How to manage cigarette smoking in kidney transplant candidates and recipients?

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ABSTRACT

Tobacco smoking is a frequent problem affecting many kidney transplant (KT) candidates and recipients. The negative impact of active smoking on KT outcomes has been demonstrated. Consequently, most guidelines strongly recommend quitting smoking before considering kidney transplantation. However, nicotine addiction is a complex multifactorial disease and only 3-5% of patients who try to quit by themselves, achieve prolonged abstinence. Smoking cessation programs (SCP) have proven their efficacy in the general population to increase the rate of quitting and should therefore be proposed to all smoking KT candidates and recipients. Nevertheless, SCP have not been evaluated in the KT field and not all KT centers have an easy access to these programs. In this work, we aim to review the current knowledge on the subject and provide an overview of available interventions to help smoking patients to quit. We detail non-pharmaceutical and pharmaceutical approaches and discuss their use in KT candidates and recipients.

**Keywords**: bupropion, kidney transplantation, nicotine replacement therapy, smoking cessation, varenicline
INTRODUCTION

Tobacco smoking is one of the major drivers of premature death and disability. It was responsible for 7.1 million deaths worldwide in 2017 (1). In the kidney transplant (KT) field, there are high-quality evidences that smokers have poorer outcomes after transplantation compared to non-smokers (2-7). Consequently, smoking cessation is strongly recommended in KT candidates and recipients (8-13).

Smoking cessation programs (SCP) have proven their efficacy and safety in young adults (14), in patients with cardiovascular diseases (CVD) (15), and in patients with chronic obstructive pulmonary disease (16). Three meta-analyses confirmed effectiveness of SCP to aid smoking cessation (17-19). Therefore, the recently published Kidney Disease Improving Global Outcomes (KDIGO) guidelines (8) recommend offering SCP to all KT candidates who are using tobacco products. Unfortunately, not all KT centers have access to SCP (20). The present work aims to 1/ review the current knowledge on this topic, 2/ detail available SCP and 3/ discuss their application for smoking KT candidates/recipients.

Epidemiology of smoking kidney transplant candidates/recipients.

Cigarette smoking is an independent risk factor for kidney failure (KF) (21,22). Moreover, chronic kidney disease (CKD) progression is accelerated by active smoking, most likely because of endothelial dysfunction caused by vascular production of reactive oxygen species, as well as transient increases in blood pressure accompanied by a decrease in both glomerular filtration rate and effective renal plasma flow (23-25). Data derived from two Dialysis Outcomes and Practice Patterns Study (DOPPS) analysis showed an incidence of active smokers in dialysis units around 15% (26,27). Rates of active smokers in kidney transplant candidates were reported between 24% and 33%, with 90% who continue to smoke after KT (28,29). Moreover, it has been suggested that 12% of patients who stopped smoking before KT
relapsed after (30). A meta-analysis has shown that younger individuals, men, and those with lower body mass index were more likely to smoke after KT (3). Other studies however suggest that these incidences might be lower. Indeed, Van Laecke et al reported in a single centre retrospective study including 1013 KT recipients (KTR) an incidence of active smokers after transplantation at 7% (31). Also, a study including 4110 KTR revealed an 11% incidence of current smokers (32). Though lower, these incidence rates are not optimal considering the well-established and highly unfavorable outcome of active smoking after kidney transplantation (see below). So there is room for improvement. Moreover, these incidences might be underestimated as they arise mainly from self-reported smoking history, which depends on patient honesty. Thus, a study aiming to confront cotinine serum level (the gold standard for the detection of active smokers) and self-reported smoking history in a single-center cohort of kidney transplant recipients, showed that 34% of patients were diagnosed as current smokers despite claiming to be non-smokers (33).

