OPEN

Poor Practitioner Adherence to Clinical Tobacco Use Guidelines in Liver Transplant Recipients

Claire Harrington, MD,[1] Megan Kosirog, MD,[1] Patrick Campbell, MD,[1] Dyanna Gregory, MS,[1] Amna Daud, MD, MPH,[4] Josh Levitsky, MD,[1] Jane L. Holl, MD, MPH,[5] Donald M. Lloyd-Jones, MD, ScM,[2,3] and Lisa B. VanWagner, MD, MSc[1,3]

Background. Tobacco use is a modifiable risk factor for cardiovascular events (CVEs) in liver transplant recipients (LTRs), but there is a paucity of data about practitioner adherence to tobacco cessation guidelines for LTRs. We sought to assess adherence to these guidelines as a predictor of CVEs after liver transplant. **Methods.** We conducted a retrospective, observational, cohort study of adult LTRs from 2010 to 2016 at a large urban, tertiary care transplant network. **Results.** Of 572 LTRs (mean age, 56.9; 64.1% male), 325 (56.8%) were never, 191 (33.4%) were former, and 56 (9.8%) were current tobacco users before liver transplant. Most LTRs (59%) had their tobacco use assessed annually by transplant providers. Among current users, documented tobacco cessation interventions decreased over time, and <25% were offered pharmacologic treatment or referral to counseling. There was no difference in CVEs between tobacco users who received cessation interventions compared with those who did not. **Conclusions.** This single-center study suggests that although tobacco use cessation counseling and interventions were not associated with a decrease in CVEs, evidence-based interventions for tobacco use were under utilized in this high cardiac risk population. These findings underscore missed opportunities for transplant practitioners to provide tobacco use cessation interventions to LTRs, which potentially could reduce CVEs.

(*Transplantation Direct* 2022;8: e1288; doi: 10.1097/TXD.0000000000001288).

INTRODUCTION

Use of tobacco products, which is a modifiable behavioral risk factor, remains the primary cause of preventable death in the general population in the United States.[1] There is a well-documented association between tobacco use and risk for cardiovascular events (CVEs), which are also a major cause of adverse outcomes after liver transplant (LT).[2,3] Smoking is known to cause inflammation, endothelial dysfunction, and alterations in lipid profiles in the general population that are all significant in the pathogenesis of atherothrombotic disease and cardiovascular

(CV) diseases.[4] Therefore, it is reasonable to extrapolate that tobacco use is a significant risk factor for CVEs in LT recipients (LTRs). This is important because the prevalence of tobacco use in LTRs due to alcohol-related liver disease has been documented to be as high as 58%.[5] Although this population may be at higher risk for tobacco use because alcohol and tobacco use are known to be associated, Ehlers et al found that 15% of LTRs (for any indication) still used tobacco after LT.[6] Despite this, there is a paucity of data about practitioner adherence in LTRs to the Surgeon General's guidelines,[1] a set of guidelines for tobacco cessation in the general population. Unfortunately, to date,

there are no guidance documents specifically written to address tobacco cessation in transplant populations. The purpose of this study was to assess practitioner adherence to the guidelines for tobacco cessation as a predictor of CVEs after LT.

