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REVIEW

Therapeutic Options in Smoking Cessation

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Abstract: Tobacco use has complex and closely interrelated psychological and physiological determinants, nicotine appearing the main addictive agent in its compulsive use. Nicotine dependence is a life threatening disorder that requires long-term management. The most effective approach to increase the smoking cessation rate combines both pharmacotherapy and no pharmacological interventions. The three major pharmacotherapies (nicotine replacement therapy, varenicline and bupropion) for which efficacy as aid to stop smoking has been proved, are summarized in this review according to their mechanism of action, metabolism, pharmacokinetic profile, efficacy, adverse events and safety. NRT has no contraindications of its use in any patient, varenicline is until now the most effective medication and bupropion allows preventing weight gain during the smoking cessation attempt. Nortriptyline is briefly described as a potential second-line medication. However there is not now one medication most effective for all smokers and there is not one standard therapy schedule: the place of these therapies must be considered according to the characteristics and the preference of the patients.

Keywords: tobacco smoking cessation, nicotine replacement therapy, varenicline, bupropion

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Introduction

Tobacco use has complex and closely interrelated physiological and psychological determinants such as neurological, individual and environmental factors that must be taken into account for the successful treatment of tobacco dependence. Although exposure to many components of tobacco smoke is significantly related to an increased risk of health disorders and deaths from cancers, cardiovascular and respiratory diseases, nicotine appears to be the main addictive agent in the compulsive use of tobacco. The frequent and rapid action of inhaled smoke nicotine contributes to the high degree of addictiveness of tobacco smoke:a bolus of inhaled nicotine reaches the brain in 7 to 10 seconds, the pulmonary absorption from inhaled smoke being more rapide than by other routes. The blood concentration peak is observed within 5 minutes.[1] Nicotine stimulates the sympathico-adrenal system leading to various hemodynamic and metabolic changes and acts as a cholinergic agent responsible for psychotropic action, relaxation of the skeletal muscles and increase in gastro-intestinal motility and secretion.[2] In the brain, nicotine binds the $\alpha 4\beta 2$ nicotinic acetylcholine receptors, the main receptors mediating nicotine dependence[3] which are located on the ventral tegmental area neurons and lead to release dopamine in the nucleus accumbens.[4–6] Prefrontal cortex, amygdala and hippocampus through the $\alpha 7$ nicotinic receptors and the glutamate and γ-aminobutyric acid neurons play also a role in the drug-seeking behaviour.[7] Tobacco abstinence can produce several withdrawal symptoms (DSM) characterized by fatigue, impatience, insomnia, restlessness, irritability, anger, concentration difficulty, increased hunger, depressed mode, anxiety and craving. These symptoms that vary widely in intensity and duration between smokers may severely challenge the smoker's resolve to quit. Furthermore there is a well-known strong tendency to relapse after tobacco smoking cessation.[8] Pharmacotherapy and behavioural interventions have strong evidence of efficacy to help smoker to stop. The best results are obtained when the two approaches are combined, the main task of smoking cessation being to change behavioural patterns and to learn to life without smoking cigarettes. Some medications are until now recommended to treat the nicotine dependence like nicotine replacement therapy, bupropion, varenicline, and in second-line nortriptyline.[9,10]

Nicotine Replacement Therapy

Mechanism of action

Nicotine replacement therapy (NRT) provides an alternative form of nicotine to relieve cravings for nicotine and to reduce the severity of physical withdrawal symptoms allowing smokers to focus on the behavioural and psychological aspects of quitting before fully abstinent from nicotine. The various forms of NRT actually available, transdermal patch, oral forms (gum, sublingual tablet, lozenge, inhaler) and nasal spray, differ in nominal dose and in the method and speed of nicotine delivery. Although high and rapid peaks of nicotine plasma concentration reinforce the effects of nicotine obtained through smoking, the nicotine replacement formulations provide a low-level nicotine release and a slower delivery of nicotine than tobacco smoking, less attractive to smokers allowing reducing their willingness to continue using nicotine.[11–13] Nicotine supplementation is prescribed usually for two to six months and tapered off gradually, the patients adjusting to non-smoking lifestyle changes.[14]

Metabolism

Nicotine is absorbed, with considerable inter-individual variability, from skin for the patch, and mainly from nasal and buccal mucosa for oral NRT forms. In the gastrointestinal tract, nicotine undergoes extensive first-bypass hepatic metabolism resulting in lowest nicotine systemic level. In order to obtain higher systemic concentrations in basal conditions, buffered agents are added to the different forms of NRT to increase their absorption.

