Review Article

Smoking resumption after heart or lung transplantation: a systematic review and suggestions for screening and management

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Abstract: Smoking remains the leading cause of preventable disease and death in the developed world and kills half of all long-term users. Smoking resumption after heart or lung transplantation is associated with allograft dysfunction, higher incidence of cancer, and reduced overall survival. Although self-reporting is considered an unreliable method for tobacco use detection, implementing systematic cotinine-based screening has proven challenging. This review examines the prevalence of smoking resumption in thoracic transplant patients, explores the risk factors associated with a post-transplant smoking resumption and discusses the currently available smoking cessation interventions for transplant patients.

Keywords: Smoking resumption; heart and lung transplantation; smoking cessation; nicotine replacement; bupropion; varenicline

Submitted Nov 28, 2017. Accepted for publication May 10, 2018.
doi: 10.21037/jtd.2018.07.16
View this article at: http://dx.doi.org/10.21037/jtd.2018.07.16

Introduction

According to projections of the World Health Organization (WHO), an estimated 1.1 billion people will smoke tobacco by 2025 (1). Tobacco smoking increases the risk for cardiovascular disease, stroke, peripheral vascular and lung disease, bacterial or viral infections and cancer (2,3). Despite a considerable rise in awareness and the implementation of smoking prevention strategies, combustible tobacco continues to be the major risk for preventable disease and death in the developed world, killing half of all long-term users (2,4).

Thoracic organ transplant (TOT) including heart transplantation (TPL), lung TPL or combined heart/lung TPL is an established treatment option for several non-malignant end-stage heart and lung diseases such as ischemic and non-ischemic cardiomyopathy, valvular cardiomyopathy, congenital heart disease, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), cystic fibrosis (CF) and pulmonary arterial hypertension (PAH) (5).

This review does not address other solid organ recipients (e.g., liver, kidney, pancreas), due to different TPL-waiting list requirements accepting current smokers.

Owing to the current shortage of donor organs, improving allograft outcomes is a pivotal aspect of ongoing clinical TPL research (6,7). Depending on the national organ donation organizations and TPL centers, patients are normally required to be smoke-free for a minimum of 6 months before being placed on the TPL-waiting list for thoracic organs TPL (8-10). Because smoking is an addictive disorder, relapse may occur post-transplant despite being smoke-free prior to TPL. Previous studies have demonstrated higher incidences of allograft dysfunction, development of *de novo* malignancies and reduced overall

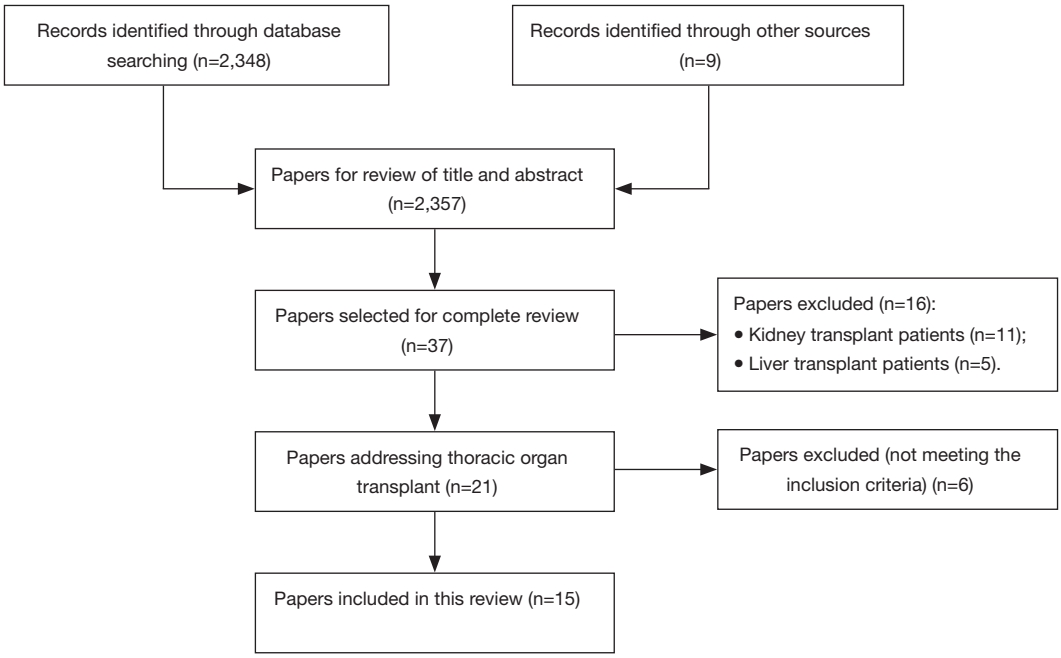

Figure 1 Flow chart of process of systematic literature search.

survival in smoking organ recipients (11-17).