MATERIALS AND METHODS

We conducted a retrospective, observational, cohort study using patient data from an electronic health record (EHR) from an urban, tertiary care hospital. IRB committee approval was obtained from Northwestern University for this study. Inclusion criteria included all patients 18 to 79 y old who underwent LT between January 1, 2010, and December 21, 2016. Patients who died within the first 6 mo after LT were excluded to assess CVEs in patients with stable immunosuppression and graft function. At this center, visits for LTRs are protocolized and established to occur weekly during the first month after LT, then at month 1, 2, 3, 4, 6, 9, 12, 18, 24, 30, and 36, and then yearly thereafter. Eligible LTRs were identified using International Classification of Diseases ninth or tenth revision (ICD-9 or ICD-10) codes, and clinical information was ascertained from the Northwestern Medicine Enterprise Data Warehouse, which contains clinical data for 7.5 million unique patients at all Northwestern Medicine sites. Supplemental manual chart review was used for data elements not easily captured in an EHR, such as clinical reasoning for not adhering to a clinical guideline (eg, documentation of why it would be inappropriate). Tobacco use was assessed using natural language processing to convert free text about tobacco use in clinical documentation in the EHR into a structured data for analysis, as described previously.[7] We utilized a combination of "cTAKES" for preprocessing and smoking status detection as well as "Textractor," which allowed for dictionary-based lookup.[7] This application has been shown to be very accurate with an overall microaveraged-F1-measure of 87.47%,[7] which is higher than any other current indicator type. Tobacco use status at time of listing, time of LT, and up to 6 y following transplant was manually reviewed for all patients identified as LTRs. Patients were classified as current, former, or never tobacco users. Tobacco cessation interventions were classified as counseling, pharmacologic treatment, and referrals. Documentation of "offered" was interpreted as an intervention that was considered by the clinician even if it was not completed by the patient. If no documentation was found in the EHR, then the intervention was considered as "not offered."

Comorbidities were identified, including chronic kidney disease (CKD, ICD-9/10 code or estimated glomerular filtration rate <60 mL/min/1.73m2 on at least 2 separate outpatient visits separated by ≥90 d) and diabetes (ICD-9/10 code or hemoglobin A1c ≥6.5%, random blood glucose >200 mg/dL, or use of glucose-lowering medication and prednisone daily dose ≤10 mg). Prevalences of CKD and diabetes changed over time during the follow-up period, were analyzed at yearly intervals and were measured up until April 30, 2021. Atherosclerotic CV disease was identified by ICD-9/10 code for pretransplant acute coronary syndrome, myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease. The primary outcome was a CVE, defined as death from a CV cause or hospitalization for myocardial infarction,

revascularization, heart failure, atrial fibrillation, cardiac arrest, thromboembolism, or stroke.

Statistical analysis was carried out by calculating yearly adherence scores based upon time from LT. Adherence scores were calculated using the method established by the Center for Medicare and Medicaid Services, defined as the number of LTRs in whom the tobacco cessation metric was offered divided by the total number of LTRs who were eligible for the tobacco cessation metric.[8,9] Clinical characteristics of the study sample of LTRs were described using frequency counts and percentages for categorical variables and means ± SDs for continuous variables. Chi-square analysis or Fisher exact test was used to assess associations between pretransplant clinical characteristics by smoking status. CVE rates per 1000 person-y were calculated according to documented smoking status in the EHR, and chi-square analysis was used to compare the standardized CVE rates. Cox proportional hazard models were used to estimate hazard of CVEs between LTRs who had tobacco use assessed at least once within the first year following LT and those who did not and between active and former/never smokers. Only CVEs that occurred at ≥360 d following LT were included in the analysis. Models were adjusted for sex and pretransplant atherosclerotic CV disease status and time-varying age, diabetes, or CKD.

RESULTS

Of 705 identified LTRs, 56 died within 6 mo of transplant (CV death n = 22), 47 had <1 y follow-up data (CVE n = 12), and 30 had no documented tobacco use status and were all excluded from the study sample. Of the remaining 572 LTRs (mean age, 56 y; 64% male, 61% non-Hispanic White) (Table 1), 325 (56.8%) were never tobacco users, 191 (33.4%) were former tobacco users, and 56 (9.8%) were current tobacco users pre-LT. There was no significant difference in tobacco use status between included and excluded LTRs (data not shown). Most LTRs (59%) had tobacco use assessed annually by LT practitioners, most commonly during the first year after LT (n = 352, 58.5%). Among current tobacco users, documented tobacco cessation counseling decreased over time from 50% in year 1 to 25% in year 6 with no significant decrease in the proportion of LTRs who were current tobacco users. Less than 25% of LTRs who were actively using tobacco after LT were offered pharmacologic treatment or referral for treatment (Figure 1).

