Table 1

DIRECTIONS FOR USE OF NICOTINE GUM

Place a piece of nicotine gum in the mouth. Don't chew nicotine gum like ordinary chewing gum. Chew the gum slowly, until you feel a tingling sensation or a 'peppery' taste (usually after about 10 chews). Then rest it for one minute under your tongue, or between your cheek and gum. Continue this 'chew - rest' sequence for 30 minutes, then throw away the gum. If a user chews without holding it in their gums, the nicotine will be released directly into the saliva, which may cause a stomach ache or throat irritation. Do not swallow nicotine gum.

Avoid eating and drinking 15 minutes before, and during, use of the gum (except for water). *Acidic foods or drinks, such as orange juice, coffee, beer and soft drink, interfere with the amount of nicotine passing through the lining of your mouth from the gum*. Do not use more than 24 doses of gum per day. Do not smoke during use.

Advantages are available over the counter in several flavors and satisfies cravings quickly. Keeps the mouth occupied. *Disadvantages:* More difficult to chew than normal chewing gum.

Side effects: Hiccups, sore mouth or jaw, headache, indigestion and nausea.

VII. NICOTINE PATCH

The nicotine patch is a transdermal delivery system which is used as an aid to overcome nicotine dependence during attempts to stop smoking. It is supplied as a course of treatment with the intent of "weaning" the user off nicotine dependence by gradually reducing the amount/dose of nicotine delivered through the skin.

The patch works by replacing some of the nicotine smokers would normally inhale from cigarettes, by offering three patches with different nicotine dose levels. These patches uses a *step-down dosing system* that allows smokers to gradually reduce their nicotine level by changing the patch they wear (moving to a lower dose) over an eight-week period.

Types of patches available on Pharmaceutical Benefits Scheme are:

- ✓ Nicorette - 16 hour patch containing 15mg of nicotine
- ✓ Nicabate P - 24 hour patch containing 21 mg of nicotine
- ✓ Nicotinell - 24 hour patch containing 21 mg of nicotine

DIRECTIONS FOR USE

Stop smoking completely when begin to use the patch. If a person smokes 10 or less cigarettes per day, start with Step 2 for 6 weeks, then Step 3 for 2 weeks and then stop. Apply one new patch every 24 hours on skin that is dry, clean and hairless. The used patch should be removed and a new one applied to a different skin site at the same time each day.

Advantage: Place and forget; no Prescription needed in most countries; can decrease morning cravings if worn at night. Disadvantage: Passive—no action to take when craving occurs

Side effects: Rash on the skin where the patch is worn, sleep disturbances or vivid dreams, particularly with the high dose 24 hour patch. Headache, nausea and indigestion.

VIII. NICOTINE LOZENGES

The lozenge provides an alternative to the gum for persons who need intermittent and controllable nicotine dosing, but who do not find gum chewing acceptable. It is a tablet that slowly releases nicotine, which absorb through the lining of mouth. The lozenge works best for addicted smokers, who smoke 10 or more cigarettes per day and who want to quit.

Before buying the lozenge, quitter should tell to their pharmacist or doctor if they have an illness or if they are taking any other medicines. The manufacturer's list of illnesses (May 2007) for which the need of medical advice includes: *heart disease, high blood pressure, any blood circulation disorder, stroke, kidney disease, liver disease, stomach ulcer or pain, hyperthyroidism, diabetes, and pheochromocytoma.* They should not take the lozenge if they react to *aspartame or phenylalanine*.

DOSAGE

- ✓ 2mg if first tobacco is used after 30 min. after walking
- ✓ 4mg if first tobacco used within 30 min of walking. For first 6 weeks use at least 9 lozenges per day.

INSTRUCTIONS FOR USING LOZENGES

Use one lozenge at a time. Place a lozenge in the mouth and let it dissolve. Move the lozenge in mouth from time to time. Do not chew or swallow.

Avoid eating or drinking while using a lozenge (except for water).

Advantage: Ease of use, Oral substitute, Antidepressant effect, Good for irregular smoker, No Prescription needed in most countries. *Disadvantage:* Poor compliance, Consuming too fast can cause side effects, No food or drink before or

while using. *Side effects:* Hiccups, headache, indigestion, nausea, diarrhoea, sore throat and mouth irritation.