**Impact of tobacco use on kidney transplant recipient outcomes.**

Cigarette smoking has a dramatic impact on the outcome of KTR. The correlation between post-KT CVD and cigarette smoking has been demonstrated. Kasiske et al. showed that KTR who smoke have a 90% increased risk to develop coronary artery disease (34). Ponticelli et al also showed that the risk of CVD is linked to the pack-years of smoking per year. Indeed the relative risks for major CVD event after KT were 1.5 and 2.14 in 11 to 25 pack-years and > 25 pack-years smokers at transplantation, respectively (35). Active smoking KTR are also more commonly affected by other atherogenic risk factors such as diabetes, hypertension and dyslipidemia (36).

Active smoking negatively impacts allograft survival (34,37-39) with reported relative risks of 1.3-2.3 for graft loss (37,40). Interestingly, quitting cigarette smoking for more than 5 years
before KT was associated with a 34% relative risk reduction for graft failure (34). In addition, although former smokers have increased long-term graft and death-censored graft loss rates compared to never smokers, this association is much stronger in patients who restarted or continued smoking after KT (31).

Mortality rate is also impacted by tobacco use in kidney transplant recipients (5,34,41) with a 2.26 fold increased risk of death after KT (5). However, the effect of cigarette smoking on mortality vanishes after 5 years of quitting (34).

Cigarette smoking is also a risk factor for post KT invasive malignancies, mostly lung (34) and bladder cancers (42). Cancer risk increases by 1.12 and 2.56 after 10 and 25 pack-year smoking history, respectively (43).

Cigarette smoking has also been associated with vascular renal problems, such as fibrous intimal thickening of small arteries (44) and allograft rejection (28).

**Exclusion of smokers from kidney transplant programs?**

Some transplant programs worldwide are very strict regarding smoking cessation and block temporarily active smokers from being listed (45, 46). Indeed, growing evidence shows that not only KTR, but also lung, liver and heart transplant recipients who smoke have poorer outcomes than non-smokers (3). Several arguments could justify such a strong policy for smoking candidates. First, considering the scarcity of organs and the poor clinical outcomes associated with cigarette smoking, it may seem logical to allocate precious organs to the patients who will benefit most: non-smoker or former smoker patients. Second, the perspective of an organ transplantation is an important event in life. So, it can be postulated that smoker candidates will show high motivation to quit, especially if the demand is an official one for listing rather than a gentle suggestion. More strict policy for organ transplantation for smoker candidates might lead to more frequent referral to SCP, as reported for liver transplantation (47). Another issue
is the association between cigarette smoking and nonadherence that has been suggested in kidney transplantation (30) and in heart transplantation (48). This is a concern regarding the association between nonadherence and poorer allograft outcomes (49).

However, though cigarette cessation should undoubtedly be the ultimate goal for smoking in kidney transplant candidates, a systematic exclusion of patients who failed quitting might not be ethically justifiable and the policies worldwide have progressively adapted their recommendations.

In patients with kidney failure, the KDIGO international guidelines strongly recommend smoking cessation at least one month before waitlisting, but do not call for excluding smokers from being transplanted (8). Likewise, the Canadian guidelines consider patients who continue to smoke to be eligible for KT with full informed consent regarding their increased risk of worse outcomes (12). Nevertheless, kidney transplant centers around the world apply individual policies while considering smoking candidates for kidney transplantation. A US survey (20) revealed indeed that only 38% of kidney transplant centers considered smoking as an absolute contraindication for waitlisting. When faced with this dilemma, many factors should be carefully weighed. First, survival of active smokers in dialysis versus active smokers after KT has not yet been addressed. Thus, despite worse post-KT outcomes in smokers compared to non-smokers, KT might still offer to active smokers a survival advantage compared to dialysis.

