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Review Article

The Effect of Varenicline on Smoking Cessation in Hospitalized Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Varenicline tartrate is a new and selective agonist of the nicotinic acetylcholine receptor (nAChR). This systematic review and meta-analysis aimed to determine varenicline efficacy in smoking cessation among hospitalized patients.

Methods: We looked through worldwide databases such as Web of Science, Embase, PubMed, Cochrane, and Scopus. Relevant pieces of research published on varenicline efficacy on smoking cessation among hospitalized patients were discovered using proper keywords. The data were analyzed using Stata software version 14 and a random-effects model meta-analysis.

Findings: Nine studies were eligible to be included in this study, with a total sample size of 2131. Generally, the point abstinence rate was significantly greater in the varenicline group than in the placebo group at weeks 12 (odds ratio [OR] = 0.59; 95% CI: 053-0.65; $P<0.001$), 24 (OR = 0.78; 95% CI: 0.72-0.84; $P<0.001$), and 52 (OR = 0.86; 95% CI: 0.80-0.92; $P<0.001$). Furthermore, the continuous abstinence rate for weeks 4 (OR = 0.70; 95% CI: 019-0.54; $P=0.000$), 12 (OR = 0.26; 95% CI: 019-0.54; $P<0.001$), 24 (OR = 0.32; 95% CI: 019-0.53; $P<0.001$), and 52 (OR = 0.32; 95% CI: 019-0.54; $P<0.001$) was significantly greater in the varenicline group than in the placebo group.

Conclusion: According to the high efficacy of varenicline in both short- and long-term smoking settings and considering the importance of smoking cessation in high-risk hospitalized patients, varenicline consumption could be considered as a main smoking cessation strategy in these patients.

Keywords: Smoking cessation, Varenicline, Hospitalized

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Introduction

Tobacco has been consumed for centuries across the world, even though it causes 8 million deaths globally each year.[1]

Nevertheless, the World Health Organization (WHO) believes that there exist 1 billion smokers throughout the world. Every day, 15 billion cigarettes are smoked. The percentage of smokers varies significantly among countries, ranging from 5% to 45%.[2] Even though approximately 40% of smokers attempt to stop, only around 10% accomplish and keep abstinence.[1]

In a survey conducted on 1000 smokers, 44% favored smoking cessation by lowering the number of cigarettes used each day, while 68% believed that drugs can help them quit smoking. Nonetheless, the US Clinical Practice Guidelines suggest that smokers stop smoking abruptly.[3] According to a population-based study, delayed withdrawal might be less beneficial than rapid abstinence.[3] The upregulation of brain nicotine receptors as a result of chronic nicotine exposure and consequent tolerance to nicotine's physiological effects increases dependency and withdrawal manifestations in the process of smoking cessation.[4] According to the obtained data, the α4β2 receptor is nicotinic acetylcholine, leading to nicotine dependence.[5]

Bupropion sustained release (SR), nicotine replacement therapy (NRT), and antidepressants are currently authorized medications for smoking abstinence.[6-8] According to a systematic review of 132 NRT trials, this therapy could lead to smoking cessation with a 50%-70%

possibility.[9] A meta-analysis of 40 bupropion studies, on the other hand, revealed that smoking cessation was more probable to happen. In addition, just 3.5% of smokers throughout 2 years effectively stop smoking. As a result, innovative treatment techniques are required to assist smokers in quitting smoking and overcoming tobacco dependency.[10]

Varenicline is a mild agonist with excellent affinity and selectivity for 42 neuronal nicotinic receptors. Varenicline dramatically improves smoking cessation in smokers who seek therapy and abruptly quit.[11] Varenicline could be a useful strategy for smokers who are not willing or unable to quit smoking immediately but tend to minimize their smoking and plan for smoking cessation (for instance, reducing to quitting method).[12] Varenicline has been proposed in some studies as a therapeutic alternative for smokers who are unable to quit smoking abruptly.[11] As its efficacy in sufferers with acute illnesses, like cardiovascular disease and acute coronary syndrome, is known to a small extent, we conducted a meta-analysis to investigate varenicline efficacy in high-risk hospitalized smokers.

