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CYTISINE THERAPY FOR TOBACCO SMOKING CESSATION: A RETROSPECTIVE OBSERVATIONAL STUDY FROM AN ITALIAN ANTI-SMOKING CENTER

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ABSTRACT – *Objective*: Tobacco smoking is recognized as one of the biggest threats to public health globally. Clinical trials conducted to date on cytisine have demonstrated its good efficacy in promoting smoking cessation. This study aims to evaluate the effectiveness and tolerability of cytisine as monotherapy in the treatment of moderate or severe tobacco use disorder in a real-world setting in Italy.

Materials and Methods: A monocentric, retrospective, observational study was conducted on 159 adult patients (≥18 years) treated with oral cytisine who were referred to the Rome Anti-Smoking Center of IRCCS Regina Elena National Cancer Institute for the first time from March 2023 to November 2023. The study used both clinical [objective examination, Visual Analogue Scale (VAS) test, Fagerström test, and Mondor test] and instrumental evaluations (spirometry and measurement of exhaled carbon monoxide). Categorical data were summarized using absolute frequencies and percentage values, while continuous variables were summarized using median values and relative range. Comparisons between categorical variables were performed by using Pearson's Chi-square test or Fisher's exact F-test. Comparisons between continuous variables were carried out using the Mann-Whitney test or the Student's *t*-test. The non-parametric Wilcoxon test was used to compare carbon monoxide values between the first visit and the first follow-up visit.

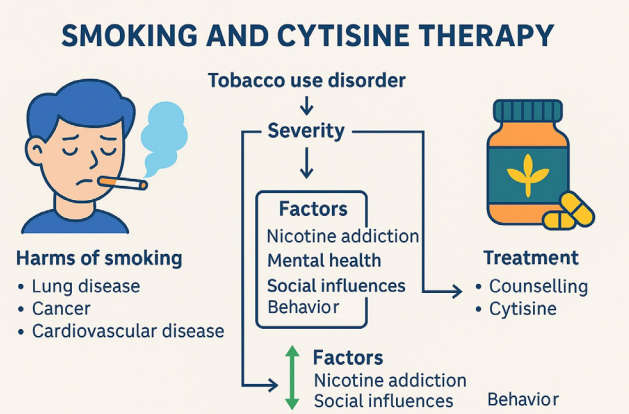
Results: 93 (58.5%) patients were males with a median age of 64 years, while 66 (42%) were females with a median age of 63 years. The median age of cigarette smoking initiation was 16 years, and the median number of packs per year was 40. After 3 months, 44 patients out of 65 (67.7%) patients who received therapy were adherent, while 21 (32.3%) patients did not follow the prescription and dropped out of the treatment. 75% (33/44) of patients who adhered to therapy successfully quit smoking, compared to just 25% (11/44) of those who did not adhere to treatment and did not stop smoking (p=0.011). No significant safety issues were identified.

Conclusions: Cytisine therapy administered in the real-life setting of a specialized anti-smoking center significantly promotes smoking abstinence. However, it has a poor therapeutic adherence profile, requiring further research on therapeutic adherence and long-term outcomes in order to optimize treatment strategies.

KEYWORDS: Cytisine, Nicotine addiction, Anti-smoking center, COPD, Abstinence, Pharmacological strategies.

INTRODUCTION

Tobacco smoking is recognized as one of the biggest threats to public health globally[1]. According to the Global Burden of Disease Study 2019[2], about 1.1 billion tobacco smokers in 2019 accounted for more than 7 million deaths worldwide. In fact, tobacco smoking is one of the main



Graphical Abstract. Overview of cytisine therapy for tobacco use disorder, its health consequences and treatment strategies.

causes of preventable mortality and morbidity, being associated with a wide range of diseases, including cancer, cardiovascular diseases, and respiratory diseases[1]. In particular, it is responsible for 85% to 90% of lung malignancies and represents the primary cause of Chronic Obstructive Pulmonary Disease (COPD)[3-5]. Furthermore, it is strongly associated with other respiratory disorders, such as asthma exacerbation[6], pneumonia[7], tuberculosis[8], and is involved in the development of less common respiratory conditions such as alpha-1 antitrypsin deficiency and histiocytosis[9].

In Italy, despite the efforts made in recent decades to raise awareness among the population about the damage caused by smoking, the rate of active tobacco smokers remains high. According to the most recent estimates[10], in 2024, approximately 24% of the Italian population (18-69 years) smokes regularly.

Tobacco smoking is a pathology influenced by multiple factors, including family influence, culture, social relationships, economic availability, and mental health. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Tobacco Use Disorder is defined as a psychiatric disorder related to the abuse or dependence on tobacco characterized by physical and psychological dependence, manifested by craving to consume tobacco, difficulty controlling or reducing tobacco use, and experiencing withdrawal symptoms when tobacco use is stopped. This severity ranges from mild to severe, depending on the number and severity of symptoms[11,12].