Moreover, participating to active smoking cessation programs before listing can also be associated with adverse effects such as prolonged waiting time for deceased-donor transplantation. Likhitsup et al recently showed that a modification of their tobacco policy in liver transplant candidates from restrictive (smoking cessation required only for patients with a history of cardiovascular disease and lung disease) to prohibitive (smoking cessation required for all liver transplant candidates) led to a significant increase of the median time to listing from 65 to 122 days (47). Nevertheless, this has to be balanced with the health benefit after
transplantation for smoking patients who achieve quitting (31) and the expected lower recurrence of active smoking if the demands for smoking cessation are more fiercely expressed. Second, smoking is detected by self-reporting in the vast majority of KT centers and not by measurement of serum/urine cotinine or exhaled carbon monoxide (CO) (20). The sensitivity of self-reporting depends on patient honesty. Denying access to transplantation to honest patients while giving it to undisclosed smokers is unfair. Third, smoking cessation therapy increases the chances of smoking cessation, but around 25% of organ transplant centers do not have access to these programs (20). Fourth, nonadherence is a complex multifactorial problem and cigarette smoking has to be interpreted among many other behavioral risk factors for noncompliance (49,50). Moreover, caution is required in order not to stigmatize all smoking candidates as « future nonadherent patients ». For example, it can be hypothesized that a smoking candidate who has demonstrated his motivation to stop (by entering in a SCP for instance) and has failed quitting is less likely susceptible to be nonadherent than a smoking candidate who simply refuses to try quitting.

In summary, cigarette cessation should undoubtedly be the ultimate goal for smoking kidney transplant candidates but a systematic exclusion of patients who failed quitting is not ethically justifiable in our point of view. Smoking cessation intervention can help and should be offered by the transplant centers.

**Nicotine addiction: a chronic multifactorial disease**

Nicotine addiction is a multifactorial disease, involving physical, psychological and behavioral dependence. Physical dependence is the need for a person to have a certain level of nicotinemia in order to function properly. Below this level, withdrawal symptoms appear, like anhedonia, insomnia, craving, irritability, depressed mood, restlessness, and anxiety (51). Nicotine acts on
the brain’s reward system, releasing notably dopamine after binding to its high-affinity nicotine cholinergic receptor. In regular smokers, the binding induces an increase of the number of nicotine binding sites while the exact mechanisms of upregulation remain unclear (52) but this could participate to addictive nicotine properties. Physical dependence can be easily and practically evaluated by questionnaires like the Fagerström test (53) but also by the measurement of exhaled CO (54), carboxyhemoglobin in the blood, or serum/urinary/salivary cotinine (Table 1). However, cotinine values have to be interpreted carefully especially in patients with KF. Indeed, cotinine is the major metabolite (70%) of nicotine that is primarily metabolized by the liver enzyme cytochrome P450 2A6 (CYP2A6). Compared to nicotine, cotinine has a longer half-life (15-19 hours vs 2-3 hours) and is eliminated over a longer period of time (55). Different assays are available and slightly differ in their diagnostic performance (55). A recent study has shown a sensitivity of 99.5% with a cotinine urinary test to detect active smokers in the general population (56). However, specificity was only around 90%, meaning a 10% rate of false positive results, secondary to environmental tobacco smoke mainly. If poorly investigated, it can be anticipated that the false positive rate might be even higher in kidney transplant candidates with KF. Indeed, it has been demonstrated that KF was associated with decreased elimination of cotinine and higher levels in blood compared to healthy people with the same level of tobacco consumption (57). Moreover, interindividual variability in the plasma concentrations of nicotine and cotinine is important among individuals with similar kidney function taking similar doses of nicotine. Indeed, a number of CYP2A6 gene variants have been described, resulting in impaired or enhanced ability to metabolize nicotine (58). Additionally, some drugs can either inhibit (amiodarone, amlodipine, clofibrate, fenofibrate, isoniazid…) or induce (barbiturates, rifampicin) CYP2A6 (59) and consequently also influence cotinine levels. Furthermore, diet, ethnicity, sex and contraceptive use can influence urinary cotinine and/or
nicotine metabolism, especially in adolescence (60,61). Hence, kidney transplant physicians should be aware of these issues, especially if cotinine measures have borderline values. Psychological dependence is mainly due to the relief of withdrawal symptoms during smoking. It gives the false belief to the smokers that smoking increase mood, concentration and performance (62). Finally, conditioned behaviors of the smokers is the third aspect of nicotine addiction. The smoker associates emotional, environmental, social stimuli to cigarette smoke, like after a meal, with a coffee or alcohol or sharing a moment with friends (63). All these features of addiction should be considered in the smoking cessation program to avoid relapses.

