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(54) Title: COMBINED USE OF HERBAL CIGARETTES AND NICOTINE REPLACEMENT THERAPY

(57) Abstract: The present invention relates to the use of herbal cigarettes within the scope of a pharmacological nicotine-withdrawal therapy or a pharmacological nicotine-substitution therapy. By the inventive combination of means of nicotine-withdrawal therapies or of nicotine-substitution therapies, the nicotine withdrawal is eased.



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COMBINED USE OF HERBAL CIGARETTES AND NICOTINE REPLACEMENT THERAPY

The present invention relates to the use of herbal cigarettes.

The tobacco smoke contains a huge number of potential physiologically active compounds (around 3000 to 4000) and nicotine has been identified as the main agent of tobacco addiction.

However, tobacco addiction is not limited to the pharmacological effect of the nicotine. Many addiction mechanisms are identified. Smoking involves the neurochemistry of the brain, Pavlovian-style conditioning, psychological factors and social factors.

Inhaling nicotine is very rewarding to parts of the mid-brain that control attention, mood, and addictive behavior. The typical smoker makes multiple attempts over many years before going even one year without a cigarette.

The physician's office is the best place to give people personalized messages about their health, offer long-term follow-up, prescribe stop-smoking medication, and offer supportive encouragement. Doing this will often require changes in clinical style, communication style, medication record system, appointment system, and duties of clinical staff.

The rewards of delivering effective clinical tobacco intervention are enormous; they include saving lives, preventing unnecessary illness and medical costs and helping patients liberate themselves from a deadly and difficult addiction.

As an example, some tobacco alkaloids were identified to have mono amine oxydase inhibitor properties and by the way a psychoactive effect.

In the scientific literature, the following factors of tobacco dependence were pointed out:

- Nicotine pharmacological effects
- Psychological and "behavioral" dependence
- Environmental stimulation
- Psychiatric morbid behavior

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- Anxiousness
- Hereditary and genetic factors (particular sensibility to previous factors)

The diagnosis to establish the main factors involved in the dependence on a patient willing to stop smoking is complicated because the treatment must take into account all of these main factors.

It is therefore important to address the pharmacological, pharmacokinetic and pharmacodynamic properties of the nicotine to understand the tobacco addiction mechanisms.

From a pharmacokinetic point of view, the nicotine is an amphiphilic molecule. Its ionic state depends on the medium pH and interferes on mechanism and absorption sites. This property is used in the different formulations used to administer the nicotine therapy (e.g. trans-mucosal or trans-dermal passage depending on the pH). Nicotine is quickly absorbed by trans-mucosal route from the cigarette smoke to reach the central nervous receptors. The maximal plasmatic concentration is reached in a few minutes. The plasmatic half life is approximately 2 hours with a great inter-individual variability.

Many pharmacokinetic parameters are involved in the addiction phenomenon, such as

- Frequency of cigarette intake
- De-sensitization of receptors during the day
- Re-sensitization of receptors during the night
- Nyctemeral cycle increasing the dependence

The nicotine acts on nicotinic receptors of acetylcholine with a release of dopamine at the central level. This mechanism is analogue to those observed with other psychotropic substances creating a dependence phenomenon such as alcohol, cannabis, cocaine, etc.. The release of dopamine induces a psycho stimulation and a "well being" and euphoria effect by activation of dopaminergic receptors. The dopamine effect is a primary step involving other neuro-mediators.

The activation process of dopaminergic receptors is complex, not well known and with inter-individual variations depending on sub-receptor repartition. This may explain the genetic factor in tobacco addiction.

These pharmacodynamic parameters explain the environmental stimulation phenomena: the intake of cigarette smoke and nicotine is often associated to an environmental event such as coffee break, end of dinner, etc., i.e. fixed events along the day. By this way, it creates endogenous or exogenous cross stimulations of receptors (internal or external stimulation). Along the nicotine weaning period, and a long time after, an external stimulation can re-activate the receptor system and create physical disorders associated to a strong smoking desire.

The nicotine induces a serotonin release. This phenomenon can currently not be explained scientifically because the nicotine has no affinity for serotonergic receptors. However this has a role in dependence phenomena.

The nicotine activates noradrenergic receptors and the hypothalamo-hypophysis axis with endorphin release. This phenomenon is preponderant in the addiction and stimulation mechanisms.

The smoker finally adjusts his cigarette consumption to his need for nicotine and to external and internal stimulations.

This explains the difficulties to adapt the treatments because of the strong link between pharmacological nicotine addiction and the behavioral, environmental and psychological parameters.

As mentioned above, the nicotine addiction is maintained for a long period of time by external and internal stimulations.

It could be linked to the pharmacological effects of the nicotine:

- Psycho-stimulating effect of the nicotine
- "Well being" sensation, euphoria effect
- Positive effects on anxious states

But also in a way not directly linked to the nicotine and which could be preponderant in many patients:

- Sensory pleasure of smoke inhalation
- Environmental stimulation and habits
- Repeated gesture
- Morbid attitudes often linked to other addictions
- Social attitudes
- Etc...

