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Helping Patients With ESRD and Earlier Stages of CKD to Quit Smoking

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Abstract

Among the many adverse effects of tobacco exposure is the increased risk for progression of kidney disease. Individuals with chronic kidney disease (CKD), who already face increased cardiovascular event rates compared to the general population, are at even greater risk if they smoke. Despite these risks and the increased focus on smoking cessation in the general population in recent years, national guidelines have not specifically targeted individuals with CKD. There are similarly sparse data specific to individuals with CKD regarding the safety and efficacy of evidence-based smoking cessation modalities. This review aims to identify the risks of nicotine dependence in individuals with CKD and the potential benefits of smoking cessation, to discuss current strategies for smoking cessation including behavioral and pharmacologic therapies such as varenicline, and to extrapolate these interventions to the unique challenges of this population. Much of the data presented stem from evidence for the general population but are described with additional consideration in dosing of nicotine replacement therapy as well as non-nicotine pharmacotherapy and treatment modality for individuals with CKD.

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In Practice is a focused review providing in-depth guidance on a clinical topic that nephrologists commonly encounter. Using clinical vignettes, these articles illustrate a complex problem for which optimal diagnostic and/or therapeutic approaches are uncertain.

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Keywords

smoking cessation; chronic kidney disease (CKD); chronic kidney failure; cigarette smoking; nicotine dependence; varenicline; tobacco; electronic cigarettes; nicotine replacement therapy (NRT); bupropion; dialysis; end-stage renal disease (ESRD); review

Background

Approximately 20% of the world's population smokes cigarettes and tobacco use is a major contributor to disease burden.¹ In 2013, six million deaths worldwide were attributable to tobacco use, making tobacco use a leading cause of death even in developed countries, despite its decreasing prevalence.² Meanwhile, the growing use of non-combustible tobacco products such as electronic cigarettes (EC) over recent years, particularly amongst current smokers and young adults³, introduces new questions about the effects of these products on long-term health. Harm begins with a single cigarette and smoking has demonstrated a dose-dependent association with all-cause mortality even after accounting for other behavioral and social determinants of health.⁴ Smoking is a known risk factor for multiple chronic conditions, including cardiovascular disease, lung disease, and cancers.

Smoking was first described as a risk factor for chronic kidney disease (CKD) in individuals with diabetes, and more recent evidence has shown it is a risk factor for the development of CKD in the general population.⁵ Furthermore, of the individuals with kidney disease requiring dialysis, around fifteen percent report current tobacco use.⁶ Despite these risks, little evidence on smoking cessation in this vulnerable population exists. Much of our understanding stems from the general population, but herein we offer a more detailed understanding of the mechanisms of harm in individuals with CKD who smoke and the associated outcomes, review best practices and evidence-based guidelines for smoking cessation, provide information for renal dosing of pharmacotherapies, and share recent evidence on non-combustible products like electronic cigarettes.

Mechanisms of harm from smoking in CKD

Observational studies demonstrate that smoking adversely affects kidney function, but the biologic mechanisms through which this occurs remain incompletely understood. A study of kidney biopsies from smokers and non-smokers does show histopathological differences between the two groups: smokers have a two-fold increase in the degree of myointimal hyperplasia of small arteries.⁷ Studies on the mechanisms of kidney injury from smoking can provide background for nephrologists interested in understanding the unique importance of smoking cessation in their at-risk patients and patients with established CKD.

Both non-hemodynamic changes and hemodynamic-mediated changes may cause kidney damage in smokers.^{8,9} Proposed non-hemodynamic-mediated mechanisms through which smoking causes kidney damage include oxidative stress, decreased bioavailability of nitric oxide, increased endothelin 1 concentration, tubular cell damage, and increased vasopressin secretion.⁹ Insulin resistance, which has been associated with smoking¹⁰ and with reduced GFR¹¹ may also contribute adversely to kidney function over time. Heightened

inflammatory state has also been shown to result from cigarette smoking¹² and to be associated with declining kidney function.¹³ The hemodynamic-mediated changes include a transient but significant increase in blood pressure from smoking initiation.^{14,15} These transient increases in systemic blood pressure have been associated with kidney disease progression.^{16–20} The role of sympathetic overactivity as a direct mediator of smoking-induced changes in renal hemodynamics was examined in a study of occasional smokers without kidney disease who were pre-treated with prazosin and atenolol.²¹ Pre-treatment with prazosin compared to placebo showed no difference in GFR, filtration fraction (FF), renal plasma flow (RPF), or renal vascular resistance (RVR). In contrast, pretreatment with atenolol compared to placebo led to smaller decreases in active renin, GFR and RVR after smoking onset. These results suggest that beta-adrenergic-mediated mechanisms and effects on the renin-angiotensin system may be partly responsible for smoking-induced changes in kidney hemodynamics. This hypothesis is also supported by data that showed a protective effect of ACE inhibitors in the progression of kidney disease in patients who smoke.²²

