Smoking Cessation Therapy Considerations for Patients with Chronic Kidney Disease

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Cigarette smoking is a readily modifiable cardiovascular and chronic kidney disease (CKD) risk factor. Smoking cessation aids include nicotine replacement therapy (NRT), bupropion, and varenicline. Several reports suggest that patients with CKD who use tobacco products be encouraged to stop; however, very little is offered to the healthcare provider as to how to successfully prescribe and monitor smoking cessation therapy for this patient population. This article reviews NRT, bupropion, and varenicline pharmacokinetics and dosing literature for patients with CKD. Evidence for the benefit of smoking cessation in patients with CKD is also reviewed.

Goal: To increase awareness about smoking cessation therapy for patients with chronic kidney disease.

Objectives
1. Explain how nicotine replacement therapy, bupropion, and varenicline are used as methods of smoking cessation therapy.
2. Describe the pharmacokinetics of bupropion and varenicline.
3. Discuss smoking cessation outcomes in patients with CKD.

This CNE article meets the Nephrology Nursing Certification Commission’s (NNCC’s) continuing nursing education requirements for certification and recertification.
mellitus, coronary heart disease, anemia, and hypertension (Brown et al., 2003; Keith, Nichols, Gullion, Brown, & Smith, 2004). Patients with CKD Stage 5 (those on dialysis) have a mean of 5 to 6 co-morbid conditions that often require complex therapeutic regimens of up to 12 different medications [Manley et al., 2004; United States Renal Data System [USRDS], 2000]. The number and severity of the aforementioned cardiovascular risk conditions increase as CKD worsens (Anavekar et al., 2004; NKF, 2002; Rahman et al., 2004). Cardiovascular-related hospitalizations and mortality also increase with worsening kidney function (Go, Chertow, Fan, McCulloch, & Hsu, 2004). Once a patient reaches CKD Stage 5, approximately 50% of deaths are cardiovascular-related (USRDS, 2004).

Since 1998, there has been a heightened awareness and call for research to reduce cardiovascular mortality in patients with CKD (Levey et al., 1998). Additionally, the NKF has published various clinical practice guidelines aimed at reducing the progression of kidney disease and cardiovascular mortality in patients with CKD through early detection and medical management of kidney disease, hyperphosphatemia, lipid abnormalities, anemia, hypertension, and cardiovascular disease (NKF, 2001, 2002, 2003b,c, 2004, 2005).

Cigarette smoking is a readily modifiable cardiovascular and CKD risk factor. It is generally accepted that smoking cessation decreases cardiovascular mortality in the general population. Smoking cessation may also decrease the progression of CKD (Chuahui et al., 2004; Halami et al., 2000; Schiff, Lang, & Fischer, 2002). Despite several reports suggesting that patients with CKD who use tobacco should be encouraged to stop their tobacco use (Brown & Keane, 2001; NKF, 2002, 2003b, 2004, 2005; St. Peter, Schoolwerth, McGowan, & McClellan, 2003; Yu, 2003), little is offered to the healthcare provider as to how to successfully prescribe and monitor smoking cessation therapy for this patient population.

Given the complexities of CKD and its affects on drug metabolism, distribution, and elimination, some clinicians may not be comfortable with or aware of the nuances of the medications prescribed for smoking cessation. In the context of CKD, this article reviews the dosing, pharmacokinetics, and side effect profiles of Food and Drug Administration-approved medications used in smoking cessation. It also reviews the literature of smoking cessation programs/clinics outcomes in patients with CKD.

Nicotine use is an addiction, and therefore, requires behavioral or non-pharmacologic interventions in addition to pharmacologic options. Many smokers report the desire to quit, whether secondary to health concerns or economics reasons, but the difficulty to quit highlights the habitual and physiological addiction (Hymowitz et al., 1997; Okuyemi et al., 2000). Effective smoking cessation programs typically include patient support programs and rely on medications to increase success. Tobacco cessation can be treated with the use of behavioral modifications in addition to drug therapy, such as nicotine replacement therapies (NRTs) bupropion, or varenicline. Behavioral strategies can include support groups, relaxation techniques, and follow-up phone calls, in addition to regular face-to-face visits with the patient’s tobacco cessation provider. The effectiveness of each of the behavioral and medication therapies has been studied, and it is reported that no one therapy is better than another (Bollinger et al., 2000; Hajak et al., 1999; Hays et al., 2001; Herrera et al., 1995; Hurt et al., 1997, 1998; Setter & Johnson, 1998; Shiffman et al., 2002). A patient’s preference is typically what defines the option the patient chooses.