To date, no international guidelines for systematic screening of post-transplant smoking recurrence exists. Therefore, it remains at the discretion of the individual TPL centers to systematically screen, question or rely on chance to detect smoking resumption after TPL. Despite considerable improvements in smoking cessation strategies including non-pharmacological (i.e., cognitive behavioral therapy, motivational interviewing) and pharmacological therapies (i.e., nicotine replacement therapy (NRT), partial nicotine agonists (varenicline, cytisine) and non-nicotine-based drugs (bupropion), its efficacy and safety transplant patients has rarely been investigated (18-22).

This review will examine the prevalence and outcome of smoking resumption in thoracic transplant recipients and how pre-transplant or post-transplant variables are associated with smoking reuptake. Such predictors, once identified, might help health care professionals and patients prevent smoking resumption after TOT in future. The importance of systematic screening of smoking resumption after TPL is discussed and tobacco cessation strategies in the context of transplant patients are reviewed.

Sources and selection criteria

We searched the electronic databases Medline, Embase, Web of Science, Cochrane Library and Google scholar from database inception until March 5, 2017. Medical subject headings (MeSH) terms included "smoking" or "smoking resumption" or "smoking recurrence" or "smoking relapse" and "heart transplant" or "lung transplant". Supplemental search was performed using keyword search for "smoking after transplant". Eligible studies had to meet the following inclusion criteria; (I) characterize smoking resumption after TPL; (II) provide data on heart or lung transplant or combined heart/lung transplant recipients; (III) be reported in English with full text available. No other restrictions were applied. Furthermore, we scanned the reference sections of the eligible articles for additional literature and selected other relevant articles for further review by author consensus. Evidence came from a variety of study types, including case reports, randomized trials, systematic reviews and meta-analysis. Abstracts of meetings and unpublished results were not considered for this review. A total of 2,356 articles were screened. Thirty-seven articles were selected for complete review based on title and abstract, 15 of these were included in this review (*Figure 1*). Owing to the paucity of literature on this topic, no studies fulfilling the inclusion criteria were excluded because of being rated poor quality, despite being rated quality during data reviewing.

Table 1 Published studies of thoracic organ transplant recipients examining smoking behavior

Author (year)	Study type	Organ	Number (n)	Pretransplant smoking (%)	Definition	Smoking resumption (%)	Diagnostic method
Ruttens *et al.*, 2014	Prosp	Lung	331	65	SR	12	SR, qUC, eCO
Vos *et al.*, 2010	Prosp	Lung	267	62	SR	11	SR, qUC, eCO
Evangelista *et al.*, 2009	Prosp	Heart	72	67	SR	25	SR, sUC
Botha *et al.*, 2008	Prosp	Heart	380	–		15–27	qUC
De Geest *et al.*, 2005	Review	Heart	–	–		6–35	SR, qUC, eCO
Evon *et al.*, 2005	Prosp	Lung	45	16–72	SR	0	SR
Basile *et al.*, 2004	Prosp	Heart	103	66	SR	12	SR
Riha *et al.*, 2001	Prosp	Heart	159	37	SR	16	SR, eCO
Nägele *et al.*, 1997	Prosp	Heart	84	–	–	26	COHb
Mehra *et al.*, 2005	Prosp	Heart	86	–	–	33	SR, qUC
Bauldoff *et al.*, 2015	Retro	Lung	34	–	–	15	SR, sUC
Rea *et al.*, 2006	Retro	Lung	554	63	SR	7	Not specified
Zmeškal *et al.*, 2015	Prosp	Lung	53	–	–	15	qUC
Dew *et al.*, 2008	Prosp	Heart, lung	126 He, 178 Lu	–	–	1–8	SR
Dew *et al.*, 1998	Prosp	Heart	145	–	–	11–23	SR

SR, self-report; prosp, prospective; retro, retrospective; He, heart; Lu, lung; sUC, semi quantitative urine cotinine; qUC, quantitative urine cotinine; eCO, exhaled carbon monoxide; COHb, carboxyhemoglobin.