Outcomes from smoking in individuals with CKD

Individuals with CKD have increased risk of cardiovascular disease²³ and smoking is a well-established risk factor for cardiovascular disease.²⁴ However, the risks of smoking specific to individuals with established kidney disease are less apparent, as there have been no randomized controlled trials and the quality of evidence is weak. A relatively small number of observational studies have examined the risk of mortality, CKD progression, and vascular events associated with smoking among patients with CKD (Table 1). Two multicenter prospective cohort studies indicated that smoking adversely affects mortality and cardiovascular events in patients with CKD; however, there is significant heterogeneity between the studies and the association of smoking with CKD progression remains unclear. While more evidence regarding the outcomes of smokers with CKD is warranted, the various outcomes described in Table 1 provide some evidence for nephrologists to identify active smokers in their patients and offer evidence-based therapeutic options.

Benefits of smoking cessation

Smoking cessation decreases proteinuria in patients with CKD and type 2 diabetes and slows progression to ESRD.^{22,25–27} Despite the benefits from smoking cessation in patients with CKD, scant data for these patients are available in guidelines on smoking cessation. Certain subgroups are addressed in national guidelines, including pregnant women, black and minority ethnic groups, children and adolescents, individuals with mental illness or substance use disorders, and individuals with cardiovascular disease. No smoking cessation guidelines specific to individuals with CKD exist.²⁸ Nevertheless, it is reasonable to assume that the benefits of smoking cessation (i.e. decreased mortality; improved lung function; and reduced rates of cardiovascular disease, stroke, and cancer) for the general population and other chronic disease conditions are also applicable to individuals with CKD.

Smoking Cessation Interventions

Overview

Data regarding the effectiveness of accepted modalities for smoking cessation applied to individuals with CKD are similarly lacking but can be extrapolated from recommendations for the general population. These recommendations vary by country, particularly in regards to recommended use of specific pharmacotherapies. The available smoking cessation guidelines from English-speaking countries are further detailed in Table 2. As discussed below, meta-analyses suggest that the best outcomes are achieved when behavioral interventions are used in combination with pharmacotherapies. The steps for smoking cessation are outlined in Fig 1.²⁹

Advice and behavioral therapies

Successful intervention begins with identifying smokers and offering appropriate interventions based upon the individual's level of motivation to quit. A recommended method endorsed by many of the clinical guidelines is the "5 A's" method: Ask, Advise, Assess, Assist, and Arrange.³⁰ Spending as little as one minute on each component is effective. The first "A" ("Ask") can be automated in the era of electronic health records. The National Health Interview Survey provides a standard two-question format to categorize patients as current every day smoker, current some day smoker, former smoker, or never smoker.³¹ The questions are as follows: (1) Have you smoked at least 100 cigarettes in your entire life? (2) If yes, do you now smoke cigarettes every day, some days, or not at all? This screening tool is recommended by the Institute of Medicine for use at screening and follow-up visits and is a simple method to quickly identify smokers.³²

The second "A" ("Advise") can be a simple recommendation to stop smoking, which has been shown to increase smoking cessation success by an additional three percent beyond an unassisted method.³³ Brief interventions offered in as little as three minutes have been shown to be more effective than usual care (RR, 1.7; 95% CI, 1.4-1.9)³³, and can help avoid early relapse as well as provide increased patient satisfaction with the provider.³³⁻³⁶ The third "A", "assessing" the patient's readiness to quit, should be performed with an understanding of the behavior change theory of "stages of change", which are briefly described in Table 3. This model identifies five different stages that individuals may go through when attempting behavior change, and has been shown to be an effective tool for identifying smoking cessation readiness, as well as assessment in readiness for other behavior change.³⁶⁻³⁹

Assessing the patient's readiness for change provides important information to help the healthcare provider understand which types of initial intervention may be effective for the patient and assist them in advancing to the next stage. For example, if a provider identifies that a patient is in the "precontemplation" stage, the goal for a single visit would not be cessation, but rather helping the patient move into the "contemplation" stage of change.³⁷