Nicotine addiction is largely involved in the development of addiction to tobacco use. Nicotine acts on the neuronal nicotinic acetylcholine receptors in the mesolimbic system. Its effects on appetite, attention, and mood seem to contribute to the establishment and maintenance of the tobacco smoking dependence[13,14].

Different strategies are available for the treatment of smoking dependence that include the use of medications to manage withdrawal symptoms and reduce nicotine intake, as well as counseling and cognitive-behavioral therapies to help the patient manage the smoking habit and maintain long-term abstinence[15]. Specifically, the combination of behavioral support and pharmacotherapy has been shown to significantly enhance long-term cessation rates[16,17]. Table I provides a comprehensive overview of the principal interventions currently available, summarizing their characteristics[18-32].

Nicotine Replacement Therapy (NRT)[17] and the use of stop-smoking medications, such as bupropion[22,23], varenicline[25,33], nortriptyline[28,29], and cytisine[30-32] are the main pharmacological strategies available for smoking cessation. According to WHO guidelines[32], the following options, which have higher likelihoods of quit success associated with their use, should be available for all tobacco users: (i) single-agent varenicline or cytisine; (ii) combination NRT (a long-acting and a short-acting agent); (iii)·combination of any medication(s) and behavioral support. Varenicline and combination NRT both have greater effectiveness compared with NRT monotherapy and bupropion. Cytisine acts similarly to varenicline, but it is demonstrated to be less effective than varenicline in smoking cessation[33-36]. Nevertheless, cytisine is considered safer and less expensive compared to other available therapeutic options at the dose currently recommended and found to be superior to NRT for smoking cessation[37,38]. Cytisine should be considered as a treatment option to help people stop smoking, also according to the National Institute for Health and Care Excellence since new evidence showed that people who took cytisine were 30% more likely not to smoke for six months or longer than those taking a placebo or no medication and significantly more likely to have higher long-term abstinence rates than NRT because patients receiving cytisine had a higher adherence to the treatment plan and a lower rate of adverse events[39].

The need to fill in the gaps in the existing literature, as recommended also by "The Italian clinical practice guideline for the treatment of

Table I. Treatment strategies of tobacco smoking cessation.

Non-pharmacological strategies
Cognitive Behavioral Therapy (CBT): psychological approach widely used in the treatment of smoking. This therapy focuses on how thoughts, emotions, and actions are interconnected and how these factors impact smoking addiction[18,19].
Motivational Therapy: patient-centered style of individual counseling with meetings with a professional. It includes evaluation and planning for stopping cigarette smoking, managing abstinence and relapses, and promoting correct lifestyle habits[20].
Nudge-Based Interventions: these techniques involve giving information or incentives, understanding mapping, setting default choices, providing feedback, reducing errors, and structuring complex choices. When applied to smoking disorder, information and feedback nudges have shown effectiveness[21].
Pharmacological strategies
Nicotine Replacement Therapy (NRT): this therapy replaces the nicotine found in cigarettes with alternative forms of nicotine. NRT reduces cravings for nicotine, as well as the physiological and psychomotor withdrawal symptoms often experienced during an attempt to stop smoking[17].
Bupropion: an inhibitor of norepinephrine and dopamine reuptake, as well as an anticholinergic nicotinic receptor inhibitor. Its action on smoking cessation is independent of its antidepressant effect. It is contraindicated in patients with cardiovascular, respiratory, renal, or epileptic disorders[22-24].
Varenicline: it acts as a selective partial agonist of the α4β2 nicotinic receptor, mimicking the action of nicotine intake and reducing withdrawal symptoms. By binding to the nicotinic receptor, it produces a release of dopamine and inhibits the nicotine-receptor binding, reducing the rewarding effect of smoking. The major side effect encountered is nausea[25-27].
Nortriptyline: a tricyclic antidepressant with potent norepinephrine reuptake inhibition, serotonin reuptake inhibition, and marked antihistaminergic effects. This medication represents the second-line pharmacological therapy in smoking cessation, whose efficacy is independent of its antidepressant action. The efficacy of Nortriptyline is comparable to Bupropion[28,29].
Cytisine: natural plant alkaloid extracted from Cytisus laburnum with a molecular structure similar to nicotine. Cytisine has a high affinity for presynaptic nicotinic acetylcholine receptors, acting as a partial agonist of α4β2 nicotinic receptors and a full agonist of α7 nicotinic receptors, which modulate dopamine and glutamate release in the mesolimbic system. Pharmacokinetic studies showed a good gastrointestinal absorption, 34% oral bioavailability, and a maximum plasma concentration after approximatively 35 minutes. Cytisine is safe at the currently recommended dose and was found to be superior to nicotine-replacement therapy for smoking cessation in clinical trials[27,30-32].

