

Pharmacotherapeutic Approaches in Tobacco Cessation and its Challenges: A Review

Akshyata Panda¹, Anurag Satpathy², Rinkee Mohanty³,
Rashmita Nayak², Abhaya Chandra Das⁴, Saurav Panda⁴, Gatha Mohanty⁵

¹Post Graduate Student, ²Professor, ³Professor and Head, ⁴Reader, ⁵Senior Lecturer, Department of Periodontics and Oral Implantology, Institute of Dental Sciences, Siksha 'O' Anusandhan (Deemed to be University), Khandagiri Square, Bhubaneswar-751003 Odisha, India

Abstract

Tobacco use is a global menace and leading cause of cancers and death. Tobacco cessation strategies are being formulated world over to curb this problem. Nicotine replacement therapy (NRT) such as chewing gum, patches and inhaler and drugs like Bupropion have shown some success in smoking cessation rates in the short and long terms.

Keywords: Tobacco cessation, Pharmacotherapy, NRT, Nicotine, Nicotine Patch, Bupropion.

Introduction

Nicotine is responsible for pathophysiological changes in smokers and also tolerance⁽¹⁾. Despite the awareness and the determined protective efforts at both national and state level, tobacco still threatens the health and well being. Oral cavity and general health are affected due to smoking and chewing tobacco. Currently, tobacco intake is one of the major etiology of oral cancer, a severe and increasing worldwide problem^(2,3).

Consumption of tobacco cause periodontal destruction with reduction in inflammation and gingival bleeding which ultimately results in delayed wound healing. It also leads to halitosis and other oral conditions⁽⁴⁻⁶⁾. Smoking causes oral cancer. Cardiovascular disease, chronic obstructive lung disease emphysema and chronic bronchitis are main cause of

smoking. Smokeless tobacco is known to cause oral cancer.

Oral cavity being the entry point for tobacco smoker, it is the first to get exposed. Therefore, it is associated with tooth stains, abrasions and condition like smoker's melanosis, nicotinic stomatitis, keratotic patches, black hairy tongue and oral carcinoma. Oral keratosis and gingival recession are due to consumption of smokeless tobacco. The prognosis for periodontal treatment is affected adversely on consumption of tobacco^(2,7). Cigarette smoking has a dramatic effect on inhalation since more than 90 percent of the nicotine present in inhaled smoke is absorbed. Absorption instantly results in an increase in arterial nicotine level⁽⁸⁾.

Pharmacotherapy in Tobacco Cessation: The objective of a pharmacological approach for tobacco cessation should ideally to blockage of positive reinforcing effect of nicotine and prevention of withdrawal symptoms. Pharmacotherapeutic treatment is mainly classified into: Nicotine replacement therapy (NRT) and non-Nicotine Replacement Therapy (n-NRT)⁽⁹⁾. NRT is not suitable in patients with history of cardiovascular conditions such as myocardial infarction, cardiac arrhythmias and angina pectoris. It is also contra indicated in pregnancy and for lactating mother. Action of NRT is by replacing nicotine component from cigarettes

Corresponding Author:

Prof. Anurag Satpathy

Department of Periodontics and Oral Implantology,
Institute of Dental Sciences, Siksha 'O' Anusandhan
(Deemed to be University), Khandagiri Square,
Bhubaneswar – 751003 Odisha, India
e- mail: drasatpathy@gmail.com

which helps in preventing withdrawal symptoms caused by nicotine component. Non-NRT also helps in reducing withdrawal symptoms as well.

Nicotine qualifies to be a highly addictive drug⁽¹⁰⁾. Regular smokers develop a dependence on tobacco smoking and not simply an addiction to nicotine⁽¹¹⁾. Dependence develops due to the temporal association of the habit and sensory inputs with the recurring stimulation and relief of withdrawal symptoms. This is the reason for minimal addictive potential of nicotine replacement therapy (NRT) products, that deliver nicotine slowly and do not produce high plasma nicotine

Types of NRTs are: Nicotine gum, Nicotine patch, Nicotine nasal spray and Nicotine inhaler

NRTs:

Nicotine gum⁽¹²⁾: This is an alternative agent which helps in cessation of smoking. It acts by principle of neuroadaptation followed by abstinence as a daily cycle. Nicotine levels fall during overnight sleep or when gum not chewed. It works best with other NRTs or bupropion hydrochloride⁽¹³⁾. Nicotine gum chewing facilitates absorption of nicotine through oral mucosa when gum placed between cheek and gum. Chewing of gum cause needle like sensation then park between cheek and gum. This chewing and parking process repeat alternately for about 30 min.