For patients who are in the precontemplation or contemplation stages of change, a valuable technique to promote behavioral change is motivational interviewing (MI).⁴⁰ Motivational interviewing is a non-judgmental and non-confrontational approach to helping patients

become more aware of potential problems or consequences of current behavior, and to allowing patients to self-identify potential benefits to changing the behavior. This method can be delivered either in-person or via telephone. While motivational interviewing may require both provider training and more time in a clinic visit, it was shown in a meta-analysis to be superior to brief advice techniques (RR, 1.3; 95% CI, 1.1-1.4).⁴¹ In patients that have spirometry available, estimation of “lung age” (the age of the average healthy individual who would perform similar to them on spirometry) is one proven motivational method for smoking cessation.⁴² In addition, describing the possible health risks for smokers with CKD (Table 1) may also motivate the patient. For patients with ESRD already receiving hemodialysis, dialysis sessions may provide a unique opportunity for extended in-person counseling on smoking cessation.

Beyond assessing the patient’s readiness to quit smoking and helping them to realize the benefits of cessation, it is crucial to address the final 2 A’s (“Assist” and “Arrange”) by providing appropriate and practical problem-solving skills for quitting and arranging follow up visits.⁴³ The provider and patient should set a quit date, and the patient should be encouraged to share this date with family and friends to garner support. Appropriate pharmacotherapy should be prescribed for patients who are ready to quit (Table 4), and patients should be counseled on nicotine withdrawal symptoms. Counseling should also be provided around anticipating and avoiding triggers (including alcohol) and utilizing evidence-based resources to achieve and maintain abstinence from smoking. For individuals who are prepared to quit, newer self-help tools such as online resources, mobile phone-based interventions, and quit lines offered by public health agencies are also helpful. Internet-based interventions have the advantages of being low- cost and accessible to patients at all times, and may be interactive and tailored to the patient.

These types of programs have demonstrated efficacy for successful smoking cessation (RR, 1.41; 95% CI, 1.11-1.78).⁴⁴ Mobile phone-based interventions are widely accessible and can be tailored to patient preferences. A meta-analysis of studies examining mobile phone-based programs not used as an adjunct to face-to-face or internet-based programs also demonstrated efficacy in achieving cessation (RR, 1.67; 95% CI, 1.46-1.90).⁴⁵ Examples of internet and phone-based resources are provided in Box 1.

Prompt follow-up should occur following the initial visit where the decision to quit was discussed because relapse risk is high within the first week from quit date.³⁶ Followup should include praise for abstinent patients and reappraisal for patients who relapse. The provider should acknowledge and accept the high likelihood of relapse in their patients attempting smoking cessation. Relapse, which constitutes smoking seven consecutive days or at least once weekly over two consecutive weeks⁴⁸, is common in smokers and providers should remain diligent in their efforts to provide smoking cessation counseling and therapy. The estimated number of quit attempts prior to successful smoking cessation varies widely in the literature, but may be as high as 30 attempts before the average smoker quits for a minimum of one year.⁴⁹ The process should be viewed as harm reduction in an attempt to achieve cessation and providers should remain diligent in their efforts with patients, maybe even more so in patients with CKD who encounter more baseline depression and anxiety and are possibly at higher risk for relapse. Furthermore, patients should be aware of discouraging

side effects during smoking cessation attempts such as weight gain or insulin resistance.⁵⁰ Weight gain can be ameliorated in the short-term with bupropion or nicotine replacement therapy (NRT).⁵¹ The patient in our case vignette is likely to resume smoking at some point, and the provider should anticipate a relapse event and a trained employee of the practice should provide close follow-up either in-person or by telephone. Again, the frequency and duration of hemodialysis sessions may provide a unique opportunity for ongoing followup for smoking cessation counseling and assessment in patients with ESRD.