During the post-LT period (mean follow-up time, 6 y; SD, 3.4 y), 175 (29.1%) LTRs who survived at least 6 mo post-LT experienced a CVE. The most common CVEs after the first year of LT were atrial fibrillation (33.1%), heart failure (26.3%), stroke (23.4%), and myocardial infarction/revascularization (12.0%). There was no difference in CVEs between LTRs with and without documentation of tobacco use status in the first year after LT (adjusted hazard ratio, 1.03; 95% confidence interval, 0.75-1.40; P = 0.38). There was a statistically significant difference in the unadjusted standardized CVE rate between active (51.8 CVE per 1000 person-y) and former/never (43.5 CVE per 1000 person-y) tobacco users (chi-square P = 0.02). In multivariable analysis adjusted for sex, pretransplant atherosclerotic CV disease status, and time-varying age, diabetes, and CKD status, there was no significant difference in CVE risk between post-LT active and former/never tobacco use (hazard ratio, 1.17; 95% confidence interval, 0.97-1.43; P = 0.10).

Pretransplant characteristics of liver transplant recipients stratified by smoking status posttransplant

	Overall (n = 572)	Never smokers (n = 325)	Former smokers (n = 191)	Current smokers (n = 56)	P
Age, mean (SD), y	56.9 (10.8)	56.0 (11.8)	59.2 (9.1)	54.4 (10.7)	0.0010
Male, n (%)	367 (64.1)	194 (59.7)	132 (69.1)	41 (73.2)	0.0325
Non-Hispanic White, n (%)	349 (61.0)	187 (57.5)	126 (66.0)	36 (64.3)	0.3370
Cause of liver disease, n (%)					
Hepatitis C	207 (36.2)	89 (27.4)	84 (44.0)	34 (60.7)	<0.0001
Alcohol	160 (28.0)	86 (26.5)	56 (29.3)	18 (32.1)	0.5994
NASH	71 (12.4)	52 (16.0)	18 (9.4)	1 (1.8)	0.0036
Myocardial infarction, n (%)	23 (4.0)	13 (4.0)	9 (4.7)	1 (1.8)	0.6183
Heart failure, n (%)	96 (16.7)	54 (16.6)	35 (18.3)	7 (12.5)	0.5865
Atrial fibrillation, n (%)	54 (9.4)	31 (9.5)	22 (11.5)	1 (1.8)	0.0904
Pulmonary embolism, n (%)	7 (1.2)	5 (1.5)	2 (1.1)	0 (0)	1.0000
Ischemic heart disease, n (%)	198 (34.6)	105 (32.3)	75 (39.3)	18 (32.1)	0.2539
Prior revascularization, n (%)	31 (5.4)	18 (5.5)	10 (5.2)	3 (5.4)	0.9891
Stroke/TIA, n (%)	70 (12.2)	33 (10.2)	30 (15.7)	7 (12.5)	0.1775

NASH, nonalcoholic steatohepatitis; TIA, transient ischemic attack.

Among post-LT active tobacco users, there was no difference in the unadjusted standardized CVE rate between those who received any cessation intervention (24.9 CVE per 1000 person-y) compared with those who did not (17.8 CVE per 1000 person-y, chi-square P=0.20). There were too few documented CVEs available to perform multivariable analysis (n=4 CVEs among LTRs who received an intervention versus n=3 CVEs among those who did not). When stratified by referral or pharmacotherapy received in the first year after LT, when such interventions were most common, there was still no statistical difference between active tobacco users who received an intervention (n=2 LTRs with documented CVEs) compared with those who did not (n=6 LTRs with documented CVEs, chi-square P=0.12).

DISCUSSION

Our study shows that although a majority of LTRs had their tobacco use assessed by LT practitioners in their first year post-LT, tobacco use cessation interventions post-LT decreased over time despite no change in the proportion of LTRs who were tobacco users and in spite of knowledge of the high CV risk in LTRs.[2,3] This phenomenon of decreased counseling over time has also been shown in patients with chronic obstructive lung disease where practitioners were frustrated by patients' lack of initiative to quit smoking despite the effect

on their health, which, in turn, hindered them from providing smoking cessation treatments.[10]

Despite the existence of evidence-based tobacco cessation treatments such as pharmacotherapy and behavioral therapy, this study shows that transplant providers caring for LTRs appear to underutilize them. Similar data have been observed in the general population in whom, according to reports from the National Ambulatory Medical Care Survey, 20.1% of current tobacco users reported receiving counseling or education on tobacco cessation, whereas only 3.8% received a prescription for tobacco cessation medication.[11] The rate of counseling provided to the general population is similar to the rate seen in our cohort at year 6 post-LT. There is a paucity of data investigating the prevalence of tobacco cessation interventions by practitioners in all transplant patients (including liver, heart, lung, and kidney transplant recipients). Although this study failed to demonstrate that tobacco cessation interventions are associated with a decrease in CVEs among LTRs, it is important to note that the low rates of tobacco cessation interventions being delivered to LTRs likely contributed to a lack of a statistically significant difference.