For smoker who smokes within 25 cigarettes per day, a dose of 2mg is advised and 4 mg dosage is advised for smokers smoking more than 25 cigarettes per day⁽¹³⁾. Patients should be instructed to chew the gum in a fixed schedule 1 piece every 1 to 2 hours. Hence around 10 to 15 pieces per day may used initially⁽¹⁴⁾. They have to avoid eating or drinking anything before to and during chewing gum. An acidic beverage hinders nicotine mucosal absorption. This treatment should be continued for 6 weeks followed by 6 weeks tapering⁽¹⁵⁾.

Advantages of chewing gum is that it acts by changing the behavior of urge to which control nicotine mood changes⁽¹⁴⁾. Common side effect includes nausea, sore throat, mouth and jaw, dysgeusia, dyspepsia, gastrointestinal discomfort etc⁽¹⁴⁻¹⁶⁾.

Nicotine Patch⁽¹⁷⁾: Nicotine patches are preferred over chewing gum because drug delivery is for long duration with high concentration than chewing gum. Patches are available in different formulation as per

strength and concentration⁽²⁾. Patches may be used 16 hours to 24 hours in a day. One day patch has advantage of controlling the morning smoking urge by increasing blood nicotine level upon awakening. 24 hour patches may cause sleep disturbances unlikely by 16 hours patch.

The patch may be put on in the morning on a hairless area between neck and waist. The initial dose is tapered after 4 to 6 weeks up to 14 mg/24 hours then to lowest dose 7 mg/24 hours in the following 2 to 4 weeks. There may be differential recommendation of dosage for the patch depending upon amount smoked, amount of nicotine dependence^(14,15,18).

A nicotine patch is easy to use with minimal side effect and more efficacy than chewing⁽¹⁴⁾. However, some side effect may be due to constant nicotine level in the body. Side effects are mainly due to localized irritation of skin causing redness, itching and burning like sensation, which may lead to discontinuation of therapy in 5% cases⁽¹⁵⁾. Most of the above side effects are self-limiting, such as redness of skin by 1 to 2 days of therapy, rashes by applying steroid creams topically. Other minor side effects are generalized skin rash, headache, nausea, vertigo and gastric discomfort^(14, 15).

Nicotine Nasal Spray⁽¹⁷⁾: Nicotine nasal spray is another type of NRT which helps in reducing nicotine crave in patients. Nicotine levels in plasma peaks within 10 minutes after intake. This is about two-thirds of the dose of nicotine in cigarettes^(14,15,19). Application of 0.5 mg equally in each nostril not more than 5 doses per hour or 40 doses per day and gradual reduction of the dose is recommended. Nasal spray may be avoided on lower nasal mucosa⁽¹⁴⁾. Sniffing, swallowing and inhalation should be avoided. Uses of one to two canisters per week don't need any follow-up. Use of more than two canisters per week should be used with caution. It is mainly used for nasal spray up to 12 weeks, then it should be tapered gradually^(14, 15).

Side effects may include headache, burning like sensation, rhinitis, increased lacrimation, pain in nose and throat, sneezing and coughing. It occurs after initiation of therapy which gradually decreases within first week⁽¹⁵⁾.

Nicotine Inhaler⁽²⁰⁾: Each puff of inhaler delivers around 13ng of nicotine. Nicotine levels due to most cigarettes is approximately 2 mg, which is about 80 puff inhaler over 20 minutes. Absorption of drug mainly occurs through mucosal membrane of oral cavity,

pharyngeal mucosa and gastrointestinal tract. It may affect throat irritation and coughing; it should not give in bronchospastic disease⁽¹⁴⁾.

