Review Article

Moderating Effect of Tobacco Dependence on Pharmacological Management of Tuberculosis : A Narrative Review

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Abstract

Tobacco dependence is one of the reasons for exacerbations of Pulmonary Tuberculosis (PTB), which is still a global health challenge. Tobacco dependence is itself highly prevalent, which makes one's body susceptible to Tuberculosis Infection (TBI). This review aims to study the moderating effect of Tobacco dependence on the pharmacological management of PTB. Tobacco smoke contains several harmful compounds that can interfere with the metabolism of anti-tuberculosis (TB) drugs, potentially alleviating their action and efficacy. Moreover, Tobacco use is a significant contributor to the development of PTB infections associated with poorer treatment outcomes, including higher rates of treatment failure and drug resistance. The immunosuppressive effects of Tobacco tend to worsen PTB symptoms and delay the healing of lung tissues. Addressing Tobacco dependence and the inclusion of Tobacco cessation should be crucial components of PTB management strategies to improve treatment outcomes and reduce the PTB burden globally.

Key words : Tobacco Dependence, Tuberculosis, Tobacco Cessation.

Global and Indian Scenarios of Tobacco Use :

Tobacco use is the most prevalent risk factor for premature mortality and morbidity that is readily preventable. Globally, Tobacco use is associated with 5,400,000 deaths every year; by 2030, this number is likely to increase to 8,300,000[1]. The Global Adult Tobacco Survey (GATS 2-2016-17) reported that the prevalence of smoking is 10.38% and SLT use is 21.38% in India[2]. More intriguingly, Tobacco use is associated with increased risks of infectious diseases, an increase in respiratory symptoms, and several adverse effects (Fig 1).

Global and Indian Scenarios of Pulmonary Tuberculosis (PTB) :

According to the WHO report, an estimated global total of 10,600,000 people fell ill with PTB in 2022, equivalent to 133 incident cases per 100,000 population. In 2022, eight countries accounted for more than two-thirds of global PTB cases, India being one of them with 27% of the global number of incident PTB cases in 2019[3]. In 2022, reported death totals of notified cases for PTB were 3,31,000[4].

Editor's Comment :

- Addressing tobacco dependence should be an integral part of PTB management to improve treatment outcomes and reduce the burden of PTB globally.

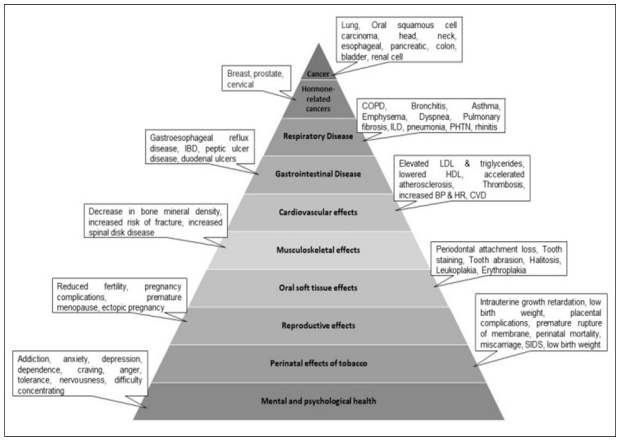

Fig 1 — Adverse health effects of Tobacco

COPD- Chronic Obstructive Pulmonary Disease, ILD- Interstitial Lung Disease, PHTN- Pulmonary Hypertension, LDL- Low-Density Lipoprotein, HDL- High-Density Lipoprotein, BP- Blood Pressure, HR- Heart Rate, CVD- Cardiovascular disease, SIDS- Sudden Infant Death Syndrome, IBD- Inflammatory Bowel Disease

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Comorbidity of Tobacco Dependence and PTB :

A study among Pulmonary Tuberculosis (PTB) patients in urban Primary Health Centres (PHCs) in Pondicherry reported a prevalence of smoking and SLT of 35.3% and 9.8%, respectively[5]. In line with these findings, a prospective study conducted in the Belgaum district of Karnataka documented the prevalence of smoking in newly diagnosed PTB patients to be 32.21%[6]. Apart from the studies conducted in the southern part of India, a study from the northern state of Haryana conducted at the Tuberculosis unit of Ballabgarh among newly diagnosed PTB patients showed that one-fifth of the patients were current Tobacco users with high Nicotine dependence levels[7].