**Smoking cessation program**

Among smokers who try to quit without treatment, only 3-5% achieve a prolonged abstinence (for 6 to 12 months) (64). Typically, SCP offer a pluridisciplinary team including doctors, nurses, social workers, psychologists and dieticians that have access to drugs and medical facilities: at least exhaled CO measurement and cotinine measurement in blood and urine. SCP have a cost, but are cost-effective, since there is strong evidence that cigarette smoking generates low productivity and smoking-attributable healthcare expenditures, affecting the patient and the society. This specific subject has been recently summarized in the report of the surgeon general in 2020 (65). In Belgium, tobacco specialist counseling is fully reimbursed (free for the patient). As it has a social purpose, financial issues should not limit the access to the programs.

Individual and group sessions are generally proposed. In our experience, kidney transplant candidates and recipients are usually referred by the nephrologist but sometimes, patients take the initiative on their own. Figure 1 proposes a practical clinical algorithm to take care of smoking KT candidates/recipients. Regular follow-up must be scheduled with the patient to monitor side effects and efficacy of the treatment and to positively reinforce the motivations of
the patient. In case of treatment failure, another therapeutic approach is proposed. Below the treatment options are detailed.

Counseling

In our center, the smoking status of every kidney transplant candidate or recipient is assessed (by self-reporting) at every appointment. SCP is offered to every smoking patient. The first approach of SCP is usually non-pharmaceutical, using behavioral, motivational and cognitive interviewing of the patient (counseling). As framework, the 5A’s methods is the gold standard intervention (66) (Table 2), and is efficient to increase the quitting rate (67). After a general overview of the medical history (including medications), the smoking history is carefully reviewed: the smoking starting date, the number of cigarettes smoked per day (to calculate the number of pack-year) and a typical day of the patient during the week and the weekend to evaluate smoking habits. Previous smoking cessation attempts are discussed, notably previous non-pharmacological methods, medications or side-effects (like weight gain) are recorded. Polyaddiction (alcohol, coffee, soda, cannabis, cocaine, heroin…) is evaluated as well as feelings of the “negative” and “positive” impacts of smoking for the patient, in order to remove false beliefs. Familial and professional status, physical and dietary habits are recorded. The physical, psychological and behavioural addiction to nicotine and motivation of the patient are evaluated via questionnaires available online (for example: Richmond test [Table 1 and 3] (68)) through a face-to-face contact. Anxiety and depression are tracked by Hospital Anxiety Depression (HAD) questionnaire which helps to choose the most appropriate medication (Figure 2) (69). At the end of this first meeting, some tools and tips are given to the patient to progress in his smoking cessation attempt (written advices, books, websites), notably to modify their automatic behaviour and help them understand their physical and psychological addiction. A regular follow-up is then arranged (one visit per month, but this can be adapted to each
patient). Then, a pharmaceutical approach is generally proposed and must be adapted to the patient’s medical history and expectations. Indeed, our approach is to discuss with the patient the available products and choose with him the therapeutic option that would be the most appropriate for him. All pharmacologic products approved by the Federal Drugs Administration (FDA) improve the probability to quit (70).

**Nicotine replacement therapy (NRT)**

Nicotine replacement therapy (NRT) have no contraindication. The more efficient treatment associates a slow (like patches) and a rapid delivery form (spray, gum, tablet and inhaler) (18). Adverse effects includes skin irritation from patches and mouth irritation from gums, inhalers and tablets. High-quality evidence studies showed that all forms of NRT increase the chance of quitting smoking by 50 to 60% (71).