NON-NRTs⁽²¹⁾: Even though the cessation of tobacco is achieved by NRT but the outcome rate is not more than 20% per year. Outcome of smoking cessation rate increases by NRT in comparison to placebo but not more than 20% per year. To increase these rates, non-nicotine agents came into consideration, which acts by noradrenergic neurotransmission (Bupropion, Nortriptyline). These drugs have more efficacy than those affecting serotonin (selective Serotonin reuptake inhibitors, Bupropione, Ondansetron etc.)⁽¹⁾.

Bupropion Hydrochloride⁽²²⁾: Bupropion hydrochloride (Zyban) which is an aminoketone antidepressant group of drug that acts by weakly obstructing both noradrenergic and dopaminergic uptake, helps in cessation of smoking. It also helps in weight loss⁽¹⁴⁾ in obese individual. It is also indicated in patient not willing to take NRT, relapse after taking NRT or failure of NRT. Starting dose of bupropion for smokers is one week prior to their cessation date. All the patients are allowed to continue smoking only for first week followed by cessation in end of 2nd week⁽¹⁾. The starting dose is 150 mg once a day for 3 days followed by 150 mg twice every day for 2 to 3 months⁽¹⁾. Minimum interval between two doses should be 8 hours. Second dose normally is advised in the late afternoon or in the evening to avoid sleeplessness. Bupropion can be used as mono therapy or in combination with other NRT (e.g., nicotine patch)^(1,23).

It can decrease sleep and cause dryness of mouth, and seizure in 0.1% of patients as it decreases seizure threshold⁽²⁴⁾. So always ask patients about seizure history and rule out other cause of seizures like cerebrovascular accident, surgical intervention or significant history of loss of consciousness due to head injury. Drug which decreases seizure threshold (e.g., alcohol, neuroleptics, patient taking monoamine oxidase inhibitor)⁽¹⁴⁾.

Clonidine⁽²⁵⁾: Clonidine is a centrally acting drug that inhibits α_2 receptor of sympathetic nervous system (primarily used as antihypertensive drug). Very few studies have stated that Clonidine may help in cessation of smoking, but side effect due to Clonidine may limit its usefulness^(1,14,26).

Antidepressants and Anxiolytics: Antidepressant

like Nortriptyline which blocks the reuptake of nortriptyline and serotonin may have some role in smoking cessation, which is yet to be approved by U.S. Food and Drug Administration⁽²⁷⁾. As smoking is mostly associated with depression and anxiety, a variety of other antidepressants and anxiolytics like (Buspirone, Doxepin and Fluoxetine) shown to have some promising effect^(1,14, 28).

Varenicline⁽²⁹⁾: To avoid addiction due to nicotine, non-nicotine containing drug came into consideration. Varenicline is a non-nicotine type drug which is recommended 1-2 weeks before quit date. Dose schedule starts with 0.5 mg daily dose for the first 3 days, then from fourth day the 1mg twice daily up to 7th day, from 8th day 2 mg twice daily up to the end of 12 weeks. To prevent relapse further 1 mg twice daily is recommended for another 12 weeks. The main side effects are nausea, headache, vomiting, gastric upset, lack of sleep and abnormal dreams which are mild in nature and decrease over time. Varenicline is found to be an effective drug in long-term relapse prevention.

Enhancing Pharmacotherapeutic Effectiveness: Safety and efficacy can be enhanced by appropriate use of drug, dose schedule and treatment duration. All patients should be monitored frequently in follow-up period and dose can be adjusted as per patient response. All patients should be instructed properly about the use of drugs^(14,30). A follow up in every 1 to 2 weeks interval should be scheduled for all patients⁽³⁰⁾. If there are no signs of improvement within⁽³¹⁾ two weeks, medications and motivations should be repeated. If the condition remains at the original level, discontinue treatment after 4 weeks or change to combination therapy

Method of Validation: Patient's smoking status can be assessed by carbon monoxide concentration in breath which is a non-invasive way and rapid method. Urine tests for Cotinine are available to assess NRT adherence⁽³²⁾. However, this test fails to distinguish between sources. Anabasine and anatabine like tobacco alkaloids may also be assessed in urine to confirm abstinence⁽³³⁾.

