Original Article

Effectiveness of Nicotine Replacement Therapy on Smoking Cessation and Reduction Among Pulmonary Tuberculosis Patients – A Randomized Controlled Trial

Jagannath Purushothama, Sanjeev Badiger[1], Jeby J. Olickal, Rahul Kunkulol[2], Nanjesh Kumar[3], Neevan D'Souza[3]

Department of Public Health, K S Hegde Medical Academy, Nitte (Deemed to be University), Mangaluru, Karnataka, India, [1]Department of Community Medicine, A J Institute of Medical Sciences and Research Centre, Mangaluru, Karnataka, India, [2]Department of Pharmacology, Pravara Institute of Medical Sciences, Loni, Maharashtra, India, [3]Department of Community Medicine, K S Hegde Medical Academy, Nitte (Deemed to be University), Mangaluru, Karnataka, India

Abstract

Background': India is ranked second in the world in terms of tobacco use and tops the list of eight high-burden countries that account for two-thirds of the new tuberculosis (TB) cases globally. As tobacco smoking among TB patients is associated with unsuccessful TB treatment outcomes, effective smoking cessation interventions for TB patients is essential to combat this double pandemic. **Aim:** The study determined the effectiveness of nicotine replacement therapy (NRT) on smoking reduction and cessation among pulmonary TB patients. **Settings and Design:** The study included 300 pulmonary TB patients undergoing antitubercular treatment in government health care centers of Dakshina Kannada district in southern India. **Materials and Methods:** The participants in this two-armed, single-blinded, placebo-controlled, block-randomized trial were divided equally (n = 150) for experimental arm (brief advice + NRT) and control arm (brief advice + placebo). The total duration of treatment and follow-up was 6 months. Unadjusted relative risk (URR) and adjusted relative risk (ARR) were calculated for treatment outcomes at 95% confidence interval (CI). Generalized linear regression analysis was performed upon variables with P value less than 0.2. **Results:** After 6 months of intervention including follow up, there was a significant reduction in self-reported smoking (ARR = 1.08, 95% CI 1.01–1.17, P = 0.03) in the experimental arm compared with the control arm. Biochemically verified smoking abstinence was not significantly different between the two arms (ARR = 1.01, 95% CI 0.72–1.38, P = 0.97). **Conclusion:** The study showed statistically significant effectiveness of NRT for self-reported smoking reduction.

Keywords: *Nicotine, pulmonary, randomized controlled trial, therapeutics, tobacco cessation, tuberculosis*

Introduction

Tobacco use and tuberculosis (TB) pose a major public health threat in low and middle-income countries.[1] Tobacco use in India has a high prevalence of 28.6% among adults aged 15 years and above and mortality is estimated at 1.3 million annually.[2] India is also the highest TB burden country in the world with an incidence of 2.69 million cases in 2019.[3] Tobacco smoking nearly doubles the risk of TB disease and TB mortality. Nearly 95% of TB cases and 80% of tobacco users reside in low- and middle-income countries.[4] However, the relationship between tobacco smoking and pulmonary TB is less recognized as a public health problem.[5] Tobacco smoking among TB patients is associated with delayed bacteriologic clearance, increased susceptibility to infection, recurrence, unsuccessful treatment outcomes, and relapse.[6,7] Furthermore, the prevalence of tobacco smoking among pulmonary TB patients is greater in comparison with non-TB individuals. Evidence suggests that tobacco smoking increases the risk of latent TB by 1.9 times, active TB by two times, and case-fatality rate by 2.6 times.[8] This disheartening evidence highlights the need for counseling and pharmacological treatment for TB patients to quit tobacco use.[8] Smoking cessation interventions such as pharmacotherapy, behavioral support, alternative therapy, etc., are available among which nicotine replacement therapy (NRT) is the most widely used pharmacotherapy that delivers nicotine thereby reducing withdrawal symptoms and smoking cravings.[9] There is tangible evidence from studies conducted on more

How to cite this article: Purushothama J, Badiger S, Olickal JJ, Kunkulol R, Kumar N, D'Souza N. Effectiveness of nicotine replacement therapy on smoking cessation and reduction among pulmonary tuberculosis patients – A randomized controlled trial. Int J Prev Med 2023;14:33.