Methods

This meta-analysis and systematic review followed the guidelines outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[13]

Search strategies

In this meta-analysis study, we conducted a thorough literature search focusing on the efficacy of varenicline in stopping smoking in patients who experienced hospitalization due to any diseases. The search encompassed international databases and search engines, including PubMed, Medline, Embase, Scopus, Cochrane, and Web of Science. In PubMed, for instance, we employed a combination of vocabulary search, subjective search strategy, and subject heading to ensure maximum sensitivity and capture relevant studies. The search strategy utilized keywords and MeSH terms such as varenicline, Chantix, Champix, hospital, hospitalization, and disease. Scope and advanced search were performed using the wildcard operator ("*") and Boolean operators ('AND,' 'OR,' 'NOT'). Additionally, we manually reviewed the references of identified studies to ensure comprehensive coverage of the literature. Screening involved assessing titles and abstracts to identify studies meeting our inclusion criteria. All authors contributed to the search process.

Study selection

To find out the eligible studies, the following inclusion criteria were considered:

1. Original studies on the effects of varenicline in stopping smoking in hospitalized patients,
2. Accessibility and presence of intended data.

Exclusion criteria were review articles, meta-analyses, preclinical studies, letters to the editor, seminar abstracts, articles in other language than English, and articles without informative data.

Initially, 2 authors independently listed the titles and abstracts of all collected articles. Each author then reviewed the list to identify relevant topics individually. Duplicate titles and articles containing redundant data were subsequently removed. Following this, the selected articles were incorporated into the research process. Finally, the articles underwent evaluation by other authors in the last step.

Data extraction and quality assessment

The data were extracted individually and then combined. Data, such as age, gender, nationality, the date of publication, the duration of smoking, and point smoking abstinence at different time intervals, continuous smoking abstinence at different time intervals, were collected. Also, we extracted the odds ratio (OR) with confidence interval (CI) from each study.

All of the authors examined and validated the retrieved data. The studies were examined methodologically, and the research quality was assessed using the Newcastle-Ottawa Scale (NOS). Based on the NOS, studies were divided into 3 subgroups based on their quality: low (scores 0-3), moderate (scores 4-6), and high (scores 7-9).[14] The NOS score for each article was over 4.

Data synthesis and analysis

The primary objective of this study was to examine the efficacy of varenicline in high-risk hospitalized smokers. Therefore, its variance was estimated using binomial distributions. A weighted average approach was used to combine the prevalence reported by various studies, with each study's weight determined by its inverse variance. To assess heterogeneity within the included studies, the Q test and I2 index were conducted at a significance level of α less than 10%. Two main methodologies (fixed- and random-effects models) were used to aggregate the results of the studies. In instances where significant heterogeneity was observed among the study results, the random-effects model was used for analysis and comparison. The OR for a 2-by-2 cross-sectional table was computed using the following formula[15]:

$OR = ad/bc$

The 95% CI was calculated using the following formula: $L(OR) \pm 1.96\,SE(Ln(OR))$ That:

$$\mathrm{SE}\left(\mathrm{Ln}\left(\mathrm{OR}\right)\right) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$$

Results

In the current investigation, we looked at 9 eligible

original publications (case-control and cohort studies) about varenicline efficacy on smoking cessation among hospitalized patients (Tables 1 and 2). Figure 1 depicts the procedures for selecting studies. The overall sample size was 2,131, with case and control subjects at the average ages of 56.5 and 54.7 years, respectively.