tobacco and nicotine dependence" published by the Italian National Guidelines System in 2023[39], served as the rationale for the design of this study. This guideline prioritizes evaluating adherence to therapy, safety, and effectiveness in scientific research on cytisine. Furthermore, if fully validated, this smoking cessation treatment could have a significant impact on the Italian National Health Service (NHS). After 15th July 2021, following the withdrawal of batches and the interruption of distribution of varenicline due to quality problems, Italy lacks a therapy with a partial agonist mechanism on nicotine cholinergic receptors. Therefore, cytisine could serve as a viable therapeutic alternative for patients seeking to quit smoking. Cytisine is a cost-effective medication with a good safety profile and the potential to significantly increase smoking cessation rates and decrease the financial burden on the NHS associated with management of smoking-related health problems[37,38,40]. Since there is the need to find effective therapeutic alternatives to varenicline after its withdrawal, and cytisine has emerged as a promising pharmacological option for smoking cessation, offering a novel mechanism of action compared to traditional therapies, we performed an observational study to evaluate effectiveness and tolerability of cytisine monotherapy for moderate or severe tobacco use disorder, as well as its capacity to reduce tobacco craving.

MATERIALS AND METHODS

Patients and study design

A monocentric retrospective observational study was conducted on adult patients (≥18 years) affected by moderate or severe tobacco use disorder and treated with oral cytisine (1.5 mg capsules) who were referred for the first time to the Rome Anti-Smoking Center of IRCCS Regina Elena National Cancer Institute - from March 2023 to November 2023.

The study was approved by the Ethical Committee Comitato Etico Territoriale Lazio of the Lazio Area 5, with protocol number 104/IRE/24, dated March 20, 2024.

Inclusion criteria

1. Adult patients (≥18 years) who have a moderate to severe tobacco use disorder,
2. Cytisine as prescribed pharmacological therapy,
3. Patients returned to the Anti-Smoking Center at the 1st follow-up on schedule.

Exclusion criteria

1. Adult patients (≥18 years) who have medical conditions that make the use of cytisine or other partial agonists of nicotinic cholinergic receptors unsafe,
2. Patients on pharmacological treatment or radiotherapy for neoplastic disorders,
3. Pregnant or breastfeeding women,
4. Patients for whom specific information for objective assessments is not available.

Pharmacological treatment

The pharmacological treatment consisted of oral cytisine (1.5 mg capsules), prepared as a galenic formulation by the hospital pharmacy. The treatment plan used included two therapeutic schemes[27]: 25 days treatment with the start of the drug at the maximum dosage (6 tablets/day in the first 3 days) and then a progressive reduction (scheme adapted from Walker et al[31]) and 40 days treatment, which included a short induction period (e.g. 4-5 days) and a longer treatment at the maximum dosage (6 tablets/day), with a prolonged progressive reduction of drug dose. The choice was based on the medical or the patient's preference.

Outcome assessment

The effectiveness of cytisine therapy was evaluated by verifying the achievement of smoking cessation after 3 months through clinical evaluation of smoking status (objective examination), measurement of the exhaled carbon monoxide (CO) value (expressed in particles per million) between the baseline visit and the first check-up visit for assessment of smoking abstinence and the evaluation of Visual Analogue Scale (VAS) score for the assessment of intensity of nicotine craving. Cytisine's safety and tolerability were evaluated by describing any adverse reactions occurring during the treatment period. The patient's physical dependence score was measured using the Nicotine Dependence Questionnaire (Fagerström test), and the patient's motivation for treatment was measured using the Mondor Motivational test. The tests were administered to evaluate whether they could be considered as a determinant of patients' adherence to the prescribed drug therapy.

The planned diagnostic and therapeutic pathway included the following steps:

- T0 – Baseline: first pneumological visit for smoking status, administration of questionnaires (Fagerström for Nicotine Dependence test and Mondor Motivational test), counseling, exhaled CO measurement, and prescription of cytisine treatment when indicated.
- T1 – after one month: pneumological follow-up visit with assessment of compliance with treatment, onset of adverse effects to the drug, detection of tobacco use status, exhaled CO measurement, and spirometry or, in alternative, a telephone follow-up with assessment of compliance with treatment, onset of adverse effects to the drug, and detection of tobacco use status.
- T2 – after three months: pulmonary follow-up visit with exhaled CO measurement, and spirometry if the patient had a telephone follow-up assessment at T1.