Pharmacotherapy

NRT and medications intended to reduce cravings (bupropion and varenicline), in conjunction with counseling and behavioral therapy, are the mainstays of treatment for smoking cessation. While no studies specific to individuals with CKD are available, the pharmacologic interventions have well-proven efficacy in the general population. Nicotine replacement therapies are available in several formulations: transdermal patch, gum, lozenges, nasal spray, and oral inhaler. The patch, gum, and lozenges are available over-the-counter. Nicotine replacement therapy increases quit rates by 50-70%.⁵² Combination NRT, using the long-acting patch in addition to a short-acting nicotine agent, is also an effective option, outperforming single-agent NRT (ORs of 1.34-1.63 depending on the single agent).⁵³ The nicotine patch can also be used in combination with bupropion, and has superior outcomes to using a single-agent pharmacotherapy. The initial dose of nicotine replacement therapy is dependent on the average number of cigarettes a patient smokes in a day. With the average nicotine content absorbed from a standard cigarette being approximately 1 mg, the patch plus gum can help quench cravings not covered by patch alone, and may be particularly useful in smokers who consume at least a pack (20 mg of nicotine) per day.⁴³ Although the goal of NRT is to taper the dose over two to three months, it can be continued for longer periods of time in patients who are at high risk for relapse. Of note, nicotine replacement therapy can be initiated while a patient is still smoking.

First-line non-nicotine replacement therapies are bupropion and varenicline, which are both available by prescription only. Sustained-release bupropion is FDA-approved for the treatment of depression and for smoking cessation, though marketed under different trade names depending on the indication. It acts to reduce cravings, likely via inhibition of nonadrenergic or dopaminergic neuronal uptake, leading to increased norepinephrine and dopamine levels.⁵⁴ One advantage to using this therapy is the potential for mood effects in patients who also suffer from depression. Bupropion therapy increases smoking cessation by approximately 80% compared to placebo and is equally effective compared to single-agent NRT.⁵³ Using the nicotine patch and bupropion in combination provides additional benefit.⁵³ Initiation of bupropion therapy should begin one to two weeks prior to a pre-defined quit date. Bupropion undergoes extensive first-pass metabolism via the *CYP2B6* gene product and reaches central nervous system concentrations 10 to 25-fold greater than plasma concentrations, with a half-life of approximately 21 hours with chronic administration. The drug is primarily excreted renally⁵⁴, and a study in patients on dialysis showed accumulation in the circulating drug levels of bupropion and its metabolites without any overt clinical manifestations or organ dysfunction.⁵⁵ In patients with reduced kidney function but not on dialysis, the accumulation of bupropion drug levels occurs in absence of accumulation of its

metabolites.⁵⁶ Because bupropion is FDA-approved as a treatment for major depressive disorder, it may be a preferred option for patients who have major depressive disorder and are interested in smoking cessation. Bupropion can lower seizure threshold and is contraindicated in patients with seizure disorder.

Varenicline acts as a partial nicotinic receptor agonist selective for the $\alpha 4\beta 2$ receptor. The odds of smoking cessation using varenicline are more than doubled when compared with placebo (OR, 2.88; 95% CI, 2.40-3.47) and it has demonstrated superiority to both bupropion alone and single-agent NRT, but not combination NRT.⁵³ The drug is excreted in the urine unmetabolized. It reaches a maximal concentration between three and four hours after administration, with a steady state within four days and a half-life of 24 hours.⁵⁴ The pharmacokinetics are unchanged in patients with mild kidney disease (creatinine clearance [CLcr] between 50 and 80 mL/min), 1.5-fold increased in those with moderate kidney disease (CLcr between 30 and 50 mL/min), and 2.1-fold increased levels in those with severe kidney disease (CLcr < 30 mL/min). Patients with ESRD treated by hemodialysis have 2.7-fold increased levels following 0.5 mg once daily administration for 12 days, and dialysis has been found to efficiently remove varenicline from circulation.⁵⁷ Table 4 presents additional details for both NRT and non-NRT therapies with important considerations for patients with CKD.

Previously, both bupropion and varenicline had black box warnings about neuropsychiatric safety and increased risk for suicidality, but these warnings were removed after a randomized controlled trial found no increase in neuropsychiatric events in either drug when compared to NRT or control.⁵⁸ The increased risk for depressive symptoms in patients with CKD is still a concern, so it is important to screen patients for depressive symptoms and to continue to monitor for depression after initiation of treatment with either drug. Although it is not evident that our patient has depression, a brief two question screening for depression can be routinely performed on all patients with CKD. Using the Patient Health Questionnaire 2 (PHQ-2) with a cutoff of greater than or equal to three has a sensitivity of 83% and specificity of 92% for major depression.⁵⁹ When patients screen positive with the PHQ-2, it is typically recommended that the longer PHQ-9 be administered. Those with mood disorders or a history of suicidal ideation should receive consultation and close monitoring.⁶⁰ We recommend first attempting combination NRT in patients with unstable mood disorders or a history of recent suicidal ideation.