Near 90% of nicotine is metabolized in the liver primarily by the cytochrome CYP2A6 and to some extent in the kidneys and lungs. The principal metabolite is cotinine, nicotine N'-oxide being one other major end product. The kidney, nicotine excretion depending on the pH of the urine with a greater excretion at low pH, rapidly excretes both nicotine and most of its metabolites. Inter-individual differences observed in nicotine metabolism could be related to CYP2A6 polymorphism.[15–18]

Pharmacokinetic Profile

Blood nicotine levels vary greatly among products because of their variability in pharmacokinetics and dose delivery but none among available

NRT delivers nicotine to circulation as fast as does inhaling cigarette smoke.[19] Transdermal systems deliver nicotine at a more constant rate than other forms achieving more stable plasma nicotine concentrations, independently of the site of application. They release nicotine slowly, over a period of 16 or 24 hours, gradually peaking in hours after placement usually within 4 to 9 hours. On each succeeding day of patch application, the trough concentration of nicotine tends to increase markedly over the first three days, the steady state plasma concentration (from 10 to 23 µg/L) being achieved within 2 to 4 days.[20] Indeed the mean half-life of nicotine after removal of the patch is longer than the 1 to 2 hours usually reported after inhalation or parenteral nicotine absorption and could be explained by the delayed absorption from the patch or by the formation of nicotine depot in the skin.[21,22] The oral forms of NRT have a more rapid onset and a shorter duration of action, allowing the users to tailor their nicotine intake. Blood nicotine levels peak within 20 to 30 minutes after use of nicotine gum, sublingual tablet, lozenge or inhaler. The inhaler has similar pharmacokinetic properties than the other oral forms, nicotine being also mainly absorbed through the oral mucosa. The nasal spray has shorter latencies of action, the blood nicotine levels peaking within 5 to 10 minutes, slower than nicotine uptake from a cigarette. The plasma nicotine concentrations reach approximately one-third with the 2 mg dose and two thirds with the 4 mg dose the concentrations achieved by smoking.[23] The amount of nicotine absorbed per polacrilex lozenge appears to be somewhat higher than that delivered by gum probably due to the residual nicotine retained in the resin of the gum. The oral inhaler is a relatively weak nicotine dosing system giving, with ordinary use, the same nicotine concentration as a 2 mg gum.[17]

Clinical Studies and Efficacy

All available forms of NRT increase the successful smoking cessation rate by 50 to 70% compared to placebo, all current NRT forms having approximately a similar efficacy in any quit attempt. The reported relative risk for all types of NRT is 1.58 (1.50–1.66; 95% CI), varying from 1.43 (1.33–1.53; 95% CI) for the gum to 2.02 (1.49–3.73; 95% CI) for the nasal spray as reported in the meta analysis included 111 trials with over 43000 participants.[24] Abstinence rates range from 19% (16.5%–21.9%, 95% CI) to 26.7% (21.5%–32.7%, 95% CI) and 36.5% (28.6%–45.3%, 95% CI) for NRT alone and combined therapy respectively compared to 13.8% abstinence rate for placebo.[9,24,25] Choice of product is largely a matter of individual smoker's preference and the optimal duration of treatment varies among smokers. In highly dependent smokers there is a benefit of 4 mg gum compared with 2 mg gum but weaker evidence of a benefit from higher doses of patch. A 24-hour NRT dosing patch was reported to afford superior relief of craving and withdrawal especially in the morning than a 16-hour NRT dosing patch.[26] Combining a steady-state nicotine delivery system like patch with a self-administrated faster-acting system is more effective [OR (95% CI): 3.6 (2.5–5.2) and 1.9 (1.3–2.7) for NRT ad libitum added to patch during more than 14 weeks vs. placebo and vs. patch alone respectively] than either agent alone.[9,13] Patch delivers relatively steady levels of nicotine and oral form allows the smokers to best respond to cravings, which are likely to contribute significantly to relapse. No evidence exists that NRT is any more or less effective in any specific subgroups of smokers. However there is little evidence of the NRT effectiveness in promoting long-term abstinence among adolescents.[9,27] NRT given during temporary abstinence periods to smokers who will not stop smoking may increase their motivation for later cessation attempts. Concomitant NRT use and smoking could also be an aid to smoking reduction before a cessation attempt preventing the smoker compensation by inhaling more from each cigarette.[9,25] In that case, NRT use must be clearly explained to the smokers and tobacco smoking cessation attempt must be planned to avoid misuse of NRT or long-term unsuccessful application.