**Bupropion**

Bupropion is an antidepressant acting by inhibition of norepinephrine and dopamine reuptake (72). Its efficiency is similar to NRT (73). Its use is more difficult in daily practice due to drug interactions (Table 4), dose adjustment in CKD stage 4-5 (Table 4) and to adverse effects (consisting in dry mouth, rash, headache, dizziness, sleep disorder) (73). Moreover, previous or risk of epilepsy, bipolar disorder, severe liver cirrhosis and the use of monoamine oxidase inhibitors (MAOIs) are absolute contraindications for this drug and must be excluded before their use.

**Nicotinic cholinergic receptor partial agonist: varenicline and cytisine.**

The third category includes nicotinic cholinergic receptor partial agonist: varenicline and cytisine. Cytisine is widely used in Eastern Europe (74) and seems to be more efficient than placebo (75) and NRT (76) for smoking cessation. However, a recent placebo-controlled trial
study did not support its efficacy in tuberculosis patients (77). Varenicline is the most effective available drug on the market (even though no studies comparing cytisine and varenicline is available). There is high evidence that it enhances the chances of successful long-term smoking cessation between two- and three-fold (78). Main side-effects of cytisine and varenicline are nausea, vomiting and sleep disorders. Varenicline was initially feared to increase the risk of depression and suicide (79). But, the EAGLES study and metanalysis have shown that even in psychiatric patients, neither varenicline, bupropion nor NRT did cause more psychiatric events than a placebo (80,81).

All these drugs (at the exception of cystisine, no data) can be used in patients with chronic kidney disease (CKD) (Table 4). However, only scarce data are available for chronic dialyzed patients (Table 5) (82-84). Varenicline is exclusively excreted by the kidney (minimally metabolized) and has almost no drug interaction (except for cimetidine). The dose should be reduced only in severe RF and the concomitant administration of cimetidine should be avoided because it induces a reduced renal clearance of varenicline (85). There is no published data about their use in KT recipients and potential interactions with immunosuppressive drugs. However, their metabolism (Table 5) makes this possibility unlikely.

In our center, the first line treatment is individualized for every patient according to his expectations and clinical situation. Figure 2 depicts our local pharmacological management for smoking patients (applicable for both candidates and recipients). As cytisine is not currently available in our country, it is not included in the algorithm. In our experience, 5% of our patients transplanted with a kidney in the last 2 years are followed in our SCP, of whom 80% achieved prolonged cessation. All were treated with varenicline without any side effect nor drug interaction (especially with immunosuppressive drugs).
A place for electronic cigarette and heat-not-burn products?

The European, American and Australian scientific societies do not support the use of electronic cigarette (e-cigarette) and heat-not-burn products for smoking cessation (86-89) and are against their recreational use by the youths and young adults. E-cigarette was reported 2-times more effective than NRT for smoking cessation with behavioural support at 52 weeks (90). However, 80% of e-cigarette users continued its use at 52 weeks compared to 9% in the NRT group (90), suggesting that the nicotine addiction was not resolved. Adding e-cigarette to nicotine patches slightly increases the rate of abstinence versus patches alone (91). But no difference for long-term abstinence was observed in studies comparing nicotine e-cigarettes plus counseling versus counseling alone (92) and nicotine e-cigarette versus NRT (93). Consequently, the use of e-cigarette in SCP is currently not recommended (94). Furthermore, although the long-term effects are unknown, the short-term respiratory side effects of e-cigarette, as the life-threatening e-cigarette or vaping-associated lung injury (EVALI), have been described in the United States (95), in Europe (96) and in the UK (97). Finally, some animal studies have showed that e-cigarette refill liquid is nephrotoxic in rats (98). In summary, we do not propose e-cigarette in kidney transplant candidates/recipients regarding all these uncertainties and the lack of data regarding its use in these patients.

