

SMOKERS' CHARACTERISTICS ASSOCIATED WITH SUCCESSFUL SMOKING CESSATION UNDERGOING PHARMACOTHERAPY IN SLOVENIA

ZNAČILNOSTI KADILCEV, POVEZANE Z USPEŠNIM OPUŠČANJEM KAJENJA S FARMAKOTERAPIJO V SLOVENIJI

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ABSTRACT

Keywords:

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Introduction: Tobacco use is a major global health problem, contributing to premature death and disability. In Slovenia, the prevalence of smoking is higher than the EU average, emphasizing the need for effective tobacco control measures. The aim of this study was to identify the characteristics of patients most likely to benefit from pharmacotherapy for smoking cessation.

Methods: We performed cross-sectional analysis of factors associated with successful smoking cessation using pharmacotherapy for Slovenian smokers. A total of 176 (24.6%) smokers with an average age of 50 years agreed to receive pharmacotherapy for their smoking cessation attempt and were enrolled in the study. Participants were followed up at 4-week intervals during treatment and for 24 weeks after completion of pharmacotherapy.

Results: Attempts to quit smoking with prescription medications were successful in 24.4% of those willing to try. Female smokers, older persons, those with more children, with a lower self-perception of health, a higher number of cigarettes per day and a higher nicotine dependence were more likely to attempt to quit smoking. However, the strongest predictors of smoking cessation success were lower nicotine dependence, which was tested using the Fagerström test for nicotine dependence, and higher adherence to pharmacotherapy.

Conclusion: Nicotine dependence and adherence to pharmacotherapy are the strongest predictors of a successful smoking cessation attempt. Identification of potential responders, prescription of pharmacotherapy and follow-up are applicable in the primary healthcare setting.

IZVLEČEK

Ključne besede:

uporaba tobaka
odvisnost od nikotina
opuščanje kajenja
farmakoterapija

Uvod: Kajenje je pomemben svetovni zdravstveni problem, ki prispeva k prezgodnji smrti in invalidnosti. Slovenija ima višjo razširjenost kajenja v primerjavi s povprečjem EU, kar poudarja potrebo po učinkovitih ukrepih za nadzor tobaka. Namen te študije je bil ugotoviti značilnosti bolnikov, ki jim bo farmakoterapija pri opuščanju kajenja najverjetneje koristila.

Metode: Opravili smo presečno analizo dejavnikov, povezanih z uspešno opustitvijo kajenja z uporabo farmakoterapije pri slovenskih kadilcih. 176 kadilcev s povprečno starostjo 50 let se je strinjalo z uporabo farmakoterapije za poskus opustitve kajenja in so bili vključeni v študijo. Udeleženci smo spremljali v 4-tedenskih intervalih med zdravljenjem in 24 tednov po zaključku farmakoterapije.

Rezultati: Poskus opustitve kajenja z zdravili na recept je bil uspešen pri 24,4 % kadilcev. Kadilke, starejše osebe, z več otroki, z nižjo samooceno zdravja, večjim številom pokajenih cigaret na dan in večjo odvisnostjo od nikotina so pogosteje poskušale opustiti kajenje. Vendar pa je bilo ugotovljeno, da sta manjša odvisnost od nikotina, preizkušena s Fagerströmovim testom za odvisnost od nikotina, in višja aderenza farmakoterapiji najmočnejša napovedna dejavnika uspeha pri opuščanju kajenja.

Zaključek: Odvisnost od nikotina in upoštevanje farmakoterapije sta najmočnejša napovedna dejavnika uspešnega poskusa opustitve kajenja. Tako identifikacija možnih odzivnikov in predpisovanje farmakoterapije kot nadaljnje spremljanje se lahko izvajajo v osnovnem zdravstvenem varstvu.