Systematic screening of smoking resumption after thoracic organ TPL

Different diagnostic methods have been suggested to identify nicotine consumption including self-report, semi quantitative and quantitative urine cotinine levels, serum cotinine levels, exhaled carbon monoxide (CO) or carboxyhemoglobin (COHb). CO can be measured in expired air or in the blood, COHb only in the blood using spectrophotometry. Both levels are highly correlated (23,24). CO has limited sensitivity in detection of light smoking because CO levels from smoking are low and can be influenced by environmental sources (i.e., air pollution, open fires) (25). Nicotine itself can be directly measured in the urine, blood or saliva and is in the absence of NRT highly specific, but not a feasible method due to its short half-life (18). Cotinine, a metabolite of nicotine, can be measured in the plasma and urine. Using a cutoff value of 15 and 50 ng/mL, respectively has the highest specificity (99%) and sensitivity (96%) for tobacco use (23,26).

At routine follow-up visits, however, smoking is mostly assessed only by questionnaire. In previous studies, self-report has shown a limited sensitivity of 25–85% for smoking resumption (27,28). Despite its high sensitivity and specificity, quantitative cotinine measurements are seldom used in routine patient encounters. Given the low prevalence of smoking resumption in a TPL cohort, systematic screening should only rely on quantitative cotinine measurements at routine follow-ups to identify smokers and thus identify patients for appropriate treatment.

Prevalence and consequences of smoking resumption

There are only few data available concerning the prevalence of smoking resumption in TOT recipients (*Table 1*). Rates of tobacco resumption range between 6–35% in heart and 0% to 15% in lung recipients (29-32). Of note, diagnostic assessments vary strongly in the considered studies (i.e., self-report, semi- and quantitative cotinine measurements, exhaled CO or COHb) (*Table 1*).

In mouse models, immunologic pathways potentially

linking tobacco smoking to organ rejection have been identified. Messenger-RNA (mRNA) and protein expression of indoleamine 2,3-dioxygenase (IDO) is suppressed by tobacco smoking (17). IDO is expressed by antigen-presenting cells and metabolizes tryptophan to serotonin and kynurenine, both of which are involved in T-cell apoptosis and induction of regulatory T cells, pivotal aspects in allograft regulation and survival (17). Combustible tobacco contains over 60 well-established carcinogens, including polycyclic aromatic hydrocarbons, aromatic amines, aldehydes, *N*-nitrosamines, volatile organic compounds (VOCs) and metals (33). Through metabolic activation, generally catalyzed by CYP-450, carcinogens can covalently bind to DNA and form DNA-adducts leading to miscoding during replication (4). Other pathways (e.g., activation of cytogenetic pathways or enzymatic hypermethylation) have been identified as drivers in smoking related carcinogenesis (33). Furthermore, the carcinogenic effects of tobacco combustion appear to have synergistic effects with immunosuppressive therapy (33). While an increasing number of studies have shown the carcinogenic adverse effects of smoking in liver transplant recipients, clinical trials regarding smoking resumption in heart or lung recipients, however, have been controversial (*Table 2*) (34-36). Only three prospective studies involving a total number of 795 patients have shown significantly higher rates of malignancy, but only Nägele *et al.* have described a reduced overall survival among patients with post-transplant nicotine resumption (27,37,38). These findings could be biased by the fact that patients with allograft dysfunction may be less prone to restart smoking than patients without such complications (*Figure 2*).

Risk factors associated with post-transplant smoking resumption

Prospective and retrospective studies of TOT patients examining risk factors for tobacco resumption are listed in *Table 2*. Interestingly, gender and age were not found to correlate with smoking resumption in any of the studies (27,28,31,37-42). Underlying diagnosis was found to be an independent risk factor for smoking resumption (27,37,39,42). This concurs with the implication of tobacco consumption in the pathogenesis of various pulmonary diseases, typical examples being emphysema and COPD. Regarding the smoking behavior before TPL, a short abstinence period before TPL was found to be an independent risk factor for resumption in all studies addressing this issue (27,28,37,39-42). Of interest, the number of packyears, a well-known surrogate for the degree of tobacco exposure and correlated risk of disease, was not shown to be a risk factor for resumption in 3 of 4 studies (27,39,41,42). Exposure to secondhand smoking (ESHS) was found to be a risk factor in two studies (27,39,41). Very little is known about pretransplant psychological testing of the risk for tobacco use resumption. In 2004, Basile *et al.* assessed patients before heart TPL using the Minnesota Multiphasic Personality Inventory (MMPI) (40,43). MMPI is a standardized psychometric test used to evaluate and describe personality and psychopathology. The authors concluded that patients who ceased smoking within one year before being included in the waiting list in combination with a lower degree of self-control and difficult adaptation scales are at risk for tobacco resumption (*Table 2*).