**Nicotine Replacement Therapy**

Nicotine is rapidly absorbed in the lung (Pomerleau & Pomerleau, 1998). On average, smokers absorb 1mg of nicotine per cigarette smoked; however, this can vary by the smoker and the level of inhalation. Nicotine then enters the pulmonary and arterial circulation. Nicotine is a weak base and is non-ionized, leading to easier absorption in alkaline environments. Nicotine undergoes extensive first pass metabolism when ingested orally (for example, with gum or lozenge). Nicotine is largely metabolized by the liver, with renal excretion depending on urinary pH and flow. The half-life (t1/2) is approximately two hours. The main metabolites include cotinine and nicotine-N-oxide.

The pharmacokinetics of intravenously administered nicotine (0.028 mg/kg) in nine healthy subjects (glomerular filtration rate [GFR], 84 to 143 mL/min/1.73m²), four patients with mild kidney failure (GFR, 63 to 73 mL/min/1.73m²), five patients with moderate kidney failure (GFR, 18 to 36 mL/min/1.73m²), and six patients with severe kidney failure (GFR, 1 to 10 mL/min/1.73m²) were reported (Pomerleau & Pomerleau, 1998). Three patients were on peritoneal dialysis. Nicotine and cotinine concentrations were measured in plasma, urine, and peritoneal dialysate from 0 to 24 hours after start of infusion. There were significant correlations between GFR and total clearance (p < 0.01, r = 0.79), and renal clearance (p = 0.047, r = 0.56) of nicotine. There were no differences between normal healthy subjects and those with mild renal insufficiency regarding nicotine total clearance and non-renal clearance. Nicotine total and non-renal clearances were reduced by 30% and 50% in patients with moderate and severe kidney failure, respectively, when compared to healthy patients. Non-renal clearance was 1,303 mL/minute in healthy subjects and 661 mL/minute in patients with severe kidney failure. Overall, the renal clearance of nicotine was 5% of total clearance in healthy patients, 2% in patients with mild kidney failure, 3% in patients with moderate kidney failure, and less than 1% in patients with severe kidney failure. Nicotine adverse effects, such as an increase in heart rate and blood pressure, were of the same magnitude in all groups.

In trials evaluating the efficacy of
NRTs, the appearance of cotinine in the blood, urine, or saliva is typically used as a measure of adherence to smoking cessation. In the United States, there are five NRT formulations currently available; these are the patch, gum, lozenge, inhaler, and nasal spray (Henningfield, Fant, Buchhalter, & Stitzer, 2005). Table 1 provides information on all available NRTs, the usual dose and the dose for patients with CKD, and the cost for a one-month supply. The most common adverse effects associated with NRT include dizziness, headache, and nausea. The patch is available over the counter without a prescription, and it provides patients with the option to “step-down” with the dose of their nicotine. Since it is a transdermal option, it leads to minimal stimulation (Henningfield et al., 2005). The typical dose available with the patch can vary with the brand or generic version, and it has minimal side effects, primarily local skin irritations.

Gum and the lozenge NRTs are similar in their administration and dosage availability (2mg and 4mg) (see Table 1). They are also available without a prescription. The most common side effects include gastrointestinal discomfort, but these products are generally tolerated well (Molander et al., 2000). Gum and lozenge NRTs are also useful in targeting the “hand-to-mouth” routine of many smokers; the gum or lozenge provides patients with something to place in their mouths where they would normally place a cigarette. These products have also been shown to assist in reducing weight gain, which can be a concern or potential barrier for many smokers trying to quit (Eliasson, Taskinen, & Smith, 1996; Herrera et al., 1995; Shiffman et al., 2002; Thompson & Hunter, 1998).

The NRT inhaler is another option that aims to target a patient’s “hand-to-mouth” routine. The inhaler is available as a 10mg cartridge that delivers 4mg of nicotine. It also provides flexible dosing for patients, who typically