In this study, patients were deemed point abstinent when they had not smoked in the 7 days before the visit, as evidenced by a self-report of zero cigarettes smoked per day, verified through a carbon monoxide monitor reading of ≤ 10 ppm. Overall, the varenicline group had a significantly higher point abstinence rate from weeks 12 (OR = 0.59; 95% CI: 053-0.65; $P < 0.001$), 24 (OR = 0.78; 95% CI: 0.72-0.84; $P < 0.001$), and 52 (OR = 0.86; 95% CI: 0.80-0.92; $P < 0.001$) than the placebo group (Table 3). Thus, varenicline reduced smoking rates (point abstinence) by 41%, 22%, and 14% during weeks 12, 24, and 52 in turn.

Furthermore, patients were regarded as continuously abstinent in case they avoided smoking based on a self-report of zero cigarettes smoked daily, which was validated by a carbon monoxide monitor reading of ≤ 10 ppm. According to fixed-effects models, the rate of continuous abstinence from weeks 4 (OR = 0.70; 95% CI: 0.19-0.54; $P < 0.001$), 12 (OR = 0.26; 95% CI: 0.19-0.54; $P < 0.001$), 24 (OR = 0.32; 95% CI: 0.19-0.53; $P < 0.001$), and 52 (OR = 0.32; 95% CI: 019-0.54; $P < 0.001$) was significantly lower in the placebo group than in the varenicline group (Figures 2, 3, and 4 and Table 4). Varenicline reduced smoking rates (continuous abstinence) by 74%, 68%, and 68% during weeks 12, 24, and 52, respectively.

Publication bias

The results from Begg's funnel plot indicated no evidence of publication bias ($P = 0.17$; Figure 5).

Discussion

This meta-analysis study was designed to evaluate the efficacy of varenicline in patients who have experienced hospitalization due to conditions such as cardiovascular disease and chronic obstructive pulmonary disease (COPD). Considering the main results of the current meta-analysis study, varenicline seems an effective choice for hospitalized patients with smoking-related conditions. In terms of the mechanism, varenicline mainly binds to the α4β2 receptor, which in turn results in dopamine secretion. Also, it does not upregulate nicotinic acetylcholine receptors (nAChRs).[24,25] These 2 functional properties of

Table 1. Characterizations of case-control articles reviewed in this study

First author (reference)	Country	Year	Samples size		Mean age ± SD		Type of disease	Gender (Male %)		Number of smoking years (Mean ± SD)	
			Case	Control	Case	Control		Case	Control	Case	Control
Windle[16]	Canada, USA	2018	151	151	54.7 ± 8.4	55.3 ± 8.3	Acute coronary syndrome	74.2	76.2	35.1 ± 11.4	36.7 ± 11.8
Rigotti[12]	USA	2010	355	359	55 ± 8.6	55.9 ± 8.4	Cardiovascular disease	75.2	78.2	40	39
Tashkin [17]	USA	2011	248	251	57.2 ± 9.1	57.1 ± 9	COPD	62.5	62.2	40.4	40.6
Steinberg [18]	USA	2011	39	49			Various diagnosis	60	59		
Politis [19]	Greece	2018	44	57	51.56 ± 11.55	50.32 ± 13	COPD	63.4	71.9		
Total			837	867	56.5	54.7					

Table 2. Characterizations of cohort articles reviewed in this study

First author (reference)	Country	Year	Samples size	Mean age ± SD	Type of disease	Gender (Male %)	Number of smoking years (Mean ± SD)
Jiménez Ruiz [20]	Spain	2012	159	58.24 ± 8.93	COPD	71	40.58 ± 9.1
Shin [21]	Korea	2016	52		COPD	96.2	
Melzer [22]	USA	2016	36		COPD	96.3	
Reina [23]	Spain	2013	180	58.34 ± 11.89	Cardiovascular disease	78	
Total			427	58.29 ± 10.43			