Combination behavioral and pharmacotherapy

The most effective method to achieve smoking cessation is combination behavioral and pharmacotherapy. A meta-analysis of 47 studies with > 18,000 participants analyzed combining pharmacotherapies (primarily NRT) with behavioral intervention (including tailored materials, brief advice, and in-person or telephone counseling) found a small but positive benefit from adding behavioral intervention to pharmacotherapy as compared to using pharmacotherapy alone (RR, 1.17; 95% CI, 1.11-1.24).²⁹

As previously mentioned, combining multiple pharmacotherapies also provides benefit. Using two forms of NRT outperforms single-agent NRT.⁵³ One non-blinded randomized trial showed that triple-combination therapy with a nicotine patch, nicotine oral inhaler, and

bupropion was more effective than the nicotine patch alone, with a relapse reduction of 16%.⁶¹ In contrast, varenicline plus NRT does not provide known additional benefit; one randomized trial comparing varenicline plus placebo patch to varenicline plus nicotine patch showed no improvement in cessation rates at 1, 4 or 12 weeks with combination therapy.⁶² The role of combination therapy with varenicline and bupropion remains unclear. A randomized control trial comparing varenicline plus bupropion to varenicline monotherapy showed improved prolonged abstinence (defined as no smoking from two weeks after target quit date), but not 7-day point prevalence at 12 or 26 weeks (defined as no smoking in past 7 days), and with neither outcome different at 52 weeks. Additionally, participants in the combination varenicline and bupropion therapy group reported more anxiety and depressive symptoms⁶³, which may be a major concern in individuals with CKD, who are at greater risk for depression and anxiety than the general population.^{64–66}

Non-combustible products

ECs are devices that use heat to aerosolize a liquid for inhalation. The liquid typically contains propylene glycol and glycerol, with or without nicotine and additional flavoring. Some people report using ECs to reduce the risks of smoking cigarettes.³ In the absence of government regulation over the last decade, extensive advertisement to youth and general public, and a rapidly expanding industry, EC sales have steadily grown. In the United States, this has led to a Surgeon General's report focusing on the public health harm from youth EC exposure and recent regulation by the FDA of EC products. Prior to this, hundreds of flavoring extracts, multiple formulations of various nicotine concentrations, and variability in delivery mechanisms contributed to substantial heterogeneity that prevented comparison across studies. One meta-analysis of studies comparing nicotine EC with placebo (non-nicotine) EC smokers found that participants in the nicotine EC group had higher rates of smoking cessation at six months than the placebo group (RR, 2.29; 95% CI, 1.05–4.96), with no increased risk for serious adverse events. However, the quality of the evidence was low or very low due to the heterogeneity mentioned above.⁶⁷ The largest randomized controlled trial in the study that examined 657 smokers in New Zealand found no differences in smoking cessation rates among the following groups: nicotine ECs, placebo (non-nicotine) ECs, and nicotine patches. The authors concluded that because abstinence was lower than anticipated, larger sample sizes are needed to be powered to detect a difference.⁶⁸ A more recent meta-analysis including studies of EC use in smokers irrespective of their reason for using EC showed that EC use was associated with lower rate of smoking cessation (OR, 0.72; 95% CI, 0.57–0.91).⁶⁹ Use of ECs is not endorsed by the United States Preventive Services Task Force (Grade I) and preliminary evidence suggests harm from additives and other chemicals that are added to the nicotine.⁷⁰ The role for EC in smoking cessation remains understudied, but with little known about the potential harms, we believe the focus should remain on pharmacotherapies and behavioral interventions currently approved by the FDA for smoking cessation. Therefore, we do not recommend the use of ECs until all other therapy options have been exhausted and multiple quit attempts have been made. In the case that a patient is only willing to use ECs as a cessation method, they should be advised that little is known about the long-term effects associated with EC use.

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Case Presentation

A 67-year-old male with a history of cerebrovascular accident with left upper and lower residual hemiparesis presents for evaluation of elevated serum creatinine. He has a history of hypertension, which was untreated until his cerebrovascular accident event. Serum creatinine ranged between 0.9 mg/dl and 1.2 mg/dl until he underwent a four-vessel coronary artery bypass surgery one year prior. Since then, his serum creatinine has increased and is now between 1.3 mg/dl and 1.6 mg/dl. Urinalysis is normal and the albumin-creatinine ratio is 13 mg/g. He does not have diabetes and his last hemoglobin A1C level was 5.4%. He smokes two packs of cigarettes per day. He did quit smoking for several months after the cerebrovascular accident event, but relapsed after his divorce four years ago and states he now feels unable to quit despite being motivated to do so. On exam, his blood pressure is 128/70 mmHg and he has no edema. His medications include metoprolol 50 mg twice daily, losartan 25 mg daily and furosemide 40 mg daily. The patient is extremely anxious about needing dialysis in the future and asks what he can do to prevent kidney failure.