Statistical analysis

Descriptive statistics were generated for all variables of interest. Categorical data were summarized using absolute frequencies and percentage values, while continuous variables were summarized using median values and relative range, since they were not normally distributed. Comparisons between categorical variables were performed using non-parametric tests, such as Pearson's Chi-square test or Fisher's exact F-test, when appropriate. Comparisons between continuous variables were carried out using the non-parametric Mann-Whitney test or the Student's *t*-test, after testing the normality condition of the distributions. The comparison between carbon monoxide values at the first visit and the first follow-up was evaluated using the non-parametric Wilcoxon test. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS software v. 29.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 159 patients who had a first access to Rome Anti-Smoking Center was identified (Table II): 93 (58.5%) were males with a median age of 64 years (min: 34-max: 76), while 66 (42%) were females with a median age of 63 years (min: 46-max: 78). The median age of cigarette smoking initiation was 16 years (min: 9-max: 35) and the

Table II. Demographic and clinical characteristics of patients who accessed the Anti-Smoking Center between March and December 2023 (n=159).

	No.	%
	159	100
Sex		
F	66	41.5
M	93	58.5
Age		
Median (Min-Max)	63 (34-78)	-
Median (Min-Max) Female	63 (46-78)	-
Median (Min-Max) Male	64 (34-76)	-
Age of cigarette smoking initiation		
Median (Min-Max)	16 (9-35)	-
No. of packs per year		
Median (Min-Max)	40 (9-107.5)	-
Occupational status		
Employed	66	41.5
Unemployed	11	6.9
Retired	66	41.5
Other	12	7.6
Missing	*4*	*2.5*
Level of education		
None/primary school	24	15.1
Secondary school	84	52.9
Bachelor's degree	46	28.9
Missing	*5*	*3.1*
Co-morbidities		
Respiratory diseases	63	39.6
Cardiovascular diseases	60	37.7
Both respiratory and cardiovascular disease	38	23.9
Missing	*34*	*21.4*
Previous therapy		
Pharmacological	6	3.8
Psychological	9	5.7
Acupuncture	5	3.1
Other	47	29.6
Missing	*100*	*62.9*
Proposed therapy		
Cytisine	103	65
Other therapies	9	6
Missing	*47*	*29*

median number of packs per year was 40 (min: 9-max: 107.5). The majority of patients who accessed the Anti-Smoking Center were employed (66, 41.5%) or retired (66, 41.5%), while 11 patients (6.9%) were unemployed. The 52.9% (84 patients) attended secondary school, 28.9% (46 patients) had a bachelor's degree, while 15.1% (24 patients) attended only primary school. Most of them had a respiratory disease (39.6%, 63 patients) or a cardiovascular disease (37.7%, 60 patients), while 23.9% (38 patients) had both.

103 (65%) patients out of 159 were proposed with a cytisine therapy at baseline visit-T0, and 65 of them (63.1% of those proposed with a cytisine therapy) returned to the Anti-Smoking Center after 1 month for the first follow-up visit-T1 (Figure 1). Overall, 44 patients out of 65 (67.7%) were adherent to cytisine therapy prescription, while 21 patients did not follow the prescription (17 interrupted cytisine therapy, 4 had counseling only) and dropped out of the treatment at the three-month follow-up visit-T2.

All 65 patients had information on their smoking situation after 3 months at the second follow-up visit-T2 (Table III): 42 patients (65%)

Table III. Outcomes of patients who returned to the Anti-Smoking Center in the study period were dichotomized by adherence to prescribed cytisine therapy (n=65).

Outcomes	No. (%)	Cytisine therapy		
		yes	no	*p*-value
Intensity of nicotine craving (VAS score test) at T0	**44 (67.7%)**	**8 (3-10)**	**8 (0-10)**	**0.610**
Nicotine Dependence score (Fagerström test) at T0	**65 (100%)**	**6 (1-9)**	**4.5 (0-8)**	**0.012***
Motivation test (Mondor score test) at T0	**65 (100%)**	**13 (9-17)**	**13 (8-19)**	**0.488**
CO value difference T1-T0	**20 (30.8%)**	**17**	**3**	**<0.001**
T0	14 (4-37)			
T1	6.5 (0-16)			
Smoking cessation at T2	**65 (100%)**	**44 (67.7%)**	**21 (32.3%)**	
Yes	42 (64.6%)	33	9	0.011*
No	23 (35.4%)	11	12	

Data are presented as median value (range) or number (proportion, %). *statistically significant.

stopped smoking, and 23 (35%) did not. In all, 75% (33/44) of patients who received therapy successfully quit smoking, compared to just 25% (11/44) of those who did not follow the therapy. This result was statistically significant (p=0.011) and confirmed the effectiveness of the therapy.