Table 3. Number of patients who did not smoke for at least 7 days

First author	Samples size		Point abstinence							
			Week 4		Week 12		Week 24		Week 52	
	Case	Control	Case (%)	Control	Case	Control	Case	Control	Case	Control
Windle[16]	151	151	90	57	86	55	70	49	59	44
Rigotti[12]	355	359			192	64	124	57	99	57
Reina[23]	180				94		85		67	

Table 4. Number of patients who did not smoke any cigarette

First Author	Samples Size		Continuous abstinence							
			Week 4		Week 12		Week 24		Week 52	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Windle[16]	151	151	78	49	66	45	53	39	46	32
Tashkin[17]	248	251			105	22	64	18	46	14
Rigotti[12]	355	359			167	50	100	34	68	26
Steinberg[18]	39	49	15	14	13	12	12	9		
Politis[19]	44	57	25	10	24	9	23	8	23	8
Jiménez Ruiz[20]	159						97			
Shin[21]	52						19			
Melzer, AC[22]	36								11	
Reina, SS[23]	180									

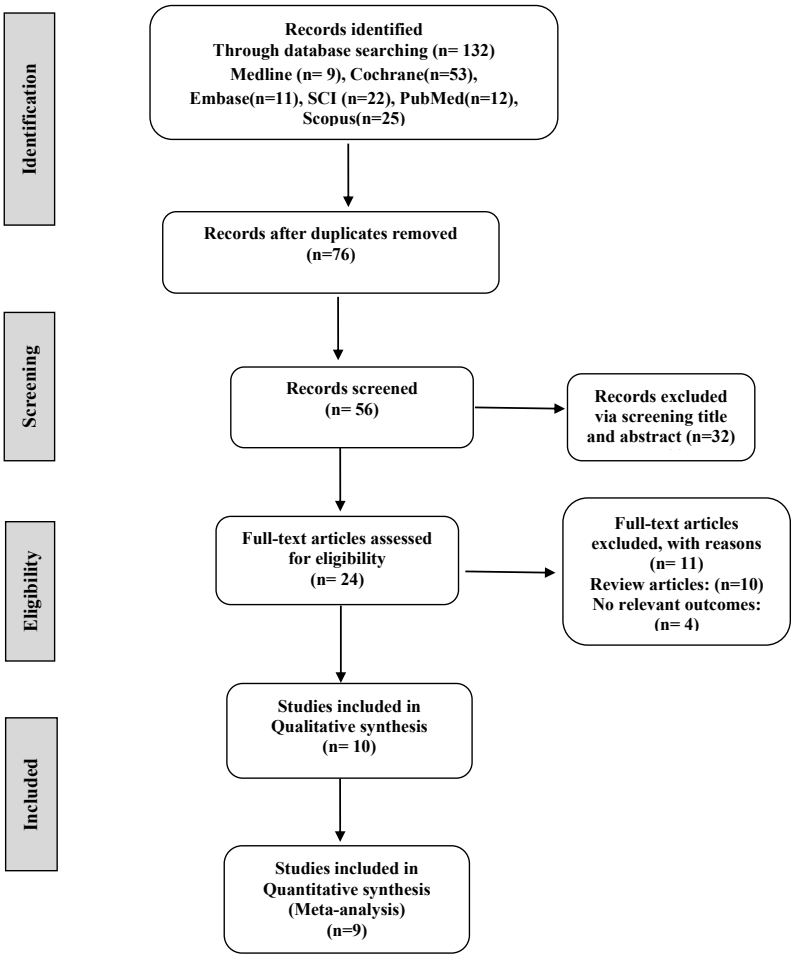

Figure 1. The PRISMA flow diagram illustrating the selection of articles

varenicline help patients to quit smoking with minimum nicotine withdrawal symptoms. In addition, compared with nicotine, varenicline has a longer half-life and plays a role as a stable nicotine antagonist.[25,26] Varenicline is also a stable component that mainly remains unmetabolized, making it a considerable drug for long-term smoking cessation.[27]