Nicotine-substitution therapies are means for increasing the prospects of the success of a tobacco-smoking withdrawal. Depending on the method used, both the mental and also the physical addiction to smoking tobacco are treated. The addiction-mediating active substance of the tobacco plant is the toxic alkaloid nicotine. Already 50 mg of nicotine are lethal for a human being, an amount which, however, is never reached with smoking. One tobacco cigarette commonly contains between 6 and 11 mg of nicotine, 1 to 3 mg of which are absorbed.

Nicotine is a water-soluble and lipid-soluble base. If taken up by alkaline tobacco smoke as it occurs with cigars or with the tobacco of a pipe, nicotine gets into the blood stream via the oral mucosa. Cigarette smoke, however, is acidic, i.a. because of the use of cellulose diacetate filters, and must be inhaled in order to enable the nicotine uptake. When smoking cigarettes, nicotine, bound to minute tar particles, gets into the lungs, and from there it is taken up into the blood stream, distributed within the body and finally reaches the site of activity on nerve cells. On these cells, primarily those of the brain, nicotine unfolds its activity. In low amounts it has a stimulating effect, at higher doses it has a sedating and relaxing influence. Moreover, a mental addiction to this toxin develops.

The addiction-developing effects of nicotine are linked to the increased expression of nicotine receptors in the brain, changes in the glucose metabolism of the brain, electro-encephalographic changes, the release of catecholamines and psychological addiction. These effects increase the craving to smoke by positive

rewarding reactions in the brain during smoking, and withdrawal symptoms during abstinence.

A further harmful component of tobacco smoke is tar which consists of many carcinogenic components. In commercially available cigarettes, the tar content of the smoke is reduced by filters. By this, however, also the amount of nicotine of the smoke bound thereto is reduced, causing the nicotine addict to smoke even more cigarettes per day. Likewise, a lowering of the nicotine content (light cigarettes) usually causes more intensive inhaling and the consumption of a greater number of cigarettes, whereby finally the harmful effect is not reduced. To reduce harmful effects or to cause other beneficial effects a light cigarette can be combined with herbs in a tobacco light cigarette according to US 2002/0153018 A1.

Further harmful components of tobacco smoke are, i.a., carbon monoxide, hydrocyanic acid, acetic aldehyde and formic aldehyde, nitrosamines, sulphur dioxide, phenols, nickel, cadmium and arsenic compounds.

Among other things, it is because of the health-damaging effects that many smokers want to stop smoking. However, due to the addiction to nicotine and the habit of smoking something, only very few succeed in stopping abruptly without having a relapse. The method of gently stopping to smoke, in which the amount of tobacco smoked is continuously reduced, is an alternative which, however, is not mastered by every smoker, either. Inter alia, diverse nicotine-withdrawal symptoms are an obstacle. Common withdrawal symptoms during an extended withdrawal are restlessness, irritability and concentration disturbances as well as an increase in weight by an increased appetite (particularly the craving for sweets).

In order to facilitate the tobacco withdrawal, diverse nicotine-substitution therapies and withdrawal therapies are available. Common auxiliaries used in nicotine-substitution therapies are transdermal nicotine patches, nicotine chewing gum, sublingual nicotine tablets, nicotine lozenges and other nicotine-admixed sweets, nicotine nose sprays, nicotine inhalers. These nicotine-

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containing means are used to controllably reduce the daily administered dose and to thereby reduce the withdrawal effect. Yet, the habit of smoking something must be abandoned at once, something that often is very difficult for many smokers because of the mental addiction to the smoking of tobacco.

Other therapeutic agents deal with the nicotine-withdrawal symptoms themselves, such as, e.g., the antidepressant Bupropion hydrochloride (Zyban®) only sold by pharmacies, yet not without possible medicament-caused side effects. Among them are headaches, aggressiveness, mood changes and eating disorders, tachycardia, hypertension, dizziness and sleep disturbances, depression, concentration disturbances, epileptic seizures, skin rashes, shortness of breath, muscular pain and fever. Due to these manifold undesired side effects, Bupropion is prescribed for very heavy smokers only.

Herbal cigarettes consisting of various components of diverse herbs are a nicotine-free alternative to tobacco cigarettes. It is the object of herbal cigarettes to meet the smoker's desire to smoke something, yet without administering the addictive drug nicotine. Often herbal compositions are chosen which, while being smoked, have a sedating effect on the smoker. In the U.S. Patent of Coy-Herbert (US 6,497,234 A), a herbal composition consisting of *Viburnum thapsus*, a component of algae, *Medicago sativa* and *Symphytum officinale* have been described as a tobacco substitute for cigarettes and pipes. These herbal cigarettes are suitable as an auxiliary for the withdrawal from tobacco-containing products, with nicotine-caused withdrawal symptoms, however, occurring. Lagrue (Tempo Médical 269 (1987) 35-38) has shown that the use of herbal cigarettes can be superior for smoking cessation compared to normal pharmacological treatment, especially when combined with psychological treatment and acupuncture. Further herbal cigarettes and their components have been described in publications WO 2004/049837 A or DE 44 02 148 A. In contrast to tobacco cigarettes, the smoke of these cigarettes contains only few carcinogenic compounds, such as, e.g., benzpyrene. Furthermore, the composition of the tar in suitable herbal compositions is less harmful than in tobacco cigarettes whose tar can glue and paralyse the cilia.