IX. NICOTINE INHALER

Nicotine inhaler works by replacing some of the nicotine that would normally inhale from cigarettes. It consists of a mouthpiece which attaches to a cartridge containing nicotine. Unlike nicotine patches and gum, the nicotine inhaler is designed to mimic the *hand-to-mouth ritual of smoking*. The inhaler works best for addicted smokers, who smoke 10 or more cigarettes per day and who want to quit.

DOSAGE: 6-16 cartridges/ day, gradual reduction is done after 12 weeks.

DOSE: 10 mg per cartridge; Duration: 6-12 cartridges a day for 8 weeks then halve use over 2 weeks and stop in the next 2 week

USING THE INHALER

Draw a breath through the mouthpiece. Either take shallow sucking breaths every two seconds or a deep strong breath every 15 seconds (four per minute). Nicotine is absorbed more slowly through your mouth than the lung and will not reach your brain as quickly as if would if you were smoking. Each "puff" on the inhalator gives you much less nicotine than a puff from a cigarette. To substitute for one cigarette, you need to take about 80 deep puffs on the inhalator – this takes about 20 minutes. No more than six cartridges should be use within 24 hours.

Avoid eating and drinking 15 minutes before, and during, use of the inhalator (except for water). Air temperature affects the amount of nicotine you get from the inhalator. In warmer weather the inhalator delivers larger amounts of nicotine and smaller amounts in cooler weather. In very cold temperatures, you may not get enough nicotine. The inhalator works best in temperatures over 15°C.

If the smokers had any of the following medical conditions, like Asthma, Chronic throat diseases, Angina or any other problem with their heart or blood vessels such as pain in one or more legs on walk, High blood pressure, Previous stroke, Kidney disease, Liver disease, Stomach ulcer or pain, Hyperthyroidism, Phaeochromocytoma, Diabetes, they should take doctor or pharmacist's advice before using it.

Advantage: Can use as needed; Mimics hand – mouth behavior. *Disadvantages:* Costly, visible; requires very frequent puffing to achieve therapeutic levels; poor compliance; prescription in some countries. *Side effects:* Burning sensation in the mouth and throat, coughing, sneezing, running nose, headache, nausea, heartburn and hiccups.

X. NICOTINE NASAL SPRAY

Nicotine nasal spray was designed to deliver doses of nicotine to the smoker more rapidly than was possible with use of the gum or patch. One of the main objectives of developing a nasal nicotine spray was to produce a smoking cessation aid that more closely mimicked the rapid delivery of nicotine produced by smoking cigarettes. Approximately 56% of one dose of nicotine nasal spray enters the systemic circulation with peak plasma concentrations achieved after only 10 minutes.

Nicotine nasal spray dispenses nicotine through a spray device similar to over-the-counter decongestant sprays. Nicotine is delivered through the nostrils, and is rapidly absorbed through the nasal membranes. With nasal spray, nicotine reaches the blood stream faster than any other nicotine replacement product; however, it is still slower than cigarettes. This product can be very useful to people who smoke heavily because of the fast nicotine delivery. The recommended period for use for is up to eight weeks, after which a tapered dose is recommended for four to six weeks.

NICOTROL NS 10ML BOTTLES (10MG/ML)

DIRECTIONS FOR USE

Tilt smoker's head back slightly. Hold the breath and spray once in each side of the nose. Put the tip in to the nose and point the tip to the outer side of nostril and spray once in each nostril. Breathe out through mouth and don't sniff or breathe in while spraying. Wait 2-3 minutes before blowing nose. Do not smoke during use and don't stop using the nasal spray before the recommended time.

Advantages: User-controlled dose and easy to use. This medication gets rid of symptoms faster than any other medication. *Disadvantage:* Costly, and there is no generic form currently on the market. Requires a prescription. *Side effects:* Fast or pounding heartbeats, fluttering in your chest, extreme weakness or dizziness, severe nausea and vomiting, bronchospasm, burning, or other irritation in your nose, mouth, or throat, or blistering, ulcerations, or bleeding in your nose.