In this study, most of the subjected cases were patients with hospitalization experience due to conditions such as cardiovascular diseases and COPD. In such cases, the efficacy and safety of smoking cessation drugs should be considered simultaneously. Varenicline is reported to have no major drug-drug interactions.[28] This is much more important in patients who receive medications. In terms of safety, in clinical trials, adverse effects (such as nausea, headache, insomnia, and abnormal dreams) have been

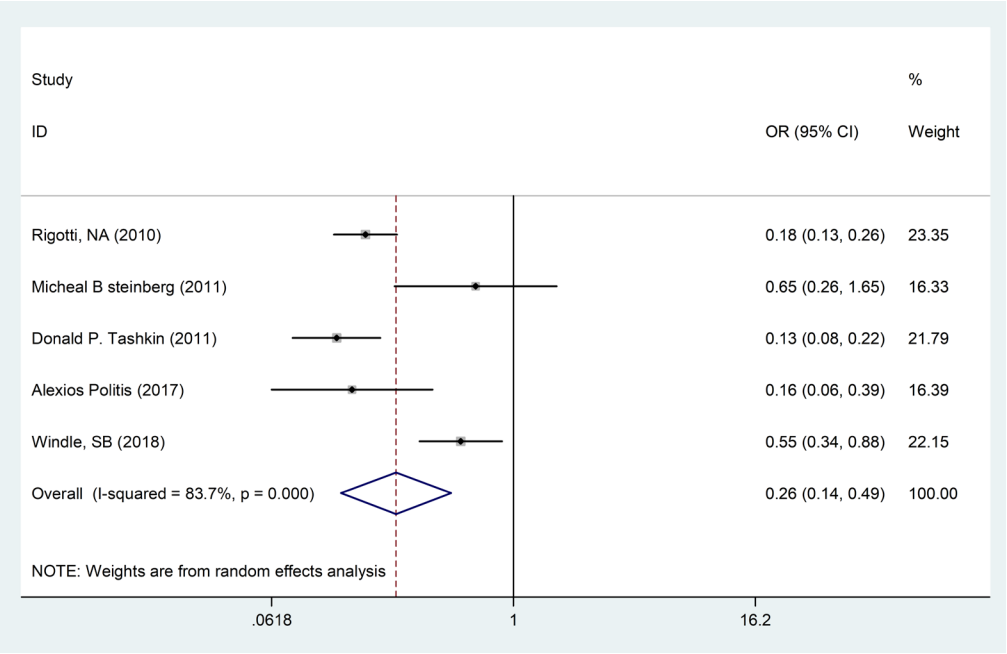

Figure 2. Forest plots of the studies focused on associations between smoking cessation and varenicline-related variables from week 12