Smoking cessation interventions in transplant recipients

In recent years, considerable improvements in non-pharmacological and pharmacological interventions for smoking cessation have been made (44). Studies on interventions for TOT are scarce. A large meta-analysis by Cahill *et al.* involving a total of 267 studies (from non-transplant settings) and over 100,000 patients analyzed the treatment effects of the most relevant and widely used pharmacotherapies for smoking cessation (45).Varenicline has shown the highest probability of biochemically validated abstinence at 6 and 12 months [odds ratio (OR) 2.88, 95% confidence interval (CI): 2.40–3.47], followed by NRT (OR 1.84, 95% CI: 1.71–1.99) and bupropion (OR 1.82, 95% CI: 1.60–2.06) (45).

Counseling strategies alone, including motivational interviewing and cognitive behavioral therapy, have shown limited efficacy in smoking cessation (brief advice to quit: OR 1.66, 95% CI: 1.42–1.94; telephone counseling: OR 1.56, 95% CI: 1.38–1.77 and a combination of pharmacotherapies and counseling: OR 1.83, 95% CI: 1.68–1.98) (46-48).

None of the reviewed studies suggested or described smoking cessation strategies, safety, tolerance and effectiveness in TOT patients. This lack of information concerning smoking cessation interventions in this population draws attention to a field that needs to be investigated in future clinical trials.

Nicotine acts on nicotinic cholinergic receptors in the mesolimbic system releasing dopamine and serotonin, which

Table 2 Patient characteristics and outcomes associated with posttransplant nicotine resumption

Author (year)	Study type	Organ	Number (n)	Sex	Age	Underlying diagnosis	Packyears	Cessation duration prior to TPL	ESHS	Outcome
Ruttens *et al.*, 2014	Prosp	Lung	331	No correlation	No correlation	Emphysema (P<0.001)	No correlation	Short (12 *vs.* 72 months, P<0.001)	Yes (P<0.001)	Higher incidence of malignancy (P=0.048)
Vos *et al.*, 2010	Prosp	Lung	267	No correlation	No correlation	Emphysema (P<0.001)	No correlation	Short (12 *vs.* 60 months, P<0.001)	Yes (P<0.001)	–
Evangelista *et al.*, 2009	Prosp	Heart	72	–	No correlation	–	–	<12 months (P=0.008)	–	–
Botha *et al.*, 2008	Prosp	Heart	380	No correlation	–	No correlation	–	<6 months (P<0.001)	–	Higher incidence of GCAD and malignancy (P=0.006)
Basile *et al.*, 2004	Prosp	Heart	103	–	–	–	–	<12 months (P=0.006)	–	–
Nägele *et al.*, 1997	Prosp	Heart	84	No correlation	No correlation	–	–	–	–	Reduced 5- and 10-year survival (P<0.001), higher prevalence of transplant vasculopathy (P<0.001), higher incidence of malignancy (P<0.001)
Mehra *et al.*, 2005	Prosp	Heart	86	No correlation	No correlation	–	No correlation	<6 months (P<0.01)	No correlation	–
Bauldoff *et al.*, 2015	Retro	Lung	34	–	–	–	–	–	–	Decreased PFT (P=0.09)
Rea *et al.*, 2006	Retro	Lung	554	–	–	COPD	High packyear history	Short (38 *vs.* 107 months, P<0.001)	–	No impact on overall survival or development of BOS

Prosp, prospective; retro, retrospective; COPD, chronic obstructive pulmonary disease; packyears, cigarette packs smoked per day multiplied by the number of years as a smoker; TPL, transplantation; ESHS, exposure to secondhand smoking; GCAD, graft coronary artery disease; PFT, pulmonary function testing; BOS, bronchitis obliterans syndrome.