Tobacco Dependence and PTB : A Double Whammy :

Tobacco use not only contributes to adverse health effects but is also an important risk factor for PTB. Recent epidemiological evidence indicating a link between Tobacco and PTB has now been established.

Tobacco smoke contains numerous harmful chemicals that weaken the body's immune response to combat the Tuberculosis (TB) bacteria (*Mycobacterium tuberculosis*). Nicotine, a major component of Tobacco, has immunosuppressive effects that impair the ability of the body's immune cells to defend against TB bacteria. Thus, a weakened immune system exacerbates the susceptibility of an individual to TBI upon exposure to TB bacteria[8]. Mechanistically, Tobacco smoke, upon entering the respiratory tract, causes chronic inflammation in the lungs and airways, causing structural changes and impairing the function of cilia (tiny, hair-like structures that help to clear pathogens and debris from the Lungs). This damage is conducive for TB bacteria to establish an infection in the respiratory tract, which leads to disease progression[9].

Moreover, inhaling smoke as a passive smoker causes serious harm to the health of second-hand smokers and poses a risk factor for TBI caused by TB bacteria and developing PTB disease[10]. Studies indicate a high prevalence of Tobacco use among PTB patients, negatively influencing their response to TB treatment.

Thus, the current narrative review aims to study the effect of Tobacco dependence on the symptoms, course, outcome and management of tuberculosis.

Moderating Effect of Tobacco Dependence :

Tobacco dependence can significantly impact the use of pharmaceuticals in the treatment of PTB in several ways discussed below:

(1) Drug Metabolism Interference

Tobacco smoke contains numerous chemicals, such as Polycyclic Aromatic Hydrocarbons (PAHs) and benzopyrene, that can induce the activity of certain Liver enzymes responsible for drug metabolism, particularly the enzyme cytochrome P450 (CYP). These enzymes play a crucial role in metabolizing many drugs, including those used in PTB treatment (rifampicin and isoniazid)[11]. When Tobacco smoke induces these enzymes, it accelerates the TB drug metabolism, leading to decreased drug concentrations in the bloodstream and potentially reducing the effectiveness of TB medications to kill TB bacteria. This results in treatment failure or relapse[12].

(2) Reduced Treatment Efficacy

Tobacco dependence can alter the pharmacokinetics of TB drugs in the body, affecting their absorption, distribution, metabolism and excretion[13]. Tobacco smoke contains nicotine, which can affect the permeability of cell membranes and alter the absorption of drugs in the Gastrointestinal tract. Additionally, Nicotine can influence blood flow and tissue distribution, potentially impacting the distribution of TB drugs to target sites of infection. These changes in pharmacokinetics can lead to variability in subtherapeutic drug levels in the body and efficacy, particularly in patients who are highly dependent on Tobacco[14].

(3) Increased Drug Resistance

Tobacco use is known to weaken the immune system. A compromised immune response in PTB patients who smoke may lead to slower recovery and clearance of TB bacteria, providing a longer exposure time for the bacteria to mutate and develop resistance to the drugs being used[8]. Subtherapeutic drug levels may fail to effectively suppress the growth of TB bacteria, potentially giving rise to drug-resistant strains. Other factors, such as the specific drugs used in treatment, the presence of multidrug-resistant TB strains and individual variations in drug metabolism, also play significant roles[15].

(4) Worsened Respiratory Symptoms

When individuals with PTB smoke Tobacco, the exposure to these irritants exacerbates existing airway inflammation, airflow obstruction, lung capacity, a reduced ability of the cilia to remove mucus and trapped particles out of the lungs and impaired gas exchange, which worsens respiratory symptoms such as persistent coughing, sputum production, and shortness of breath, which are already common in PTB patients[16]. The existing damage to the respiratory epithelium makes PTB patients more susceptible to respiratory infections such as Pneumonia, Bronchitis, Influenza, etc, complicating the ongoing PTB treatment[17]. The combination of TB-induced lung inflammation and Tobacco smoke-induced airway irritation can result in a synergistic effect, making respiratory symptoms more severe. Smoking-related respiratory problems might make people uncomfortable or reluctant to take their medicine, which can further lower their quality of life and treatment compliance for Tuberculosis[16].