The median values of exhaled CO, measured in 20 (30.8%) patients for which the information was available, decreased from 14 at the baseline visit-T0 to 6.5 at the first follow-up visit-T1 with a statistically significant difference (p<0.001). Out of these 20 patients, 17 who adhered to cytisine therapy showed a significant difference in exhaled CO (Wilcoxon test: p=0.001), while 3 patients who did not adhere to cytisine therapy showed a statistically nonsignificant difference in CO emitted.

The VAS score was evaluated at baseline visit-T0 in 44 patients and no statistically significant differences were found between patients on cytisine therapy and those who were not. The difference in scores of two different tests (Fagerström test and Mondor test) measured at baseline visit-T0 between patients who followed cytisine therapy and those who did not follow cytisine therapy was significant (p=0.012) only for physical dependence measured with the nicotine test (Fagerström test) but not for patients' motivation to stop smoking (Mondor test). Among 44

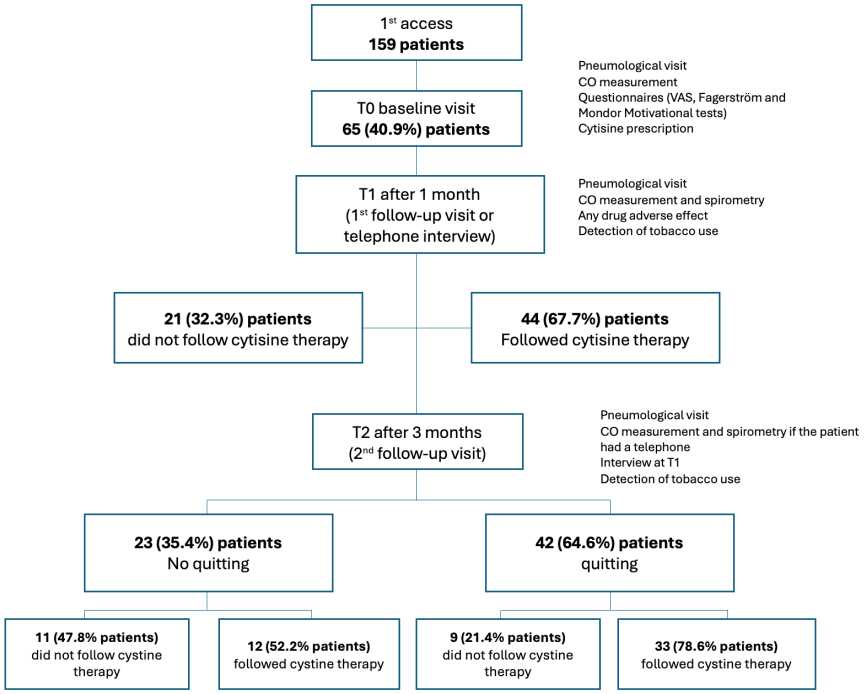


Figure 1. Diagnostic and therapeutic pathway.

patients who received cytisine treatment, only 2 patients (4.5%) developed a non-serious adverse event; one had to discontinue the treatment regimen because of headache, whereas the other ceased therapy due to the appearance of a skin rash.

DISCUSSION

Our study assessed the effectiveness and tolerability of cytisine therapy for smoking cessation in a real-world observational setting in Italy, thus contributing to improving the knowledge about the use of this medication in daily clinical practice to promote smoking abstinence, as part of an integrated smoking cessation intervention and relapse prevention.

Based on our study results, we found that after 3 months from the start of cytisine therapy on 25 days scheme or 40 days regimen, the proportion of patients who stopped smoking was significant in those who followed the therapy compared to those who did not follow the therapy (67.7 *vs.* 32.3%), thus showing the effectiveness of cytisine use in clinical practice for promoting smoking cessation in patients who adhered to the therapy. These results confirmed the data obtained from another retrospective observational study[41] recently published by another Italian research group, where smoking abstinence at three months was 68.7%.

The evaluation of the scores obtained through the VAS test (measuring the intensity of nicotine craving) and the Motivation test (measuring the patients' motivation to quit) administered to patients at baseline visit-T0 showed no statistically significant differences between patients who followed the therapy and those who did not follow it. This is in accordance with a recent study[42], which found no association between measuring motivation to quit smoking through motivational scales alone with success or failure in quitting smoking, thus suggesting that patients' motivation alone should not be considered as a predictor of abstinence maintenance among smokers who wanted to quit.

On the contrary, the score measuring the nicotine physical dependence through the Fagerström test resulted significantly higher in patients who follow the therapy. Since the two dimensions of nicotine physical dependence are the degree of urgency to restore nicotine to a threshold level after nighttime abstinence and the persistence with which one maintains nicotine levels at this threshold during waking hours[43], this result seemed to support the demonstration of the effectiveness of cytisine therapy.