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1 INTRODUCTION

Tobacco use is a leading preventable risk factor for noncommunicable chronic diseases and premature death worldwide, leading to more than eight million deaths and 170.9 million disability-adjusted life-years lost each year (1). In 2019, more than one billion individuals worldwide were tobacco users. In Slovenia, the prevalence of smoking is 27.9%, which is higher than the EU average of 26.1% (2). According to the Global Burden of Disease study, in 2019 smoking was the second most important risk factor for female deaths and most important factor for male deaths worldwide (3). There is strong scientific evidence that tobacco use inflicts harm on almost every organ in the human body and has detrimental effects on overall health throughout one's lifetime (4), but tobacco users are most at risk for developing lung cancer, chronic obstructive pulmonary disease (COPD) and ischemic heart disease due to smoking (5). Therefore, reducing tobacco use is essential for improving public health and limiting the tobacco epidemic (6).

Smoking also represents a heavy economic burden for healthcare systems throughout the world (3). This includes direct costs (costs of inpatient care, outpatient visits, drugs and diagnostic tests, transportation costs) and indirect costs (productivity lost, the cost of premature retirement and morbidity costs) (7). There are different approaches to limiting tobacco consumption and lowering the cost of treating patients for the effects of tobacco use. These efforts include various non-pharmacological smoking cessation programmes (8), the use of nicotine substitutes and pharmacotherapy (9). Thus smokers in the European Union (EU) approach smoking cessation differently (8-10). In Slovenia, the screening for smoking and tobacco use is carried out by registered nurses who are part of the family medicine (FM) team. Smokers are invited to attend individual or group smoking cessation programmes in Health Promotion Centres. In countries where prescription medicines are available, smokers may be offered this therapy to support the smoking cessation process.

In recent literature, successful smoking cessation has been correlated to factors such as age, gender, education level, cigarette consumption, past quitting attempts, self-efficacy in quitting, presence of smoking family members, household smoking restrictions and nicotine dependency (11-14). Identifying potential respondents for smoking cessation pharmacotherapy based on nicotine dependency involves assessing the level of nicotine dependency of individuals. The two most used questionnaires used to evaluate nicotine dependency are the Fagerström Test for Nicotine Dependence (FTND) and Heaviness of Smoking Index (HSI). FTND and HIS questionnaires had substantial agreement in measuring high levels of nicotine dependency (15).

There is strong scientific evidence that FTND score is associated with smoking cessation success (16-18). However, the association of nicotine dependency and the role of pharmacotherapy to support the smoking cessation process has not yet been studied in Slovenia. Therefore, the aim of this study was to explore the association between the smokers' characteristics and the success of pharmacotherapy for smoking cessation in Slovenian smokers.

2 METHODS

2.1 Study design

The data used in this study come from part of a multicentre prospective non-inferiority clinical intervention supported by the Global Research Awards for Nicotine Dependence foundation (GRAND) (19). In this paper we describe the cross-sectional analysis of factors associated with successful smoking cessation using pharmacotherapy. The data for this analysis derived only from the Slovenian arm of the GRAND study and therefore reflect the setting and the population of Slovenian smokers.

2.2 Setting

FM practices in Slovenia were invited to recruit patients for participation in the study, and purposive sampling was applied. Email invitations to the practices were sent using two databases: The Association of Family Medicine Doctors, which has 351 email addresses, and the Praktik. Um family medicine physicians' union, which has 725 email addresses. The first 24 responding practices were included in the study. The average number of registered patients per FM practice in Slovenia is approximately 1,600 patients, hence the FM practices included in the study reached out to approximately 38,400 appointed patients.

2.3 Study population

The research sample consisted of tobacco users identified in the FM practice by their appointed FM specialist or registered nurse. Convenience sampling was used for recruiting the patients. A total of 715 consecutive tobacco users were asked if they were willing to attend a smoking cessation programme using pharmacotherapy. Out of these, 176 patients agreed to receive pharmacotherapy for their smoking cessation attempt and were enrolled in the study. Enrolment in the study took place from 14 July 2020 to 4 November 2022.