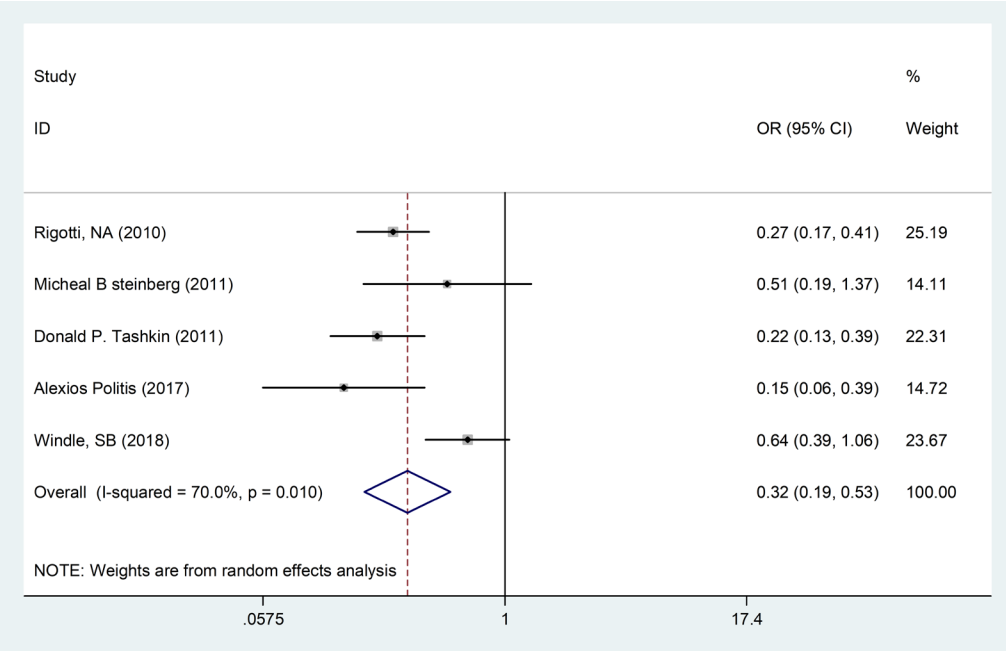

Figure 3. Forest plots of the studies focused on associations between smoking cessation and varenicline-related variables from week 24

reported in association with varenicline consumption.[29] By the way, in the most recent meta-analysis study investigating the adverse effects of cardiovascular disease, no significant adverse effect was reported in varenicline-treated cases compared to the placebo group. Interestingly, they also showed varenicline as a safe smoking cessation agent, even in patients with cardiovascular conditions.[30] However, there are some reports accusing varenicline of having cardiovascular adverse effects.[31]

In another study investigating the long-term (1 year) safety of varenicline, the authors showed that it could be prescribed safely for 1 year.[32] There are several clinical trials that have studied the efficacy of varenicline in smoking cessation programs in the general population.[28] The most important ones to be mentioned are those clinical trials that led to the US Food and Drug Administration (FDA) approval of varenicline in 2006; the first 2 clinical trials were designed to investigate the efficacy of varenicline in comparison to bupropion and placebo. These 2 multicenter trials were performed to survey the effect of varenicline at different time points after 12 weeks of treatment.[28,33] The third trial was structured to assess the impact of extending the use of varenicline from 12 to 24 weeks on the relapse rate.[29] Both trials showed similarly

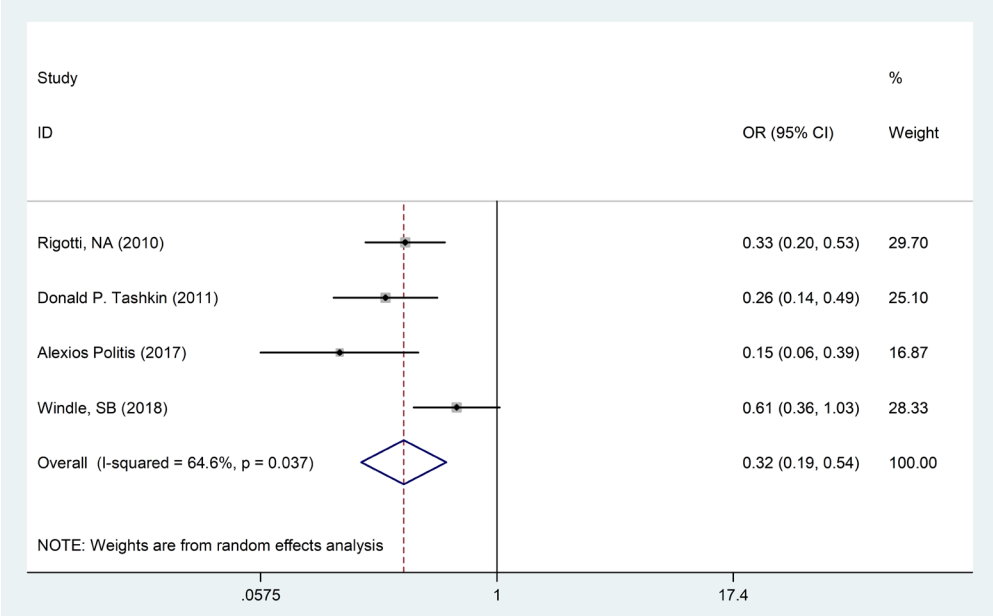

Figure 4. Forest plots of the studies focused on associations between smoking cessation and varenicline-related variables from week 52