Another possible way of checking the nicotine intake have been nicotine-reduced tobacco cigarettes. In contrast to nicotine-free herbal cigarettes, all tobacco-based nicotine-reduced cigarettes have at least an intentional or unintentional residual amount of nicotine. Since the nicotine-caused effects occur in combination with smoking, there is no substantial withdrawal effect in nicotine-addicted smokers. As with light cigarettes, the smoker is tempted to smoke more cigarettes. To minimize this detrimental effect, additives are added. In US patent 5,383,478 A, tar and nicotine-reduced cigarettes are described to which capsaicinoids are admixed, the hot ingredients of pepper grains and chilli peppers. By these irritants sensations are caused in the respiratory tract which correspond to those of a normal cigarette.

US 2004/0103908 A1 generally describes herbal cigarettes, free of tobacco or nicotine. These herbal cigarettes can be used for the de-addiction of tobacco cigarette smoking.

Tar is one of the most harmful ingredients of tobacco smoke and is mainly responsible for the carcinogenic property of smoke. Therefore, the attempt has been made in some cigarettes to reduce the tar content of the smoke, e.g. by filters or by an altered tobacco composition. Tar-reduced methods also reduce the taste and the nicotine content of tobacco cigarettes. A tobacco composition which is said to retain the taste has been described i.a. in WO 93/02575. Therein, primarily the nicotine-rich parts of the tobacco plant are used. To increase the nicotine content of the smoke, compositions have been described in US 6,497,234 A in which nicotine is provided in the form of inclusion complexes which are added to the tobacco or to the filter. When the temperature is increased, nicotine is released from the carrier material and transits into the smoke.

A further harmful ingredient of smoke is carbon monoxide (CO). Carbon monoxide is gaseous and is not captured by conventional filters.

The common means for a nicotine or smoke withdrawal often are

insufficient to liberate smokers from their nicotine addiction. The substitution of the conventional nicotine cigarettes by herbal cigarettes also requires the nicotine-addicted smoker to accept the nicotine-withdrawal symptoms occurring during a withdrawal. The use of medicaments (Zyban®) against these withdrawal symptoms often is accompanied by severe side effects. The use of so-called "nicotine-free" tobacco cigarettes which, however, always still contain a residual amount of nicotine does not result in a satisfactory withdrawal, since an - even though reduced - nicotine-caused stimulus does always still occur together with the cigarette. Furthermore, in many nicotine-withdrawal therapies it is strictly forbidden to take in even the slightest amounts of nicotine during the therapy, since this may result in severe side effects and at least the success of the therapy may not occur (also comparable with an alcohol withdrawal in which the supply of the slightest amounts of alcohol might have disastrous consequences). The use of nicotine-withdrawal means, such as nicotine skin patches, chewing gums, aerosol sprays, inhalers or nicotine-containing foodstuffs does not meet the smokers' desire or habit to use something that can be smoked.

As mentioned before, current treatments (nicotine replacement therapy (NRT), psychotropic products, psychological assistance, tobacco free cigarettes, etc.) only take into account one aspect of the tobacco addiction:

- The pharmacological dependence to the nicotine or
- The behavioral and/or environmental dependence.

The tobacco addiction removal is not treated globally and it stays a physically and psychologically difficult event.

An analysis of clinical results obtained with various available treatments shows a limited success: more than 80 % of the patients present a total relapse in the one year period after the end of the treatment. Pierce et al. (JAMA 288 (2002), 1260-1264) concluded that since becoming available over the counter, NRT appears no longer effective in increasing long-term successful smoking cessation.

According to addiction mechanisms described previously, this

failure percentage is explained by:

- A persistence of environmental and behavioral cross stimulation effects,
- A "memory" of sedative and psycho stimulating effect of the nicotine,
- A persistence of anxious or morbid state,
- A need for the smoking pleasure, etc.

At the relapse of tobacco consumption, the negative effects of nicotine on the central receptors (nausea, vertigo, headache, etc.) quickly disappear and only leave "positive" effects (sedation, psycho stimulation, "well being" sensation, etc.). The addiction is quickly re-induced due to an increased sensitivity of the receptors and cross mechanisms.

For these reasons, it is very important to set up an accurate diagnosis with regard to the main dependence factors of the patient and bring the more adapted and global treatment.

For smokers with a long tobacco history, the more stimulation factors are cumulated, the more difficult and the longer is the weaning period.

The object of the present invention is therefore to help this kind of patients during this period and prevent them from a relapse inducing nicotine re-addiction.