The inclusion criteria for participants were a) active smoking, defined by smoking more than 1 cigarette per day in the 30 days prior to inclusion, b) self-declared motivation for quitting smoking, c) having an appointed FM specialist and d) consent to participate in the study. Exclusion criteria were a) age below 18 years, b) cognitive impairment that results in not being able to answer the

questionnaire, c) hypersensitivity or contraindications to pharmacotherapy for smoking cessation, specifically to cytisine or varenicline.

Participants were enrolled in the study on a voluntary basis, were fully informed about the research procedures before signing the informed consent and were able to withdraw from the study at any point without explanation or consequence. The study was approved by the Slovenian National Medical Ethics Committee (KME 0120/133/2019/4).

2.4 Study protocol

176 smokers who expressed motivation to quit smoking using pharmacotherapy were randomly prescribed one of the two smoking cessation medications that were available at the time of the study (varenicline or cytisine). The envelope technique was used for randomization. Neither doctor nor patient knew what the allocated medication was, until opening the envelope. Participants were followed at 4-week intervals during treatment and for 24 weeks after completion of pharmacotherapy, i.e. a total of 28 weeks for cytisine and 36 weeks for varenicline due to the difference in treatment duration. There was no control group and no follow-up for smokers who did not receive pharmacotherapy.

2.5 Data collection

All smokers were invited to complete the set of questionnaires: The baseline interview questionnaire on smoking habits, FTND and sociodemographic information. The Slovenian version of FTND has been previously used in publications (20) issued by the Slovenian National Institute of Public Health (NIJZ). The FTND questionnaire is presented in supplement 1.

Variables age, gender, education level, cigarette consumption, past quitting attempts, self-efficacy in quitting, presence of smoking family members, household smoking restrictions and scores on the FTND scale were included in the data analysis. Self-assessment of "general health" was subjectively rated by the subjects in five categories from 1 (excellent) to 5 (poor). Adherence to pharmacotherapy was operationally defined as taking $\geq 80\%$ of the prescribed medication until completion of the treatment regimen.

2.6 Data analysis

The sample was calculated to ensure a representative cross-section of smokers in Slovenia utilising Cochran's formula. According to data from the Statistical Office of the Republic of Slovenia, the prevalence of adult smokers in 2019 was 17.4% ($n=233922$). Therefore, a representative sample of smokers necessitated a minimum of 384 participants ($e=95\%$; $z=5\%$). We anticipated that about 40% of smokers would express interest in pharmacotherapy to assist their smoking cessation attempt, therefore our target was to enroll at least 150 smokers for the analysis. The study utilised Research Electronic Data Capture (REDCap) database management technology for real-time data monitoring. Statistical analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics 29. Descriptive statistics, including frequencies, means and standard deviations or ranges and medians, were used to summarize demographic characteristics and FTND items. Variables associated with smoking cessation success were identified through univariate analysis. Furthermore, a multivariate logistic regression model between successful smoking cessation and potential predictors was constructed. A statistical significance level of $p<0.05$ was assumed for the hypothesis test.

Prior to the analysis, multicollinearity was evaluated by calculating the tolerance values and the variance inflation factor (VIF). In all cases, the VIF values were in the range of 1 to 2, indicating that there was no multicollinearity between the variables.

In total, the data set contained 1.71% missing values, which affected only four variables, with no discernible pattern. To compensate for these missing values and obtain unbiased estimates, multiple imputation was performed. The assumption of normal distribution was checked using a Kolmogorov-Smirnov test with a random sample.

3 RESULTS

3.1 Demographic characteristics

A total of 715 smokers were invited to participate in the study. Of these, 24.6% were willing to attempt smoking cessation (responders), and the majority did not attempt smoking cessation (non-responders). The demographic and clinical characteristics of responders and non-responders are presented in Table 1.