Adverse Events and Safety

NRT has an extremely good safety profile, the incidence of clinically significant harmful effects being very low even after a long-term use. Nicotine medications generally provide lower doses than cigarette smoking and the nicotine arterial blood rate is slower for NRT than that achieved from inhaled tobacco smoke. The most frequently side effect after nicotine application is moderate skin irritation responding to topical steroids or oral antihistamines treatment. The side effects reported with the oral use

of NRT mainly include mouth and throat irritation, cough, nausea, vomiting and hiccups. However some adverse local or systemic side effects can in rare cases lead to discontinuation of the treatment. A small minority of smokers, who successfully stop smoking, do become long-term users.[13]

A recent epidemiological study suggests that maternal use of NRT monotherapy during pregnancy does not significantly affect birthweight[28] although there are several animals studies indicating that foetal and neonatal nicotine exposure alone may be harmful to the developing foetus. Nicotine use has been reported to contribute to adverse pulmonary and hemodynamic effects, obstetric complications, foetal, neonatal and long-term injuries.[29,30] Futhermore there is insufficient evidence supporting the NRT efficacy in pregnant women.[9] However it is believed that the risks of NRT are small relative to the risks of continued smoking, the nicotine dose being reduced and the developing foetus not exposed to other tobacco smoke toxic components. NRT could thus be used for pregnant and breast-feeding women who are unable to quit without treatment. In these cases, oral forms or, if necessary, nicotine patch taken off at night to limit nicotine concentration in the amniotic liquid, could be prescribed.[9,25]

Several studies assessing the cardiovascular safety of NRT in clinical setting[31–33] suggest that NRT is safe in smokers with stable cardiovascular diseases and should be used in acute diseases to help in smoking cessation patients who continue to smoke, the benefits of quitting outweighing the potential risk of the medication.[9,25,34]

Although the effectiveness of NRT in adolescent remains to be clearly demonstrated, NRT therapy could be a help for nicotine dependent young smokers who are motivated to quit.

Varenicline

Mechanism of action

Structurally related to cytisine extracted from the plant Cytisa Viburnum, varenicline is a selective partial agonist of the α4β2 nicotinic receptor, a full agonist of the monomeric α7 receptor subtype and also an antagonist of the α4β2-receptor depending on the state of activation of the nicotinic receptor.[35,36] It may both attenuate the craving and withdrawal symptoms associated with tobacco smoking cessation by stimulating a moderate and sustained release of dopamine, and block nicotine uptake that decreases the reinforcing effects of nicotine thereby reducing the psychogenic reward associated with smoking if relapse.[37,38]

The therapy should be started between 8 to 10 days before tobacco cessation and is prescribed at a dose of 0.5 mg once daily for three days, 0.5 mg twice daily for the next 4 days and then 1 mg twice daily for a total duration of usually 12 weeks.[39] However varenicline could be safely used for long-term administration of up to one year to prevent relapse[40] particularly in patient non confident of remaining abstinent at the end of the usual treatment.[41]

Metabolism and Pharmacokinetic Profile

Varenicline is highly absorbed after oral administration without influence of food intake or time-of-day dosing and is weakly bound to plasma protein (<20%). The maximum concentration occurs within 3 to 4 hours after oral administration, the elimination half-life turning out about 17 to 30 hours and the steady-state being reach within 4 days. Less than 10% is metabolised in the liver into varenicline N-carbamoylglucuronide and hydroxyvarenicline, dose adjustments being thus not required for hepatic impairment. The compound is excreted primarily unchanged in the urine through glomerular filtration along with an active tubular secretion. The pharmacokinetic properties are not affected by age, gender, race, smoking status or use of concomitant medications.[42–44]