XI. NICOTINE MOUTH SPRAY

The nicotine vapour inhaler, which consists of a mouthpiece and a plastic cartridge containing nicotine, was first marketed in the United States in 1998 as a prescription smoking-cessation medication. 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 randomized controlled trial in healthy smokers who wanted to stop smoking and its efficacy was found to be comparable to nicotine gum and nicotine inhaler. Smokers were also reported to prefer nicotine mouth spray over other formulations.

The mouth spray works by replacing some of the nicotine you would normally inhale from cigarettes. The pump sprays a fine mist onto the inside of your cheek or under your tongue. The nicotine is absorbed through the lining of mouth. Nicotine withdrawal should get better within 1 minute (60 seconds). Each bottle of NRT mouth spray provides about 150 sprays. One spray will give about 1mg of nicotine.

USING THE MOUTH SPRAY

Use the spray when you would normally have a cigarette or have a craving to smoke. Do not spray directly into your throat. Do not breathe in while spraying to avoid getting it on your throat – this can cause hiccups or a burning feeling in the throat. Try not to swallow for a few seconds after spraying, as doing so will reduce how much nicotine you absorb.

Avoid eating and drinking 15 minutes before, and during, use of the mouth spray (except for water). Do not use more than 64 sprays within a 24 hour period. After six weeks, start cutting down the number of sprays you use. See your doctor if you need to use it for longer than six months. *Side effects:* Throat and mouth irritation, a change in the way things taste. Headache, nausea, vomiting, Indigestion, increased salivation, burning lips, dry mouth, Hiccups, Tingling sensation in the mouth, inflammation of the lining of the mouth.

XII. NICOTINE SUBLINGUAL TABLETS

A small nicotine tablet has been developed, and is currently being marketed in many European countries. Sublingual tablets may be useful in situations where chewing gum is inappropriate.

The tablet works by replacing some of the nicotine you would normally inhale from cigarettes. Nicotine is released slowly and absorbed through the lining of the mouth as the tablet dissolves. Using the tablet can help to reduce some withdrawal symptoms when you quit, such as cravings, irritability, and anxiety.[15] One can buy nicotine sublingual tablets without prescription from pharmacies and some supermarkets.

Place the tablet under tongue, and allow it to dissolve. This usually takes about 30 minutes. To start with, take one tablet every one to two hours during the day. Most people use between eight and 12 tablets per day. However, if a person usually smoke within 30 minutes of waking and smoke more than 20 cigarettes per day, he/she should take more tablets for them to be effective. No one should use more than 40 tablets per day. It should not be swallowed or chewed, as it works best when it is dissolved in the mouth. The acidity of drinks and food will not affect how the tablet works, so it should be taken after eating or drinking. *Side effects*: sore mouth or throat, and a dry or burning sensation in the mouth, when beginning to use the tablet. Other: hiccups, headache, coughing, mild indigestion and nausea.

XIII. COMBINATION MEDICATION

Certain combinations of first-line medications have been shown to be effective smoking cessation treatments**.** The possibility has been raised that combining the medications may increase treatment efficacy. Effective combination medications are

- ✓ Long-term (> 14 weeks) nicotine patch + other NRT (gum and spray)
- ✓ The nicotine patch + the nicotine inhaler
- ✓ The nicotine patch + bupropion SR

NICOTINE PATCH AND DIFFERENT COMBINATIONS

Combination therapy has been approved for the use of the 15 mg 16 hour patch or the 21 mg 24 hour patch with the mouth spray, 2 mg nicotine gum, 2mg nicotine lozenge, or the 1.5 mg mini lozenge.