To date, several clinical trials[36,44-46] conducted in many European countries explored the efficacy and the safety of cytisine in smoking cessation, as compared to placebo or to the approved first-line tobacco cessation treatments [nicotine replacement therapy (NRT), bupropion and varenicline, recently withdrawn from the market], suggesting a growing recognition of cytisine's potential worldwide.

A recent systematic review and meta-analysis[47] that included studies from various countries (including European nations, Australia, and New Zealand) found that cytisine is associated with higher quit rates compared to placebo and is comparable in efficacy to NRT and varenicline, but with fewer adverse events, thus suggesting that cytisine could be a valuable addition to the global arsenal of smoking cessation treatments.

These findings are also supported by observational studies[41,48] primarily focusing on the effectiveness and safety of cytisine use for smoking cessation in real-world settings in Italy. These studies suggested that combining cytisine therapy with behavioral interventions may enhance the effectiveness of smoking cessation strategies, supporting its use as an effective and safe tool in smoking cessation programs in a real-world population.

CONCLUSIONS

The findings from this study confirmed that cytisine could be an effective therapy for nicotine addiction when following the adequate dosing schedule without treatment interruption. The data we gathered indicates that cytisine is a drug that effectively aids in smoking cessation, both during the initial treatment period and after three months of therapy. It is also safe and well-tolerated; in fact, only two patients had only mild adverse events. We found that cytisine exhibited a harmless safety profile without any indication of significant safety issues. However, it has a poor therapeutic adherence profile, requiring further research on therapeutic adherence and long-term outcomes in order to optimize treatment strategies.

It is important to emphasize that cytisine may be an attractive choice for tobacco smokers due to its lower cost in comparison to other available pharmacological options, making it particularly appreciated, especially by heavy smokers, who generally require higher therapeutic doses and longer treatment periods[49]. In conclusion, cytisine therapy appears to be a promising and cost-effective option for smoking cessation, supported by both European and global research. Further studies may help solidify its role in smoking cessation programs worldwide.

Conflict of Interest
The authors declare that they have no conflict of interest to disclose.

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Authors' Contributions
Andrea Mastrostefano, Luisa Petraccia and Filomena Fortinguerra: conceptualization, methodology, supervision, validation, writing – review and editing. Irene Terrenato: formal analysis, validation. Maria Papale: conceptualization, supervision, validation, writing. Vincenzo Cilenti, Giorgio Piperno, Eliuccia Mastropasqua, Enrica Ciarciaglini: validation, writing – supervision.

Informed Consent
All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki.

Ethics Approval
The study was approved by the Ethical Committee Comitato Etico Territoriale Lazio, of the Lazio Area 5, with protocol number 104/IRE/24, dated 20 March 2024.

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AI Disclosure
The authors disclose that they did not use artificial intelligence or any assistive technologies for text revision.