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### Table 1

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Dose for Patients with CKD</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nicotine Containing</strong></td>
<td></td>
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<tr>
<td>Nicoderm CQ</td>
<td>Transdermal</td>
<td>7 to 21mg daily Regimen: 21mg daily x 6 weeks, then 14mg daily x 2 weeks, then 7mg daily x 2 weeks</td>
<td>OTC</td>
</tr>
<tr>
<td>Nicorette</td>
<td>Gum</td>
<td>2mg (for those that smoke less than 25 cigarettes per day) and 4mg (for those that smoke greater than 25 cigarettes per day) Regimen: 1 piece every 1-2 hours for first 6 weeks, then 1 piece every 2-4 hours for 3 weeks, then 1 piece every 4-8 hours for 3 weeks</td>
<td>OTC</td>
</tr>
<tr>
<td>Commit</td>
<td>Lozenge</td>
<td>2mg and 4mg Regimen: Frequency depends on level of nicotine dependence</td>
<td>OTC</td>
</tr>
<tr>
<td>Nicotrol</td>
<td>Inhaler</td>
<td>10mg cartridge that delivers 4mg of nicotine Regimen: up to 16 cartridges per day with continuous puffing over 20 minutes. Treat for 3 months then wean over 6-12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal spray</td>
<td>0.5mg nicotine per spray Regimen: Initiate with 1 to 2 doses per hour as needed; maximum 40 doses per day</td>
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<tr>
<td></td>
<td>Transdermal</td>
<td>5-15mg daily for 16 hours; taper regimen: 15mg daily x 6 weeks; 10mg daily x 2 weeks; 5mg daily x 2 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Nicotine Containing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buproprion (Zyban®)</td>
<td>Oral tablet</td>
<td>Renal Impairment: 150mg bupropion every day Hemodialysis: 150mg every 3 days</td>
<td></td>
</tr>
<tr>
<td>Varenicline (Chantix®)</td>
<td>Oral tablet</td>
<td>Renal Impairment (CrCl less than 30mL/minute) 0.5mg twice daily</td>
<td></td>
</tr>
</tbody>
</table>

**Key**: CKD – chronic kidney disease; OTC – over the counter; Job – prescription only; CrCl = creatine clearance.
use 6 to 16 cartridges per day based on their level of nicotine dependence (Bollinger et al., 2000; Hjalmarson, Nilsson, Sjostrom, & Wiklund, 1997; Okuyemi et al., 2000).

The last NRT option is the nasal spray. The nasal spray is available as 0.5mg nicotine per spray. Patients are recommended to use 1 to 2 doses per hour (Henningfield et al., 2005). This formulation also provides flexible dosing and is the only NRT option that is closest to a cigarette in terms of the rapid rise in nicotine stimulation (Hurt et al., 1998; Okuyemi et al., 2000; Thompson & Hunter, 1998). Both the inhaler and nasal spray are well tolerated with mild side effects, such as coughing or nasal irritation, respectively.

**Bupropion**

The first non-nicotine-containing medication approved by the Food and Drug Administration for smoking cessation is bupropion. Bupropion is indicated for the treatment of depression and also as an aide to smoking cessation (GlaxoSmithKline, 2007). This option focuses more on reducing a patient’s craving rather than supplementing the need for nicotine, such as an NRT (Hays et al., 2001; Hurt et al., 1997). Bupropion use is warranted in patients who are willing to quit and have tried the NRTs without success, are unwilling to use an NRT, and have a potential precaution that precludes them from using one of the NRTs (such as cardiac conditions, pregnancy). The purported mechanism of bupropion in assisting patients in smoking cessation is unknown, but is probably related to inhibition of noradrenergic or dopa-minergic neuronal uptake (GlaxoSmithKline, 2007). The resultant increase in norepinephrine and dopamine attenuates nicotine withdrawal symptoms and cravings, respectively. Bupropion should be started 1 to 2 weeks prior to the patient’s chosen “quit day” because the onset of activity usually occurs after the first week of initiation. Patients who have not stopped smoking after seven weeks of bupropion therapy are generally considered non-responsive to this treatment (Glaxo-SmithKline, 2007). The most common side effect with bupropion use is dry mouth and insomnia. Bupropion increases the risk of seizure. Doses should not exceed 300mg per day, and bupropion should not be prescribed in patients with seizure disorder or who are at risk for seizures (GlaxoSmithKline, 2007; Henningfield et al., 2005).