Address for correspondence:
Dr. Sanjeev Badiger, Department of Community Medicine, A J Institute of Medical Sciences and Research Centre, Mangaluru, Karnataka, India.
E-mail: badiger1971@gmail.com

Access this article online

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/ijpvm.ijpvm_3_22

Quick Response Code:

than 40,000 patients regarding NRT for tobacco smokers enhancing the likelihood of success when compared with support without NRT.[10] Systematic reviews also support the evidence that NRT is effective when compared with placebo or no intervention.[11] Thus, it is feasible and imperative for smoking cessation to be amalgamated as a standard therapy along with anti-TB treatment for tobacco users smokers.[12] This study was conducted to determine the effectiveness of NRT with brief advice on smoking reduction and cessation among pulmonary TB patients undergoing anti-TB treatment in government primary health care settings.

Materials and Methods

Methods

This two-armed, single-blinded, randomized, placebo-controlled, study was designed based on CONsolidated Standards of Reporting Trials 2010 guidelines with a 1:1 allocation ratio. The primary objective of the study was to determine the effectiveness of nicotine replacement therapy on smoking cessation among the pulmonary tuberculosis (TB) patients. The study was conducted in the primary health centers (PHCs) of Mangaluru Taluk, Dakshina Kannada District of Southern India between January 2019 and October 2021.[13] Considering a self-reported 6-month abstinence rate of 21.5% and 9.3%, respectively, in the experimental and control arm reported by Louwagie *et al*.,[14] our sample size was estimated at 136 and then rounded off to 150 per arm anticipating a loss to follow up of 10%. Block randomization was done to obtain four participants in each of the 75 blocks to ensure a balance in sample size across groups over time and to keep the numbers of subjects in each group similar at all times (i.e., equal number for the experimental and control arm within the block). Block randomization was done to obtain the two arms using a computer-generated table (www.blockrandomizer.org). The participants were blinded, and concealment of arm allocation was done by sealed envelopes. The pretested, semi-structured questionnaire had participants' sociodemographic factors, smoking history, current smoking status, tobacco dependence score, and follow-up details of treatment.

Participants

Microbiologically confirmed pulmonary TB patients registered under Nikshay (a government managed TB portal) with history of tobacco use in the past one year undergoing antitubercular treatment were enrolled for the study. Their smoking status was biochemically verified with semi-quantitative urine cotinine rapid test kits (Brand: Juscheck). Pediatric TB, mono or multidrug-resistant TB patients, smokeless tobacco users, patients contraindicated for NRT (recent history of myocardial infarction, angina; pregnancy, lactation) were excluded before randomization. Smokeless tobacco users were excluded from the study as the available literature suggests high evidence of smoking tobacco associated with TB but limited evidence with smokeless tobacco.

Intervention and ethics

The experimental arm was administered NRT containing 2 mg nicotine gums for 3 months with a standard tapering dosage along with brief advice. The prescribed dosage was standardized for all the participants with 12 gums per day for the first week and slowly tapered by reducing one gum per day every week from the previous week's dosage. Hence, during the 12th week, the dosage reduced to only one gum per day. The control arm was given non-nicotine chewing gums (placebo) with brief advice. The 5As (ask, advise, assess, assist, and arrange) summarized all the activities that a primary care provider can do to help a tobacco user within 3 − 5 min in a primary care setting. The gums were dispensed in sterile, plain-packaged drug container boxes. Carbon monoxide (CO) monitoring, and urine cotinine test was done to assess the smoking status at baseline and end line of the study. The first author (J.P.) recruited the participants, administered the questionnaire, recorded the nicotine dependence, carbon monoxide levels, provided the treatment and follow up. The corresponding author (S.B.) monitored the recruitment and randomization of the participants. Urine cotinine tests were conducted by the laboratory technician of the respective PHCs. Secondary outcomes were self-reported daily smoking reduction (at least 50%), and self-reported sustained abstinence of at least 3 months prior to the end of follow up. Approval was obtained from the Institutional Ethics Committee (NU/CEC/2019/209 dated January 30, 2019), and the study was registered prospectively with Clinical Trials Registry of India (CTRI) (CTRI/2018/11/016457 dated December 1, 2018). The study was conducted according to the principles of Declaration of Helsinki. Written informed consent was obtained from all the participants and their identity was anonymized. Participants were free to withdraw from the study at any point of time. All the participants were given brief advice. The cost of treatment was borne by the investigator.