CONTRAINDICATIONS (TABLE 1)

NRT	Contraindications
Patch	✓ Non tobacco users ✓ Generalised chronic dermatological disorders, such as psoriasis, chronic dermatitis, or urticaria ✓ Patients with known hypersensitivity to nicotine or any components of the patch ✓ Recent myocardial infarction ✓ Unstable or progressive angina pectoris ✓ Severe cardiac arrhythmias ✓ Acute phase stroke ✓ Patients who weigh less than 45 kilograms ✓ Lactation – with caution – gum and inhaler preferred. ✓ hildren under 12 years
Inhaler	✓ Non-tobacco users ✓ Patients with known hypersensitivity to nicotine or menthol ✓ hildren under 12 years
Gum	✓ Non-tobacco users ✓ Hypersensitivity to nicotine ✓ Recent myocardial infarction ✓ Unstable or progressive angina pectoris ✓ Severe cardiac arrhythmias ✓ Acute phase stroke ✓ Children under 12 years

Table 1: Contraindications For Nicotine Replacement Therapy

ABSOLUTE CONTRAINDICATIONS

- ✓ *ALL FREE FLAP PATIENTS:* NRT and tobacco products must not be used by these patients for at least 2 weeks before and 2 weeks after free flap surgery. For planned procedures involving face and breast, tobacco and NRT use should be avoided 4 weeks before and 4 weeks after surgery.

RELATIVE CONTRAINDICATIONS

- ✓ Patients who may continue to use tobacco if not prescribed NRT but are in the immediate (within 2 weeks) post myocardial infarction period or have serious arrhythmias or have unstable angina pectoris or are hemodynamically or electrically unstable or have had orthopedic surgery or a serious fracture.

Abstinence without NRT is preferred, but NRT may be safer than continued use of tobacco in the above circumstances - individual clinical judgment required.

CAUTIONS

✓ WOMEN WHO ARE PREGNANT OR BREAST FEEDING

Abstinence or cessation without NRT is preferred since NRT in pregnant and lactating women has not been well studied. However, NRT is safer than continued use of tobacco in the above circumstances- individual clinical judgment required.

✓ ADOLESCENTS

Although nicotine replacement has been shown to be safe in adolescents, there is little evidence that NRT is effective in promoting long-term abstinence among adolescent smokers.

Abstinence or cessation without NRT is preferred. For some physically mature youth who are continuing to use tobacco despite attempts to support them to be abstinent or quit without NRT, NRT can be considered.

XIV. CONCLUSION

The rationale for nicotine-assisted reduction to quit is that using NRT boosts nicotine levels, making it easier for the smoker to smoke fewer cigarettes, and making compensation less likely, which in turn should mean that the smoker will inhale fewer toxins. The safety profile of nicotine replacement therapy is well established and the available evidence can be concluded as: *using nicotine replacement therapy to quit is always safer than continuing to smoke.*