We did observe higher CVE rates among current compared with former/never tobacco users, though this association was attenuated in fully adjusted models. There has been a strong correlation in the literature between CV disease and smoking in renal transplant recipients with higher risk based on the amount of tobacco smoked over time.[12] Although the risk of tobacco use in LTRs is often extrapolated from the general and renal transplant populations, Leithead et al showed that active smoking is associated with greater mortality in LTRs.[3] Interestingly, the increased mortality was mostly attributed to nongraft-related causes, primarily CV and sepsis-related causes.[3]

This is significant because tobacco use, more so than many other risk factors for CVEs, is a preventable and modifiable risk factor that can impact mortality in this already high-risk population for CVEs. In the renal transplant population, one study showed that at 5 and 10 y posttransplant, the numbers needed to treat to prevent CVEs with smoking cessation were 7 and 4, respectively.[13]

Not only has tobacco use been shown to be associated with higher mortality due to CV conditions in LTRs; it has also
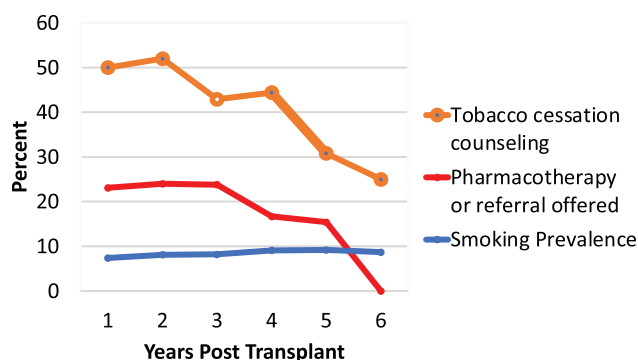

FIGURE 1. Tobacco cessation counseling and therapies offered over time among current tobacco users postliver transplant (n=589).

been shown to increase the risk for hepatic artery thrombosis and other vascular complications after LT.[14] In addition, smoking contributes to the development of bacterial cholangitis, lung, and oropharyngeal cancer, as well as other neoplasia after LT.[15-17] Tobacco use in the general population has also been associated with increased likelihood of alcohol use relapse, which is an important consideration with further implications in LTRs who required transplant secondary to alcohol-related liver disease.[18]

Therefore, tobacco use is clearly a significant risk factor that impacts mortality and morbidity in LTRs. The Surgeon General's guidelines for treatment of tobacco dependence provide guidelines for the general population and include behavior counseling and pharmacologic interventions.[1] Effective behavioral counseling includes cognitive behavioral therapy,[19] motivational interviewing,[20] and incentive-based interventions.[21] Behavioral therapies have been shown to have a significant "dose response," meaning that with longer duration and time invested in counseling, patients have more sustained tobacco cessation.[22] There are also several FDA-approved medications to assist in tobacco cessation, including 5 nicotine-based medications (gum, patch, lozenge, nasal spray, oral inhaler) in addition to bupropion and varenicline.[1] There are no absolute contraindications to any of the nicotine-based medications.