**The Pharmacokinetics Of Bupropion**

Bupropion is rapidly absorbed after oral administration; however, only a small proportion of the oral drug reaches the systemic circulation intact. Bupropion is extensively protein bound (84%). The volume of distribution is 19 to 21 L/kg, and central nervous system concentrations are 10 to 25 times greater than in plasma concentrations (Findlay et al., 1981; Preskorn & Othmer, 1984). Bupropion undergoes extensive first-pass metabolism primarily by the CYP2B6 isoenzyme (GlaxoSmithKline, 2007). There are three active metabolites – hydroxy-bupropion, threohydrobupropion, and erythrohydrobupropion. The metabolite potency, relative to bupropion, is estimated to be 50%, 20%, and 20% respectively (Glaxo-SmithKline, 2007). The kidney is responsible for 87% bupropion excretion; 10% is excreted via the feces (GlaxoSmithKline, 2007). With chronic administration, bupropion elimination half-life is 21 hours; metabolite elimination half-lives range from 20 to 37 hours. All half-lives are prolonged in patients with liver disease (GlaxoSmithKline, 2007).

In the general population, the recommended dose is 150mg daily for 3 days then increasing to 150mg twice a day (GlaxoSmithKline, 2007; Henningfield et al., 2005). Common adverse effects include general gastrointestinal discomfort, agitation, and insomnia (Henningfield et al., 2005). Patients prescribed bupropion should be advised to take the second dose earlier in the evening to minimize any associated insomnia.

The pharmacokinetics of bupropion and two of its major metabolites, hydroxybupropion and threohydrobupropion, were studied in eight patients on hemodialysis (HD) following a single oral dose of 150 mg bupropion hydrochloride sustained-release (Worrall, Almond, & Dhillon, 2004). The bupropion results were similar to those for individuals with normal renal function. The metabolites demonstrated increased areas under the curve, indicating accumulation. Dialysis clearance of hydroxybupropion is unlikely. The results suggest significant accumulation of the metabolites in patients with renal failure. Due to the uncertainty of the clinical importance of bupropion metabolite accumulation and potential associated toxic plasma levels, the authors recommend that a dose of 150mg bupropion every three days in patients receiving HD may be more appropriate than the current manufacturer’s recommendation (in renal-impaired patients) of 150 mg daily then increased to twice daily after 3 days. Further investigation of the safety and efficacy of this dosing recommendation is warranted.

**Varenicline**

The latest non-nicotine containing medication approved and available for use in tobacco cessation is varenicline (Chantix®). Varenicline has a novel mechanism of action in targeting tobacco dependence. It works as a partial nicotinic receptor agonist selective for the α4β2 nicotinic receptor. By binding to α4β2 receptors, varenicline induces two results: 1) it signals the release of dopamine to create similar reinforcing effects due to its partial binding at the receptor, and 2) it acts as a physical antagonist by binding to the nicotine receptor to potentially block the effects of nicotine (Foulds, 2006; Pfizer, 2008). Varenicline’s dosing is 1mg twice daily for 12 weeks after a one-week dose titration. The recommended dosing titration is 0.5mg once daily for days 1 to 3, 0.5mg twice daily for days 4 to 7, and 1.0mg twice daily for day 8 through completion of treatment (Pfizer, 2008). Varenicline should be taken after eating and with a full glass of water to minimize possible side effects.
effects. The treatment duration may also be expanded to 24 weeks and has been shown increase efficacy and abstinence rates (Gonzales et al., 2006).

The most common adverse effects associated with varenicline include nausea, headaches, insomnia, and abnormal dreams (Pfizer, 2008). Nausea has been reported as primarily mild to moderate (Gonzales et al., 2006; Jorenby et al., 2006; Tomstad et al., 2006) and can be minimized by using the recommended dose titration.

The Pharmacokinetics Of Varenicline

Varenicline reaches maximum plasma concentrations within 3 to 4 hours after oral administration and typically achieves steady state within 4 days (Pfizer, 2008). Oral administration of varenicline has been shown to be unaffected by food or the time of administration (Faessel et al., 2006). Varenicline exhibits minimal metabolism with 92% of varenicline excreted unchanged in the urine and has a half-life of approximately 24 hours (Pfizer, 2008). Dosage adjustments have been recommended with varenicline in patients with severe renal impairment, which is defined as a creatinine clearance less than 30 mL/minute due to a 2-fold increase in varenicline levels (Pfizer, 2008). The recommended dosage adjustment is to titrate the patient from 0.5mg daily up to a maximum dose of 0.5mg twice daily. Currently, dosage adjustments have not been recommended for patients with hepatic impairment due to the minimal hepatic metabolism and are not recommended based on the age of the patient (Pfizer, 2008). Further data are still needed to evaluate the safety profile and potential for dosage adjustments in these special populations.