Statistical analysis

The data were entered into SPSS (Statistical Packages for Social Sciences; v. 20) and analyzed using STATA (statistics and data) version 14. Missing data were confirmed as missing completely at random using Little's Missing Completely at Random test and were computed using multiple imputation for intention to treat analysis. Probability of mean differences and median differences between arms were calculated using independent "*t*" test and Mann–Whitney *U* test, respectively. The association of demographic characteristics based on arm allocation was performed using Chi-squared test and relative risk (RR) with 95% Confidence interval (CI) was calculated.

Generalized linear regression analysis was performed upon variable having *P* value <0.2 in the unadjusted analysis and adjusted relative risk (ARR) with 95% CI was calculated. Statistical significance was determined at $P < 0.05$.

Results

Figure 1 depicts the flow of participants through assessment for eligibility, exclusion, randomization, arm allocation, loss to follow-up, and intention to treat analysis. Seventy-nine participants lost to follow-up at the end of 6 months. Hence, the missing data were processed for multiple imputation.

Table 1 describes the distribution of participants in the two arms based on sociodemographic characteristics. Majority of the participants were males (94%); mean age was 46.27 (±12.23) years and 45.49 (±11.94) years in the experimental and control arms, respectively. Majority belonged to the age group of 31–45 years.

Table 2 shows cessation outcomes in the two arms. Quit rates are higher in the experimental arm (34.0%) when compared with the control arm (29.33%). The RR of biochemically verified smoking abstinence in the experimental arm was 1.15 times the control arm (0.83–1.61 95 CI; $P = 0.38$). With confounding variables, the ARR was 1.01 (95% CI 0.72–1.38; $P = 0.97$). Self-reported reduction of daily smoking frequency at the end of 6 months was significantly higher in the experimental arm (ARR = 1.08, 95% CI 1.01–1.17; $P = 0.03$). The ARR for sustained abstinence of at least three consecutive months preceding the end-line was 1.48 (95% CI 1.03–2.11; $P = 0.03$).

Table 3 shows the mean, standard deviation, and effect size between the baseline and endline for the two arms in terms of harm reduction. At the end-line in the control arm (brief advice), mean Carbon monoxide (CO) level (1.68 ppm), median smoking frequency (two per day), and median Fagerstorm score (one) were higher in comparison to their respective variables in the experimental arm (1.59 ppm, zero per day, and zero). There was a statistically significant difference between the baseline and endline for all the variables in both the arms. No adverse events were reported in the trial.

Figure 2 shows the trend of self-reported 7-day point prevalence smoking abstinence in both the arms. The experimental arm has a consistent increase in the quit rates when compared with the control arm. The end-line abstinence was 52.7% and 44.7% in the experimental and control arm, respectively. There was no statistically significant association between the two arms for prevalence of self-reported smoking abstinence for the follow up periods [chi-sq (df)= 42 (36); $P = 0.16$].