REFERENCES

[1] Kaleta D, Polańska K, Wojtysiak P, Kozieł A, Kwaśniewska M, Miśkiewicz P, Drygas W. Effective protection from exposure to environmental tobacco smoke in Poland: The World Health Organization perspective. Int J Occup Med Environ Health. 2010;23(2):123-31.
[2] Kumar R, Prakash S, Kushwah A.S, Kumar H. Smoking cessation-control measures. Lung India 2005; 22: 68-73.
[3] Vijayan V.K. and Kumar R. Tobacco Cessation in India. Indian J Chest Dis Allied Sci 2005; 47: 5-8.
[4] National Tobacco control Programme. Tobacco Dependence Treatment Guidelines. 2011: 1-22.
[5] Zwar N, Bell J, Peters M, Christie M, Mendelsohn C. Nicotine and nicotine replacement therapy – the facts. Australian Pharmacist 2006;25:969-73.
[6] Kotlyar M, Hatsukami D.K. Managing Nicotine Addiction. Journal of Dental Education Sep 2002; 66(9):1061-73.
[7] UK: Adis International Limited and Pharmacia & Upjohn. Nicorette(R) nicotine inhaler monograph. Chester: 1996.
[8] Johnson & Johnson Pacific. Nicorette(R) chewing gum 2mg & 4mg [product information]. Ultimo, NSW: 2007.
[9] Medicated chewing gum delivery system for nicotine. http://www.google.co.in/patents/CA2346330A1?cl=en. [accessed on 23/05/15 at 18:52]
[10] Nicorette gum. http://sites.hamline.edu/~rkagan/Pictures_and_others/PDF/NicoretteMonoGUM.pdf [accessed on 18/04/2015 at 18:00]
[11] Nicotine patches. Fact sheet. www.quit.org.au. [accessed on 22/12/2015 at 16/05/2015]
[12] NPS RADAr. Nicotine patches (Nicabate P, Nicorette, Nicotinell Step 1). April 2011 https://www.nps.org.au/__data/assets/pdf_file/0017/122732/NPS_RADAR_April_2011_Nicotine_patches_-_Published.pdf [accessed on 22/12/2014 at 16:05]
[13] Nicotine Skin Patches. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/meds/.[accessed on 22/12/2014 at 16:00]
[14] Nicobate lozenges: 2 mg and 4 mg nicotine. Consumer medicine information [package insert]. Ermington, NSW: GlaxoSmithKl ine Australia Pty Ltd: 2008.
[15] Quiting services and products http://www.medi7.com.au/media/Quitting%20Help.pdf [accessed on 17/05/2015 at 11:00].
[16] Shiffman S, Dresler CM, Hajek P, Gilburt SJ, Targett DA, Strahs KR. Efficacy of a nicotine lozenge for smoking cessation. Arch Intern Med. 2002; 162: 1267-76.
[17] Fact sheet, Quit Victoria. http://www.quittas.org.au/sites/quittas/files/media/FS_Nicotine_inhalator_Jun_2013_EN_final.pdf [accessed on 11/04/2015].
[18] Nicotine replacement therapy. Guidance for health professionals on changes in the licensing arrangements for nicotine replacement therapy ash, London, December 2005 guidance first issued.
[19] The nicotine inhaler smoking cessation Aid. Alberta health services. Available from: https://www.albertahealthservices.ca/facilities/images/Mazankowksi/maz-meds-nicotine-inhaler.pdf [accessed on 11/04/2015].
[20] Nicotrol NS http://www.rxlist.com/nicotrol-ns-drug.htm [accessed on 12/04/2015 at 11:13]
[21] U.S. Department of Health and Human Services. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guidlines. Public health services; May 2008.
[22] Nicotine mouth spray. Quit Victoria. http://www.quit.org.au/downloads/resource/facts-evidence/nicotine-mouth-spray-fact-sheet.pdf. [accessed on 13/05/2015 at 20:10].
[23] Karin A. Kasza1, Andrew J. Hyland, Ron Borland, Ann D. McNeill, Maansi Bansal-Travers, Brian V. Fix, David Hammond, Geoffrey T. Fong, and K. Michael Cummings. Effectiveness of Stop-Smoking Medications: Findings from the International Tobacco Control (ITC) Four Country Survey. Addiction. 2013 January; 108(1): 193–202.
[24] Johnson & Johnson Pacific. Nicorette QuickMist-Nicotine Replacement Therapy. Ultimo, NSW:2007. http://colinmendelsohn.com.au/files/2713/5394/6524/Nic

orette_QuickMist_CMI_8_2012.pdf. [Accessed on 13/05/2015 at 20:05].
[25] Fact Sheet. http://www.ideas.org.au/uploads/resources/309/Quit%20Smoking%20pdf.pdf. [accessed on 17/o5/2015 at 11:00]
[26] Johnson and Johnson pacific. Microtab. http://www.substance.org.au/imagesDB/wysiwyg/MicrotabPackInsert.pdf. [accessed on 17/05/2015 at 11:00]
[27] Proposal for Inclusion of Nicotine Replacement Therapy in the WHO Model List of Essential Medicines. 17th Expert Committee on the Selection and Use of Essential Medicines.Geneva, March 2009
[28] Northern Territory Government. Department of Health and Families. https://www.google.co.in/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwjy4rCsqdjJAhXERI4KHWgADVAQFggcMAA&url=http%3A%2F%2Fwww.health.nt.gov.au%2Flibrary%2Fscripts%2FobjectifyMedia.aspx%3Ffile%3Doffice%2F38%2F64.doc&usg=AFQjCNG64raVrtsfmO6jjyLqGqh-c9oPiw&sig2=wW5Fn42E4mATcS9eJQ9Wxw. [accessed on 1/10/15 at 19:53]
[29] Nicotine Replacement Therapy Guidance Document. www.ipp.gov.bc.ca [accessed on 29/10/2015 at 21:30].