(5) Delayed Healing of Lung Tissues

Smoking slows down the healing process and prolongs the recovery time of lung tissues, which is crucial for recovery from TBI[8]. Additionally, delayed healing of TB-related lung lesions may result in chronic lung damage, impaired lung function and increased susceptibility to secondary respiratory infections such as lung abscesses and bronchiectasis, leading to long-term respiratory complications[18].

(6) Incomplete Treatment and Poor Adherence

Tobacco dependence is often associated with behavioural factors that can impact treatment adherence. Tobacco dependence can also indirectly interfere with TB drug metabolism by affecting treatment adherence. Smokers may be more likely to miss doses of PTB medications or have irregular treatment schedules due to the addictive nature of Tobacco and the associated cravings as well as withdrawal symptoms. Discontinued treatment or poor treatment adherence can result in subtherapeutic drug levels in the body, allowing TB bacteria to survive and potentially develop drug resistance[19].

Management Strategies for Tobacco Use in Patients with PTB :

There are several strategies for smoking or Tobacco cessation (Fig 2).

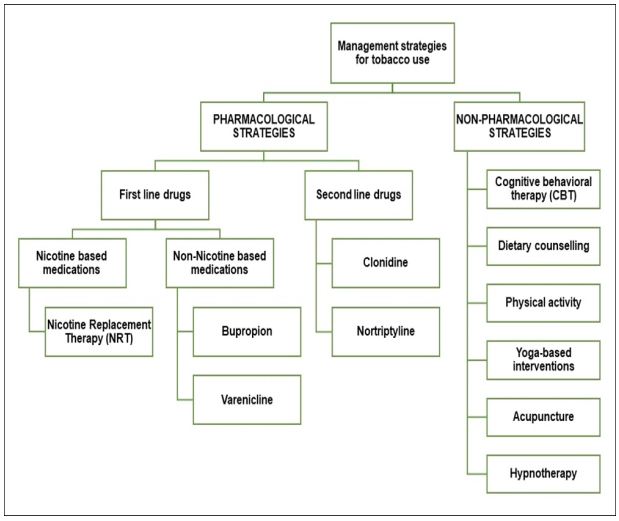

Fig 2 — Management strategies for tobacco use in patients with PTB

Pharmacological Strategies :

Pharmacological strategies for smoking or tobacco cessation are preferably used because of their higher efficacy. These include both first-line and second-line drugs. Among the first-line treatments, Nicotine Replacement Therapy (NRT) is commonly used to help individuals reduce their dependence on Nicotine. NRT works by delivering controlled doses of nicotine through various NRT products like gums, patches, lozenges, nasal sprays, inhalers, tablets or injections, gradually decreasing nicotine receptor activity and reducing psychological cravings[20]. Besides nicotine-based medications, non-nicotine-based alternatives like bupropion are also effective. Originally developed as an antidepressant, bupropion helps manage Nicotine addiction by inhibiting the neuronal reuptake of norepinephrine and dopamine neurotransmitters in the brain, which improves neurotransmission and reduces nicotine cravings as well as withdrawal symptoms. Its action as an antagonist at nicotinic acetylcholine receptors (nAChRs) further supports tobacco cessation[21]. Another first-line option is varenicline, a partial agonist of $\alpha 4\beta 2$ nAChRs. It partially stimulates these nAChRs to a lesser extent than Nicotine, competing with Nicotine for the same binding spots, which causes a moderate dopamine release while blocking nicotine's binding to nAChRs, thereby diminishing the reward response associated with Nicotine intake and easing withdrawal symptoms[22]. Second-line medications include clonidine, which acts on the Central Nervous System by stimulating alpha-2 adrenergic receptors in the

brain, thereby lowering the release of norepinephrine and reducing the severity of Tobacco withdrawal symptoms experienced during Tobacco cessation, making Nicotine intake less rewarding[23]. Lastly, nortriptyline, a tricyclic antidepressant, is used off-label to assist in tobacco cessation. It increases norepinephrine and serotonin levels, which potentially improves mood and reduces depressive symptoms, thereby attenuating Nicotine urges, making it easier for Tobacco users to abstain from Tobacco use[23].