Case Review

The patient is counseled that smoking likely increases his lifetime risk for needing renal replacement therapy. He acknowledges these risks and further discussion reveals that he is in the preparation stage of change; he has told his co-workers that he would like to quit smoking and was referred to his local public health agency to receive free nicotine patches. He also purchased over-the-counter nicotine gum, but does not like the taste. A PHQ-2 screen is administered and is negative for depression. He is amenable to pharmacotherapy, and agrees to try varenicline following a discussion of the FDA-approved therapies. He chooses a quit date one week from the visit, and a member of the provider team agrees to call him on this day to check in, as well as communicate the quit date to the patient's primary care provider. The patient is also provided with a list of suggested phone apps to aid in smoking cessation. A two-week nurse follow up visit is scheduled prior to the patient's departure.

Box 1**internet and phone-based resources for smoking cessation**

- Smokefree.gov⁴⁶ (<https://smokefree.gov>): A National Cancer Institute-based web site that provides information and multiple free tools targeted to specific demographics (veterans, women, teens, Spanish speaking persons, and adults over age 60 years) including a quit plan guide, a text messaging program, and other mobile phone applications
- 1-800-QUIT-NOW: A free quitline with coaches and referrals to local resources
- 1-855-DEJALO-YA: A free quitline for Spanish-speaking persons
- Freedom From Smoking⁴⁷ (www.lung.org/stop-smoking): An American Lung Association-based program with online resources, group clinics, a phone HelpLine, and an online support community
- How to Quit Smoking or Smokeless Tobacco (www.cancer.org/healthy/stay-away-from-tobacco/guide-quit-smoking.html): An American Cancer Society-based web site with information for current smokers and people who have quit smoking as well as a link to Quit For Life, a web and phone-based cessation program available through some states and employers

Figure 1.
Steps for smoking cessation.

Table 1
Clinical Studies on Smoking Exposure and Outcomes in Patients with Reduced Kidney Function

Reference	Study design	Kidney disease definition	N	Smoking categorization	Primary Outcome	Findings
Chapman et al ⁷¹ (‘85–’93)	Single-center prospective cohort	ADPKD	270	No. of pack-years	Proteinuria level	Pack-year smoking history significant in adjusted model (p<0.05)
Ward et al ⁷² (‘69–’83)	Single-center retrospective cohort	Lupus nephritis	160	Never, current, former	Development of ESRD	Current smokers had shorter time to ESRD: 145 vs 273 mo in ****
Foley et al ⁷³ (‘96–’98)	National prospective cohort	Medicare patients initiating dialysis	3941	Never, current	New-onset CV events	HRs for new-onset CV events in current smokers: <i>CHF</i> : 1.59 (p < 0.004) <i>PVD</i> : 1.68 (p<0.001)
Stengel et al ⁷⁴ (‘85–’90)	Multicenter case control study	CKD and biopsy- proven GN	537	Never, current, former	Environment al risk factors	In men, higher % of current smokers with CKD vs without (OR, 2.4 [1.2–4.5])
Grams et al ⁷⁵ (‘89–’93)	Multicenter prospective cohort study	Ser 1.2–1.7, ESRD, or kidney transplant	1722	Not provided	All-cause mortality	HR for all-cause mortality for current smokers: 1.50 (p = 0.04)
Ricardo et al ⁷⁶ (‘03–’08)	Multicenter prospective cohort study	eGFR 20/70	300 6	Never, Current, Former	CKD progression, atherosclerotic CV events, all-cause mortality	HRs vs current smokers: <i>Mortality</i> : 0.45 (0.34–0.60) for never; 0.63 (0.48–0.81) for former <i>CV events</i> : 0.55 (0.40–0.75) for never; 0.73 (0.54–0.99) for former <i>CKD progression</i> : 0.68 (0.55–0.84) for never; 0.79 (0.64–0.98) for former
Staplin et al ⁷⁷ (‘03–’06)	Multicenter prospective cohort study	Dialysis or elevated Scr	927 0	Never, current, former	All-cause mortality, CV events, progression to ESRD	RRs vs never smokers: <i>All-cause mortality</i> : 1.48 (1.30–1.70) for current; 1.08 (0.98–1.19) for former <i>CV events</i> : 1.36 (1.19–1.55) for current (atherosclerotic: 1.49 [1.26–1.76]; non-atherosclerotic: 1.25 [1.05–1.50]); 1.12 (1.05–1.50) for former Similar rates of progression to ESRD in all smoker categories