It is important to note that both bupropion and varenicline have not been studied in the LTR population. Varenicline is a partial agonist of the α4ß2 nicotine acetylcholine receptor subtype, which is the main receptor that mediates tobacco use and nicotine addiction.[1] By having only 50% of the activity of nicotine, it is able to alleviate some of the symptoms of nicotine withdrawal without activating the reward circuit.[23] Varenicline may be favorable in LTRs, as 92% of it is excreted as urine, and it is largely not metabolized by the liver.[24] It is recommended to initiate varenicline 1 wk before tobacco cessation starting at 0.5 mg/d and then increasing to 0.5 mg twice a day on day 4 and to 1 mg twice a day on day 7, which is the maximum recommended daily dosing.[25] There are no absolute contraindications to administering varenicline, and the primary side effects are headache, nausea, depression, and suicidal ideation.[24] Of note, the EAGLES trial showed that the frequencies of neuropsychiatric events in both a nonpsychiatric and psychiatric cohort were 3% and 7%, respectively, allowing the FDA to remove this as a boxed warning in 2016.[26]

Bupropion is a medication that was initially marketed as an antidepressant but was found to have some nicotine receptor-blocking activity with the ability to help aid tobacco cessation in the absence of depression.[27,28] Contraindications to bupropion include seizure disorder, concomitant diagnosis of bulimia or anorexia nervosa, use of monoamine oxidase inhibitors in the prior 14 d, and any other conditions that would decrease one's seizure threshold.[1] It is also important to note that bupropion should also be used with caution in LTRs, as it is rarely associated with clinically significant liver injury.[29]

Behavioral therapy and pharmacological interventions are known to be synergistic, and the combination is considered as the "gold standard" in tobacco cessation treatment in the general population.[22] In addition to these interventions, Seijo-Bestilleiro et al have shown that the measurement of exhaled carbon monoxide by co-oximetry, in addition to brief advice for smoking cessation, leads to a significant decrease in tobacco use in renal transplant recipients,[30] which could potentially be extrapolated to the LTR population.

Multiple factors may contribute to poor adherence to tobacco use cessation guidelines, including clinical time constraints and a lack of awareness or insufficient expertise in providing effective counseling. One proposed strategy suggests that hepatologists could assist with implementing tobacco cessation interventions by using the US Public Health Service guidelines of the "five A's" (Ask about tobacco use, Advise smoker to quit, Assess willingness to quit, Assist with quitting, and Arrange for follow-up) during the frequent office visits required pre-LT.[31]

Another barrier may be a failure in allocation of roles. A study in 2009 revealed that a majority of transplant hepatologists usually assume long-term overall care of their LTRs.[32] Interestingly, although, most hepatologists also noted that hypertension, diabetes, and hyperlipidemia should be managed by a primary care physician (PCP), which in reality was happening less frequently. Only 2% of hepatologists identified a PCP as a member of the posttransplant care team.[32] More recently, our group published a study that characterized perceptions about CV care after LT to inform the design of solutions to improve care, such as tobacco cessation. Notably, only 13.6% of providers (transplant and nontransplant) were confident in their ability to help the LTR stop tobacco use.[33] Also, when asked which healthcare team should be primarily responsible for treating risk factors for heart disease (including tobacco use) after LT, there was a discrepancy where a majority of LTRs and their caregivers felt that the transplant provider should be responsible for providing this care, whereas the vast majority of healthcare providers felt that PCPs should be performing this care.[33] These data highlight a miscommunication and gap in care between the PCP, the transplant team, and LTRs. Future studies aiming to improve care delivery must address this barrier to tobacco cessation interventions.

As the volume of LTRs increases, it is also imperative to emphasize the importance of interprofessional collaboration with the patient's PCP as well as psychosocial colleagues ranging from psychiatry, psychology, social work, and addiction medicine to assist in the effective implementation of tobacco cessation interventions. Therefore, although the onus of tobacco cessation does not fall completely on the transplant hepatologist, it is important to emphasize the need for close communication between the PCP and the hepatologist to ensure that the patient is receiving the tobacco cessation counseling that he/she deserves from at least 1 member of their care team.

This issue of tobacco cessation becomes more pressing as transplant centers begin to account for the increase in tobacco-associated mortality pre- and post-LT. In a 2015 study, 75% of LT centers that responded to a survey had a policy on smoking with a majority of those centers requiring complete cessation before transplant[34]; however, whether these policies are durable and result in long-term smoking cessation after LT is not known. Our center does not have a tobacco cessation policy, and tobacco use has never been an absolute contraindication to transplant. This study may be a helpful catalyst to help advocate for a structured tobacco cessation counseling process both pre- and posttransplant.