Other interventions

Numerous technological interventions (websites, applications, sms, video games, social media) emerge on the market to help smokers to quit. Websites (like (99)) offer free applications to support the smokers. Advancing faster than evidence, the efficacy seems moderate (due also to low engagement) and probably lower than medications but may help some smokers (100,101). Taylor et al reviewed 68 randomized controlled trials (some of them at high risk of bias)
suggesting that interactive and tailored internet-based interventions are moderately more effective than non-active controls at six months or longer (102).

CONCLUSION

Smoking has a negative impact on kidney graft outcomes and patient survival after kidney transplantation. Therefore, smoking cessation is strongly recommended in kidney transplant candidates and recipients. However, nicotine addiction is a complex affection and the rate of successful prolonged abstinence without any intervention is dramatically low. Different therapeutic approaches for smoking patients are available and have proven their efficacy. They should be offered whenever possible to all kidney transplant candidates/recipients suffering from smoking addiction.

CONFLICT OF INTEREST STATEMENT

SG declares congress travel fees and educational events from Pfizer (payment to her institution) and drugs samples for patients from Johnson and Johnson and Omega; AD, AR, NK declare no conflict of interest.

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AUTHORS’ CONTRIBUTIONS

AD and SG realized the conception and design of the research; drafted and wrote the manuscript; AR provided the data for dialyzed patients; NK revised and edited the manuscript; all authors approved final version.

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Table 1. Evaluation of physical dependence

| Fagerström questionnaire: | 1. How soon after you wake up do you smoke your first cigarette? |
|--------------------------|---------------------------------------------------------------|
|                          | (0) >60min; (1) 31-60min; (2) 6-30min; (3) ≤5min             |
| 0-2: no dependence       | 2. Do you find it difficult to refrain from smoking in places where it is forbidden? |
|                          | (0) No; (1) Yes                                              |
| 3-4: low dependence      | 3. Which cigarette would you hate most to give up?            |
|                          | (1) The first in the morning; (0) Any other                  |
| 5-6: moderate dependence | 4. How many cigarettes per day do you smoke?                  |
|                          | (0) ≤10; (1) 11-20; (2) 21-30; (3) >30                        |
| 7-8: high dependence     | 5. Do you smoke more frequently during the first hours after awakening than during the rest of the day? |
|                          | (0) No; (1) Yes                                              |
| 9-10: very high dependence | 6. Do you smoke even if you are so ill that you are in bed most of the day? |
|                          | (0) No; (1) Yes                                              |

| Exhaled CO               | 0-5 ppm: Non-smoker (at least for 24 hrs)                     |
|                         | 5-10 ppm: Light exposure, more than 6 hrs from the last cigarette, passive smoking or exposure to other environmental CO. |
|                         | > 10 ppm: current smoker                                       |

| Carboxyhemoglobin        | > 1.7% in the blood: active smoker                             |

| Urinary cotinine         | Inhaled nicotine (mg/24h)= 0.013x urinary cotinine (µg/L)     |
|                         | <10µg/L: non-smoker and <50µg/L: passive smoker               |
Table 2. 5A’s methods

| Ask            | Systematically identify the smoking status at every visit |
|----------------|----------------------------------------------------------|
| Advice         | Provide a very brief, non-threatening recommendations to quit |
| Assess         | Evaluate if the patient is ready to stop                 |
| Assist         | Offer practical help for quitting                        |
| Arrange        | Ensure the follow-up of the patient                      |
Table 3. Richmond test

| Question                                                                 | Interpretation                                      |
|--------------------------------------------------------------------------|-----------------------------------------------------|
| 1. Would you like to quit smoking if you could do it easily? (0) No; (1) Yes | ≥8: high motivation to quit                           |
| 2. Do you really want to quit smoking? (0) Not a bit; (1) A little; (2) Moderately; (3) Very Much | 6-8: moderate motivation to quit                     |
| 3. Do you think that you can quit smoking in the following two weeks? (0) Not a bit; (1) A little; (2) Moderately; (3) Very Much | ≤5: low motivation to quit                           |
| 4. Do you think that you will still be a former smoker in 6 months? (0) Not a bit; (1) A little; (2) Moderately; (3) Very Much |                                                     |
Table 4. Dose adjustment and drug interactions with pharmacologic drugs used for smoking cessation