Clinical Studies and Efficacy

Ten randomized controlled trials with a follow up 12, 24 and 52 weeks are reported covering nearly 8000 participants from which more than 5000 used varenicline. Seven trials compared varenicline with placebo, three including a bupropion arm; one concerned early smoking cessation trial, one the relapse prevention and one an open-label trial comparing varenicline to NRT.[45,46] Varenicline was more effective than placebo considering validated continuous abstinence six months or more from the start of the intervention (RR: 2.33; 95% CI: 1.95 to 2.80). The pooled RR at 12 months for the three trials comparing varenicline to bupropion was 1.52 (95% CI: 1.22 to 1.88), remaining significant even after exclusion of previous users of bupropion

(RR: 1.46; 95% CI: 1.17 to 1.83). A significant benefit of varenicline over placebo in preventing smoking relapse was also reported with a risk ratio for validated continuous abstinence at 52 weeks of 1.18 (95% CI: 1.03 to 1.36).[40] Finally, a weak benefit of varenicline over NRT has been also reported (RR: 1.31; 95% CI: 1.01 to 1.71).[47]

Safety and Adverse Events

Varenicline is usually well tolerated at doses up to 2 mg daily except nausea occurring in about 30% of patients (29 to 44% following the clinical trials). This symptom, the main side effect of the therapy, remains generally mild to moderate, is dose-related and often attenuates over time and when the drug is given with food. The other main adverse events include abnormal dreams, insomnia and headache with a risk ratio for varenicline versus placebo of 2.79 (95% CI: 2.09 to 3.72), 1.45 (05% CI: 1.21 to 1.75) and 1.20 (95% CI: 0.98 to 1.46) respectively. The side effects do not result in a significantly higher drop out rate than that observed with placebo. Clinical studies didn't report any treatment-related deaths during treatment or follow up phases.[40,45–47]

No worsening of neuropsychiatric symptoms or new mood disturbance have been observed in patients with mental illness.[48,49] However post-marketing data reported events like depression, suicidal ideation and suicide attempts in patients treated with varenicline. Consequently, the US Food and Drug Administration issued in 2008 a public health advisory note reporting that patients must stop taking varenicline and call their doctor if they or their family observe depressed mood, suicidal thoughts or behavioural change.[50] Nevertheless it remains difficult to quantify the risk of such events which are naturally more frequently described in smokers and which may also be associated with nicotine withdrawal symptoms. The data of the UK General Practice Research Database including 80660 subjects did not demonstrated that varenicline was associated with an increased risk of self harm, suicidal thoughts or depression in varenicline-treated subjects (n = 10973) compared to those with bupropion (n = 6422) or NRT (n = 63265).[51] Furthermore a meta-analysis of the data from 10 randomized, double-blind, placebo-controlled trials including 3091 varenicline-treated subjects without current psychiatric disorders and 2005 participants receiving a placebo did also not show a significant increase in overall psychiatric disorders other than sleep disorders and disturbances (RR: 1.02; 95% CI: 0.86 to 1.12) nor any cases of suicidal ideation or behaviour in varenicline-treated subjects.[52] However it could be important to continue to evaluate the potential increased risk of suicide or suicidal thoughts and major behavioural change associated with varenicline in clinical practice. Safety and efficacy of varenicline must also be more studied in patients with serious psychiatric illness as schizophrenia, bipolar disorder and major depressive disorder.