REFERENCES

1) World Health Organization (WHO). Tobacco. Accessed April 29, 2024. Available at: https://www.who.int/news-room/fact-sheets/detail/tobacco (Accessed on April 14, 2025).
2) GBD 2019 Tobacco Collaborators. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet 2021; 397: 2337-2360.
3) O'Keeffe LM, Taylor G, Huxley RR, Mitchell P, Woodward M, PetersSAE. Smoking as a risk factor for lung cancer in women and men: asystematic review and meta-analysis. BMJ Open 2018: e021611.
4) Terzikhan N, Verhamme KM, Hofman A, Stricker BH, Brusselle GG, Lahousse L. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam Study. Eur J Epidemiol 2016; 31: 785-792.
5) Lu W, Aarsand R, Schotte K, Han J, Lebedeva E, Tsoy E, Maglakelidze N, Soriano JB, Bill W, Halpin DMG, Rivera MP, Fong KM, Kathuria H, Yorgancıoğlu A, Gappa M, Lam DC, Rylance S, Sohal SS. Tobacco and COPD: presenting the World Health Organization (WHO) Tobacco Knowledge Summary. Respir Res 2024; 25: 338.
6) Bellou V, Gogali A, Kostikas K. Asthma and Tobacco Smoking. J Pers Med. 2022; 12: 1231.
7) Chan JY, Stern DA, Guerra S, Wright AL, Morgan WJ, Martinez FD. Pneumonia in childhood and impaired lung function in adults: a longitudinal study. Pediatrics 2015; 135: 607-616,
8) Bai X, Aerts SL, Verma D, Ordway DJ, Chan ED. Epidemiologic Evidence of and Potential Mechanisms by Which Second-Hand Smoke Causes Predisposition to Latent and Active Tuberculosis. Immune Netw 2018; 18: e22.
9) Franciosi AN, Alkhunaizi MA, Woodsmith A, Aldaihani L, Alkandari H, Lee SE, Fee LT, McElvaney NG, Carroll TP. Alpha-1 Antitrypsin Deficiency and Tobacco Smoking: Exploring Risk Factors and Smoking Cessation in a Registry Population. COPD 2021; 18: 76-82.
10) The Italian National Institute of Health. National Report on Tobacco and Nicotine Use in Italy, World No-Tobacco Day 2025. Rome, 31 March 2025 Available at https://www.salute.gov.it/new/it/news-e-media/notizie/31-maggio-2025-giornata-mondiale-senza-tabacco/ (Accessed on July 31, 2025).
11) American Psychiatric Association, American Psychiatric Association, eds. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association; 2013.
12) Ziedonis D, Das S, Larkin C. Tobacco use disorder and treatment: new challenges and opportunities. Dialogues Clin Neurosci 2017; 19: 271-280.
13) Galiatsatos P, Kaplan B, Lansey DG, Ellison-Barnes A. Tobacco Use and Tobacco Dependence Management. Clin Chest Med 2023; 44: 479-488.
14) Picciotto MR, Kenny PJ. Mechanisms of Nicotine Addiction. Cold Spring Harb Perspect Med 2021; 11: a039610.
15) Giulietti F, Filipponi A, Rosettani G, Giordano P, Iacoacci C, Spannella F, Sarzani R. Pharmacological Approach to Smoking Cessation: An Updated Review for Daily Clinical Practice. High Blood Press Cardiovasc Prev 2020; 27: 349-362.
16) GBD 2017 Italy Collaborators. Italy's health performance, 1990-2017: findings from the Global Burden of Disease Study 2017. Lancet Public Health 2019; 4: e645-e657.
17) Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2012; 11: CD000146.
18) Tudor-Sfetea C, Rabee R, Najim M, Amin N, Chadha M, Jain M, Karia K, Kothari V, Patel T, Suseeharan M, Ahmed M, Sherwani Y, Siddiqui S, Lin Y, Eisingerich AB. Evaluation of Two Mobile Health Apps in the Context of Smoking Cessation: Qualitative Study of Cognitive Behavioral Therapy (CBT) Versus Non-CBT-Based Digital Solutions. JMIR MHealth UHealth 2018; 6: e98.