3.2 Factors associated with successful smoking cessation

Potential predictors in successful smoking cessation using pharmacotherapy are presented in Table 2. Fewer cigarettes per day, lower nicotine dependence and higher adherence to pharmacotherapy were associated with successful smoking cessation.

Table 1. Demographic and clinical characteristics of responders and non-responders (n=715).

Characteristics	Responders n (%)	Non-responders n (%)	P value
No. of smokers	176 (24.6)	539 (75.4)	<0.01
Age, mean (SD)	50.9 (11.7)	47.2 (14.2)	
Range in years	23-73	18-84	
Missing values		11 (2.0)	
Gender			
Female	96 (54.5)	242 (45.8)	<0.05
Male	80 (45.5)	297 (54.2)	
Education			
Primary school or less	38 (21.6)	103 (19.1)	0.83
Completed secondary school	118 (67.0)	362 (67.2)	
Completed university	20 (11.4)	64 (11.9)	
Missing values		10 (1.9)	
Marital status			
Married	82 (46.6)	205 (38.0)	0.16
In relationship	54 (30.7)	162 (30.1)	
Single	24 (13.6)	90 (16.7)	
Widowed/divorced	16 (9.1)	71 (13.2)	
Missing values		11 (2.0)	
No. of children, mean (SD)	1.65 (1.1)	1.34 (1.0)	<0.01
Missing values		14 (2.6)	
General health, mean (SD)	3.1 (1.0)	2.70 (0.97)	<0.01
Missing values		11 (2.0)	
No. of cigarettes per day, mean (SD)	19.2 (8.8)	15.7 (9.1)	<0.01
Missing values		21 (3.9)	
Age at start of smoking, mean (SD)	19.5 (3.3)	18.9 (5.0)	0.69
Missing values		8 (1.5)	
Dependence (FTND, 0-10), mean (SD)	4.72 (2.1)	3.89 (2.0)	<0.01
Missing values		15 (2.8)	

Legend: FTND - Fagerström Test for Nicotine Dependence; SD - standard deviation.

Table 2. Univariate analysis exploring potential predictors in successful smoking cessation (n=176).

Variables	OR	95% CI	P value
Age	1.02	0.99-1.05	0.17
Gender	0.95	0.47-1.88	0.87
Education (ref. Primary School)			
Completed secondary school	0.47	0.15-1.49	0.19
Completed university	0.42	0.16-1.15	0.09
Partnered (yes/no)	1.23	0.55-2.74	0.61
No. of children	1.00	0.73-1.36	0.99
Age of starting to smoke	1.04	0.97-1.11	0.28
No. of cigarettes per day	0.96	0.91-1.00	0.04
No. of quit attempts	1.08	0.98-1.20	0.13
Confidence in quitting (0-10)	0.97	0.97-1.29	0.19
Other family members smoking (no/yes)	1.69	0.84-3.38	0.14
Household smoking restrictions (ref. smoking everywhere)			
Nobody smokes inside	2.92	0.62-13.70	0.17
Smoking in some areas	2.67	0.56-12.74	0.22
Dependence (FTND, 0-10)	0.73	0.31-0.74	<0.01
Adherence	2.55	1.20-5.38	<0.01
Treatment type (Varenicline/Cytisine)	0.69	0.34-1.38	0.29
General health (0-5)	0.73	0.51-1.04	0.08

Legend: FTND - Fagerström Test for Nicotine Dependence; OR - odds ratio; CI - Confidence interval.

A multivariate logistic regression model between successful smoking cessation and potential predictors was constructed (Table 3). Dependence and adherence were proven to be the statistically significant predictors for successful smoking cessation.

Table 3. Multivariate logistic regression between successful smoking cessation and potential predictors (n=176).