Furthermore, non-pharmacological strategies for Tobacco cessation can be highly effective and can complement pharmacological treatments or be used alone.

Non-pharmacological Strategies :

In the primary care setting, a brief strategy, following the "rule of 5A's (Ask, Advise, Assess, Assist, and Arrange)," is recommended for Tobacco users who are willing to quit, and the "rule of 5 R's (Relevance, Risks, Rewards, Roadblocks, and Repetition)" helps encourage the motivation to quit Tobacco use.

Among the Non-pharmacological strategies, one widely used method is Cognitive Behavioural Therapy, which helps Tobacco users identify their Tobacco triggers–such as specific situations, thoughts, or activities –that prompt Tobacco use and teaches them coping techniques to manage their Tobacco urges and prevent relapse[20]. Dietary counselling also plays a crucial role by promoting a balanced diet that includes complex carbohydrates, lean proteins, healthy fats, and a variety of fruits and vegetables, preventing weight gain and helping manage withdrawal symptoms. Healthy snacking and increased omega-3 fatty acid consumption have been associated with reduced Tobacco dependence, while adequate hydration supports detoxification and abstaining from the consumption of dehydrating drinks such as alcohol and caffeinated drinks[20,24,25]. Physical activity is another powerful tool that acts as a natural stress reliever and mood enhancer. Exercise not only distracts from cravings but also stimulates the production of neurotransmitters such as serotonin and dopamine, alleviating Nicotine withdrawal symptoms and thus decreasing the likelihood of Tobacco use. Yoga-based interventions, which combine deep breathing, meditation, physical movement and relaxation exercises, enhance mindfulness and stress reduction, facilitating individuals' recognition and management of Tobacco use triggers. The calming effects of yoga practice support emotional well-being, the body's natural detoxification, and overcoming addictive behaviours, making the cessation process more manageable. Acupuncture, through stimulation of specific acupoints, modulates the release of neurotransmitters (such as dopamine, serotonin, and endorphins) to reduce Stress, Anxiety and Cravings, easing the Tobacco withdrawal process. Lastly, hypnotherapy works by accessing the subconscious mind to induce a change in the perception towards tobacco use among Tobacco users, instilling motivation, confidence and self-efficacy to quit tobacco use while addressing the root causes of tobacco urges and highlighting the negative consequences of Tobacco use[20]. Together, these holistic strategies significantly support long-term Tobacco cessation.

Conclusion

Healthcare providers should be aware of the moderating effects of Tobacco use on the conventional treatment of PTB patients as well as consider the same while prescribing TB medications. In addition to TB medications, professional counselling explaining the negative impact of Tobacco on the current health status of the patient must be ensured by the physician directing the patient to quit tobacco. Subsequently, the concept of the 5D's, ie, Delay, Distract, Deep breathing, Drink water and Discuss; could be elucidated to the patients to ride out the craving when encountering Tobacco urges. Moreover, if a PTB patient needs assistance with Tobacco cessation, pharmacological or non-pharmacological strategies could be given as per the need.

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References

1 Mathers CD, Loncar D — Projections of Global Mortality and Burden of Disease from 2002 to 2030. Samet J, editor. *PLoS Med* 2006; **3(11):** e442.

2 Tata Institute of Social Sciences (TISS), Mumbai and Ministry of Health and Family Welfare, Government of India. Global-Adult-Tobacco-Survey-Second-Round-India-2016-2017. Available from: https://ntcp.mohfw.gov.in/assets/document/surveys-reports-publications/Global-Adult-Tobacco-Survey-Second-Round-India-2016-2017.pdf

3 World Health Organization. Global Tuberculosis Report 2023. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023/tb-disease-burden/1-1-tb-incidence

4 Ministry of Health and Family Welfare. 2023. Available from: https://www.pib.gov.in/PressReleaseIframePage.aspx?PRID=1975724

5 Mariappan VA, Sahu SK, Sarkar S, Kattimani S, Soundappan G — Smoked and smokeless tobacco use among pulmonary tuberculosis patients under RNTCP in urban Puducherry, India. *Indian Journal of Tuberculosis* 2016; **63(3):** 158-66.

6 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(2):** 86.