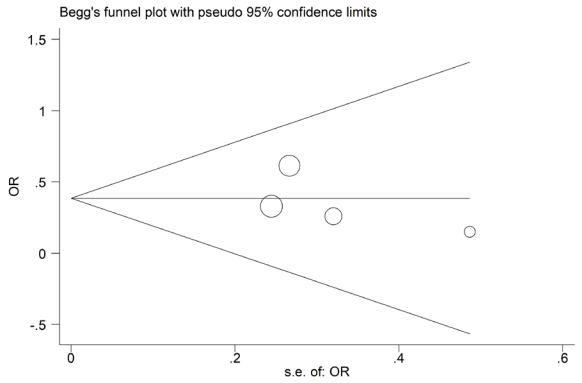

Figure 5. Begg's funnel plot for publication bias, indicating pseudo 95% confidence limits

significant outcomes and higher efficacy of varenicline. Their main results indicated 44% abstinence at the end of the 24th week of the trials in individuals receiving varenicline, while 30% of the bupropion group and 18% of the placebo group stopped smoking. Even after 1 year, 22%-23% of the varenicline group were still abstinent, while 15%-16% of the bupropion group and 8%-10% of the placebo group remained abstinent. In the phase III trial, 1,927 smokers were enrolled and received 1.0 mg of open-label varenicline twice a day for 12 weeks.64.1% of cases stopped smoking by the end of the 12th week. After that, the abstinent cases were divided into 2 groups to receive double-blind varenicline or placebo for another 12 weeks. Interestingly, smoking abstinence rates were significantly higher in the varenicline group. This difference may indicate the importance of long-term consumption of varenicline to achieve a higher rate of smoking abstinence in smokers who do not show adverse effects.

In the case of meta-analysis studies, a meta-analysis in 2012 investigated the efficacy of varenicline in 6,375 smokers and showed that the chance of smoking abstinence is 2.83 times more than placebo at week 52. They also showed that the chance of smoking abstinence in patients with COPD and cardiovascular diseases was higher than in healthy cases.[34]

Also, the efficacy and safety of varenicline have been investigated in patients with neuropsychological conditions. In a meta-analysis surveying the efficacy of varenicline in outpatients with schizophrenia, researchers showed that varenicline not only reduces the rate of smoking in subject cases but also does not cause any severe side effects in these patients.[35]

An important outcome of the current study is the significant efficacy of varenicline in both short-and long-term smoking cessation programs. Our results show that although the rate of smoking abstinence in both continuous and point forms declines during smoking cessation programs in patients receiving varenicline, it remains significantly effective compared to placebo, even in the 52th week. As mentioned earlier, this long-term effectiveness of varenicline seems to be associated with its stability and high affinity of its receptor, as well as with the fact that it does not sensitize or upregulate the α4β2 receptor.[28]

Like any other study, our meta-analysis has its limitations. Since we excluded studies on outpatient cases, the investigated studies were mostly limited to patients with COPD or cardiovascular diseases. Also, the efficacy of varenicline was evaluated in comparison to placebo while considering other smoking cessation regimes and programs, and comparing their effectiveness will provide a more conclusive outcome.

Conclusion

Finally, considering the high efficacy of varenicline in enrolled patients and previous studies indicating its

acceptable safety, as well as the high risk of smoking in patients with cardiovascular or COPD conditions, it is suggested to use varenicline as a main component of the smoking cessation program in these patients.

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Writing–review & editing: All of the authors.

Competing Interests
No competing interest

Ethical Approval
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