19) Lindson N, Thompson TP, Ferrey A, Lambert JD, Aveyard P. Motivational interviewing for smoking cessation. Cochrane Database Syst Rev 2019; 7: CD006936.
20) Nurchis MC, Di Pumpo M, Perilli A, Greco G, Damiani G. Nudging Interventions on Alcohol and Tobacco Consumption in Adults: A Scoping Review of the Literature. Int J Environ Res Public Health 2023; 20: 1675.
21) Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation: a meta-analysis. J Am Med Ass 1994; 271: 1940-1947.
22) Costa R, Oliveira NG, Dinis-Oliveira RJ. Pharmacokinetic and pharmacodynamic of bupropion:integrative overview of relevant clinical and forensic aspects. Drug Metab Rev 2019; 51: 293-313.
23) Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. Antidepressants for smoking cessation. Cochrane Database Syst Rev 2023; 5: CD000031.
24) Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013; 2013: CD009329.
25) Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev 2016; 2016: CD006103.
26) Sönmez TG, Fidanci I. Cytisine as an Emerging Tool for Smoking Cessation and Addiction Treatment. Iran J Public Health 2024; 53: 2823-2824.
27) Tinghino B, Baraldo M, Mangiaracina G, Zagà V. La citisina nel trattamento del tabagismo. Tabaccologia 2015; 2: 1-8
28) Hughes JR, Stead LF, Lancaster T. Nortriptyline for smoking cessation: a review. Nicotine Tob Res Off J Soc Res Nicotine Tob 2005; 7: 491-499.
29) Tutka P, Zatoński W. Cytisine for the treatment of nicotine addiction: from a molecule to therapeutic efficacy. Pharmacol Rep PR 2006; 58: 777-798.
30) Etter JF, Lukas RJ, Benowitz NL, West R, Dresler CM. Cytisine for smoking cessation: a research agenda. Drug Alcohol Depend 2008; 92: 3-8.
31) Walker N, Howe C, Glover M, McRobbie H, Barnes J, Nosa V, Parag V, Bassett B, Bullen C. Cytisine versus nicotine for smoking cessation. N Engl J Med 2014; 371: 2353-2362.
32) WHO clinical treatment guideline for tobacco cessation in adults. Geneva: World Health Organization; 2024. Available at: https://www.who.int/publications/i/item/9789240096431.
33) Aubin HJ, Luquiens A, Berlin I. Pharmacotherapy for smoking cessation: pharmacological principles and clinical practice. Br J Clin Pharmacol 2014; 77: 324-336.
34) Oreskovic T, Percac-Lima S, Ashburner JM, Tiljak H, Rifel J, Klemenc Ketiš Z, Oreskovic S. Cytisine Versus Varenicline for Smoking Cessation in a Primary Care Setting: A Randomized Non-inferiority Trial. Nicotine Tob Res 2023; 25: 1547-1555.
35) Courtney RJ, McRobbie H, Tutka P, Weaver NA, Petrie D, Mendelsohn CP, Shakeshaft A, Talukder S, Macdonald C, Thomas D, Kwan BCH, Walker N, Gartner C, Mattick RP, Paul C, Ferguson SG, Zwar NA, Richmond RL, Doran CM, Boland VC, Hall W, West R, Farrell M. Effect of Cytisine vs Varenicline on Smoking Cessation: A Randomized Clinical Trial. JAMA 2021; 326: 56-64.
36) De Santi O, Orellana M, Di Niro CA, Greco V. Evaluation of the effectiveness of cytisine for the treatment of smoking cessation: A systematic review and meta-analysis. Addict Abingdon Engl 2024; 119: 649-663.
37) Puljević C, Stjepanović D, Meciar I, Kang H, Chan G, Morphett K, Bendotti H, Kunwar G, Gartner C. Systematic review and meta-analyses of cytisine to support tobacco cessation. Addiction 2024; 119: 1713-1725.
38) Wise J. NICE proposes adding cytisine as treatment option for smoking cessation. BMJ 2024; 387: q2563.
39) Solimini R, Vecchi S, Fauci AJ, Napoletano A, Coclite D, Mastrobattista L, Mortali C, Palmi I, Amato L, Pacifici R, Experts Panel Group, Evidence Review Team, Pichini S. The Italian clinical practice guideline for the treatment of tobacco and nicotine dependence. Tob Prev Cessation 2023; 9(Supplement 2): A17
40) Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. Cochrane Database Syst Rev 2017; 3: CD001292.
41) Pozzi P, Boffi R, Veronese C, Trussardo S, Valsecchi C, Sabia F, Pastorino U, Apolone G, Cardani E, Tarantini F, Munarini E. Cytisine as a smoking cessation aid: Preliminary observations with a modified therapeutic scheme in real life. Tumori 2024; 110: 124-131.
42) Granda-Orive R, Lledó JF, Asensio-Sánchez S, Solano-Reina S, García-Rueda M, Martínez-Muñiz MÁ, Lázaro-Asegurado L, Buljubasich D, Luhning S, Pendino RL, Cienfuegos-Agustín I, Jiménez-Ruiz CA. Is the motivation to quit smoking a predictor of abstinence maintenance? Tob Prev Cessat 2021; 7: 48.
43) Fagerstrom KO, Schneider NG. Measuring nicotine dependence: A review of the Fagerstrom Tolerance Questionnaire. J Behav Med 1989; 12: 159-182.
44) Zatonski W, Cedzynska M, Tutka P, West R. An uncontrolled trial of cytisine (Tabex) for smoking cessation. Tob Control 2006; 15: 481-484.
45) Walker N, Smith B, Barnes J, Verbiest M, Parag V, Pokhrel S, Wharakura MK, Lees T, Cubillos Gutierrez H, Jones B, Bullen C. Cytisine versus varenicline for smoking cessation in New Zealand indigenous Māori: a randomized controlled trial. Addiction 2021; 116: 2847-2858.
46) Rigotti NA, Benowitz NL, Prochaska J, Leischow S, Nides M, Blumenstein B, Clarke A, Cain D, Jacobs C. Cytisinicline for smoking cessation: a randomized clinical trial. JAMA 2023; 330: 152-160.
47) Ofori S, Lu C, Olasupo OO, Dennis BB, Fairbairn N, Devereaux PJ, Mbuagbaw L. Cytisine for smoking cessation: A systematic review and meta-analysis. Drug Alcohol Depend 2023; 251: 110936.
48) Tedesco E, Ceccato S, Torazzi A, Santin L, Losso L, Bottardi A, Casari R, Melchiori S, Secchettin E, Ferrero V, Arzenton E, Marini P, Lugoboni F, Chiamulera C. Cytisine for smoking cessation in hospitalised smokers with cardiovascular diseases: an observational study. Intern Emerg Med 2025; 20: 817-828.
49) Leaviss J, Sullivan W, Ren S, Everson-Hock E, Stevenson M, Stevens JW, Strong M, Cantrell A. What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? A systematic review and economic evaluation. Health Technol Assess 2014; 18: 1-120.