There are several potential limitations to this study. It is a single transplant center study, which limits the generalizability. Therefore, our findings need to be corroborated in larger studies. Also, due to the lack of power of this study, we did not include other outcomes related to tobacco use such as chronic obstructive pulmonary disease or malignancy. In addition, this

is a retrospective study and, therefore, is unable to accurately assess how much and what type (cognitive behavioral therapy, motivational interviewing, or incentive-based) of counseling or therapy was delivered during any specific visit, as well as if and what type of pharmacotherapy was ultimately used by the patient. Due to the retrospective study design, we were also unable to assess the reason for practitioners' poor adherence to clinical tobacco use guidelines as well as the possibility that patients could have received counseling from another healthcare provider, which would not be captured by our study. We also recognize a potential for detection bias, as some patients may have been offered tobacco cessation interventions by other providers not captured by the EHR.

In conclusion, we have demonstrated that current tobacco use among LTRs is associated with increased rates of CVEs, which is a leading cause of morbidity and mortality after LT. Unfortunately, we also demonstrate that tobacco cessation interventions are inconsistently delivered by transplant providers at a large, urban, transplant center. These findings provide the critical scientific rationale to study health interventions with the potential to increase identification, timely referral, and interventions for tobacco cessation in this high CV-risk population. Future multicenter studies with adequate power to determine the effectiveness and efficacy of tobacco use interventions, including behavioral counseling as well as pharmacotherapy, in LTRs are needed to demonstrate clinical benefit, particularly in terms of reducing CVEs as well as mortality, malignancy, and chronic obstructive pulmonary disease. Such studies ideally would use mixed method approaches to further elucidate the barriers and facilitators for transplant providers to offer and deliver tobacco cessation interventions to LTRs. There is a glaring need for the identification of and effect of quality improvement efforts aimed at improving adherence to evidence-based interventions, such as tobacco use cessation, to reduce CVEs and improve long-term outcomes after liver transplantation; our study is the first to highlight this pressing need.