It is also an object of the present invention to provide means which shall enable the smokers to free themselves from their nicotine addiction in as convenient a manner as possible, without having to endure mental or physical withdrawal symptoms.

Therefore, the present invention provides for the use of herbal cigarettes (HC) in combination with a nicotine replacement therapy (NRT). According to the present invention "nicotine replacement therapy" means any pharmacological nicotine-substitution therapy, or nicotine-withdrawal therapy, respectively. Any psychological way or means of treatment are not to be included in these terms, yet combinations of the herbal cigarettes and pharmacological nicotine replacement therapies according to the

present invention with such psychological treatments is also preferred.

In the present invention, nicotine-free herbal cigarettes are used within the scope of a nicotine-withdrawal therapy or a nicotine-substitution therapy. It is, of course, clear that the function of the herbal cigarettes is not to wean a smoker from smoking, but to act in support of the nicotine withdrawal. Thus, the smoker can meet his mental desire of smoking - in spite of an ongoing nicotine withdrawal. So far, this has not been possible for nicotine-withdrawal therapies, since they are based on strict adherence to the administration of nicotine or nicotine surrogates. If the smoker smokes (nicotine-containing) cigarettes during the therapy, this will lead to severe side effects and to a failure of the nicotine-withdrawal therapy. In contrast, with the present invention a nicotine withdrawal is possible without having to abandon the habit of smoking. The present invention also has essential advantages over a mere changing over from nicotine cigarettes to herbal cigarettes (which naturally are free from nicotine), since by this the side effects of the nicotine withdrawal cannot be fought. During the smoking of tobacco, the subconscious of the smoker is being and has been trained to taking up nicotine by smoking tobacco. The inventive use of herbal cigarettes now provides a means for re-training the smoker so that the addiction to nicotine-containing cigarettes is eliminated. To counteract the nicotine-withdrawal symptoms, nicotine is administered by a conventional means known in the prior art in doses decreased little by little. By this method, the addiction to nicotine finally is overcome. To meet the desire for smoking, according to the invention additionally a nicotine-free herbal cigarette is provided. For many smokers the desire to smoke something is a reason to break off an ongoing nicotine-withdrawal therapy. By the inventive approach, this reason is counteracted, whereby the prospects of a success of a nicotine-withdrawal therapy, or a nicotine-substitution therapy are considerably increased. In contrast to tobacco cigarettes, these herbal cigarettes do not cause any (further) increase of the nicotine content in blood (because no additional nicotine gets into the body by herbal cigarettes), whereby the smoker does not experience an above-described nicotine-caused stimulus

and the complications and side-effects caused by the supply of nicotine by smoking cannot occur. Over time, this may even have the consequence that, by this therapy, the smoker loses the addiction to the activity of smoking in addition to the addiction to nicotine and finally will no longer be dependent on tobacco or herbal cigarettes. By using synthetic cigarettes, a hand-mouth movement similar to smoking is imitated, yet this experience is not satisfying for most smokers. In contrast to these smoke-free synthetic cigarettes, with the combination therapy according to the invention the smoker has the feeling of smoking something, an advantage which may be beneficial to the mental and social (image) circumstances of the addiction to smoking. Preferably the herbal cigarette is nicotine-free and/or tobacco-free, most preferably the smokable main ingredient (besides, e.g. a paper envelope or a filter) is exclusively constituted of herbs.

The publication EP 1 201 142 A1 discloses a method to stop or reduce a smoking habit. The underlying goal of this method is similar as for the present invention, since the authors have also noticed that the use of common nicotine-withdrawal means like nicotine tablets or transdermal patches do not take away the smoker's urge towards taking a cigarette. However, the goal is achieved completely different to the present invention: According to this document, cigarettes with a mixture of herbs and tobacco are used, wherein in four phases of the therapy the tobacco content is gradually reduced in the cigarette. No combination of standard nicotine-withdrawal means like nicotine tablets and patches with herbal cigarettes is suggested in this document, since common therapeutic means like tablets and patches have been associated with certain adverse effects like mouth ulcers, heart burns and skin diseases, such as pruritus.

The present invention provides methods and means for combating nicotine addiction which addresses the most important factors of tobacco dependence and total relapse reasons: the pharmacological effects of nicotine, the psychological and "behavioral" dependence and the environmental stimulation ("Pavlovian" type of reaction). In nicotine replacement therapies according to the prior art, such a holistic approach using pharmacological means

and herbal cigarettes has never been suggested.

What is provided is also the inventive use of nicotine-free herbal cigarettes for producing a therapeutic kit for carrying out a nicotine-withdrawal therapy or a nicotine-substitution therapy. Such a kit allows for the simple handling of the therapy at any point of time during the withdrawal. The dosing of the nicotine surrogate or nicotine-withdrawal means in combination with the checking of the consumption of the herbal cigarettes is a practical advantage of this embodiment.