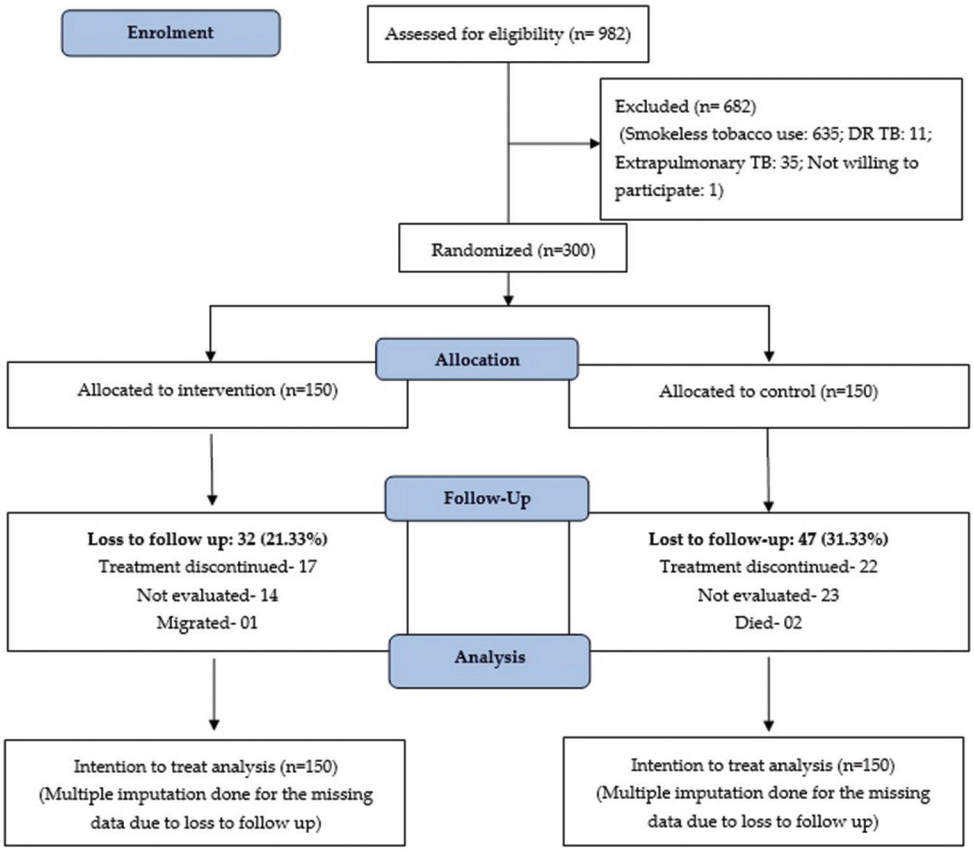

Figure 1: Consort flow chart of participant enrolment, randomization, and allocation

Table 1: Association between sociodemographic of participants and arm allocation

Sociodemographic factors	NRT + Brief advice (*n*=150)	Placebo + Brief advice (*n*=150)	Chi square Statistic	*P*
Gender				
Male	138 (92%)	144 (96%)	2.12	0.14
Female	12 (8%)	06 (4%)		
Age group (years)	Mean: 46.27 (±12.23)	Mean: 45.49 (±11.94)		
18-30	15 (10%)	18 (12%)	1.66	0.64
31-45	60 (40%)	62 (41.3%)		
46-60	53 (35.3%)	55 (36.7%)		
More than 60	22 (14.7%)	15 (10%)		
Education				
Illiterate	6 (4%)	14 (9.3%)	3.59	0.30
Class 1-7	14 (9.3%)	14 (9.3%)		
Class 8-12	117 (78%)	108 (72.1%)		
Degree and above	13 (8.7%)	14 (9.3%)		
Marital status				
Unmarried	44 (29.3%)	48 (32%)	0.55	0.75
Married	104 (69.3%)	101 (67.3%)		
Divorced/widowed	2 (1.4%)	1 (0.7%)		
Occupation				
Professional	40 (26.7%)	39 (26%)	2.44	0.48
Clerical/skilled	22 (14.7%)	26 (17.3%)		
Unskilled	53 (35.3%)	60 (40%)		
Unemployed	35 (23.3%)	25 (16.7%)		

Table 2: Strength of association between trial arms and treatment outcome

Outcome	NRT + Brief Advice (*n*=150)	Placebo + Brief advice (*n*=150)	URR (95%CI)	*P*	ARR (95% CI)	*P*
Biochemically verified smoking abstinence, *n* (%)	51 (34.0%)	44 (29.33%)	1.15 (0.83-1.61)	0.38	1.011 (0.72-1.38)[a]	0.97
Self-reported smoking reduction, *n* (%)	139 (92.66%)	126 (84%)	1.10 (1.01-1.19)	0.02	1.082 (1.01-1.17)[b]	0.03
Self- reported sustained abstinence, *n* (%)	51 (34.0%)	34 (22.66%)	1.50 (1.03-2.17)	0.03	1.483 (1.03-2.11)[c]	0.03

[a]Adjusted for occupation, type of tobacco product used, alcohol use, daily smoking frequency, and nicotine dependence. [b]Adjusted for residence, occupation, type of tobacco product used, alcohol use, level of motivation, and daily smoking frequency. [c]Adjusted for residence, type of smoker, type of tobacco product used, level of motivation, and daily smoking frequency

Discussion

Smoking cessation

This study was conducted to determine the effectiveness of NRT on smoking cessation and reduction among pulmonary TB patients undergoing antitubercular treatment. The sociodemographic characteristics such as gender, age group, education, etc., did not show significant difference between the allocated arms. This proves a reasonably balanced distribution between the arms, thus reducing the possibility of affecting the cessation outcomes.[15] Aryanpur M *et al.*,[6] showed no significant intergroup difference in the demographic characteristics of the subjects.