Future Approaches: A vaccine is being developed which is helpful to avoid nicotine from crossing the blood-brain barrier. Some drugs are being developed to modify the metabolism of nicotine. The discovery of gamma-vinyl GABA (GVG) is quite promising⁽³⁴⁾. Although it is yet to be tested, it acts by three chief

mechanism: Drug addiction direct neurochemical effects, Behavioral effects and Neurochemical changes.

Nicotine toxicity: Acute toxicity at high doses (40 -60 mg) and very high dosage up to 500mg may cause sudden death due to respiratory blockade. Usual symptoms of nicotine toxicity may varies as Nausea, salivation, abdominal pain, sweating, headache, diarrhea, dizziness, delayed wound healing etc⁽³⁵⁾.

Conclusion

Tobacco is a major risk factor for most of the cancer deaths worldwide. Tobacco addicts can greatly be benefited by pharmacological approach.

Conflict of Interests: None

Ethical Permission: Approved

Funding: Nil

References

- Jiloha RC. Pharmacotherapy of smoking cessation. *Indian journal of psychiatry*. 2014;56(1):87-95.
- Shaik SS, Doshi D, Bandari SR, Madupu PR, Kulkarni S. Tobacco Use Cessation and Prevention - A Review. *Journal of clinical and diagnostic research : JCDR*. 2016;10(5):ZE13-7.
- Baishya B, Satpathy A, Nayak R, Mohanty R. Oral hygiene status, oral hygiene practices and periodontal health of brick kiln workers of Odisha. *Journal of Indian Society of Periodontology*. 2019;23(2):163-7.
- Borojevic T. Smoking and periodontal disease. *Materia socio-medica*. 2012;24(4):274-6.
- Satpathy A, Ravindra S, Thakur S, Kulkarni S, Porwal A, Panda S. Serum interleukin-1beta in subjects with abdominal obesity and periodontitis. *Obesity research & clinical practice*. 2015;9(5):513-21.
- Satpathy A, Panda G, Gogula R, Sharma R. Low complexity adaptive nonlinear models for diagnosis of periodontal disease. *International Journal of Sensors, Wireless Communications and Control*. 2019;09.
- Satpathy A, Ravindra S, Porwal A, Das AC, Kumar M, Mukhopadhyay I. Effect of alcohol consumption status and alcohol concentration on oral pain induced by alcohol-containing mouthwash. *Journal of oral science*. 2013;55(2):99-105.
- Jiloha RC. Biological basis of tobacco addiction: Implications for smoking-cessation treatment. *Indian journal of psychiatry*. 2010;52(4):301.
- Pontieri FE, Tanda G, Orzi F, Chiara GD. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature*. 1996;382(6588):255-7.
- Benowitz NL, Schwartz RS. Nicotine Addiction. *New England Journal of Medicine*. 2010;362(24):2295-303.
- Tomkins DM, Sellers EM. Addiction and the brain: the role of neurotransmitters in the cause and treatment of drug dependence. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2001;164(6):817-21.
- Du D. A Single-Dose, Crossover-Design Bioequivalence Study Comparing Two Nicotine Gum Formulations in Healthy Subjects. *Advances in therapy*. 2018;35(8):1169-80.
- Wadgave U, Nagesh L. Nicotine Replacement Therapy: An Overview. *International journal of health sciences*. 2016;10(3):425-35.
- Anczak JD, Nogler RA, 2nd. Tobacco cessation in primary care: maximizing intervention strategies. *Clinical medicine & research*. 2003;1(3):201-16.
- Maseeh A, Kwatra G. A review of smoking cessation interventions. *MedGenMed : Medscape general medicine*. 2005;7(2):24.
- Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *The Cochrane database of systematic reviews*. 2018;5:CD000146.
- Perkins KA, Karelitz JL, Boldry MC. Reinforcement Enhancing Effects of Nicotine Via Patch and Nasal Spray. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*. 2019;21(6):778-83.
- Hughes JR, Solomon LJ, Peasley-Miklus CE, Callas PW, Fingar JR. Effectiveness of continuing nicotine replacement after a lapse: A randomized trial. *Addictive behaviors*. 2018;76:68-81.
- Myers CS, Taylor RC, Moolchan ET, Heishman SJ. Dose-related enhancement of mood and cognition in smokers administered nicotine nasal spray. *Neuropsychopharmacology*:

- official publication of the American College of Neuropsychopharmacology. 2008;33(3):588-98.
20. Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, et al. Nicotine replacement therapy for smoking cessation. The Cochrane database of systematic reviews. 2012;11:CD000146.
 21. McRobbie H, Lee M, Juniper Z. Non-nicotine pharmacotherapies for smoking cessation. *Respiratory Medicine*. 2005;99(10):1203-12.
 22. Stapleton J, West R, Hajek P, Wheeler J, Vangeli E, Abdi Z, et al. Randomized trial of nicotine replacement therapy (NRT), bupropion and NRT plus bupropion for smoking cessation: effectiveness in clinical practice. *Addiction*. 2013;108(12):2193-201.
 23. Bupropion alone or with a nicotine patch increased smoking cessation rates. *Evidence-Based Mental Health*. 1999;2(3):74-.
 24. Dale LC, Ebbert JO, Glover ED, Croghan IT, Schroeder DR, Severson HH, et al. Bupropion SR for the treatment of smokeless tobacco use. *Drug and alcohol dependence*. 2007;90(1):56-63.
 25. Gourlay SG, Stead LF, Benowitz NL. Clonidine for smoking cessation. The Cochrane database of systematic reviews. 2004(3):CD000058.
 26. Franks P. Randomized, Controlled Trial of Clonidine for Smoking Cessation in a Primary Care Setting. *JAMA: The Journal of the American Medical Association*. 1989;262(21):3011.
 27. Mooney ME, Reus VI, Gorecki J, Hall SM, Humfleet GL, Muñoz RF, et al. Therapeutic Drug Monitoring of Nortriptyline in Smoking Cessation: A Multistudy Analysis. *Clinical Pharmacology & Therapeutics*. 2007;83(3):436-42.
 28. Moret C. Combination/augmentation strategies for improving the treatment of depression. *Neuropsychiatric disease and treatment*. 2005;1(4):301-9.
 29. Fagerstrom K, Hughes J. Varenicline in the treatment of tobacco dependence. *Neuropsychiatric disease and treatment*. 2008;4(2):353-63.
 30. Nides M, Leischow S, Sarna L, Evans SE. Maximizing Smoking Cessation in Clinical Practice: Pharmacologic and Behavioral Interventions. *Preventive Cardiology*. 2007;10(s2):23-30.
 31. Ebbert JO, Wyatt KD, Hays JT, Klee EW, Hurt RD. Varenicline for smoking cessation: efficacy, safety, and treatment recommendations. *Patient preference and adherence*. 2010;4:355-62.
 32. Raja M, Garg A, Yadav P, Jha K, Handa S. Diagnostic Method for Detection of Cotinine Level in Tobacco Users: A Review. *Journal of clinical and diagnostic research : JCDR*. 2016;10(3):ZE04-6.
 33. Levin ED, Hao I, Burke DA, Cauley M, Hall BJ, Rezvani AH. Effects of tobacco smoke constituents, anabasine and anatabine, on memory and attention in female rats. *Journal of psychopharmacology*. 2014;28(10):915-22.
 34. Janes AC, Jensen JE, Farmer SL, Frederick Bd, Pizzagalli DA, Lukas SE. GABA Levels in The Dorsal Anterior Cingulate Cortex Associated with Difficulty Ignoring Smoking-Related Cues in Tobacco-Dependent Volunteers. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology*. 2013;38(6):1113-20.
 35. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annual review of pharmacology and toxicology*. 2009;49:57-71.