ADPKD, autosomal dominant polycystic kidney disease; CHF, congestive heart failure; CV, cardiovascular; ESRD = end stage renal disease; CKD = chronic kidney disease; eGFR, estimated glomerular filtration rate (in mL/min/1.73 m²); GN, glomerulonephritis; RR = risk ratio; Scr = serum creatinine (in mg/dL); HR = hazard ratio; OR = odds ratio; PVD, peripheral vascular disease

Table 2

A sample of smoking cessation guidelines

	Royal Australian College of General Practitioners ⁷⁸ (2014 ^{***})	CAN- ADAP T ⁷⁹ (2012)	New Zealand Ministry of Health, ⁸⁰ (2014 ^{***})	NHS Scotland ⁸¹ (2017 ^{***})	South African Thoracic Society ⁸² (2013)	UK Health Education Authority ⁸³ (2000)	US Public Health Service ⁸⁴ (2008)	US Preventiv e Health Services Task Force ⁸³ (2015)
Brief advice	Y	Y	Y	Y	Y	Y	Y	Y
Assess motivation	Y	Y	N	Y	Y	Y	Y	Y
5 A's	Y	Y	— ^{**}	— ^{**}	Y	Y	Y	Y
NRT	Y	Y	Y	Y	Y	Y	Y	Y
Combined NRT	Y	— ^{**}	Y	Y	Y	Y	Y	Y
NRT + bupropion	I	— ^{**}	I	N	Y	I	Y	Y
Nortriptyline [*]	Y	— ^{**}	Y	— ^{**}	Y	— ^{**}	— ^{**}	— ^{**}
E-cigarettes	I	— ^{**}	N	— ^{**}	I	— ^{**}	— ^{**}	I
Renal consideratio ns	— ^{**}	— ^{**}	— ^{**}	— ^{**}	— ^{**}	— ^{**}	— ^{**}	— ^{**}

Y: Recommended. N: Not recommended against. I: Noted insufficient evidence to make recommendation; NHS, National Health Service; CAN-ADAPT, Canadian Action Network; 5 A's = Ask, advise, assess, assist, arrange follow up; NRT = Nicotine replacement therapy; e-cigarettes = electronic cigarettes

^{*} not FDA-approved for smoking cessation in the U.S.

^{**} not addressed

^{***} Year updated.

Table 3

Stages of change

Stage	Clinical assessment for stage	Meaning of stage	Provider interventions
Precontemplation	The patient does not intend to quit smoking.	Patient has no intention to change behavior in the near future. Friends and family may be aware of the problem, but patient does not acknowledge it as a problem and may be defensive.	<ul style="list-style-type: none"> • Motivational interviewing • Follow-up discussion at future appointments
Contemplation	The patient is considering behavior change—often weighing pros and cons of cessation.	Patient is aware of problem and is thinking about addressing the issue, but has not yet made a firm decision to take action and may seem ambivalent about attempts to quit.	(Same as for previous stage)
Preparation	The patient has committed to attempt to quit, and may be experimenting with small behavior changes.	Patient is making plans and has committed to make a change. Patients in this stage may have looked into treatment options or already made plans for how they will stop.	<ul style="list-style-type: none"> • Set quit date • Discuss pharmacologic and behavioral strategies to improve abstinence • Provide information for online and phone resources • Follow-up discussion at future appointments
Action	The patient already has made actions toward quitting.	Patient is actively modifying behavior in order to address the problem. Patients in this stage are at high risk for relapse.	(Same as for previous stage)
Maintenance	The patient is maintaining behavior change (not smoking).	Patient has been able to abstain from smoking and has acquired new skills to avoid relapse.	<ul style="list-style-type: none"> • Encourage continued abstinence • Follow-up discussion at future appointments