Variables	OR	95% CI	P value
Age	1.04	0.99-1.08	0.06
Education (ref. Primary School)			
Completed secondary school	0.60	0.21-1.69	0.32
Completed university	1.61	0.38-6.81	0.52
Other family members smoking (no/yes)	1.02	0.44-2.35	0.96
Household smoking restrictions (ref. smoking everywhere)			
Nobody smokes inside	2.47	0.45-13.61	0.30
No. of days of smoking	0.96	0.85-1.08	0.50
No. of cigarettes per day	1.00	0.95-1.06	0.97
No. of quit attempts	1.00	0.88-1.14	0.94
Confidence in quitting (0-10)	1.09	0.92-1.28	0.33
Dependence (FTND, 0-10)	0.75	0.58-0.96	0.02
Adherence	3.53	1.47-8.51	<0.01
General health (0-5)	0.70	0.43-1.16	0.17

Legend: FTND - Fagerström Test for Nicotine Dependence; OR - odds ratio; CI - Confidence interval.

The model was found to be statistically significant ($p < 0.01$), overall showing a good model fit. The predictors explained by the model were better explained in the group that did not successfully complete the treatment (97% correct prediction). Nevertheless, the model was able to explain 24% of the variability of the dependent variable.

4 DISCUSSION

This study showed that almost a quarter of smokers undergoing pharmacotherapy successfully quit smoking for a 24-week interval. The statistically significant predictors of smoking cessation success were nicotine dependence and adherence to pharmacotherapy.

The cross-sectional analysis that was performed aimed to investigate factors associated with the success of smoking cessation facilitated by pharmacotherapy. Out of 715 invited participants, 24.6% opted to attempt smoking cessation using prescription medications, specifically cytisine and varenicline, with a success rate of 24.3% over the 24-week observation period.

The univariate analysis among 715 invited participants (Table 1) showed that female smokers, older smokers and smokers with a higher number of children were more likely to try to quit smoking. In addition, those who reported poorer general health, higher daily cigarette consumption and higher nicotine dependence were more likely to engage in smoking cessation initiatives.

A multivariate logistic regression model between successful smoking cessation and potential predictors was constructed (Table 3). Dependence and adherence were proven to be the statistically significant predictors for successful smoking cessation.

In 176 patients who used prescription medicine, univariate analysis identified dependence, adherence and lower daily cigarette consumption to be correlated with the smoking cessation. However, lower daily cigarette consumption did not prove significant in the multivariate model. In this study, the FTND served as a critical measure for assessing nicotine dependence and showed a robust association with the effectiveness of smoking cessation using the prescribed medications studied. The results of our study also show that treatment adherence to non-NRT pharmacological therapy is essential for smoking cessation, regardless of the medication used (cytisine or varenicline).

Our findings align with prior research indicating that various demographic factors correlate with the likelihood of successfully quitting smoking through pharmacotherapy. These factors include age, gender, level of education, marital status, presence of children and self-assessment of health status (11, 12, 21, 22). However, after adjusting for other variables in the multivariate regression model, only nicotine dependence and adherence to pharmacotherapy protocols were found to be statistically significant predictors of smoking cessation success. A larger sample size would probably confirm or reject the significance of previous sociodemographic variables. This observation is consistent with several studies indicating that FTND scores are an indicator of successful smoking cessation (16-18). Indeed, Fagerström's study has shown that higher FTND scores correlate with a lower probability of being abstinent at week 24 (16). Our study confirms this relationship in the context of pharmacotherapeutic interventions. Furthermore, our results highlight the utility of FTND scores in the assessment phase in identifying smokers at increased risk of non-adherence to subsequent treatment sessions (23). Studies on adherence to nicotine replacement therapy (NRT) have shown that adherence doubles the rate of successful smoking cessation (24), and there is a positive correlation between adherence to treatment and tobacco abstinence, with early abstinence experience being a strong driver of adherence (25). Several studies have found a strong relationship between the number of cigarettes smoked and smoking cessation (26, 27), and a longitudinal study of 17,155 persistent smokers who were followed over a six-year period showed that higher daily cigarette consumption, shorter intervals before the first cigarette of the day and regular daily smoking patterns resulted in a lower probability of smoking cessation (13). Regarding prescription medications, Noor et al. showed that lower daily cigarette consumption is associated with a higher likelihood of becoming smoke-

free in people undergoing varenicline treatment (28). However, in the multivariate logistic model of our study, this variable was no longer recognized as a significant factor associated with smoking cessation. It is possible that FTND and adherence to treatment might mediate or moderate the relationship between daily cigarette consumption and smoking cessation.