In our study, the prevalence of biochemically verified self-reported smoking abstinence at the end of six months is 31.66%. Although higher quit rates were seen in the experimental arm than the control arm [unadjusted relative risk (URR) = 1.15; 0.83–1.61 95% CI; *P* = 0.38], there was no statistically significant difference between the two arms.

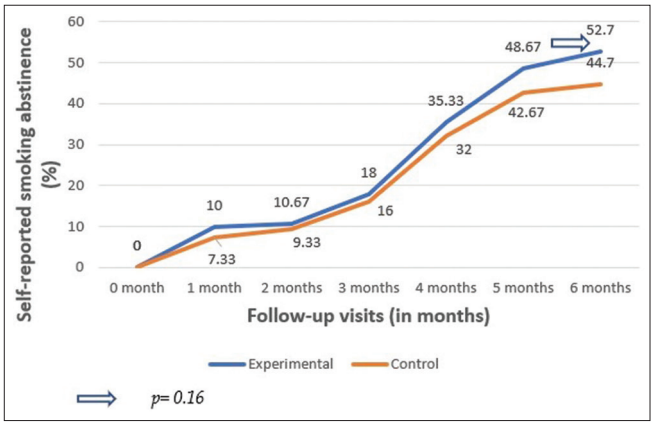

Figure 2: Linear trends of self-reported 7-day point prevalence of smoking abstinence

Table 3: Monitoring of harm reduction based on group allocation

Category	NRT + Brief Advice (*n*=150)	Brief advice (*n*=150)
Exhaled CO (in ppm)	Mean±S.D	Mean±S.D
Baseline	4.09±1.62	4.27±1.83
Endline (6 months)	1.59±0.97	1.68±1.19
Mean difference between baseline and endline	2.50±1.70	2.59±1.93
Paired '*t*' test statistic:		
t(df); effect size;	17.89 (149); 1.18;	16.62 (149); 1.1;
P	*P*<0.01	*P*<0.01
Daily smoking frequency	Median (IQR)	Median (IQR)
Baseline	10 (5-15)	10 (5-15)
Endline (6 months)	0 (0-4)	2 (0-4)
Wilcoxon test:		
z statistic; *P*	−10.15; *P*<0.001	−10.28; *P*<0.001
Fagerstorm Score	Median (IQR)	Median (IQR)
Baseline	02 (1-4)	02 (1-5)
Endline (6 months)	0 (0-1)	01 (0-1.25)
Wilcoxon test:		
z statistic; *P*	−9.75; *P*<0.01	−9.63; *P*<0.001

A subsample of 53 studies with about 19,000 participants of a systematic review showed a pooled effect size of smoking cessation at 6 + months for nicotine gums as 1.43 (1.33–1.53).[16] The variation in the results between our study and systematic review may be due to the different study populations as ours was specific to TB patients and the latter was in general population. Ellerbeck *et al.,*[17] showed biochemically verified 7-day point prevalence abstinence at 6 months as 12.7% among COPD patients undergoing smoking cessation for 10 weeks. The study claimed difficulty in achieving cessation due to high risk for treatment failure among the COPD group. Papadakis *et al.,*[18] showed quit rates of 33.3% at 26 weeks in the cost-free NRT group versus 15.4% in the prescription-only NRT group for seven-day point prevalence abstinence. Cost-free smoking cessation medications increased the motivation to quit. Our study results are similar to the former as NRT was provided free of cost to all the participants. Goel *et al.,* worked on ABC smoking cessation for TB patients (Ask about smoking, Brief advice, and Cessation). In the study, 80.2% and 57.5% of the patients had quit smoking in the ABC and control group, respectively (ARR = 1.56; 95% CI = 1.24–1.93; $P < 0.0001$). Repeated brief cessation advice is a feasible and inexpensive addition to routine TB case management.[19] Our study showed a RR reduction of 15% for smoking cessation in the experimental arm as all the participants received brief advice several times by healthcare personnel which motivated them to quit smoking. However, our study did not suggest a statistically significant effectiveness of NRT for smoking cessation when compared with brief advice alone.

Smoking reduction

Harm reduction indicators such as daily smoking frequency, carbon monoxide levels, and Fagerstorm score on nicotine dependence, were measured between baseline and end-line. The mean/median difference and the effect size was not statistically significant between the two arms. Ellerbeck E *et al.,*[17] showed significant reductions in smoking cigarettes per day (CPD) relative to baseline (long term-NRT group, −14.5; standard cessation group, −12.4 CPD), and expired CO level (long term-NRT group, −7.8 ppm; standard cessation group, −5.5 ppm). Reductions of 50% or more CPD is linked to improvements in cardiovascular risk factors, respiratory symptoms, and lung cancer risk.