Varenicline therapy has been recently evaluated among patients (n = 355) with stable cardiovascular diseases compared to placebo (n = 350) showing that varenicline was effective, well tolerated and not associated with significant increases in cardiovascular events, deaths, hemodynamic effects and heart arrhythmias.[53]

Preliminary studies showed that varenicline is well tolerated in healthy adolescent smokers during a 14-day treatment period[54] and that varenicline combined with bupropion may be more effective than monotherapy.[55]

Bupropion

Mechanism of action

Bupropion is an atypical antidepressant chemically unrelated to nicotine which, by inhibiting selectively the neuronal re-uptake of dopamine and noradrenaline with minimal effect on the re-uptake of serotonin, is believed to decrease craving and withdrawal symptoms. Furthermore, bupropion could act as an antagonist of the nicotinic receptors.[56,57] Started about one week prior to the quit date, the therapy should be usually prescribed at 150 mg once a day for 6 days and then increased to 150 mg twice daily for 7 to 9 weeks, with a minimum of 8 hours between doses.[58,59] Analysis of pooled results from studies comparing 300 mg versus 150 mg failed to demonstrate significant difference in long-term abstinence between the two doses.[60]

Metabolism

Bupropion is metabolised to three clinical active metabolites, hydroxybupropion primarily via CYP2B6, threohydrobupropion and erythrohydrobupropion; it should thus be used with care when combined

with medications known to inhibit or induce this isoenzyme.[58] Furthermore bupropion and hydroxybupropion inhibit the CYP2D6 and lead thus to possible increase in plasma concentrations of some antidepressants, antipsychotics, beta-blockers and antiarrhythmics. Bupropion and its active metabolites are conjugated within the liver to inactive metabolites which are excreted in the urine (84%), only a small amount (0.5%) of bupropion being excreted unchanged in the urine and 9% in the faeces. A reduced alcohol tolerance has been reported in patients treated with bupropion, avoiding alcohol intake whilst taking this therapy.[59]

Pharmacokinetic Profile

After initial daily dosing with sustained-release tablet of bupropion, the peak of plasma concentration is reached after 3 hours for bupropion, approximately 6 hours for hydroxybupropion and 5 hours for threohydrobupropion and erythrohydrobupropion. After a second dose administrated at least 8 hours following the first one, a second peak is observed in the evening prior to bedtime. The absorption is not significantly influenced by food. The steady state for bupropion and its metabolites is reached within 8 days, the mean t½ turning out about 20 ± 9 hours.[58,59]

Clinical Studies and Efficacy

Bupropion like NRT has been shown to approximately double quit rates compared with placebo. A recent Cochrane review analyses the results of 49 trials of bupropion in smoking cessation.[61] In 36 studies, bupropion used as the sole pharmacotherapy increases the long-term cessation rate (n = 11140; RR: 1.69; 95% CI: 1.53 to 1.85). Pooled analyses of studies comparing bupropion and NRT[62–64] or varenicline,[39,65,66] did not show a significant difference between bupropion and NRT but demonstrated a significantly lower tobacco smoking cessation rate with bupropion than with varenicline (14% vs. 21% abstinence). Based on the pooled studies which combined bupropion and NRT, most of them concerning population who are potentially hard to treat like adolescents or patients with schizophrenia or alcohol dependence,[62,67–71] it was reported a slightly higher abstinence rate than with bupropion alone that failed to reach statistical significance (n = 1106; RR: 1.23, 95% CI: 0.67 to 2.26).

An extended bupropion treatment until 12 months to delay smoking relapse in people who stopped smoking with 7 weeks of treatment,[72] showed a small benefit being confirmed after pooling studies (n = 1587; RR: 1.17; 95% CI: 0.99 to 1.39).[73] Several studies reported a low overall success rate in smokers offered further pharmacotherapy soon after treatment failure although others showed that bupropion was an effective therapy for smokers who have previously attempted to quit.[74,75] This effectiveness discrepancy of bupropion as second treatment after cessation attempt failure could be explained by the gap between the different attempts.[61]

Bupropion has been studied in patients' subgroups, particularly in patients with mental disorders for which a significant benefit from the addition of bupropion has not yet been demonstrated.[59] In patients with chronic obstructive pulmonary disease, bupropion was reported as an effective aid to smoking cessation at 6 months abstinence[76] without sustaining effect at one-year abstinence.[59]

Bupropion has been associated with absolute less weight gain than placebo, a benefit inversely related to dose. Although this effect is lost after treatment is stopped,[60,62] it allows smokers, in the early phase, to stop smoking without excessive worry about their weight.