Smoking Cessation Outcomes In CKD: The Evidence

To date, only three studies were identified via a MEDLINE search that investigate the effects of smoking cessation on preservation of kidney function (Chuahirun et al., 2004; Halimi et al., 2000; Schiff et al., 2002). Unfortunately, the trials do not mention whether or not nicotine or bupropion therapy was used to facilitate smoking cessation.

Smoking cessation effects on GFR decline in patients with type 2 diabetes with and without macroalbuminuria were reported (Chuahirun et al., 2004). All patients had a normal plasma creatinine, were prescribed an angiotensin-converting enzyme inhibitor, and had adequate blood pressure control. Non-smokers and smokers with normo-, micro-, and macroalbuminuria (n = 157) and a separate cohort (n = 80) with microalbuminuria, were followed for six months. Urine excretion of transforming growth factor-beta 1 (TGF-β1), measured as TGF-β1, is associated with the development of scarring and fibrous crescents in the glomerulus via activation of myofibroblasts from glomerular parietal epithelial cells (El Nahas, 1996; Ng et al., 1999). TGF-β1 increased in macroalbuminuric but not in nonmacroalbuminuric nonsmokers and TGF-β1 rate was higher in smokers than nonsmokers within each albuminuria group. In the separate microalbuminuric cohort, the rate of TGF-β1 change for quitting smokers was not different from nonsmokers (0.093 versus -0.123 ng/g of creatine/week, P = not significant) but for non-quitting smokers (0.970) was higher than non-smokers (P = 0.017). Patients with type 2 diabetes who are at high risk compared with low risk for nephropathy progression have progressive renal injury as measured by increasing TGF-β1. Cigarette smoking exacerbates renal injury in type 2 diabetes despite blood pressure control and ACEI, but its cessation in those with microalbuminuria ameliorates the progressive renal injury caused by continued smoking.

The second trial is a report of 45 patients with progressive primary nephropathies (glomerulonephritis or tubulointerstitial nephritis) and moderate renal failure (Schiff et al., 2002). All patients were encouraged to stop cigarette smoking (1 to 2 packs per day); 26 patients refused to change their smoking habits (current smokers), and 16 successfully stopped (ex-smokers). Over a 24-month study period, carboxyhemoglobin and creatinine clearance were measured every six months. The primary end-point of the study was end-stage renal disease requiring dialysis. Current smokers and ex-smokers had similar rates of creatinine clearance decline in the preceding 24 months prior to the investigation. Compared to ex-smokers or matched non-smoking patients with CKD, individuals who continued to smoke had a significantly faster decline in creatinine clearance during the 24-month study period. Dialysis therapy was started in seven individuals (6 smokers; 1 ex-smoker) over the study period. The authors concluded that smoking cessation slowed the progression of renal failure but did not reverse any renal function caused by previous smoking.

Investigators determined creatinine clearance (Cockcroft-Gault formula) and proteinuria (dipstick) of an overnight urine sample in large observational trial (n = 28,409) in the general population of the la Sante region in France (Halimi et al., 2000). Adjusted creatinine clearance was higher in current smokers than in former smokers and never smokers (100.6 ± 13.6 vs. 98.8 ± 13.9 mL/min/1.73m², P < 0.0001, and vs. 98.5 ± 14.0 mL/min/1.73m², P < 0.0001, respectively). This difference was predominant in men (HR and p value) and weak in women (HR and p value), and was associated with the number of cigarettes smoked daily (HR and p value). The slope of the projected age-related decline in the creatinine clearance accelerated with age, but it was similar in current smokers, former smokers, and never smokers. Current and former smokers had a marked risk of 2 or higher proteinuria (adjusted RR [95% CI], 3.26 [1.66 to 6.80], P = 0.0009, and 2.69 [1.24 to 5.99], respectively, P = 0.013, vs. never smoking), which was independent of the daily or cumulative cigarette consumption.
Conclusion

Increased efforts should be made to encourage patients with CKD to stop smoking in order to preserve kidney function and potentially delay dialysis therapy. Clinicians recommending smoking cessation pharmacotherapy should use reduced doses of bupropion and varenicline, and may use recommended doses of NRT.

References


nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. *Archives of Internal Medicine, 159,* 2003-2038.


Tobacco Control, 6(Suppl 2), S57-S62.


To increase awareness about smoking cessation therapy for patients with chronic kidney disease.

Please note that this continuing nursing education activity does not contain multiple-choice questions. This posttest substitutes the multiple-choice questions with an open-ended question. Simply answer the open-ended question(s) directly above the evaluation portion of the Answer/Evaluation Form and return the form, with payment, to the National Office as usual.