In a preferred embodiment of the invention, transdermal nicotine patches, nicotine chewing gums, sublingual nicotine tablets, nicotine lozenges, nicotine-admixed foodstuffs, in particular sweets, nicotine sprays or nicotine inhalers are employed as a nicotine-withdrawal therapy means or nicotine-substitution therapy means in combination with the above-indicated herbal cigarettes. These means are simple to use and already are largely known to most smokers, since they are means established in the market. Transdermal patches i.a. are known from US 4,597,961 A, US 4,781,924 A, US 4,839,174 A and EP 0 289 342 B. Such patches are applied to the skin and from there continuously release a certain amount of nicotine to the smoker. Nicotine patches are provided with different nicotine contents, as required. In this instance, nicotine is slowly and uniformly released over an extended period of time. Thus, nicotine patches are suitable to keep the patient's nicotine level constant over a long period of time. Nicotine chewing gums i.a. are known from GB 1,401,585 B. Here, nicotine is dissolved from the chewing gum during the chewing procedure, the nicotine delivery being highly dependent on the intensity of chewing. Nicotine is directly taken up by the body via the oral mucosa. Also with this nicotine therapy means, various nicotine concentrations are available. Nicotine lozenges and other nicotine-containing sweets have been described i.a. in GB 2,299,756 A. Similar to nicotine chewing gums, here the uptake of nicotine is enabled via the oral mucosa during consumption of the lozenges or sweets, respectively. Other nicotine-containing sweets are described in U.S. application US 2004/0115244 A. There, an appetite suppressor (Chromium picolinate) was additionally added to the sweet, so as to counteract

a gain in weight during the withdrawal. For the nasal administration of nicotine, nicotine aerosol sprays i.a. have been described in US 4,945,928 A, US 4,945,929 A or in US 4,953,572 A. By the uptake of the nicotine via the mucosa of the nose, the effect occurs within a few minutes. The urge to smoke and the withdrawal symptoms are quickly alleviated by these methods so that according to the invention it also quickly reduces the amount of herbal cigarettes consumed. Nicotine nose sprays thus are also suitable for smokers with a pronounced nicotine addiction. With nicotine inhalers, nicotine-containing vapours are transported into the lung so as to be absorbed there. Alternatively, it is also possible with such an inhaler device as described i.a. in JP 9,075,058 A, US 4,284,089 A or in DE 19854009 A, to simply take up the vapour in the oral cavity and not to inhale it, the nicotine being absorbed via the oral mucosa. In order to additionally reduce the desire for glucose, the U.S. patent of Reynolds (US 6,409,991 A) provides a kit which, in addition to a nicotine-containing means, e.g. an inhaler, contains a xylitol-containing agent. The purpose of this composition is to reduce a gain in weight during the tobacco withdrawal.

The nicotine amount in all these nicotine surrogates or nicotine-withdrawal means can vary as required in their inventive use in combination with herbal cigarettes. Usually, nicotine amounts of from 2 to 4 mg per use (in the patch, chewing gum, lozenge, nicotine capsule in the spray or inhaler) are used. Within the scope of the inventive nicotine-substitution therapy, or nicotine-withdrawal therapy, respectively, this amount may also deviate from these levels. In a preferred embodiment, according to the invention nicotine surrogate, or nicotine withdrawing agent with a nicotine amount of from 0 to 10 mg of nicotine are used. During the therapy, the nicotine amount is gradually reduced until finally no nicotine is administered any more. The use of placebos, i.e. nicotine surrogates or nicotine withdrawing means free from nicotine, as described above, is also an element of the nicotine-substitution therapy, or the nicotine-withdrawal therapy, respectively.

Particularly preferred is the inventive use in nicotine surrog-

ate therapies (such as, e.g., with Zyban®), since in such therapies any supply of nicotine must be avoided. In this type of therapy, already one single nicotine-containing cigarette could entail severe side effects, or lastingly jeopardize the success of the therapy, respectively.

Preferably, the means and methods according to the present invention are combined with psychological means and methods, specifically the psychological treatments currently applied together with nicotine replacement therapies. Whereas those psychological treatments have had improving, yet still limited effect in classical NRT, such psychological methods can be applied according to the present invention in a more successful way. Examples of such psychological methods to be combined with HC and pharmacological NRT according to the present invention are described by Fiore et al. (JAMA 268(19) (1992), 2687-2694; adjuvant smoking cessation counselling), Shiffman et al. (Drug Alcohol Depend. 64 (2001), 35-46); computer-tailored smoking cessation material), Riley et al. (Nicotine and Tobacco Res. 4(supp2) (2002), 183-188; computer and manual self-help behavioral strategies for smoking reduction), acupuncture, acupressure, yoga, qi gong, meditation therapy, autogenous training, etc..