Adverse Events and Safety

Bupropion treatment can be related to adverse events. If most commonly reported side effects include insomnia (30% to 45%) and dry mouth (5%–15%), gastrointestinal disorders (nausea, vomiting, abdominal pain, constipation), headache, dizziness, anxiety, depression, sweating, chest pain, arthralgia, myalgia, pyrexia and hypersensitivity reactions (rash, pruritis, urticaria, in rare cases angio-oedema, bronchospasm, and anaphylaxis) were also occasionally reported as withdrawal symptoms.[59,61]

An increased risk of seizure, a well known adverse event of many antidepressants, has been associated with bupropion with an overall seizure rate remaining in clinical trials less than 0.1% Half of the reported seizure cases were related to a previous history of seizure or to a risk factor for seizures such as an history of head injury, alcohol withdrawal or abuse, and anorexia. Consequently, bupropion is contraindicated in these patients. Care is needed when bupropion is

used concomitantly with other medications that can lower seizure threshold such as glucose-lowering drug, insulin or stimulants.[39,65,61,77] Although several studies have reported the use of bupropion in the treatment of patients with bipolar disorder, this treatment could induce maniac phase that must be closely followed. Following the manufacturer recommendations, bupropion remains contraindicated for these patients. It remains also contraindicated for patients with a history of eating disorder, during pregnancy and breastfeeding and with concurrent use of monoamine oxidase inhibitor in past 14 days (product safety data). There is neither a pharmacological nor a clinical reason for suspecting bupropion to be causally associated with depression or suicide. However, some cases of suicide or suicidal ideations having been reported among patients treated with bupropion, it is recommended to be aware of the possible emergence of significant depressive symptoms in patients undergoing a smoking cessation attempt.[61]

Finally, an increase in blood pressure has been reported, particularly in combination with NRT leading to avoid this association in patients with hypertension.[58]

Nortriptyline

Mechanism of action

Nortriptyline is a tricyclic antidepressant which inhibits the neuronal re-uptake of noradrenaline and weakly of serotonin and could be used as a second line medication in tobacco smoke cessation. Nortriptyline is prescribed during up to 3 months at the dose of 75 to 100 mg once a day taken at bedtime, started 10 to 28 days prior to stop smoking.

Metabolism and Pharmacokinetic Profile

Nortriptyline is completely metabolised by N-demethylation, hydroxylation and glucurono-conjugaison within the liver and excreted in urine. Nortriptyline is also secreted into maternal milk at a concentration similar than that observed in the blood. The peak of plasma concentration is reached 5 hours after oral absorption, the mean t1/2 turning out about 36 hours with a great individual variations.

Clinical Studies and Efficacy

Nortriptyline is an effective medication in treating tobacco dependence, showing a significant benefit over placebo (n = 975; RR: 2.03; 95% CI: 1.48–8.78) without evidence of an additional benefit to combine this therapy with NRT (n = 1219; RR: 1.29; 95% CI: 0.97–1.72).[61] Nortriptyline is recommended as a second line medication and should thus be considered for patients unable to use first line therapies according to the contraindications or who are unable to quit using these therapies.[61]

Adverse Events and Safety

Related to the anticholinergic nature of the product, several side effects are reported like dry mouth, blurred vision, urinary retention, light-headedness, tremor, constipation, dysgeusia, sedation, arrhythmia.[10,17] Nortriptyline is contraindicated for patients after acute myocardial infarction or cardiac rhythm disorders, with glaucoma, alcohol, opiate or barbituric addiction, prostatic hypertrophy, acute urinary retention, during pregnancy, breast feeding and with concurrent use of monoamine oxidase inhibitor in past 14 days (product safety data).

Place in Therapy

Tobacco smoking is a chronic, relapsing disease that must be treated to prevent health side effects and that requires long-term management. The most effective aid to stop smoking includes behavioural support and a pharmacological therapy for the nicotine physical dependence. Actually there are available medications for which efficacy has been demonstrated,[17] three of them (NRT, bupropion and varenicline) are recommended as first line treatment[9] and an other as a second line (Table 1). There is not one medication most effective for all smokers and there is not one standard therapy schedule. Considering the contraindications and potential adverse events of each therapy related to the current medical conditions of the patient, the medication must be selected according to the individual preference of the patient for various formulations, his previous use of smoking cessation aids and his degree of dependence. According to the perception of the previously used treatments, the same therapy can be prescribed for patients who report a positive experience considering some modifications in the therapeutic formulation (dose, frequency, duration and association of therapies), an alternative product being recommended for patients with a previously negative experience. Pharmacotherapy may be continued for periods longer than usually recommended to prevent relapse. It should be interesting, especially in heavy

Table 1. Comparison of the four therapeutic options according to their profile, efficacy and side effects.