Table 4

Pharmacotherapy for smoking cessation

Product	Dosing	Renal considerations	Precautions	Sideeffects	Advantages
Long-acting agents					
Nicotine patch	By cigarettes per day: >10: 21 mg/d for 6 wk, then 14 mg/d for 2 wk, then 7 mg/d for 2 wk; <10: 14 mg/d for 6 wk, then 7 mg/d for 2 wk	Caution in severe kidney disease, no defined dosing adjustments	MI in past 2 wk, serious or worsening angina, serious arrhythmia	Local skin reaction, headache, sleep disturbances (may remove patch at bedtime if needed)	Constant dosing over 24 h, may reduce AM cravings, OTC, 1x/d dosing, easily concealed
Bupropion	Begin 1-2 wk prior to set quit date; 150 mg every AM for 3 d, then 150 mg 2x/d for 7-12 wk, with maintenance up to 6 mo in selected pts; avoid bedtime dosing	Consider dose reduction to 150 mg every 3 d in dialysis pts due to accumulation of metabolites; consider dose reduction to 150 mg daily in non-ESRD pts with kidney disease due to accumulation of parent compound	Severe liver disease, unstable mental health condition or recent history of suicidal ideation; <i>contraindications</i> : seizure disorder, MAOI therapy in past 2 wk, current or prior dx of anorexia nervosa or bulimia, simultaneous abrupt cessation of alcohol or benzodiazepines (due to lowered seizure threshold)	Insomnia, dry mouth, rash, constipation, anxiety	May delay or decrease weight gain, also FDA-approved for treating depression, can be combined with NRT
Varenicline	Begin 1 wk prior to set quit date: 0.5 mg each AM for days 1-3; 0.5 mg 2x/d for days 4-7; weeks 2-12: 1 mg 2x/d; additional 12-wk course may be used in select pts	Renal dosing per manufacturer recommendations; CL _{cr} < 30: start at 0.5 mg/d with max of 0.5 mg 2x/d; HD: max of 0.5 mg/d	Unstable mental health condition or recent history of suicidal ideation, pre-existing CV disease	Nausea/vomiting, sleep disturbances, constipation	May be effective option for pts who have failed other agents
Short-acting agents					
Nicotine gum	By timing of first cigarette after waking: 4 mg if <30 min, 2 mg if >30 min; weeks 1-6: 1 piece every 1-2 h; weeks 7-9: 1 piece every 2-4 h; weeks 10-12: 1 piece every 4-8 h; max of 24 pieces per day [*]	Caution in severe kidney disease, no defined dosing adjustments	MI in past 2 wk, serious or worsening angina, serious arrhythmia, TJD, may be difficult for pts with poor dentition or dentures	Mouth/jaw soreness, dyspepsia, hypersalivation	OTC, may satisfy oral cravings, may delay or decrease weight gain
Nicotine lozenge	By timing of first cigarette after waking: 4 mg if <30 min, 2 mg if >30 min; weeks 1-6: 1 lozenge every 1-2 h; weeks 7-9: 1 lozenge every 2-4 h; weeks 10-12: 1 lozenge every 4-8 h; max of 20 lozenges per day	Caution in severe kidney disease, no defined dosing adjustments	MI in 2 past wk, serious or worsening angina, serious arrhythmia	Nausea, heartburn, insomnia, cough	OTC, may satisfy oral cravings, may delay or decrease weight gain, can be used in pts with poor dentition or dentures
Nicotine inhaler	10 mg cartridge (delivers 4 mg nicotine vapor) every 1-2 h; individualized dosing: 6-16 cartridges per day; 3-6 mo duration	Caution in severe kidney disease, no defined dosing adjustments	MI in past 2 wk, serious or worsening angina, serious arrhythmia, bronchospasm	Mouth/throat irritation, nausea, dyspepsia, cough, headache, rhinitis	Titratable to manage cravings and withdrawal
Nicotine nasal spray	1 spray (0.5 mg nicotine) each nostril very 0.5-1 h; max of 5 doses per hour or 40 doses per day; 3-6 mo duration	Caution in severe kidney disease, no defined dosing adjustments	MI in past 2 wk, serious or worsening angina, serious arrhythmia, chronic rhinitis or sinusitis, severe reactive airways disease	Nasal/sinus/throat irritation, rhinitis, cough, headache	Titratable to manage cravings and withdrawal

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CV, cardiovascular; pt, patient; TJD, temporomandibular joint disease; OTC, over the counter; MI, myocardial infarction; MAOI, _____; dx, diagnosis; FDA, Food and Drug Administration; CLer, creatinine clearance (in mL/min); HD, hemodialysis

* It is important that patients “chew and park” the gum, to optimize buccal absorption