| GFR:                        | NRT | Bupropion       | Cytisine       | Varenicline     |
|-----------------------------|-----|-----------------|----------------|-----------------|
| > 50 ml/min                 | No adjustment | No adjustment | No adjustment | No adjustment |
| 50 -30ml/min                | No adjustment | No adjustment | No Data        | No adjustment  |
| <30ml/min                   | No adjustment | Maximum 150mg 1x/day | No Data        | Maximum 1mg 1x/day |

Drug interactions

- ° ↑ bupropion
  - Voriconazole, clopidogrel, ticlopidine:
  - ° ↓ bupropion
  - Rifampicin, carba, efavirenz, isavuconazole, ritonavir, telotristat

Caution with anti-tuberculosis medications; clozapine; ropinirole; oral contraception
cimetidine

Abbreviations: GFR, glomerular filtration rate; NRT, nicotine replacement therapy.
Table 5. Dose adjustment in dialyzed patients

| Drug      | Metabolism                                      | PD                        | CVVH                      | HD-HDF                    |
|-----------|-------------------------------------------------|---------------------------|---------------------------|---------------------------|
| Bupropion | Renal elimination after hepatic metabolism by CYP2B6 | Not dialyzed              | Unlikely dialyzed         | Not dialyzed              |
|           | 1% excreted unchanged in urine.                 | Daily dose : 150 mg       | Daily dose : 150 mg       | Daily dose : 150 mg       |
| Cytisine  | Renal elimination                               | No data                   | No data                   | No data                   |
| Varenicline | Renal elimination                           | Dialyzed                  | Dialyzed                  | Dialyzed                  |
|           | Daily dose : 0.5 mg (after dialysis)            | Daily dose : 0.5 to 1 mg   | Daily dose : 0.5 mg (after dialysis) |
| Nicotine  | Hepatic metabolism                              | Not dialyzed              | Not dialyzed              | Not dialyzed              |
|           | 10% excreted unchanged in urine.                |                           |                           |                           |

Abbreviations: CVVH, Continuous Veno-Venous Hemofiltration; HD, hemodialysis; HDF, hemodiafiltration; PD, peritoneal dialysis
Legend to Figures.

**Figure 1:** Practical clinical algorithm to take care of smoking KT candidates/recipients
Abbreviation: SCP, smoking cessation program.

**Figure 2:** Local pharmacological management for smoking KT candidates and recipients
Abbreviations: HAD, Hospital Anxiety Depression; NRT, nicotine replacement therapy.
At every visit, ask “Do you want to quit?”

**YES**
- No SCP available
  - Counseling
  - “Do you want pharmacological help?”
    - No
      - Follow-up and monitor
    - YES
      - Choose a therapeutic option with the patient
        - Follow-up and monitor
- SCP available
  - Ensure early access to SCP
  - Follow-up and monitor

**No**
- Advice/information
  - Motivation
  - Roadblock
*Check for drug interaction and dose adjustment (Table 4 and Table 5). Buproprion should not be used if previous or risk of seizures, bipolar disorder, severe liver impairment and concomitant treatment with monoamine oxidase inhibitors.
Patient agrees to take additional pills?

- No
- Yes

NRT

Need for mood support (HAD questionnaire > 8)?

- No
- Yes

- Varenicline*
- Bupropion*

If the first line fails, consider another pharmacological option according to the patient’s expectations

*Check for drug interaction and dose adjustment (Table 4 and Table 5). Bupropion should not be used if previous or risk of epilepsy, bipolar disorder, severe liver cirrhosis and concomitant treatment with monoamine oxidase inhibitors.