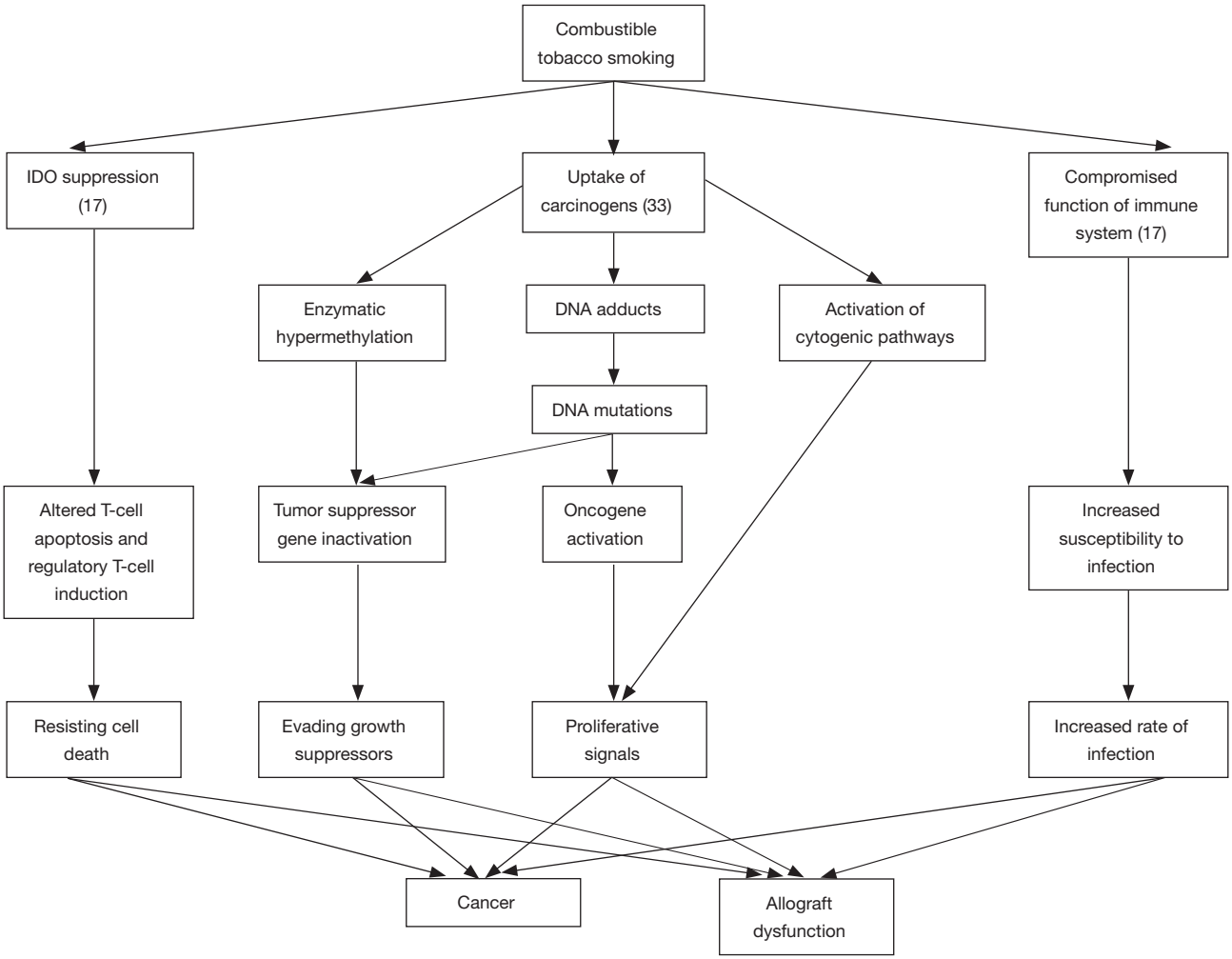

Figure 2 Link between cigarette smoking, allograft dysfunction and cancer (17,33). IDO, indoleamine 2,3-dioxygenase.

sustains addiction (21). Nicotine is metabolized primarily by cytochrome P-2A6 (CYP2A6) (18). Pharmacologic studies have observed a slight induction of CYP2A6 by commonly used immunosuppressive drugs (i.e., cyclosporine A, tacrolimus, mycophenolate mofetil). However, a clinically relevant increased nicotine metabolism or withdrawal symptoms remains under question (49). NRT therapy is generally considered to be safe and can be used in transplant recipients as in the general population (50).

Varenicline, a nicotinic acetylcholine receptor partial agonist, is the most widely used and most efficient smoking cessation drug available (51). Because of its reported side effect profile, it should be prescribed in patients with a history of neuropsychiatric disorders (e.g., depression, suicidal ideation, dysthymia) only when in a stable condition with or without medication (44,52). A large meta-analysis of randomized controlled trials did not find relevant adverse effects of varenicline on cardiovascular safety that had previously been considered problematic (53). This finding is especially relevant for transplant recipients, who are already at an increased risk for cardiovascular events due to their immunosuppressive regimen (54). Varenicline is reported to have a low interaction potential (to date reported to be limited to cimetidine) (55). Although this has not specifically been studied in transplant recipients this lack of pharmacological interactions in the context of polymedicated transplant recipients may be considered an advantage for smoking cessation interventions in this population.