Preferably, the herbal cigarettes to be used according to the present invention contain plants, herbs and legumes in smokeable form that can be smoked without exercising to the human organism a pharmacological action. In a preferred use according to the invention of the herbal cigarettes, the herbal cigarettes are comprised of one or more of (herbal) components selected from *Althaea officinalis*, *Trifolium pratense*, *Trifolium repens*, *Trifolium incarnatum*, *Trifolium alpestre*, *Trifolium arvense*, *Glycine max*, *Glycine soja*, rose petals, *Laminaria digitata*, *Hibiscus rosa Sinensis*, *Medicago sativa*, *Symphytum officinale*, algae, *Cnicus benedictus*, *Centella asiatica*, *Mentha piperita*, *Glycyrrhiza glabra*, *Pulmonaria officinalis*, *Ilex paraguaiensis*, *Lobelia inflata*, *Hypericum perforatum*, *Lawsonia inermis* L., *Nelumbo garetin*, *Ocimum santum* L., *Piper methysticum*, *Plantago major*, *Passiflora*, *Saussurea lappa*, *Areca catechu*, *Terminalia catappa*, *Curcuma longa*, *Centella asiatica*, *Hydrocotyle asiatica*,

Ribes indica, *Terminalia chebula*, *Elettaria cardamomum*, *Zingiber officinale*, sandalwood (*Santalum*), *Cinnamomum zeylanicum*, *Bdelium indica*, *Aegopodium podagraria*, *Ammi visnaga*, *Ocimum basilicum*, *Trigonella foenum-graecum*, *Turnera aphrodisiaca*, *Turnera diffusa*, *Laurus nobilis*, *Umbellularia californica*, *Vigna radiata*, *Potentilla* sp., *Rosa* sp., *Spirea* sp., *Chimaphila* sp., *Pyrola* sp., *Arctostaphylos uva-ursi*, *Arbutus menziesii*, *Rubus* sp., *Verbascum thapsus*, *Marrubium vulgare*, Herbaceous *Artemisia* sp., *Melissa officinalis*, *Uva-ursi*, *Menyanthes trifoliata*, *Chorophyllum sativum*, *Tussilago farfara*, *Stigneta maidis*, *Cunila mariana*, *Euphrasia officinalis*, *Antennaria dioica*, *Origanum marjorana*, *Rubus strigosus*, *Rosmarinus officinalis*, *Salvia officinalis*, *Betonica officinalis*, *Eriodictyon californicum*, *Corylus americana* Walt., *Carica papaya*, *Mentha piperita* L., *Althaea officinalis* L. oder *Cinnamomum tejpata*. These are known herbs for herbal cigarettes which form a preferred aspect of the invention in connection with a nicotine-substitution therapy or a nicotine-withdrawal therapy.

In order to reduce the carbon monoxide in the smoke of herbal cigarettes, means or methods for reducing carbon monoxide (CO) in the smoke are used in herbal cigarettes preferably to be used. Each arbitrary means or method from the prior art may be used for this purpose. In particular, when applying these means to herbal cigarettes, no attention must be paid to the nicotine-reducing effect that is undesired in nicotine-containing tobacco cigarettes. Examples of this are metal catalysts in the herbal material, in the paper sheath or in the filter. Such catalysts are described for instance in FR 2,841,438 A. There, the metals from the group of rare earths, such as, e.g., zirconium or manganese in the form of oxides or hydroxides, and/or zinc aluminate, and/or metals of the IIIA to IIB-groups of the periodic system on a silicon or titanium oxide carrier are described for such a use. These catalysts do not only reduce the CO concentration of the smoke, but they are also capable of respectively eliminating or rendering harmless other toxic ingredients, such as, e.g., nitrogen oxides (NO_x), of the smoke. Furthermore, these catalysts are capable of binding numerous organic carbohydrates and eliminating them from the smoke.

Common methods for reducing the CO content of smoke are based on changing the combustion equilibrium between carbon monoxide and carbon dioxide in favour of carbon dioxide (CO₂). In normal cigarettes, CO mainly forms in the interior of the cigarette, while in the outer layers less CO develops on account of the better access of air, or oxygen, respectively. To equalize this, US 4,986,287 A describes a coaxially layered cigarette, constructed with paper having little to medium air permeability as a sheath. Other air-permeable, perforated cigarette papers are described in US 4,088,142 A. Here, a compromise has to be found which sufficiently prevents CO formation, yet does not make the cigarette burn too quickly because of the better access of air. Another approach for reducing CO in cigarette smoke is described in US 4,120,309 A, where a metal rod or a tube is described which is longitudinally slid into a cigarette. As metal rod, the core of the combustion zone is cooled so much that the formation of CO₂ relative to CO is promoted. In the embodiment as a tube, the oxygen supply in the center of the combustion zone is additionally increased, whereby also more CO₂ is formed. Other approaches for minimizing CO are based on the use of metal oxide reagents in the filter material or in filter attachments. Such devices have long been known and are found e.g. in GB 685,822 A. However, these materials reduce also the nicotine content of the smoke. Filter materials based on metals, such as Fe²⁺, Cu²⁺ or Mg²⁺, occurring complexed by porphyrine rings, are described in WO 96/00019 A. These filter materials are capable of retaining a number of harmful ingredients of the smoke, among them NO, NO_x, carcinogenic nitroso compounds, free radicals, H₂O₂, CO, aldehydes and trace elements. Further metal complex materials for reducing the CO or NO_x contents of the smoke which are employed in filters are described in US 4,182,348 A and in GB 2,150,806 A.