REFERENCES

1. U.S. Department of Health and Human Services. *Smoking cessation: a report of the Surgeon General*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2020.
2. van der Heide F, Dijkstra G, Porte RJ, et al. Smoking behavior in liver transplant recipients. *Liver Transpl.* 2009;15:648–655.
3. Leithead JA, Ferguson JW, Hayes PC. Smoking-related morbidity and mortality following liver transplantation. *Liver Transpl.* 2008;14:1159–1164.
4. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol.* 2004;43:1731–1737.
5. DiMartini A, Javed L, Russell S, et al. Tobacco use following liver transplantation for alcoholic liver disease: an underestimated problem. *Liver Transpl.* 2005;11:679–683.
6. Ehlers SL, Rodrigue JR, Widows MR, et al. Tobacco use before and after liver transplantation: a single center survey and implications for clinical practice and research. *Liver Transpl.* 2004;10:412–417.
7. Khalifa A, Meystre S. Adapting existing natural language processing resources for cardiovascular risk factors identification in clinical notes. *J Biomed Inform.* 2015;58(Suppl):S128–S132.
8. Nolan T, Berwick DM. All-or-none measurement raises the bar on performance. *JAMA.* 2006;295:1168–1170.
9. Ryan AM. Effects of the premier hospital quality incentive demonstration on medicare patient mortality and cost. *Health Serv Res.* 2009;44:821–842.
10. van Eerd EAM, Bech Risør M, Spigt M, et al. Why do physicians lack engagement with smoking cessation treatment in their COPD patients? A multinational qualitative study. *NPJ Prim Care Respir Med.* 2017;27:41.
11. Jamal A, Dube SR, Malarcher AM, et al; Centers for Disease Control and Prevention (CDC). Tobacco use screening and counseling during physician office visits among adults–National Ambulatory Medical Care Survey and National Health Interview Survey, United States, 2005-2009. *MMWR Suppl.* 2012;61:38–45.
12. Kasiske BL, Klinger D. Cigarette smoking in renal transplant recipients. *J Am Soc Nephrol.* 2000;11:753–759.
13. Valdés-Cañedo F, Pita-Fernández S, Seijo-Bestilleiro R, et al. Incidence of cardiovascular events in renal transplant recipients and clinical relevance of modifiable variables. *Transplant Proc.* 2007;39:2239–2241.
14. Pungpapong S, Manzarbeitia C, Ortiz J, et al. Cigarette smoking is associated with an increased incidence of vascular complications after liver transplantation. *Liver Transpl.* 2002;8:582–587.
15. Herrero JI, Lorenzo M, Quiroga J, et al. De novo neoplasia after liver transplantation: an analysis of risk factors and influence on survival. *Liver Transpl.* 2005;11:89–97.
16. Perney P, Segalas F, Nalpas B, et al. Impact of tobacco and alcohol consumption in patients registered on waiting list on early morbidity following liver transplantation. *Clin Res Hepatol Gastroenterol.* 2013;37:473–478.
17. Johnston SD, Morris JK, Cramb R, et al. Cardiovascular morbidity and mortality after orthotopic liver transplantation. *Transplantation.* 2002;73:901–906.
18. Weinberger AH, Platt J, Jiang B, et al. Cigarette smoking and risk of alcohol use relapse among adults in recovery from alcohol use disorders. *Alcohol Clin Exp Res.* 2015;39:1989–1996.
19. Perkins KA, Conklin CA, Levine MD. *Cognitive-behavioral Therapy for Smoking Cessation: A Practical Guidebook to the Most Effective Treatments*. 1st ed. Routledge; 2008.
20. Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. *Cochrane Database Syst Rev.* 2015;2:CD006936.
21. Cahill K, Hartmann-Boyce J, Perera R. Incentives for smoking cessation. *Cochrane Database Syst Rev.* 2015;18:CD004307.
22. Tobacco Use and Dependence Guideline Panel. *Treating Tobacco Use and Dependence: 2008 Update*. U.S. Department of Health and Human Services; 2008.
23. Aubin HJ, Luquiens A, Berlin I. Pharmacotherapy for smoking cessation: pharmacological principles and clinical practice. *Br J Clin Pharmacol.* 2014;77:324–336.
24. UpToDate. *Varenicline: drug information*. 2021. Available at https://www-uptodate-com.ezproxy.galter.northwestern.edu/contents/varenicline-systemic-drug-information?search=varenicline&source=panel_search_result&selectedTitle=1~33&usage_type=panel&display_rank=1&showDrugLabel=true. Accessed October 21, 2021.
25. Pfizer. *Medication guide: Chantix (varenicline) tablets*. 2019. Available at http://labeling.pfizer.com/ShowLabeling.aspx?id=557&section=MedGuide. Accessed October 21, 2021.
26. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomized, placebo-controlled clinical trial. *Lancet.* 2016;387:2507–2520.
27. Slemmer JE, Martin BR, Damaj MI. Bupropion is a nicotinic antagonist. *J Pharmacol Exp Ther.* 2000;295:321–327.
28. Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med.* 1997;337:1195–1202.
29. Little MA, Ebbert JO. The safety of treatments for tobacco use disorder. *Expert Opin Drug Saf.* 2016;15:333–341.
30. Seijo-Bestilleiro R, Seoane-Pillado T, Pertega-Diaz S, et al. Randomized clinical trial to determine the effectiveness of CO-oximetry and anti-smoking brief advice in a cohort of kidney transplant patients who smoke. *Int J Med Sci.* 2020;17:2673–2684.
31. Muñoz SJ. Tobacco use by liver transplant recipients: grappling with a smoking gun. *Liver Transpl.* 2005;11:606–609.
32. Heller JC, Prochazka AV, Everson GT, et al. Long-term management after liver transplantation: primary care physician versus hepatologist. *Liver Transpl.* 2009;15:1330–1335.
33. VanWagner LB, Gordon E, Adamski L, et al. Liver transplant recipient, caregiver, and provider perceptions of cardiovascular disease and related risk factors after transplant. *Liver Transpl.* 2021;27:668–683.
34. Fleetwood VA, Hertl M, Chan EY. Liver transplantation to the active smoker: transplant provider opinions and how they have changed: transplantation in smokers: a survey. *J Gastrointest Surg.* 2015;19:2223–2227.