Apart from smoking cessation, smoking reduction is also a favorable outcome because NRT manages craving symptoms better.[20] This can help smokers to reduce frequency although unable or unwilling to quit. Smoking reduction could be a first step toward cessation as this encourages subsequent quit attempts.[21] In our study, self-reported reduction of daily smoking frequency (by at least 50%) at six months was high both in the experimental (92.66%) and control arm (84%) with an RR of 1.10 (95% 1.01–1.19; $P = 0.02$), and ARR of 1.08 (1.01–1.17; $P = 0.03$). Lam *et al.,*[22] reported smoking reduction (at least 50%) of 50.9% and 25.7% in the NRT and placebo arm, respectively (OR 3.0; 95% CI, 2.16–4.15). Our study showed relatively higher reduction rates in both the arms as the participants were motivated by healthcare providers to reduce cough symptoms due to smoking. However, smoking reduction may undermine cessation and motivation to quit because smokers may perceive reduction as an alternative to cessation. Sustained abstinence (at least three months) preceding the end-line in the experimental arm and control arm had an RR of 1.50 (95% CI 1.03–2.17; $P = 0.03$), and ARR of 1.48 (95% CI 1.03–2.11; $P = 0.03$) in our study. Awaisu *et al.,*[12] reported 77.5% continuous four-week abstinence at six months when compared with 8.7% in the non-NRT group. The difference between the two study findings is due to the varying durations of sustained abstinence. Self-reported smoking abstinence in our study was higher in the experimental arm than control arm consistently from the first month (10.0 vs. 7.33%) to the sixth month (52.7 vs. 44.7%). If smokers could reduce the frequency and sustain it due to NRT, it might help them quit as they would be starting from a lower level of nicotine dependence.[21] Hence, this study supports NRT along with brief advice as a first line of treatment for smoking reduction in primary health care settings.

Conclusion

This study demonstrates an effective intervention for smoking reduction sans smoking cessation. National Tuberculosis Elimination Program and National Tobacco Control Program are the two national health programs in India that requires a collaborative approach starting from the primary health care level. Identification of tobacco smokers

among the newly diagnosed TB cases shall pave the way for effective and timely smoking cessation interventions which may improve the TB treatment outcomes.

Strengths and limitations of the study: Bio-verification of self-reported smoking status of the study participants with urine cotinine test, and multiple imputation done to overcome the uncertainly of the missing data are the strengths of the study. The study limitation is a possible interaction with NRT/placebo due to regular counselling of the participants for ethical considerations may have affected the cessation rates.

Informed consent statement

Written informed consent was obtained from all the participants involved in the study both for therapeutic and research purpose.

Acknowledgments

The authors acknowledge the District Health and Family Welfare Society, Dakshina Kannada District, Government of Karnataka, for the administrative and technical support given to the authors.

The study is registered prospectively with the Clinical Trials Registry of India (CTRI/2018/11/016457 dated 1st December 2018). http://ctri.nic.in/Clinicaltrials/advsearch.php.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Received: 03 Jan 22 **Accepted:** 28 Oct 22
Published: 17 Mar 23