Among other factors investigated, including age, gender, self-perceived general health and number of children, none emerged as a predictive factor for smoking cessation success in our study population, although they were associated with a higher likelihood of attempting smoking cessation. Several other predictors for both trying to quit and successful cessation were described in the literature (29), but none demonstrated statistical significance in our population. There are several possible reasons for this outcome, including complex interactions between variables that could not be fully explored due to a limited sample size.

The pharmacological approach to smoking cessation is widely acknowledged as safe and efficacious, warranting consideration for all individuals committed to quit smoking (9, 19). Notably, varenicline, cytisine treatment and NRT are all effective methods for smoking cessation (30). Although a trial by Courtney et al. failed to demonstrate noninferiority of cytisine compared with varenicline regarding smoking cessation (31), the standard 4-week cytisine treatment was shown to be less effective than the standard 12-week varenicline treatment for smoking cessation in the trial by Orešković et al. (19).

Our study has several notable strengths. While references demonstrate the importance of nicotine dependence for smoking cessation success, the significance of adherence to smoking cessation medications is novel in this context. Our study's key advantage is demonstrating how medication adherence can improve smoking cessation effectiveness in real-world clinical settings. The biggest strength of our research is its practical application in a real family medicine setting. The tools we used to identify candidates for smoking cessation medication can be easily integrated into routine primary care. Additionally, using two different types of smoking cessation medications underscores the thoroughness of our study.

However, our study also has some limitations. First, the small sample size limits the statistical robustness required for an individualized analysis of the efficacy of each medication. Nonetheless, the observed similarity in outcomes between the two medications supports the generalisability of our findings to different pharmacotherapeutic approaches to smoking cessation. There was no control group and no follow-up for smokers who did not receive pharmacotherapy. Furthermore, because we rely on cross-sectional data, we are limited in our ability to establish definitive causal relationships or

temporal sequences between smoking cessation success and associated factors. This limitation underscores the need for future longitudinal studies to elucidate the dynamic interplay of these variables over time.

There was no connection with real participant data, which limited the interpretation of results, particularly concerning non-respondents in the context of mental health, previous addiction diseases and socioeconomic status, all of which heavily influence continued smoking according to findings from previous studies (21). Also, the success of quitting smoking can be affected by the condition during or after treatment and by recovering from a serious illness (32, 33). Moreover, it is possible that more motivated FM enrolled patients participated in the study, and this can also be reflected in the population of their patients. While we have not included these variables in our data collection, we want to emphasize their importance and acknowledge their potential impact on the outcomes.

5 CONCLUSION

This study highlights the central role of reduced nicotine dependence and higher adherence to pharmacotherapy as robust predictors of smoking cessation success when using pharmacotherapy. This finding enables the identification of potential responders to pharmacotherapeutic interventions and facilitates targeted prescribing and follow-up in primary healthcare. Moving forward, it is imperative to investigate the efficacy and outcomes of targeted pharmacotherapy prescription for smoking cessation through further research efforts. Such investigations will not only improve our understanding of the role of pharmacotherapy in smoking cessation, but will also enable the development of tailored interventions to optimise smoking cessation outcomes more broadly (20).

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CONFLICTS OF INTEREST

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ETHICAL APPROVAL

The authors of this paper hereby declare that the study complies with the Declaration of Helsinki and has been approved by the Slovenian National Medical Ethics Committee (KME 0120/133/2019/4).

AVAILABILITY OF DATA AND MATERIALS

Access to the data is subject to approval and a data-sharing agreement.

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