	Profile	Efficacy vs. placebo (RR, [95% CI])	Main side effects
NRT	Alternative forms of nicotine		Skin or respiratory irritation
	— Any form	1.58, [1.50–1.66]	
	— Gum	1.43, [1.33–1.53]	
	— Patch	1.66, [1.53–1.81]	
	— Inhaler	1.90, [1.36–2.67]	
	— Oral tablets	2.00, [1.63–2.45]	
	— Nasal spray	2.02, [1.49–2.73]	
Varenicline	Selective partial agonist and antagonist of the $\alpha 4\beta 2$ nicotinic receptors	2.33, [1.95–2.80]	Nausea, abnormal dreams, insomnia, headache
Bupropion	Inhibitor of re-uptake of dopamine and noradrenaline	1.69, [1.53–1.85]	Insomnia, dry mouth, gastrointestinal disorders, increased risk of seizure
Nortriptyline	Antidepressant	2.03, [1.48–2.78]	Anticholinergic side effects

dependent smokers, to combine various therapeutic formulations.

The main advantage of NRT is that there isn't any contraindication to its use even in patients with respiratory, mental and cardiovascular diseases. The choice of the most appropriate form, the optimal dose and duration of treatment might enhance the efficacy of this therapy. The combination of patch used during a longer period (>14 weeks) with an oral NRT formulation selected by the smoker produces greater likelihood of long-term abstinence than does the use of single medication. A short acting NRT is proposed as often as necessary to control craving and intermittent withdrawal symptoms. For optimal efficacy, the doses of nicotine must be adapted to achieve the inhaled nicotine concentration. It is important to explain to each smoker how to use each type of NRT correctly. These medications have been shown to be safe in adolescents and remains available for nicotine dependent adolescents who cannot stop smoking without pharmacological therapy regarding their urges and withdrawal symptoms. NRT is also the only therapy that can be prescribed to pregnant or breastfeeding women in second intention if women failed their cessation attempt with non-pharmaceutical interventions. The harm of NRT during pregnancy remains controversial but seems less hazardous than continuing to smoke thereby exposing the foetus and its mother to the other toxins of tobacco smoke.

Varenicline is until now the most effective medication for smoking cessation and could be a first-line treatment according to the preference of the subjects and their tolerance and contraindications to the other therapies such as bupropion and NRT. At the present time, it is not recommended to associate varenicline with other therapies. However, in daily practice, varenicline is sometimes combined with NRT for heavy smokers, the effectiveness of this association remaining to be studied. The standard duration of the treatment could be extended for patients for whom the quit attempt was not stabilised. Its efficacy in adolescents remains to be more investigated.

Bupropion is an effective alternative therapy for smokers who prefer a treatment without nicotine or who did not tolerated vanenicline. It could also be an useful therapeutic option regarding to its ability to be used in combination with NRT and its potential action to prevent weight gain after smoking cessation, particularly for patients most concerned with their weight.

Finally, nortriptyline is a second-line effective medication for patients who failed their tobacco smoking cessation attempts with the other recommended medications or who did not tolerate them.

Conclusion

Nicotine dependence is a life threatening disorder that requires long-term management. Physicians should routinely identify patients' smoking status and help them to stop smoking. There is now a strong evidence for the efficacy of several medications like NRT, varenicline, bupropion, and nortriptyline, especially when associated with a specialist behavioural support. Varenicline is the most effective therapy until now, NRT products having the advantage of the absence of any formal contraindication. Various formulations of NRT can be safely combined as well as the association with bupropion. However the choice of the therapy should be taken according to the patient's preferences, potential contraindications and past experiences. Any health risk of the therapy must be balanced against the likely long-term benefits of smoking cessation and the evidence of the effectiveness of medication as an aid to smoking cessation.

Disclosure

This manuscript has been read and approved by all author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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