In a preferred use of herbal cigarettes, means or methods for reducing tar in the smoke are employed. As described above in the case of carbon monoxide-reducing means, the reduction of the nicotine content of the smoke that is undesired in tobacco cigarettes is no obstacle for using them in herbal cigarettes. Tar-reducing means or methods are, i.a., common cellulose filters, charcoal, metal oxides (e.g. Al₂O₃), cigarette papers hav-

ing a higher air-permeability or the choice of low-tar-forming herbs or herbal products.

In order to remove as many of the harmful substances of the herbal cigarette smoke as possible, also combinations of filter materials are provided. Possible uses of composite filters have been described in GB 2,294,861 A, where CO and tar reducing layers are incorporated in a filter. A further combined filter which may be used according to the invention is found in EP 1,442,667 B. There, filter layers with i.a. liquid materials, among them liquid fatty acid esters or fatty acids, glycerol and charcoal, are described for purifying the cigarette smoke. In general usable filter materials are not limited to solids. Both volatile and also non-volatile liquids may form a component of filters, wherein in the case of volatile liquids methods known in the prior art are used so as to preserve the liquid in the filter until the time the cigarette is smoked. One mode of use is found in GB 1,065,204 A, where a filter is described which contains a capsule capable of bursting under pressure and containing a liquid adsorbent (e.g. water or glycerol). JP 2000-014377 A describes a similar device in which a dissolved perfume is enclosed in the capsule. Various filter compositions, in particular with a tar-degrading catalyst, are i.a. described in WO 2004/034825 A and in US 2004/025890 A. The smoke passing the cigarette filter described therein is characterized by a highly reduced tar content.

To improve the smoking experience and to induce the smoker to use the herbal cigarette rather than the tobacco cigarette, in a preferred embodiment of the invention additives, in particular flavoring agents and/or irritants, can be added to the herbal cigarette. Diverse additives for this purpose are known in the prior art. Also additives originally developed for tobacco cigarettes may be used for herbal cigarettes. Examples of suitable additives are i.a. menthol, glycerol, olive oil, sugar, honey, vanilla, cocoa, wine or wine products, maple syrup, licorice, capsaicinoids, ginger or ascorbic acid.

In a further aspect, the present invention relates to a kit for carrying out a nicotine-withdrawal therapy or a nicotine-substi-

tution therapy, comprising

- one or more pharmacological nicotine surrogates or pharmacological nicotine-withdrawal therapy means and
- one or more herbal cigarettes.

This kit makes carrying out the therapy easy for any tobacco smoker who wants to get rid of his/her nicotine addiction.

In a preferred embodiment of this kit, the nicotine surrogate or the nicotine-withdrawal therapy means from one or several of the nicotine surrogates or the nicotine-withdrawal therapy means selected from transdermal nicotine patches, nicotine chewing gum, sublingual nicotine tablets, nicotine lozenges, nicotine-admixed sweets, nicotine sprays or nicotine inhalers, is used.

In a further preferred embodiment of the kit, herbal cigarettes are used which comprise one of the above described herbal compositions and/or additives for carbon monoxide reduction and/or means for tar reduction.

The invention will be explained in more detail by way of the following examples to which, however, it shall not be restricted.

A clinical treatment schedule is organized in 2 steps:

- The nicotine addiction treatment with decreasing NRT doses according to patients needs still keeping the smoking gesture and habits (HC). It is the pharmacological addiction treatment period. This period is short (3 to 4 weeks) and will represent a less heavy effort with the help of HC gesture.
- In a second period, the behavioral and environmental treatment is conducted by progressive reduction of the number of HC according to external stimulations and with patient habits adjustment or re-education.

A psychological support helps patients to identify external stimulation and organize his treatment profile.

Relapses could occur for various reasons:

- Stress period
- Relapse or persistence of anxious state
- Desire of smoking pleasure
- ...

Anyway, if the desire or the need for smoking is too strong, the use of HC in the healing period prevents patients from re-induction of nicotine addiction by the tobacco smoke. HC are an interesting alternative because they could be transitory taken to help patient to cross a critical period with relapse risks.

Claims:

1. The use of nicotine-free herbal cigarettes within the scope of a pharmacological nicotine-withdrawal therapy or a pharmacological nicotine-substitution therapy.
2. The use of nicotine-free herbal cigarettes for producing a therapeutic kit for carrying out a pharmacological nicotine-withdrawal therapy or a pharmacological nicotine-substitution therapy.
3. The use of herbal cigarettes according to claim 1 or 2, characterized in that one or more means selected from transdermal nicotine patches, nicotine chewing gum, sublingual nicotine tablets, nicotine lozenges, nicotine-admixed sweets, nicotine sprays, nicotine inhalers are used for the nicotine-withdrawal therapy or the nicotine-substitution therapy.
4. The use of herbal cigarettes according to any one of claims 1 to 3, characterized in that the amount of nicotine of the nicotine surrogate or of the nicotine-withdrawal means is between 0 and 10 mg of nicotine per application.
5. The use of herbal cigarettes according to any one of claims 1 to 4, characterized in that the herbal cigarettes are comprised of one or more of herbal components selected from *Althaea officinalis*, *Trifolium pratense*, *Trifolium repens*, *Trifolium incarnatum*, *Trifolium alpestre*, *Trifolium arvense*, *Glycine max*, *Glycine soja*, rose petals, *Laminaria digitata*, *Hibiscus rosa Sinensis*, *Medicago sativa*, *Symphytum officinale*, algae, *Cnicus benedictus*, *Centella asiatica*, *Mentha piperita*, *Glycyrrhiza glabra*, *Pulmonaria officinalis*, *Ilex paraguaiensis*, *Lobelia inflata*, *Hypericum perforatum*, *Lawsonia inermis* L., *Nelumbo garetin*, *Ocimum santum* L., *Piper methysticum*, *Plantago major*, *Passiflora*, *Saussurea lappa*, *Areca catechu*, *Terminalia catappa*, *Curcuma longa*, *Centella asiatica*, *Hydrocotyle asiatica*, *Ribes indica*, *Terminalia chebula*, *Elettaria cardamomum*, *Zingiber officinale*, sandalwood (*Santalum*), *Cinnamomum zeylanicum*, *Bdellium indica*, *Aegopodium podagraria*, *Ammi visnaga*, *Ocimum basilicum*, *Trigonella foenum-graecum*, *Turnera aphrodisiaca*, *Turnera dif-*

fusa, Laurus nobilis, Umbellularia californica, Vigna radiata, Potentilla sp., Rosa sp., Spirea sp., Chimaphila sp., Pyrola sp., Arctostaphylos uva-ursi, Arbutus menziesii, Rubus sp., Verbascum thapsus, Marrubium vulgare, Herbaceous Artemisia sp., Melissa officinalis, Uva-ursi, Menyanthes trifoliata, Choerophyllum sativum, Tussilago farfara, Stigneta maidis, Cunila mariana, Euphrasia officinalis, Antennaria dioica, Origanum marjorana, Rubus strigosus, Rosmarinus officinalis, Salvia officinalis, Betonica officinalis, Eriodictyon californicum, Corylus americana Walt., Carica papaya, Mentha piperita L., Althaea officinalis L. oder Cinnamomum tejpata.

6. The use of herbal cigarettes according to any one of claims 1 to 5, characterized in that means or methods are used for reducing CO (carbon monoxide) in the smoke.

7. The use of herbal cigarettes according to any one of claims 1 to 6, characterized in that the means or methods are used for reducing tar in the smoke.

8. The use of herbal cigarettes according to any one of claims 1 to 7, characterized in that additives, in particular flavouring agents and/or irritants are admixed to the herbal cigarette.

9. A kit for carrying out a pharmacological nicotine-withdrawal therapy or a pharmacological nicotine-substitution therapy, comprising

- one or more pharmacological nicotine surrogates or pharmacological nicotine-withdrawal therapy means and
- one or more nicotine-free herbal cigarettes.

10. A kit according to claim 9, characterized in that the nicotine surrogate or the nicotine-withdrawal therapy means is comprised of one or more of the nicotine surrogates or the nicotine-withdrawal therapy means selected from transdermal nicotine patches, nicotine chewing gum, sublingual nicotine tablets, nicotine lozenges, nicotine-admixed sweets, nicotine sprays, nicotine inhalers.

11. A kit according to claim 9 or 10, characterized in that

the amount of nicotine of the nicotine surrogate or of the nicotine-withdrawal means is between 0 and 10 mg of nicotine per application.

12. A kit according to any one of claims 9 to 11, characterized in that the herbal cigarettes contained therein are as defined in any one of claims 5 to 9.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/060659

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K36/00 A61K31/465 A24D1/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A24D A24B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WESTMAN ERIC C ET AL: "Airway sensory replacement as a treatment for smoking cessation" DRUG DEVELOPMENT RESEARCH, vol. 38, no. 3-4, 1996, pages 257-262, XP009067330 ISSN: 0272-4391 abstract table 2 page 262, paragraph 2	1-12
Y,A	US 2003/111088 A1 (FOX BARBARA S) 19 June 2003 (2003-06-19) claims 1,2,6 paragraphs [0009] - [0014], [0021] ----- -/--	1-12

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* & * document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/060659

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 201 142 A (RAES, JAN) 2 May 2002 (2002-05-02) cited in the application claims 1-3 paragraphs [0002] - [0006] -----	1-12
Y	US 2004/103908 A1 (PRAKASH ROHIT ET AL) 3 June 2004 (2004-06-03) cited in the application claim 1 -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/060659

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2003111088	A1	19-06-2003	NONE	
EP 1201142	A	02-05-2002	NONE	
US 2004103908	A1	03-06-2004	WO 2004049837 A2	17-06-2004