References

1. Marshall AM, Barua D, Mitchell A, Keding A, Huque R, Khan A, *et al*. Smoking prevalence among tuberculosis patients: A cross-sectional study in Bangladesh and Pakistan. Tob Induc Dis 2020;18:1–7.
2. Ministry of Health and Family Welfare; Government of India. Global adult tobacco survey, India 2016-17 [Internet]. 2017. Available from: https://ntcp.nhp.gov.in/assets/document/surveys-reports-publications/Global-Adult-Tobacco-Survey-Second-Round-India-2016-2017.pdf.
3. Central TB Division-Directorate General of Health Services. India Tb Report National Tuberculosis. 2020. p. 292.
4. Amere GA, Nayak P, Salindri AD, Narayan KMV, Magee MJ. Contribution of smoking to tuberculosis incidence and mortality in high-tuberculosis-burden countries. Am J Epidemiol 2018;187:1846–55.
5. Van Zyl Smit RN, Pai M, Yew WW, Leung CC, Zumla A, Bateman ED DK. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. Eur Respir J 2010;35:27-33.
6. Aryanpur M, Hosseini M, Masjedi MR, Mortaz E, Tabarsi P, Soori H, *et al*. A randomized controlled trial of smoking cessation methods in patients newly-diagnosed with pulmonary tuberculosis. BMC Infect Dis 2016;16:1–9.
7. Leung CC, Yew WW, Chan CK, Chang KC, Law WS, Lee SN, *et al*. Smoking adversely affects treatment response, outcome and relapse in tuberculosis. Eur Respir J 2015;45:738–45.
8. Mahishale V, Patil B, Lolly M, Eti A, Khan S. Prevalence of smoking and its impact on treatment outcomes in newly diagnosed pulmonary tuberculosis patients: A hospital-based prospective study. Chonnam Med J 2015;51:86-90.
9. Hersi M, Traversy G, Thombs BD, Beck A, Skidmore B, Groulx S, *et al*. Effectiveness of stop smoking interventions among adults: Protocol for an overview of systematic reviews and an updated systematic review. Syst Rev 2019;8:1–21.
10. Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, *et al*. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2012. Available from: https://doi.wiley.com/10.1002/14651858.CD000146.pub4.
11. Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*. The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: A systematic review and economic evaluation. Health Technol Assess (Rockv) 2002;6. Available from: https://www.journalslibrary.nihr.ac.uk/hta/hta6160/#/abstract.
12. Awaisu A, Nik Mohamed MH, Mohamad Noordin N, Abd Aziz N, Syed Sulaiman SA, Muttalif AR, *et al*. The SCIDOTS Project: Evidence of benefits of an integrated tobacco cessation intervention in tuberculosis care on treatment outcomes. Subst Abus Treat Prev Policy 2011;6:1–13.
13. Purushothama J, Badiger S. A Randomized Trial Protocol to Determine Effectiveness of Nicotine Replacement Therapy on Smoking Cessation of Tuberculosis Patients in Coastal India. Ann Rom Soc Cell Biol 2021;25:3525-34.
14. Louwagie GMC, Okuyemi KS, Ayo-Yusuf OA. Efficacy of brief motivational interviewing on smoking cessation at tuberculosis clinics in Tshwane, South Africa: A randomized controlled trial. Addiction 2014;109:1942–52.
15. Edjoc RK, Reid RD, Sharma M. The effectiveness of smoking cessation interventions in smokers with cerebrovascular disease: A systematic review. BMJ Open 2012;2:1–5.
16. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation [Internet]. In: Stead LF, editor. Cochrane Database of Systematic Reviews.Chichester, UK: John Wiley & Sons, Ltd; 2008. Available from: https://doi.wiley.com/10.1002/14651858.CD000146.pub3 [Last accessed on 2022 Nov 15].
17. Ellerbeck EF, Nollen N, Hutcheson TD, Phadnis M, Fitzgerald SA, Vacek J, *et al*. Effect of long-term nicotine replacement therapy vs standard smoking cessation for smokers with chronic lung disease: A randomized clinical trial. JAMA Netw Open 2018;1:e181843.
18. Papadakis S, Aitken D, Gocan S, Riley D, Laplante MA, Bhatnagar-Bost A, *et al*. A randomised controlled pilot study of standardised counselling and cost-free pharmacotherapy for smoking cessation among stroke and TIA patients. BMJ Open 2011;1:1–8.
19. Goel S, Kathiresan J, Singh P, Singh RJ. Effect of a brief smoking cessation intervention on adult tobacco smokers with pulmonary tuberculosis: A cluster randomized controlled trial from North India. Indian J Public Health 2017;61:S47–53.
20. Fagerström KO, Tejding R, Westin Å, Lunell E. Aiding reduction of smoking with nicotine replacement medications: Hope for the recalcitrant smoker? Tob Control 1997;6:311–6.
21. Kralikova E, Kozak JT, Rasmussen T, Gustavsson G, Le Houezec J. Smoking cessation or reduction with nicotine replacement therapy: A placebo-controlled double-blind trial with nicotine gum and inhaler. BMC Public Health 2009;9:4–11.
22. Lam TH, Chan SSC, Abdullah ASM, Taam Wong V, Chan AYW, Hedley AJ. Smoking reduction intervention for smokers not willing to quit smoking: A randomised controlled trial. Hong Kong Med J 2012;18:S4–8.