The most important side effect of bupropion, a norepinephrine-dopamine reuptake inhibitor (NDRI) and nicotinic antagonist, is an increased risk for epileptic seizures (19). In addition to drug interactions, some

common drugs in TPL medicine (e.g., cyclosporine, tacrolimus, prednisone and beta-lactam antibiotics) can also lower seizure threshold (56). Another contraindication for bupropion is a decreased liver function. Patients with CF, the third most common underlying diagnosis for lung TPL after COPD and ILD worldwide, commonly have hepatobiliary dysfunction (i.e., biliary cirrhosis, cholelithiasis, cholestasis and portal hypertension) (5,10,57). Additionally, macrolides and sulfonamides, being well-established antibiotics also used post-transplant, are associated with acute and chronic drug induced liver injury (DILI), characterized by continued elevation (>2× the upper limit of normal) in alanine aminotransferase (ALT) (58,59). In case reports, the use of bupropion has also been linked to a reduced clinically effective concentration of cyclosporine (60).

Electronic cigarettes (e-cigarettes), are increasingly popular devices that produce an aerosol by heating a liquid containing solvents (glycerin, propylene glycol), flavorings and nicotine (61). The efficacy of e-cigarettes as a smoking cessation or reduction intervention remains uncertain due to the limited data available from randomized controlled trials. Dual consumption of tobacco cigarettes and e-cigarettes is a common finding, thus, making e-cigarettes a questionable smoking cessation aid for transplant recipients, who should achieve immediate and complete tobacco abstinence (62,63).

Cytisine acts, like varenicline, as a partial agonist of nicotinic acetylcholine receptors. Despite its proven efficacy and favorable cost-benefit ratio, its application in clinical settings, outside resource poor countries, is still very limited (64). In 2014, Walker *et al.* conducted a large noninferiority trial comparing cytisine versus NRT for smoking cessation (65). In this study, self-reported continuous abstinence from smoking at 1 month was reported in 40% of participants receiving cytisine (264 of 655) and 31% of participants receiving NRT (203 of 655) (95% CI of difference: 4.2–14.5). A main limitation of this trial remains the nicotine abstinence assessment relying only on self-report, instead of cotinine or exhaled CO measurements. In certain transplant patients, in whom varenicline or bupropion may be contraindicated, cytisine may be considered an alternative. However, studies supporting the effectiveness and safety of cytisine for smoking cessation in transplant recipients are missing.

Conclusion and future directions

Smoking resumption is an underestimated and under investigated issue in TPL medicine. Systematic screening of nicotine consumption based on quantitative cotinine measurements should be implemented in routine follow-up visits. As alternative, exhaled CO may be considered. Self-report or relying on clinical suspicion have a low sensitivity for tobacco detection and are inadequate methods without a systematic cotinine screening.

An increasing number of evidence suggests that smoking within 6 months prior to listing for TPL is a marker of poor outcome and may be associated with posttransplant smoking resumption. These findings challenge the 6-month abstinence rule in TPL enrollment of thoracic transplant recipients. However, instead of only considering prolonging the abstinence interval, more effort and resources should be invested in intensive smoking cessation interventions for patients with severe and end-stage lung diseases as routine standard of care. Other factors associated with smoking resumption are underlying diagnosis (COPD, emphysema) and ESHS. This highlights the importance of involving the patient's family in the smoking cessation programs prior to TPL. Future research should focus on the pre-transplant psychological assessment to better identify and understand high-risk patient profiles that are strongly associated with smoking resumption after TPL.

Due to the side effect profile and possible interactions, an experienced TPL physician familiar with both pharmacological and behavioral smoking cessation interventions should ideally provide pharmacological smoking cessation interventions for TOT recipients. Future clinical trials should assess safety, efficiency and tolerance of pharmacological smoking cessation drugs in TOT. If not contraindicated, NRT and varenicline should be preferred over bupropion based on efficacy and potential for interactions.

Patients and their relatives require access to professional smoking cessation interventions even long before being assessed for TOT, since a long abstinence period prior to TPL appears to be beneficial for relapse prevention.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Hofmann P, Benden C, Kohler M, Schuurmans MM. Smoking resumption after heart or lung transplantation: a systematic review and suggestions for screening and management. J Thorac Dis 2018;10(7):4609-4618. doi: 10.21037/jtd.2018.07.16