7 Kumar R, Kant S, Chandra A, Krishnan A — Tobacco use and nicotine dependence among newly diagnosed pulmonary tuberculosis patients in Ballabgarh tuberculosis unit, Haryana. *J Family Med Prim Care* 2020; **9(6):** 2860.

8 Bai X, Stitzel JA, Bai A, Zambrano CA, Phillips M, Marrack P, *et al* — Nicotine Impairs Macrophage Control of *Mycobacterium tuberculosis*. *Am J Respir Cell Mol Biol* 2017; **57(3):** 324-33.

9 Leopold PL, O'Mahony MJ, Lian XJ, Tilley AE, Harvey BG, Crystal RG — Smoking is associated with shortened airway cilia. *PLoS One* 2009; **4(12):** e8157.

10 Öberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A — Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. The Lancet 2011; **377(9760):** 139-46.

11 Luo K, Luo X, Cao W, Hochalter JB, Paiano V, Sipe CJ, *et al*— Cigarette smoking enhances the metabolic activation of the polycyclic aromatic hydrocarbon phenanthrene in humans. *Carcinogenesis* 2021; **42(4):** 570-7.

12 Hukkanen J, Jacob Iii P, Peng M, Dempsey D, Benowitz NL — Effect of nicotine on cytochrome P450 1A2 activity. *Brit J Clinical Pharma* 2011; **72(5):** 836-8.

13 Miller LG — Cigarettes and drug therapy: pharmacokinetic and pharmacodynamic considerations. *Clin Pharm* 1990; **9(2):** 125-35.

14 Wang EY, Arrazola RA, Mathema B, Ahluwalia IB, Mase SR — The impact of smoking on tuberculosis treatment outcomes: a meta-analysis. *Int J Tuberc Lung Dis* 2020; **24(2):** 170-5.

15 Khan A, Fox G, Menzies D — Drug-Resistant Tuberculosis. In: Gotte M, Berghuis A, Matlashewski G, Wainberg M, Sheppard D (eds). In: Handbook of Antimicrobial Resistance. Springer, New York, NY; 2014. Available from: 10.1007/978-1-4939-0667-3_13-1

16 Perriot J, Underner M, Peiffer G — Tuberculosis and tobacco smoking. *Journal of Tuberculosis* 2018; **1(01):** 17-22.

17 Dasaraju PV, Liu C — Infections of the respiratory system. Medical Microbiology 4th edition. 1996;

18 Arcavi L, Benowitz NL — Cigarette smoking and infection. Archives of Internal Medicine 2004; **164(20):** 2206-16.

19 Burusie A, Enquesilassie F, Addissie A, Dessalegn B, Lamaro T — Effect of smoking on tuberculosis treatment outcomes: A systematic review and meta-analysis. Glantz SA, editor. *PLoS ONE* 2020; **15(9):** e0239333.

20 Kant S, Singh A, Verma N, Kumar Verma A, Tripathi A — Non-pharmacological Modalities for Tobacco Cessation: An Overview. *IJAR* 2022; **10(05):** 176-86.

21 Mooney ME, Sofuoglu M — Bupropion for the treatment of nicotine withdrawal and craving. *Expert Review of Neurotherapeutics* 2006; **6(7):** 965-81.

22 De Moura FB, McMahon LR — The contribution of á4â2 and non-á4â2 nicotinic acetylcholine receptors to the discriminative stimulus effects of nicotine and varenicline in mice. *Psychopharmacology* 2017; **234(5):** 781-92.

23 Pajai DD, Paul P, Reche A — Pharmacotherapy in Tobacco Cessation: A Narrative Review. *Cureus* 2023; **15(2):** e35086.

24 Singh A, Verma N, Kant S, Verma AK, Tripathi A, Bhardwaj K — Impact of Flaxseed Oil Supplementation on Tobacco Dependence, Craving, and Haematological Parameters in Tobacco-Dependent Subjects. *Cureus* 2024; **16(3):** e57101.

25 Singh A, Verma N, Kant S, Verma AK, Tripathi A, Bhardwaj K — The Effects of Alpha Linolenic Acid (Omega-3 Fatty Acid) on Tobacco Craving Intensity, Withdrawal Symptoms and Biochemical Markers in Tobacco Users. *Ind J Clin Biochem* 2024; 30.